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# Studies of Food Intake: Lessons from Nontraditionally Studied Species

Timothy J. Bartness and Gregory E. Demas

## Introduction

A reasonable question for a reader to ask is "Why should I care about the controls of food intake in animals other than rats, mice, or humans and how can researchers justify studying species other than these three?" Indeed, one of the authors (TJB) posed this question to his first postdoctoral advisor when asked to help solve the riddle of a lack of increased food intake after a fast by Syrian golden hamsters (*Mesocricetus auratus*)—a response primarily shared with other hamster species (see below). To continue in this vein, it would seem that further study of laboratory rats and mice is most warranted based on the shear volume of accumulated knowledge on the controls of food intake for these species. With the advent of gene knockouts and knock-ins that have largely been accomplished in mice, a strong case could be made for further narrowing of our research species to laboratory mice as a means of understanding human food intake.

One answer to the initially posed question is that, despite the considerable knowledge already achieved from food intake studies of laboratory rats and mice, and from humans, many or most of the fundamental problems in ingestive behavior

Timothy J. Bartness Departments of Biology and Center for Behavioral Neuroscience, Georgia State University, Atlanta, GA 30303. Gregory E. Demas Department of Biology and Program in Neural Science, Indiana University, Bloomington, IN 47405.

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have not been satisfactorily solved. Perhaps new approaches using more ecologically relevant animal species might yield insights into solving the puzzles of ingestive behavior—and this is precisely the underlying premise of this review. Therefore, we hope that the reader may find some useful lessons learned via the study of "experiments of nature" (i.e., species-specific food intake behaviors that have been shaped by evolution, that occur in the real world and many of which can be conveniently studied in the laboratory). For example, a negative consequence of sustained exposure to a calorically dense high fat diet (HFD) is overeating (Ramirez & Friedman, 1990), consequent obesity, and its associated health problems (Satcher, 2001). Some animals have evolved to be naturally resistant to the almost reflexive overeating triggered by HFD exposure for many species including humans (Blundell, Lawton, Cotton, & Macdiarmid, 1996). Perhaps by studying the physiological mechanisms underlying food intake in these less-studied species that have been shaped by evolutionary forces, we might gain greater insight into the functional and adaptive significance of resistance to dietary obesity. Similarly, by studying animals that go through self-imposed fasts for weeks or months at a time, even in the presence of food (see below), we might gain insight into mechanisms underlying satiety.

With that focus in mind, note that this chapter will not be a 'Noah's Ark' of food intake across the wide spectrum of animal species, or even covering any one taxonomic order such as *Rodentia*—there are ~1,700 species of rodents (Vaughan, 1978). Thus, given space constraints, any comparative study of food intake in rodents must focus on only a relatively small number of species and largely ignore the others. We have attempted, however, to highlight some selected examples of the feeding responses of nontraditionally studied species that may allow us to identify and isolate specific physiological states, ingestive responses, and/or environmental conditions controlling food intake that are so often inextricably intertwined in laboratory rat and mouse eating behavior. In some cases, experimenters explicitly chose animals as potential models of human food intake/physiology (e.g., HFD feeding by Syrian hamsters), whereas other species were chosen based on the commercial value of the species (e.g., chickens, pigs, and sheep). Still others were studied as part of behavioral ecological experiments, the focus of which often is to better understand the behavior and physiology of the particular species (e.g., penguins). Nevertheless, in retrospect, it appears that at least some of these species-specific responses lend themselves well as models to study long-standing problems in the field of ingestive behavior.

We divided the chapter into sections that focus on contemporary issues in the study of food intake, including: (1) responses to fasting and satiety as viewed from self-imposed reductions in food intake, (2) metabolic control of food intake, (3) peptidergic control of food intake, (4) responses to HFDs, and (5) appetitive ingestive behaviors (foraging/hoarding).

## Responses to Fasting, Voluntary Fasting/Reductions in Food intake and Satiety

Shortfalls in food are common in nature and strategies to cope with energy deficits are diverse across animal species (e.g., mobilization of triglyceride or glycogen, decreases in energy expenditure, use of external energy stores; for review

see Le Maho, 1989). In addition, although one might envision that the subsequent feeding response to a fast is a highly conserved behavior across most, if not all species, this is not the case. For example, hamster species differ in that they do not overeat after a fast as mentioned above (Bartness, 1997; Bartness & Clein, 1994; Borer, Rowland, Mirow, Borer, & Kelch, 1979; Day, Mintz, & Bartness, 1999; Rowland, 1982; Silverman & Zucker, 1976; Simek & Petrasek, 1974; Wong & Jones, 1985). Because absence of a post-fast hyperphagia by hamsters has been most thoroughly studied from a mechanistic standpoint, we will take an in-depth look into this phenomenon and attempt to answer the seemingly perplexing questions: Why don't hamsters overeat after a fast and how is this an adaptive response? We will first look at the less studied, but fascinating cases of prolonged involuntary fasting.

Researchers studying mechanisms of food satiation in laboratory rats and mice typically fast animals and then, just before refeeding, administer a naturally occurring chemical found in the CNS (e.g., neuropeptides such as cocaine- and amphetamine-regulated transcript [CART] (Kristensen *et al.*, 1998; Lambert *et al.*, 1998) or in the periphery (e.g., cholecystokinin [CCK] (Gibbs & Smith, 1982; Waldbillig & Bartness, 1982) ) in an attempt to inhibit the post-fast hyperphagia. What was made abundantly clear in the insightful review by Mrosovsky and Sherry on animal anorexias (Mrosovsky & Sherry, 1980) is that several species exhibit prolonged period of fasting *voluntarily*. Naturally occurring reduced food intake can take one of several forms including complete inhibition of feeding for months (e.g., marmots [*Marmota monax*, Kortner & Heldmaier, 1995]; artic ground squirrels [Galster & Morrison, 1976]; emperor penguins [*Aptenodytes forsteri*, Dewasmes, Le Maho, Cornet, & Groscolas, 1980]) or reduced food intake (e.g., golden-mantled ground squirrels [*Citellus lateralis*, Barnes & Mrosovsky, 1974; Zucker & Boshes, 1982]). Perhaps these impressive voluntary fasts by various penguin species, some occurring for several months (Castellini, Costa, & Huntley, 1987; Cherel, Leloup, & Le Maho, 1988; Cherel *et al.*, 1988; Le Maho, Delclitte, & Chatonnet, 1976; Nordoy & Blix, 1991), might be useful to explore in our attempts to understand the systems engaged in the termination of a meal. Unfortunately, information on the feeding responses after voluntary fasting is severely limited because few studies have measured food intake in these species (for review see Davis, 1976)

In order to understand voluntary food intake reductions, it is important to determine the metabolic consequences of food deprivation because it is generally thought that alterations in fuel oxidation *per se*, a metabolic by-product of these oxidation changes, or the resulting modifications of brain neurotransmitter systems, are the factors responsible for triggering post fast increases in food intake. To this end, fasting has been classically parceled into four phases indicated by the predominant status of lipid, carbohydrate and most importantly, protein metabolism (for review see Newsholme & Leech, 1983, and for a schematized view of the many interrelations between lipid, protein, and carbohydrate utilization during fasting in birds, see Figure 1). Briefly, Phase I (i.e., the post-absorptive period), starts when food has been fully absorbed by the intestine after a meal, the duration of which varies with the caloric content of the meal among other factors. For most animals, this lasts for several hours. Relatively quickly once absorption ends, mobilization of liver and muscle glycogen begins in an apparent attempt to counter the slow decline in blood glucose concentrations after their post-meal peak. Because glycogen stores are rapidly depleted with fasting (Newsholme & Leech, 1983), this source of energy is not even sustainable for relatively short fasts (e.g., Syrian hamsters and laboratory rats

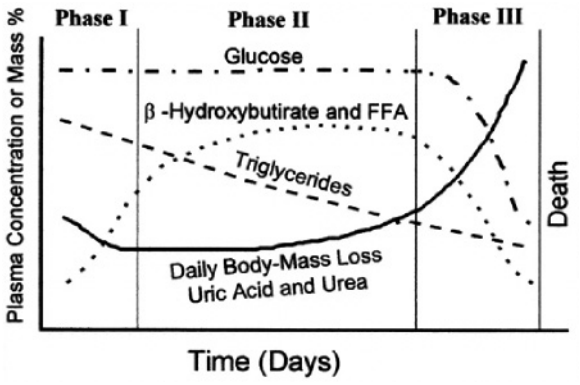


Figure 1. Stylized view of the interrelations among several metabolic measures and body mass during fasting in bird species, especially penguins and gulls (from Alonso-Alvarez & Ferrer, 2001).

[Rowland, 1984] and certainly not for fasts lasting for months [emperor penguins; Groscolas & Clement, 1976]). Some protein breakdown also occurs during this short phase and toward its end, body mass declines more rapidly. Phase II (i.e., early starvation) is characterized by continued and accelerated release of liver glucose into the circulation and mobilization of white adipose tissue (WAT) triglyceride stores for oxidation of their fatty acids by muscle and kidney. This utilization of fatty acids, in turn, spares glucose for use by brain and other tissues. Some gluconeogenesis (the formation of glucose from amino acids resulting from protein breakdown) is stimulated in the liver in Phase II, but this occurs very late in the phase using amino acids derived from protein catabolism and is relatively insignificant (typically this phase is known for its protein sparing). Body mass steadily declines, but at a slower rate than in Phase I. In Phase III (i.e., intermediate starvation), the gluconeogenesis begun late in Phase II begins to diminish, likely due to fulfillment of the mounting energetic needs by the conversion of the adipose-derived fatty acids to ketone bodies in the liver for use by the brain and other tissues. Despite diminished use of amino acids for gluconeogenesis, a critically high rate of protein breakdown occurs, ending the protein sparing of the earlier phases. Body mass loss during this phase is again rapid and impressive. Phase IV (i.e., prolonged starvation) is known for its steady-state rates of carbohydrate, lipid and protein metabolism, and ultimately death (Newsholme & Leech, 1983).

In the typical laboratory rat and mouse fasting–refeeding experiments alluded to above, the animals are fasted overnight or else for 24–48 hr; thus Phase II, and perhaps at the longer durations, early Phase III, is reached before food access is reinstated. With resumption of free-feeding, food intake in rats is increased and, up to a point, is positively correlated with the duration of the fast (Baker, 1955; Lawrence & Mason, 1955). After short fasts, a similar relation holds for subsequent food intake by mice (Ross & Smith, 1953); however, because they are prone to fasting-induced torpor, an energy saving response (Gavrilova *et al.*, 1999; Webb, Jagot, & Jakobson, 1982; Webb & Skinner, 1996), fasted-refed mice do not eat as much as would be expected given their high metabolic rates when fed ad libitum. This is most likely because the caloric deficit is lessened by the torpor-induced decrease in energy expenditure and the post-torpor decrease in locomotor activity.

In stark contrast to most animals across many taxa, all species of hamsters tested to date show no post-fast hyperphagia (i.e., Syrian [*M. auratus*, Silverman &

Zucker, 1976]; Turkish [*Mesocricetus brandti*, Rowland, 1982]; and Siberian [*Phodopus sungorus*, Bartness & Clein, 1994]). Substantial efforts have been made to understand this apparent "maladaptive response" to refeeding after starvation. Interestingly, clear documentation of post-fast increases in food intake in humans is incredulously missing. In a recent unpublished study of Mormons who fast once a month (Fast Saturday) for about a day, upon refeeding they do not initially increase their food intake the next day (Sunday), but rather increase their food intake the following weekend (Plunkett, 2002). How such a delayed post-fast hyperphagia might occur mechanistically is unknown.

The lack of post-fast hyperphagia in hamsters was shown initially when Syrian hamsters (*M. auratus*) were schedule-fed such that their food availability was limited each day. When access to food was restricted to only 1 hr per day, the hamsters never overate as do similarly treated laboratory rats (Simek & Petrasek, 1974), and consequently had progressive losses in body mass and fat resulting in death (Simek & Petrasek, 1974). Using a less severe test of fasting–refeeding responses, Silverman and Zucker (1976) fasted Syrian hamsters or laboratory rats for 24 hr every other day (intermittent feeding/fasting); the rats, but not the hamsters, compensated for the lost calories due to these alternating days of fasting by overeating during the days of ad libitum food access. Indeed, 80–100% of the hamsters died with this fasting/feeding regimen across several experiments, whereas all of the rats thrived (Silverman & Zucker, 1976). Syrian hamsters continue to progressively lose body mass and never overeat even after 6–20 weeks of this restricted feeding schedule (Simek, 1974, 1975, 1980; Simek & Petrasek, 1974).

Detailed analysis of food intake after fasts of varying lengths by Syrian hamsters suggests they do not cope with fasts longer than 12 hr well, or with body mass losses greater than 20% of body weight, becoming "debilitated" (Borer *et al.*, 1979). The pattern of food intake upon refeeding by fasted Syrian hamsters is not different from that of ad libitum fed hamsters with fasts of 5–12 hr (Borer *et al.*, 1979), but the latency to eat after a fast is significantly decreased (DiBattista, 1983). The type of food offered after a fast does not affect this post-fast normophagia, even if the starved hamsters are allowed to self-select their diet from foods varying in caloric density and macronutrient composition (Day *et al.*, 1999; DiBattista, 1987).

It might be argued that restricting food intake to a few hours a day, or every other day, may be contrived and that hamsters in nature would not experience this type of food availability and therefore this is the reason they do not adapt to this feeding schedule. The artificial nature of this type of manipulation, however, may be more apparent than real. That is, animals in the wild do have restrictions on foraging for food and consequently eating because of the presence of predators outside their burrows, as well as inclement weather. Why traditional laboratory animals, such as laboratory rats, are able to adapt to this feeding schedule, whereas nontraditional animals, such as hamsters, are not able to do so has remained a puzzle, although some insights have occurred (see later). Before looking at the behavioral and metabolic responses to fasting by hamsters, laboratory rats and other species more closely, note that the failure to increase food intake by hamsters during refeeding does not preclude recovery of the lost body and lipid mass. Given ample time between fasts (clearly not every other day as in the intermittent fasting models above), Syrian (Borer, Allen, Smalley, Lundell, & Stockton, 1985; Borer *et al.*, 1979; Granneman & Wade, 1982) and Siberian (Day *et al.*, 1999; Wood & Bartness, 1996) hamsters will regain fasting/food restriction-induced body and

lipid mass losses, but do so through decreased energy expenditure/increased efficiency in the utilization of their non-elevated food intakes (Borer *et al.*, 1985).

Silverman and Zucker (1976), and others (Rowland, 1982), have shown that the failure to exhibit a post-fast hyperphagia by Syrian hamsters is not a consequence of being physically unable to overeat. That is, diluted liquid or solid food triggers increases in food intake by Syrian hamsters (Rowland, 1982; Silverman & Zucker, 1976), as do lesions of certain brain areas (i.e., ventromedial hypothalamus [VMH]/paraventricular hypothalamic nucleus [PVN]; (Rowland *et al.*, 1986)), cold exposure (Bartness, Ruby, & Wade, 1984; Simek, 1980), and exercise (Bartness *et al.*, 1984; Browne & Borer, 1978; Shapiro, Borer, Fig, & Vinik, 1987; Tsai, Bach, & Borer, 1981; Tsai, Rosenberg, & Borer, 1982). Silverman and Zucker (1976) speculated that hamsters may have evolved a different strategy to counteract shortfalls in foragable food—building food caches (food hoards; for review see Bartness & Day, 2003) thereby rendering the effects of decreased food availability less costly. In addition, it should be noted that there is an increase in food hoarding accompanying the post-fast increases in food intake by laboratory rats, if they are permitted to do so (Baker, 1955), and they increase both food intake and food hoard size even with restricted access to food (Borker & Gogate, 1981). Food hoarding by laboratory rats is, at best, a secondary priority in that they eat first and then hoard (Day & Bartness, 2003); moreover, it seems that rats do not hoard food in their natural environment (Calhoun, 1962; Lore & Flannelly, 1978; Pisano & Storer, 1948; Takahhashi & Lore, 1980; Whishaw & Whishaw, 1996). In addition, unlike hamsters that possess specialized sublingual pouches to facilitate hoarding, rats lack such specializations. Fasted Syrian (Lea & Tarpy, 1986; Schneider & Buckley, 1993; Wong & Jones, 1985) and Siberian (*P. sungorus*, Bartness, 1997; Bartness & Clein, 1994; Day *et al.*, 1999; Wood & Bartness, 1996) hamsters markedly increase their food hoarding

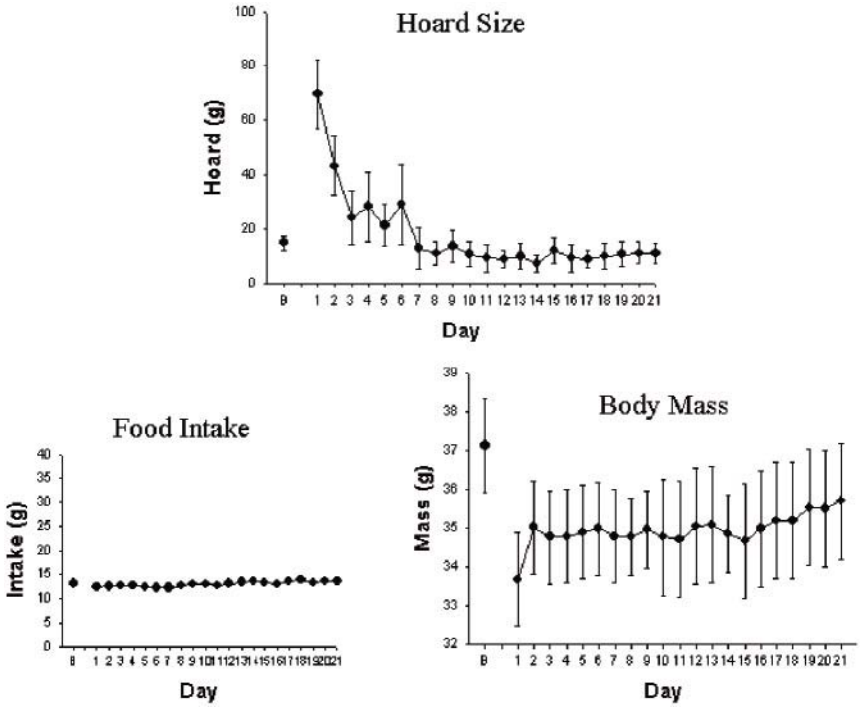


Figure 2. Stimulation of food hoarding, but not food intake by Siberian hamsters after a fast (from Day *et al.*, 1999).

during refeeding, but do not increase their food intake (Figure 2; see below for in-depth discussion).

Perhaps the failure of hamsters to increase food intake after a fast is due to a markedly different physiological metabolic response to starvation. The fasting-induced increases in circulating fatty acids, ketones, and decreases in circulating glucose, insulin, and leptin, as well as liver glycogen by Syrian hamsters (Borer *et al.*, 1979; Mercer, Lawrence, & Atkinson, 1996; Rowland, 1984; Schneider, Blum, & Wade, 2000; Simek & Petrasek, 1974) are similar to those of laboratory rats (e.g., Owens, Thompson, Shah, & DiGirolamo, 1979; Rowland, 1984), however. The lack of a post-fast hyperphagia might likewise be due to differences in the control of gene expression (and subsequent protein synthesis) for neuropeptides thought to be involved in food intake in laboratory rats and mice. Fasting-induced changes in gene expression are similar between laboratory rats and hamsters (of several species) after food deprivation, however. Specifically, food deprivation increases hypothalamic neuropeptide Y (NPY), the long form of the leptin receptor (Ob-Rb), and agouti-related protein (AgRP) gene expression while decreasing CART gene expression by hamsters (Mercer *et al.*, 1995, 1996, 2001; Mercer, Lawrence, Moar, Atkinson, & Barrett, 1997; Mercer, Moar, Ross, & Morgan, 2000; Reddy, Cronin, Ford, & Ebling, 1999).

Likewise, the lack of a post-fast hyperphagia by hamsters could be due to the presence or absence of a dominant environmental factor such as the photoperiod (daylength) or food type. The absence of a post-fast hyperphagia occurs in either long "summer-like" days or short "winter-like" days by Syrian (Granneman & Wade, 1982) and Siberian hamsters (Wood & Bartness, 1996), however. In addition, if Syrian (DiBattista, 1987) or Siberian (Day *et al.*, 1999) hamsters are given a choice of foods, significant post-fast increases in food intake also do not occur, although fat intake increases briefly 6 hr post-fast (DiBattista, 1987). As discussed below, Silverman and Zucker's speculation (Silverman & Zucker, 1976) that hamsters may respond to fasts by increasing food hoarding, rather than food intake, was correct and by increasing hoarding, these animals can accomplish the same goal as animals that overeat—acquiring food energy for current and subsequent needs. In other words, food hoarding and food intake appear to be alternate strategies for energy storage triggered by food shortages and utilized to various degrees in a species-specific manner.

Voluntary fasting seems extremely interesting in light of the tendency for humans in Western and Westernized civilizations, and nonhuman animals in the laboratory, to overeat amidst their caloric wealth. How prevalent are these voluntary fasts? Many species exhibit complete fasts, especially during certain reproductive states (e.g., egg brooding by penguin species (Pinshow, Fedak, Battles, & Schmidt-Nielsen, 1976; Williams, Siegfried, Burger, & Berruti, 1977), post-weaning by seal pups (Castellini *et al.*, 1987), molting of scales by snakes or feathers by penguins (Williams *et al.*, 1977), and hibernation by yellow-bellied marmots [*Marmota flaviventris*, Florant, Tokuyama, & Rintoul, 1989]). The fasting associated with egg brooding and molting of penguins could be viewed simply as two behaviors that are incompatible with feeding. That is, feeding during brooding requires the penguins to leave their nest areas and consequently to leave their eggs unprotected from the elements to travel often long distances to the sea to catch fish (Williams, 1995). Feeding during molting is precluded because the penguins lose all their plumage, and consequently thermal insulation, leaving nothing to combat the icy water temperatures in the Antarctic where they exclusively feed (Groscolas & Cherel, 1992). Both the brooding/ molting and hibernation associated fasts also could be viewed as a consequence of reduced food availability. This seems somewhat unlikely because, although there is a reduction in food during the winter, hibernating mammals often

have food stores in their hibernacula, especially seeds (for review see Davis & Finnie, 1975; Morton, 1975), but even in the presence of food it is not necessarily consumed (e.g., alpine marmots, Kortner & Heldmaier, 1995). If one views the obligatory cessation of food intake during hibernation as a self-imposed fast, then post-fast (arousal) intakes of garden dormice (*Eliomys quercinus*) should be increased over pre-fast (prehibernation), but they are not for the first 24 or 48 hr post-fast (Amid, Cartan, Atgie, & Nibbelink). Hibernating Turkish hamsters also do not increase their food intake over prehibernation levels during arousals when they typically feed, regardless of the length of the hibernation bout (Bartness and Goldman, unpublished observations). Perhaps this fixed rate of feeding by hamsters and dormice after a hibernation bout may help them regulate the utilization of energy stored in the form of a food cache (see later).

The ability of the avian and mammalian species discussed above to thwart the adverse consequences of absent or reduced energy intake, especially in harsh environments such as the Artic, Antarctic, and Turkish steppes, is their principal reliance on stored energy as body fat and secondarily as carcass protein. Although the topic is too complex for a thorough discussion here, for brooding and molting penguins as well as for hibernating small mammals, energy-saving responses are triggered such as huddling for the former (Prevost, 1962) and depressed body temperature/metabolic rate for the latter. An example of the importance of such energy saving responses is the fasted and cold-exposed barn owl (*Tyto alba*) that does not huddle and has relatively limited abilities to depress body temperature/metabolic rates (Thouzeau, Duchamp, & Handrich, 1999). The inability to engage in these physiological/behavioral energy saving responses apparently underlies the high mortality rate of barn owls under these conditions (Thouzeau *et al.*, 1999).

Some fasted penguins have full stomachs—a remarkable combination of conditions. For example, King penguin parents (*Aptenodytes pantagonica*) take turns incubating the eggs so that one parent can go to sea to feed, while the eggs are warmed by the other parent. Upon return from the sea with a full stomach, this parent incubates the egg holding the food in its stomach for as long as 20 days while its mate goes off to sea to eat; the food can then be regurgitated to feed the chick upon its birth (Gauthier-Klerc, LeMaho, Clerquin, Drault, & Handrich, 2000). Digestion/composition of the food during that time is unknown, but its purpose appears to be the first meal for the hatched chicks (for review see Groscolas & Robin, 2001). Clearly, the inhibition of gastric emptying in the face of a prolonged total fast is an impressive feat and its study may lead to an understanding of potent satiety factors. Finally, it is not within our space limitations to discuss the other side of this coin in depth—resumption of feeding after voluntary fasts (see peptidergic control of feeding below for some treatment of this issue). It seems clear that, because no fasting male emperor penguin has been found starved to death, at some point if its mate does not return punctually, the egg is abandoned for a trek to the sea to feed (Groscolas & Robin, 2001). It has been postulated (Groscolas & Robin, 2001) and tested recently (Bernard, Mioskowski, & Groscolas, 2002) that a decrease in the utilization of lipid fuels triggers the resumption of food intake and this, and related topics, are considered below in the section on the metabolic controls of food intake.

What triggers the complete or partial inhibition of food intake in animals that voluntarily fast or reduce their food intake? This question, of course, can be reduced to one of the questions plaguing the field of ingestive behavior—"What makes animals stop eating a meal?" We are not going to address fully this complicated and unresolved question here, except in the few studies focusing on satiety or

anorexia in these naturally occurring examples. If one takes the view that alterations in brain and/or peripheral peptides underlie changes in food intake, then there is a plethora of peptides that could contribute to these inhibitions of food intake (see Table 1 for a list of factors affecting food intake [Schneider & Watts, 2002]). One candidate hormone is pancreatic insulin (for review see Baskin *et al.*, 1999). Specifically, in the yellow-bellied marmot that ceases food intake during the hibernation season, it has been hypothesized that peripherally released insulin could be responsible for this anorexia (Florant, Richardson, Mahan, Singer, & Woods, 1991). Thus, circulating insulin could reach brain insulin and inhibit food intake; however, insulin does not readily enter the brain at times when peripheral levels are high in this species and therefore seems unlikely to participate in this process (Florant *et al.*, 1991). Another well-studied and recognized inhibitor of food intake is peripherally- and centrally-released CCK (for review see Morley *et al.*, 1985; Reidelberger, 1994; Smith, 1996). Siberian hamsters that reduce, but do not eliminate, food intake in winter (Bartness, Morley, & Levine, 1986, 1995; Drazen, Demas, & Nelson, 2001; Wade & Bartness, 1984a) are more responsive to the inhibition of food intake by CCK during short "winter-like" days when their food intake is naturally low, than in long "summer-like" days (Bartness *et al.*, 1986). This leaves open the possibility of an involvement of CCK in winter reductions in food intake for other species as well. Another, nonmutually exclusive hypothesis is that peripheral metabolic signals indicating enlarged adipose tissue lipid fuel stores may lead to a decrease or complete inhibition of food intake during these periods of natural anorexia. Later, with the waning of these signals and/or the emergence of signals reflecting protein catabolism, the resumption of normal levels of food intake may be triggered. There has been much speculation about the identity of this metabolic signal, including the possibility that it is leptin, the peripheral factor that is widely believed to inform the brain of the size of adipose tissue lipid fuel stores (Friedman, 1998). Chronic peripheral leptin infusions block both the prehibernatory decrease in food intake and body weight by arctic ground squirrels (Ormseth, Nicolson, Pelleymounter, & Boyer, 1996), as well as the post-hibernatory increase in fattening (Boyer *et al.*, 1997), two periods of naturally occurring increases in lipid energy stores. This effect of leptin could originate peripherally through the often neglected peripheral metabolic effects of this peptide (for review see Harris, 2000; Schneider & Wade, 1999). Such changes in lipid and/or carbohydrate metabolism could, in turn trigger physiological responses within the brain. Alternatively, these effects of leptin could act *directly* to affect the central sites containing leptin receptors implicated in the control of food intake and body fat (e.g., hypothalamic sites such as the arcuate nucleus [Elmquist, 2001] or brainstem sites such as the dorsal vagal complex [Grill *et al.*, 2002]). Finally, leptin could signal the size of lipid stores by stimulating putative leptin receptors located on the sensory nerves (Fishman & Dark, 1987) that innervate WAT (Niijima, 1998, 1999). Although sensory innervation of WAT has traditionally been ignored, reliable data exist in support of such innervation (Fishman & Dark, 1987; Niijima, 1998, 1999). Whether the effects of chronic peripheral leptin on prehibernatory food intake in arctic ground squirrels discussed above are a physiological reality or a pharmacological curiosity requires considerably more study.

There are several similarities between these nonhuman animal species and humans in terms of some, but not all, of the physiological responses engaged during fasting. For example, extremely malnourished humans near death increase their energy expenditure (Rigaud, Hassid, Meulemans, Poupard, & Boulier, 2000),

Table 1. Some Central Peptides that Affect Food Intake[a]

| |
|---|
| *CNS peptides that stimulate food intake* |
| Agouti-related protein |
| β-Endorphin |
| Galanin |
| Melanin-concentrating hormone |
| Moltin |
| Neuropeptide Y |
| *CNS peptides that inhibit food intake* |
| α-Melanocyte stimulating hormone |
| Bombesin-like peptides |
| Cocaine- and amphetamine-regulated transcript |
| Cholecystokinin |
| Corticotropin-releasing hormone |
| Glucagon-like peptide |
| Insulin |
| Urocortin |
| Vasopressin |

[a]Adapted from Schneider & Watts (2002).

reminiscent of the increases in energy expenditure and protein mobilization by the brooding-associated fasts of male king penguins (*Aptenodytes patagonicus*) when their mates are tardy in their return from feeding in the sea (Cherel, Charrassin, & Challet, 1994). For these humans, it appears that increases in catabolism of their remaining protein energy stores (albeit very small ones given their body mass index of $<10$) may trigger the increases in energy expenditure, although a potential mechanism remains to be elucidated. This finding is quite different from that of fasted healthy humans (Keys, Brozek, Henschel, Mickelson, & Taylor, 1950), or of human anorexia nervosa patients who are otherwise in generally good health (Melchoir, Rigaud, Rozen, Malon, & Apfelbaum, 1989), although both of these populations are generally not in as dire metabolic straights as the dying humans (Rigaud *et al.*, 2000). Some insight into the "terminal spurt" of increased energy expenditure by dying humans might be gained from further study of the prolonged fasts of male king penguins (Cherel *et al.*, 1994).

## Metabolic Control of Food Intake

One segment of research on the control of food intake has focused on alterations in utilizable metabolic fuels as triggers for the stimulation or inhibition of food intake. As with most of the research on food intake, it has been largely conducted using laboratory rats and to a lesser extent, mice. The underlying assumption is that a change in the utilization of one (usually) or more metabolic fuels is sensed either by peripheral (e.g., liver) and/or central receptors to trigger food intake so as to offset the alterations in metabolic fuel utilization. Specifically, some hypotheses have centered on key metabolic fuels such as carbohydrates or carbohydrate-related fuels (glucose, glycogen), lipids or lipid-related fuels (free fatty acids [FFA], glycerol, ketones) or proteins or protein-related fuels (amino acids) (for review see Friedman, 1995; LeMagnen, 1984; Mayer, 1953; Scheurink & Nolan, 1996). Others have posited that it is not decreases or increases in the utilization of a specific

metabolic fuel *per se* that is important, rather it is their ultimate metabolic impact such as alterations in adenosine triphosphate (ATP; Even & Nicolaidis, 1985; Friedman, 1995) that control food intake. Experimental tests of these hypotheses have been conducted using specific metabolic fuel utilization blockers alone or in combination. Thus, to produce decreases in glucose utilization (glucoprivation) so as to increase food intake, several compounds have been administered to laboratory rats, including the glucose analogs 2-deoxy-D-glucose (2DG; Berthoud & Mogenson, 1977; Naito *et al.*, 1973; Smith & Epstein, 1969; Stricker, Rowland, Saller, & Friedman, 1977) or 5-thio-D-glucose (5TG; Flynn & Grill, 1985; Slusser & Ritter, 1980) that compete for enzymes of the glycolytic pathway where glucose ultimately feeds into the tricarboxcylic acid cycle (a.k.a. Krebs cycle). To produce decreases in lipid fuel (fatty acid) utilization so as to increase food intake, blockers of key enzymes in fatty acid transport and their ultimate conversion to ATP (methyl palmoxirate [MP; Friedman, Ramirez, Bowden, & Tordoff, 1990; Friedman & Tordoff, 1986] or mercaptoacetate [MA; Ritter, & Taylor, 1989; Scharrer & Langhans, 1986]) have been used effectively with laboratory rats, especially if they are deriving most of their calories from dietary fat. Alternatively, production of ATP can be blocked to stimulate food intake by laboratory rats, regardless of whether the carbon fragments entering the tricarboxcylic acid cycle originate from carbohydrate, lipid or protein sources such as after treatment with 2,5-anhydro-D-mannitol (2′5′AM; Rawson, Blum, Osbakken, & Friedman, 1994; Rawson & Friedman, 1994; Rawson & Ulrich, 1996) or L-ethionine (Rawson, Ulrich, & Friedman, 1994). Finally, peripheral administration of insulin can be used to clear all circulating metabolic fuels from the blood to storage and thereby increase food intake in laboratory rats (e.g., Gil & Friedman, 1982). These manipulations of metabolic fuels do not stimulate food intake universally, however (for review see Bartness, 1990). Once again, hamster species are a notable exception. Specifically, injections of 2DG or 5TG (Bartness *et al.* 1995; DiBattista, 1982; Ritter & Balch, 1978; Rowland, 1978; Sclafani & Eisenstadt, 1980; Stamper, Dark, & Zucker, 1999) do not stimulate food intake as they do in laboratory rats (Berthoud & Mogenson, 1977; Ritter & Slusser, 1980; Smith & Epstein, 1969; Stricker & Rowland, 1978). Furthermore, injections of short-acting insulin produce small or no increases in feeding in hamsters or Mongolian gerbils (*Meriones unguiculatus*), but long-lasting insulin does increase food intake ([Bartness & Clein, 1994; DiBattista, 1983, 1984; Ritter & Balch, 1978; Rowland, 1978; Wade, Schneider, & Friedman, 1991]; cf., [Bartness & Clein, 1994); laboratory rats increase food intake after administration of either insulin form (Flynn & Grill, 1983; Gil & Friedman, 1982; Rowland & Bartness, 1982). Although the physiological mechanisms for the differential effects of long versus short-lasting insulin are not known, one possibility is that long-term insulin triggers hypoglycemia, that hamsters respond to by increasing food intake, whereas short-term insulin fails to induce hypoglycemia. Although this idea is intriguing, it remains to be tested. Hamster species are not the only ones that do not increase their food intake after alterations in metabolic fuel utilization or storage. For example, Shaw's jirds (*Meriones shawi*) do not increase their food intake after peripheral injections of 2DG or insulin (Demas & Bartness, 1999), nor do deer mice (*Peromyscus maniculatus,* Rowland, Watkins, & Carlton, 1985) or Mongolian gerbils (Rowland, 1978) after peripherally injected 2DG, but unlike hamsters all increase food intake after a fast (Demas & Bartness, 1999; Rowland *et al.*, 1985; Wong & Jones, 1985). Thus, no clear predictive relation exists among the metabolic fuel utilization/storage-induced or fasting-induced increases in food intake and a failure to respond to 2DG (Table 2).

Table 2. Some Nontraditional Animal Models of Food Intake (FI)

| Use | Response |
|---|---|
| **Seasonality** | |
| House mice (*Mus musculus*) | No seasonal/photoperiodic changes in FI or body mass |
| Norway rats (*Rattus norvegicus*) | No seasonal/photoperiodic changes in FI or body mass |
| Siberian hamsters (*Phodopus sungorus*) | Decreased FI and adiposity in short days |
| Syrian hamsters (*Mesocricetus auratus*) | Increased FI and adiposity in short days |
| Arctic ground squirrels (*Citellus undulates*) | Increased FI during autumnal pre-hibernation |
| Sheep (*Ovis aries*) | Increased FI in summer or long days |
| **Involuntary fasting/refeeding** | |
| House mice (*M. musculus*) | Post-fast hyperphagia |
| Norway rats (*R. norvegicus*) | Post-fast hyperphagia |
| Siberian hamsters (*P. sungorus*) | No post-fast hyperphagia |
| Syrian hamsters (*M. auratus*) | No post-fast hyperphagia |
| Shaw's jird (*Meriones shawi*) | Post-fast hyperphagia |
| Mongolian gerbils (*Meriones unguiculatus*) | Post-fast hyperphagia |
| Deer mice (*Peromyscus maniculatus*) | Post-fast hyperphagia |
| **Voluntary fasting** | |
| House mice (*M. musculus*) | No voluntary fasting |
| Norway rats (*R. norvegicus*) | No voluntary fasting |
| Marmots (*Marmota monax*) | Hibernation-induced fasting |
| Ground squirrels (*Citella lateralis*) | Hibernation-induced fasting |
| Garden dormice (*Eliomys quercinus*) | Hibernation-induced fasting |
| Turkish hamsters (*Mesocricetus brandti*) | Hibernation-induced fasting |
| Emperor penguins (*Aptenodytes forsteri*) | Fast during egg brooding or molt |
| King penguins (*Aptenodytes pantagonica*) | Fast during egg brooding |
| Elephant seals (*Mirounga angustirostris*) | Fast during post-weaning |
| **Food hoarding** | |
| House mice (*M. musculus*) | Decreased post-fast hoarding |
| Norway rats (*R. norvegicus*) | Increased post-fast hoarding |
| Siberian hamsters (*P. sungorus*) | Increased post-fast hoarding |
| Syrian hamsters (*M. auratus*) | Increased post-fast hoarding |
| Jirds (*M. shawi*) | Decreased post-fast hoarding |
| **Metabolic control of feeding** | |
| House mice (*M. musculus*) | Increased FI after 2DG or MA |
| Norway rats (*R. norvegicus*) | Increased FI after 2DG, 5TG, insulin, MA, or MP |
| Mongolian gerbils (*M. unguiculatus*) | No increases in FI after 2DG or insulin |
| Shaw's jirds (*M. shawi*) | No increase in FI after 2DG or insulin |
| Deer mice (*P. maniculatus*) | No increase in FI after 2DG or insulin; no MA-induced changes in FI |
| Siberian hamsters (*P. sungorus*) | No 2DG induced feeding, MA-induced decreases in FI, no effect of MP |
| Syrian hamsters (*M. auratus*) | No 2DG induced feeding; no effect of MP on FI |
| **Peptidergic control of feeding** | |
| *Leptin* | |
| House mice (*M. musculus*) | Decreased FI and body mass |
| Norway rats (*R. norvegicus*) | Decreased FI and body mass |
| Siberian hamsters (*P. sungorus*) | Decreased or no effect on FI in long or short days |
| Rhesus monkeys (*Macaca mulatta*) | Decreased FI after icv, but not peripheral injections |
| Domestic chickens (*Gallus domesticus*) | Dose-related decrease in FI |

TABLE 2. (*Continued*)

| Use | Response |
|---|---|
| *Neuropeptide Y (NPY)* | |
| House mice (*M. musculus*) | Increased FI after icv injections |
| Norway rats (*R. norvegicus*) | Increased FI after icv injections |
| Syrian hamsters (*M. auratus*) | Increased FI after icv infusions |
| Siberian hamsters (*P. sungorus*) | Increased FI after icv infusions |
| Sheep (*O. aries*) | Increased FI after icv infusions |
| Domestic chickens (*G. domesticus*) | Increased FI in adults, but not 2-day-old chicks |
| White-crowned sparrows (*Zonotrichia leucophrys*) | Greater increase in FI in short than long days |
| Goldfish (*Carassius auratus*) | Increased FI after icv infusions |
| *Cholecystokinin (CCK)* | |
| House mice (*M. musculus*) | Decreased FI after icv or peripheral injections |
| Norway rats (*R. norvegicus*) | Decreased FI after icv or peripheral injections |
| Siberian hamsters | Decreased FI after peripheral injections |
| Syrian hamsters | Decreased FI after icv injections |
| Sheep (*O. aries*) | Decreased FI after icv injections; CCK receptor agonist increases FI |
| Pigs (*Sus scrofa*) | Decreased FI and motivation to eat after peripheral injections |
| Domestic chickens (*G. domesticus*) | Decreased FI after iv or icv injections |
| Goldfish (*C. auratus*) | Decreased FI after icv or peripheral injections |
| **High fat diets (HFD)** | |
| House mice (*M. musculus*) | Increased body fat |
| Norway rats (*R. norvegicus*) | Increased body fat |
| Siberian hamsters (*P. sungorus*) | Slight or no effect on caloric intake; no effect on body fat |
| Syrian hamsters (*M. auratus*) | obesity without overeating |
| Meadow voles (*Microtus pennsylvanicus*) | No effect on body fat |
| Shaw's jirds (*M. shawi*) | No effect on FI, body mass or carcass lipid content |
| Mongolian gerbils (*M. unguiculatus*) | Decrease caloric intake |
| Bank voles (*Clethrionomys glareolus*) | No effect on body fat |

*Note*: References for each response are contained within this review.
MA = mercaptoacetate; MP = methyl palmoxirate; 2DG = 2-deoxy-D-glucose; icv = intracerebroventricular; iv = intravenous.

This lack of an increase in food intake after treatment with glucose utilization blockers by hamsters also applies to the blockade of lipid fuels, specifically FFAs. Whereas MA increases food intake in deer mice (Stamper & Dark, 1997) and laboratory rats (Scharrer & Langhans, 1986), it *decreases* (Stamper *et al.*, 1999) or does not affect (K. Boss-Williams and T. Bartness, unpublished observations) food intake in Siberian hamsters. Similarly, whereas MP increases food intake in laboratory rats (Friedman & Tordoff, 1986), it does not do so in Syrian (Lazzarini, Schneider, & Wade, 1988; Schneider, Lazzarini, Friedman, & Wade, 1988) or Siberian (Bartness & Clein, 1994) hamsters.

One argument made for the inability of some species, especially hamsters, to respond to glucoprivation or lipoprivation is that they can effortlessly switch between utilization of lipid and carbohydrate fuels. For example, Syrian hamsters can maintain continued estrous cyclicity (a response sensitive to alterations in metabolic fuels) following blockade either glucoprivation (2DG) or lipoprivation (MP) (Schneider & Wade, 1989). Combined treatment with 2DG and MP, however,

renders animals acyclic, suggesting that either of these metabolic pathways can be utilized to maintain normal estrous cycles in Syrian hamsters (Schneider & Wade, 1989). Thus, perhaps the combination of glucoprivation (2DG) with lipoprivation (MP), which stimulates food intake in laboratory rats, even when doses of both drugs each are below the threshold dose to stimulate food intake (Friedman & Tordoff, 1986), might increase food intake in hamsters. The combined treatment of 2DG and MP does not stimulate food intake by Syrian (Lazzarini *et al.*, 1988) or Siberian hamsters (Bartness & Clein, 1994), however, nor does a combined treatment of 2DG and MA (another fatty acid utilization blocker similar in effect to MP) in deer mice (Stamper & Dark, 1997).

The inability of these manipulations of metabolic fuels to increase food intake by Syrian and Siberian hamsters is not because these treatments are ineffective in blocking fuel utilization in these species. Thus, 2DG triggers increases in circulating glucose and/or ketone bodies in Syrian hamsters and Mongolian gerbils (Angel & Taranger, 1991; Ritter & Balch, 1978; Rowland, 1978, 1983), whereas 5TG triggers increases in circulating glucose and FFAs in Syrian hamsters (DiBattista, 1982). Short- or long-acting insulin produces profound decreases in glucose concentrations in Syrian (DiBattista, 1983; Ritter & Balch, 1978; Rowland, 1978, 1983) or Siberian hamsters (Bartness, McGriff, & Maharaj, 1991; Bartness *et al.*, 1995) to levels that would cause coma in laboratory rats (e.g., 30–50 mg/dl) yet the animals are conscious and mobile. Thus, the appropriate changes in circulating metabolic fuels appear to be generated by these blockers of fuel utilization, but these animals do not have the same sensing or subsequent response systems to trigger increases in food intake as do laboratory rats and mice. Perhaps when metabolic fuel utilization is blocked in these species, other energy-related responses are generated such as savings of energy expenditure (torpor is induced by 2DG in Syrian and Siberian hamsters) or increases in energy acquisition (food hoarding, see below).

## Peptidergic Control of Food Intake

As with other aspects of food intake, the role of peptides in the control of food intake has primarily been accomplished using laboratory rats and mice, but there is a growing body of research on other species. Unfortunately, there has been no successful attempt to integrate the effects of peptides on these nontraditionally studied species, perhaps because such a task seems daunting. Thus, unlike the other topics within this chapter, this section is divided into the effects of several well-studied peptides with subdivisions for single or related species. One point is clear, that there are striking similarities across species with respect to the ability of these peptides to stimulate or inhibit food intake. Therefore, we will make note of these consistencies across species, as well as pointing out the few exceptions to these generalities. Finally, in keeping with the overall theme of this review, we will incorporate possible functional significance of the effects of the peptides on feeding in light of the animal's behavioral ecology when possible.

### Leptin

Leptin is a peptide hormone primarily derived from WAT and belongs to the cytokine family, the discovery of which in 1994 quickly led to its attribution as a primary conveyor of body fat levels to the brain (Campfield, Smith, Guisez, Devos, &

Burn, 1995; Halaas *et al.*, 1995; Pelleymounter *et al.*, 1995). Specifically, it was initially hypothesized that as body fat level increases, leptin secretion by the expanding adipose depot increases and impacts key forebrain (arcuate nucleus, Schwartz *et al.*, 1997; Wang *et al.*, 1997) and hindbrain sites (dorsal vagal complex, Grill *et al.*, 2002) thought to be involved in the regulation of energy balance (Table 3). Stimulation of these brain areas by leptin, in turn, would trigger corrective measures opposing the increases in adiposity (e.g., decreases in food intake, Pelleymounter *et al.*, 1995; Weigle *et al.*, 1995). With additional study, the role of leptin was expanded to include involvement in reproduction, and immune and stress responses among others (for review see Harris, 2000). Since the initial observations, excitement about the role of leptin in the control of food intake and body fat levels, indirectly and directly, has diminished somewhat because of the growing number of exceptions to the original notion of its role as a feedback signal of body fat levels to the brain. For example, exogenous leptin does not always reliably decrease food intake in genetically normal laboratory mice, especially when given peripherally (its natural origin) and when physiological circulating concentrations are achieved (e.g., Harris *et al.*, 1998). In addition, leptin may not be necessary for the regulation of total body fat. For example, the induction of a lipid deficit by surgical removal of body fat (lipectomy) results in complete or nearly complete compensatory increases in fat pad mass of the non-excised lipid depots in many species, including laboratory rats and mice (Faust, Johnson, & Hirsch, 1977; Liebelt, Ichinoe, & Nicholson, 1965; Schemmel, Mickelsen, Pierce, Johnson, & Schirmer, 1971), Siberian and Syrian hamsters (Hamilton & Wade, 1988; Mauer & Bartness, 1994, 1996, 1997), and ground squirrels (Dark, Forger, Stern, & Zucker, 1985). Lipectomy of mice with alterations in leptin synthesis (*ob/ob* mice) and expression of functional leptin receptors (*db/db* mice) results in fat pad mass compensation that is complete or nearly complete (Chlouverakis, 1974; Harris, Hausman, & Bartness, 2002) despite these alterations of leptin synthesis or signal reception that render the peptide nonfunctional in these animals. Nevertheless, leptin may play a role in regulating energy expensive physiological processes such as reproduction (e.g., Ahima *et al.*, 1996).

### Leptin: Effects on Food Intake by Siberian and Syrian Hamsters

In virtually all species undergoing seasonal fluctuations in body fat, there are concomitant fluctuations in circulating leptin. Because both leptin and its receptor may be components of a body fat feedback mechanism in mammals (Berthoud, 2002), leptin also may be involved in seasonal control of body fat. Although a wide variety of mammalian species undergo seasonal cycles of body fat, the vast majority of research on the role of leptin in these seasonal responses has focused on Siberian and Syrian hamsters (Bartness & Wade, 1985). For example, serum leptin concentration correlates positively with body fat in Siberian hamsters over their yearly cycle (Drazen, Kriegsfeld, Schneider, & Nelson, 2000; Horton, Buxton, Losee-Olson, & Turek, 2000). Moreover, for this species, WAT leptin gene expression, circulating leptin concentrations, and leptin receptor gene expression all are reduced in short "winter-like" daylengths compared with long "summer-like" daylengths in accordance with short day-induced decreases in body fat (Demas, Bowers, Bartness, & Gettys, 2002; Drazen *et al.*, 2000; Klingenspor, Dickopp, Heldmaier, & Klaus, 1997; Mercer, Moar, Ross, & Morgan, 2000). Given that reduced leptin receptor gene expression contributes to a decrease in sensitivity to leptin, reduced gene expression

Table 3. Comparative Studies of the Effects of Exogenous Leptin on Food Intake

| Species | Leptin treatment | Food intake | Reference |
|---|---|---|---|
| Sheep (*Ovis aries*) | 20 μg/hr icv | ↓ | Henry *et al.* (1999) |
| | 4 μg/hr for 3 days icv | ↓ | Henry *et al.* (2001) |
| Pigs (*Sus scrofa*) | 10, 50, 100 μg icv | ↓ | Barb *et al.* (1998) |
| Syrian hamsters (*Mesocricetus auratus*) | 1 μg/day icv | ↓ | Schneider *et al.* (1999) |
| | 5 mg/day ip | ↓ | Schneider *et al.* (1998) |
| Siberian hamsters (*Phodopus sungorus*) | 15 g/day for 7 days osmotic minipump | NC | Rousseau *et al.* (2002) |
| | osmotic minipump | NC (LDs), ↑(SDs) | Drazen *et al.* (2001) |
| | ip injections | ↓LDs and SDs | Klingenspor *et al.* (2000) |
| | 15 g/day for 14 days osmotic minipump | NC (LDs and SDs) | Atcha *et al.* (2000) |
| Ground squirrels (*Spermophilus lateralis*) | 1 mg/m1 3 weeks osmotic minipump | ↓ | Boyer *et al.* (1997) |
| Rhesus monkeys (*Macaca mulatto*) | 500 ng, 2 μg, 22 μg icv | ↓ | Ramsey *et al.* (1998) |
| | 1 or 3 μg/kg sc | ↓ | Tang-Christensen *et al.* (1999) |
| Gerbils (*Psammomys obesus*) | ip injections 7–14 days | ↓ | Walder *et al.* (1999) |
| | ip injections 7d | ↓ | Sanigorski *et al.* (2000) |
| Beagle dogs (*Canis familiaris*) | 0.05–μg/kg/day sc | | LeBel *et al.* (1999) |
| Chickens (*Gallus domesticus*) | 10 μg icv | ↓ | Denbow *et al.* (2000) |
| | 0.2, 1, 5 μg icv | ↓ | Bungo *et al.* (1999) |
| | C4S recombinant leptin | ↓ | Dridi *et al.* (2000) |

in short days may reduce leptin sensitivity in short-day hamsters and indeed, this seems to be the case in Siberian hamsters (Mercer *et al.*, 2000). Note, however, that the dogma associated with the regulation of body fat by leptin states that when body fat levels decrease, the decrease in leptin triggers increases in food intake. The data above support the first portion of this dogma (i.e., short-day-induced decreases in body fat are associated with decreases in leptin gene expression by white fat [Klingenspor *et al.*, 1997] and circulating leptin concentrations [Drazen *et al.*, 2000; Horton *et al.*, 2000; Klingenspor, Niggeman, & Heldmaier, 2000]); however, food intake is *decreased* in short photoperiods *not* increased, especially when body fat is at its seasonal nadir (e.g., Wade & Bartness, 1984).

At least one of the energy-related short-day-induced changes by Siberian hamsters is reversed by peripheral chronic administration of leptin—the increase in food intake occurring when these animals are switched from short to long days is blocked by exogenous leptin (Drazen *et al.*, 2001). Unlike other species, however, such as standard strains of laboratory rats and mice, leptin administration did not affect food intake when Siberian hamsters were at the body and lipid mass peaks in long days (Drazen *et al.*, 2001). This result contrasts with the findings of two earlier studies of Siberian hamsters where peripheral leptin injections decreased food intake to the same extent in both long and short days, but reduced body and fat

pad mass to a greater extent in short days (Atcha *et al.*, 2000; Klingenspor *et al.*, 2000). The exact reasons for these discrepancies are unknown, but in part may be due to differences in leptin administration, as well as other methodological considerations (for discussion see Drazen *et al.*, 2001). The most reliable effect of leptin on food intake in rats and mice is when it is given intracerebroventricularly (icv; *vide infra*) ad to our knowledge, this has not been done in Siberian hamsters. Although Siberian hamsters do not increase food intake after a fast, release from a less than complete food restriction can stimulate food intake (Fine & Bartness, 1996; Rousseau *et al.*, 2002) and chronic peripheral leptin administration does not block this increase, nor does it have any effect on body or lipid mass in these animals (Rousseau *et al.*, 2002). Despite the varied leptin-induced responses across these experiments, there is the tendency for leptin to act differentially between the photoperiods to affect energy balance and food intake. Therefore, seasonal changes in circulating leptin concentrations, coupled with changes in leptin sensitivity, may serve as part of an adaptive mechanism for increasing the odds of winter survival when food availability is decreased and adipose tissue stores are at their nadir (for review see Rousseau, Atcha, & Loudon, 2003).

Fewer data are available on the effects of leptin on food intake *per se* by Syrian hamsters and instead the work to date has focused on its metabolic effects in this species. Fasted-refed Syrian hamsters do not increase their food intake, as do rats (*vide infra*). Fasted laboratory rats have suppressed circulating leptin concentrations (Frederich *et al.*, 1995; Moinat, Deng, & Muzzin, 1995) and consequent activation of the central NPY system thought to be involved with the post-fast increase in food intake of laboratory rats (Sahu, Kalra, & Kalra, 1988; Stanley, Magdalin, Seirafi, Nguyen, & Leibowitz, 1992; White & Kershaw, 1989). Prolonged fasting also inhibits leptin gene expression by WAT in Syrian hamsters (e.g., 48 hr) with partial restoration following refeeding despite the absence of a post-fast hypophagia (Mercer *et al.*, 1996). Unlike fasted laboratory rats, however, hypothalamic NPY mRNA expression is not increased (Mercer *et al.*, 1996). Therefore, it may be that the failure of fasting to stimulate NPY gene expression by Syrian hamsters likely reflects differences in leptin signaling between laboratory rats and Syrian hamsters, and is not due to any general inability of leptin to affect energy-sensitive brain sites *per se* (Mercer *et al.*, 1996). This view is buttressed by the series of elegant studies of Schneider and colleagues demonstrating a role of leptin in the regulation of peripheral fuel metabolism. Specifically, prolonged fasting inhibits estrous cyclicity in female Syrian hamsters (Schneider & Wade, 1989) and exogenous peripheral leptin treatment given during the fast counteracts this fasting-induced inhibition of estrous cyclicity. The possibility that this effect of leptin was sensitive to metabolic fuel utilization was supported when each leptin treatment was preceded by giving metabolic fuel blockers such as 2DG (to block glucose oxidation; Schneider *et al.*, 1998). That is, 2DG treatment blocked the ability of leptin to reinstate estrous cycles that cease due to fasting. Thus, the ability of leptin to affect reproductive status in these experiments appears to rely on sufficient metabolic fuels for oxidation in this species (Schneider *et al.*, 1998).

### Leptin: Effects on Food Intake by Ground Squirrels

Another seasonally breeding animal with annual cycles of body fat is the ground squirrel. Although the seasonal rhythms in ground squirrels can be modified by changes in the photoperiod and the pineal hormone melatonin (Hiebert

*et al.*, 2000), the photoperiod is not the primary coordinator of these seasonal energy and reproductive annual cycles, as in hamster species. Instead, the underlying timing mechanism is an endogenous circannual clock, the location of which is unknown. Chronic peripheral infusions of mouse recombinant leptin given to arctic ground squirrels (*Citellus undulates*) inhibit the increase in body fat that occur in the fall during the prehibernatory period (Ormseth *et al.*, 1996). This effect of leptin on body fat likely is caused by decreases in food intake and not increased energy expenditure because resting metabolic rate, body temperature, and locomotor activity are not affected by leptin (Boyer *et al.*, 1997). The ability of exogenous leptin to inhibit food intake likely represents a pharmacological effect of the peptide because leptin was administered when food intake is naturally increasing and the greatly expanding WAT mass likely results in increased endogenous circulating leptin concentrations. Thus, leptin was given on a background of naturally occurring elevated concentrations of native peptide. That food intake naturally *increases* when circulating leptin concentrations are high suggests that there is a seasonally induced insensitivity to leptin (Rousseau *et al.*, 2003) in arctic ground squirrels, as in Siberian hamsters (Atcha *et al.*, 2000; Klingenspor *et al.*, 2000), woodchucks (*M. monax*, Concannon, Levac, Rawson, Tennant, & Bensadoun, 2001), and sheep (Marie, Findlay, Thomas, & Adam, 2001).

### Leptin: Effects on Food Intake by Sheep

Sheep (*Ovis aries*) have annual cycles of reproduction, body/lipid mass, and food intake and although these seasonal rhythms are modified by the photoperiod, they have an unidentified circannual clock as their underlying basis, similar to ground squirrels and marmots. The effects of leptin on body fat and food intake have been extensively studied in sheep, likely because of their commercial importance (for review see Invartsen & Boisclaire, 2001). The seasonal peak in food intake of female sheep occurs in late-summer/early autumn when animals are reproductively inactive, and they reach a seasonal nadir during the spring when active breeding occurs (Clark, 2001). Exogenous icv leptin infusions inhibit food intake by sheep, but do not affect pituitary hormone secretion such that circulating levels of luteinizing hormone, follicle-stimulating hormone, prolactin, and growth hormone are normal. This suggests that the leptin-induced inhibition of food intake is not due to indirect effects on the output of pituitary hormones. As occurs in laboratory rats (Korner, Savontaus, Chua, Leibel, & Wardlaw, 2001), fasting increases arcuate nucleus NPY gene expression of sheep, an effect that decreases with leptin treatment (Henry *et al.*, 1999). Thus, it is likely that the effects of leptin on food intake are mediated, at least in part, by the central NPY system. The ability of leptin to decrease food intake is apparently coupled to available metabolic fuels as suggested above for its effects on Syrian hamster reproductive status, because food-restricted ewes given icv infusions of leptin do not inhibit their food intake (Henry, Goding, Tilbrook, Dunshea, & Clarke, 2001).

### Leptin: Effects on Food Intake by Nonhuman Primates

As with most mammalian species studied to date, leptin decreases food intake in nonhuman primates and this effect is dependent on the route of administration. For example, icv injections of leptin decrease food intake in a dose-dependent manner in male rhesus monkeys (*Macaca mulatta*, Ramsey, Kemnitz, Colman, Cunningham, & Swick, 1998), but energy expenditure is not affected by leptin treatment. By contrast, peripheral (iv) injections of leptin do not affect food intake,

despite 100-fold increases in serum leptin concentrations (Ramsey *et al.*, 1998). Similarly, central administration of leptin increases food intake by ~50% 24 hr after administration, but peripheral injections of leptin (subcutaneous) yielding physiological circulating concentrations of the peptide do not (Tang-Christensen, Havel, Jacobs, Larsen, & Cameron, 1999). The inability of peripherally administered injections to inhibit food intake when given so as to yield physiological concentrations of the peptide in blood, but for central injections to do so, is reminiscent of the effects on nongenetically obese mice discussed above (Harris *et al.*, 1998) and casts doubt on a physiologically important role of the peptide on food intake in nonprimates. It may be, however, that the transport of leptin across the blood–brain barrier under *ad libitum* feeding conditions may limit access of the peptide to its central receptors. There is, however, the typical relation between serum leptin concentrations, WAT leptin gene expression and the level of body fat (Bodkin, Nicolson, Ortmeyer, & Hansen, 1996; Chen, Ono, Yoshida, & Yoshikawa, 2002; Hotta *et al.*, 1996), but this relation may be of more importance under times of decreased lipid fuel stores, rather than when lipid stores are in balance with energy intake or are in surplus as suggested more generally (Ahima *et al.*, 1996).

### Leptin: Effects on Food Intake by Birds

Although not widely studied across species of birds, the effects of leptin have been tested in agriculturally important avian species such as domestic chickens (*Gallus domesticus*). In an initial study, mouse leptin (which shares 97% homology with chicken leptin) given icv to male broiler or male Single-Comb White Leghorn chicks did not decrease food intake at doses effective in rodents, suggesting that mouse leptin does not bind to chicken leptin receptors or that the chicken brain does not have leptin receptors (Bungo *et al.*, 1999). This latter possibility has been ruled out because a chicken leptin receptor has been discovered that is expressed in hypothalamus, along with peripheral sites such as the pancreas, and has high homology to the mammalian leptin receptor (Taouis *et al.*, 2001). Indeed, recombinant chicken leptin markedly inhibits food intake in chickens (Denbow *et al.*, 2000; Taouis *et al.*, 2001). This decrease in food intake is dose-related by icv-injected chicken leptin in both broiler and Single-Comb White Leghorn-type chickens and is a behaviorally specific effect in that water intake was not decreased (Denbow *et al.*, 2000). Food intake in chickens can be reduced by systemic leptin treatment, whereas it is not as effective, or not effective, in doing so in other species (*vide infra*). Thus, both intravenous or intraperitoneal injections of chicken leptin, ovine leptin, or a recombinant chicken leptin (C4S) reduce food intake in starved 9-day-old broiler chicks or 5-week-old layer chickens (Dridi *et al.*, 2000).

Collectively, the comparative analysis of the effects of leptin on food intake across a wide range of species discussed above suggests that leptin acts as a satiety factor in virtually all species studied to date. As with the case of most peptide hormones, the ability of leptin to inhibit feeding is largely dose-dependent, supporting the idea that food intake in these species is generally negatively correlated with total body fat, and thus, circulating leptin concentrations. Lastly, the ability to inhibit food intake with relatively small amount of centrally administered leptin supports the idea that leptin acts centrally at specific brain cites to regulate feeding, but the frequent inability of peripherally administered leptin that creates physiologically relevant circulating concentrations of the peptide questions the role of leptin in everyday food consumption.

## Neuropeptide Y (NPY)

NPY appears to be a key neuropeptide in the regulation of energy balance and reproduction (for review see Broberger & Hokfelt, 2001; Kalra, Clark, Sahu, Kalra, & Crowley, 1989). NPY is found in both central and peripheral neurons. The population of NPY neurons within the arcuate nucleus of the hypothalamus is clearly sensitive to alterations in energy balance and is involved in the metabolic and ingestive behavioral responses of this peptide (e.g., Cusin *et al.*, 1995; Wang *et al.*, 1997). Central administration of NPY has proven it to be one of the most potent stimulators of food intake (Clark, Kalra, Crowley, & Kalra, 1984; Stanley & Leibowitz, 1984), and it increases food intake in a wide variety of vertebrate species (DiBona, 2002). As with most studies of ingestive behavior, the majority of work on the orexigenic actions of NPY has focused on laboratory rats and mice; however, there is a rapidly increasing number of comparative studies suggesting that the physiological and behavioral actions of NPY are highly conserved across vertebrate taxa (Jensen, 2001).

### NPY: Effects on Food Intake by Syrian and Siberian Hamsters

Although hamsters do not increase their food intake after a fast, but are physically capable of doing so (see above), they do increase their food intake after icv NPY injections. Thus, both Syrian (Kulkosky, Glazner, Moore, Low, & Woods, 1988) and Siberian (Boss-Williams & Bartness, 1996) hamsters given icv NPY profoundly increase their food intake comparably to laboratory rats. As for laboratory rats (Clark, Kalra, & Kalra, 1985), NPY inhibits female reproductive behavior in a dose-dependent fashion and increases food intake (Corp, Greco, Powers, Bivens, & Wade, 2001). Specifically, icv NPY decreases lordosis, but increases food intake in ovariectomized, steroid-primed female Syrian hamsters (Corp, McQuade, Krasnicki, & Conze, 2001). Furthermore, the effects of NPY on reproduction and food intake appear to be mediated by separate pathways as determined by using several NPY receptor subtype antagonists in conjunction with exogenous NPY (Corp, McQuade, Krasnicki, & Conze, 2001). Thus, the effects of NPY on feeding by Syrian hamsters appears to be mediated by the NPY Y5 receptor subtype, whereas the effects of this hormone on female reproductive behavior are mediated by the NPY Y2 receptor subtype (Corp, McQuade, Krasnicki, & Conze, 2001).

As is the case for leptin, considerably more research on the effects of NPY on food intake and energy balance has been accomplished using Siberian hamsters and a related species, Djungarian hamsters (*Phodopus cambelli*). As expected, food deprivation increases both NPY and prepro-NPY gene expression in the arcuate nucleus, although these changes were less robust than those reported in laboratory rats (Mercer *et al.*, 1995). Interestingly, despite marked decreases in body and lipid mass (~30–40%) by short-day exposed Djungarian hamsters, neither arcuate NPY content nor gene expression changes there in these animals (Mercer *et al.*, 1995). Generally, similar results have been shown for short-day-housed Siberian hamsters except that the predicted increase in NPY gene expression, based on their body and lipid mass decreases, was modest compared with long-day food-restricted hamsters (Reddy *et al.*, 1999). The naturally occurring elevation of food intake by Siberian hamsters in long versus short days (Wade & Bartness, 1984a) might suggest that food intake would be more readily stimulated by NPY in long days; however, the magnitude of the NPY-stimulated food intake at all doses is similar between long- and short-day-housed hamsters (Boss-Williams & Bartness, 1996) and both groups of animals show comparable levels of NPY gene expression (Reddy *et al.*, 1999).

Furthermore, short-day-housed Siberian hamsters display increases in NPY gene expression, but this increase is modest compared with long-day food-restricted hamsters, based on their respective body and lipid mass decreases (Reddy *et al.*, 1999). Although Siberian hamster arcuate NPY gene expression is not increased after short-day exposure, despite decreases in body and lipid masses as noted above, food deprivation increases hypothalamic NPY gene expression in these animals to the same extent in both photoperiods (Reddy *et al.*, 1999).

Although maintenance in short days does not appear to affect central NPY independently, short-day-housed hamsters are more sensitive to *food deprivation-induced* changes in NPY. Short-day-housed Djungarian hamsters significantly increase arcuate NPY gene expression (~200%) when food deprived for 24 hr (Mercer *et al.*, 1997) Moreover, these results do not appear to be due to changes in gonadal steroid hormones or total body fat *per se*, as neither castrated hamsters nor juvenile long-day hamsters matched for body masses of short-day hamsters displayed significant changes in NPY mRNA. Thus, the response of Siberian hamsters to acute energetic challenges, such as food deprivation, is similar to that of laboratory rats, but the response of Siberian hamsters to naturally occurring, seasonally appropriate fluctuations in body mass is not as tightly correlated with body fat levels as it is for laboratory rats (Mercer *et al.*, 1995).

It has been effectively argued (Mercer, 1998) that that the lack of a change in NPY gene expression by short-day-housed Siberian and Djungarian hamsters makes sense in that their short-day-induced decreases in body and lipid mass *are not* a deviation from their natural state of energy balance, as occurs with food deprivation. Therefore, these animals should not be expected to show similar compensatory changes in hypothalamic neuropeptide gene expression. That these animals are experiencing a "seasonal program" of body and lipid mass changes is borne out by the return to seasonally appropriate body masses after the lifting of food restriction at different points in their short-day decline in these measures (Steinlechner, Heldmaier, & Becker, 1983). How such a seasonal program controls the changes in neuropeptides, food intake, and body fat levels is unknown, but understanding these interactions within this naturally occurring context seems likely to provide insight into a more general understanding of energy balance.

### NPY: Effects on Food Intake by Sheep

As with the long photoperiod-breeding hamster species above, short-day breeding sheep markedly increase food intake (~800%) shortly after (30 min) icv administration of NPY, whereas peripheral injections of the peptide have no effect suggesting a central site of action (Miner, Della-Fera, Paterson, & Baile, 1989). A central mode of action also is suggested by the presence of the NPY Y1 receptor subtype mRNA in the arcuate nucleus and PVN of the sheep hypothalamus (Dyer, Simmons, Matteri, & Keisler, 1997a, 1997b), a receptor subtype implicated in the stimulation of feeding by NPY in other species (e.g., Kanatani *et al.*, 1996, 1998; Lopez-Valpuesta, Nyce, Griffin-Biggs, Ice, & Myers, 1996). Furthermore, the seasonal peak in food intake (long "summer-like" days) and its nadir (short "winter-like" days; e.g., Clarke, Rao, Chilliard, Delavaud, & Lincoln, 2003; Gettys, Schanbacher, & Taylor, 1989) may be partially based on increases in the activation of the NPY system in the former given that arcuate NPY gene expression is significantly greater in long versus short days in sheep (Clarke *et al.*, 2003). Therefore, as for all other species tested (cf. Sipols *et al.*, 1996), sheep are responsive to the

orexigenic properties of NPY. Whether they are differentially susceptible to the appetite-promoting effects of NPY in long or short days, as the differential gene expression in the arcuate might suggest (Clarke *et al.*, 2003), remains to be tested.

## NPY: Effects on Food Intake by Birds

The variety of birds species tested for feeding responses to neuropeptides is narrow, with work almost exclusively focused on domestic chickens. Icv injections of NPY, or the structurally related peptide PYY, markedly stimulates food intake by broiler chicks within 1 hr post-injection (Kuenzel, Douglass, & Davison, 1987). The dose of NPY that elicits maximal feeding is greater than that of PYY (i.e., 9 vs 5 μg, respectively), suggesting a higher potency for the latter peptide (Kuenzel *et al.*, 1987) Centrally administered NPY does not increase food intake by 2-day-old Leghorn chicks (Steinman, Fujikawa, Wasterlain, Cherkin, & Morley, 1987), an effect not due to the inability of these young animals to increase their food intake because both pancreatic polypeptide and naloxone increase food intake at this age (Steinman *et al.*, 1987). This lack of a NPY-induced stimulation of feeding is likely due to the peptide stimulating convulsions in that those chicks not convulsing increase their food intake (Steinman *et al.*, 1987). As with mammals, the site of action for NPY-induced feeding is probably central in chickens. Although the cell bodies of the NPY producing neurons are not in brain areas traditionally associated with feeding in mammals (i.e., lateral thalamus, hippocampus, caudal linear nucleus, and raphe nucleus of the brainstem; Boswell, Millam, Li, & Dunn, 1998), there is hyperstriatal, archistriatal, and neostriatal regions of the telencephalon that have NPY-immunoreactivity, but not gene expression, in Japanese quail (*Coturnix coturnix japonica*) and domestic chickens (Boswell *et al.*, 1998).

Regarding other avian species, short-day-housed white-crowned sparrows (*Zonotrichia leucophrys gambelii*) given NPY icv increase food intake at the higher doses tested compared with saline-treated birds, whereas long-day-housed (photostimulation for the reproductive system) birds have increases in food intake, but at doses 4–8 times lower than in short days (Richardson *et al.*, 1995) Therefore, increases in sensitivity to the appetite promoting effects of NPY seem to occur during the breeding season, a time when energy investments are high and seasonal body mass and fat peak (Wingfield, Hahn, Wada, & Schoech, 1997). Finally, icv NPY increases food intake by ring doves (*Streptopelia risoria*) at the same low doses as in long-day-housed white-crowned sparrows (Strader & Buntin, 2001).

## NPY: Effects on Food Intake by Fish

Goldfish (*Carassiua auratus*), as with the other species discussed above, show increases in brain NPY gene expression after a fast (e.g., 72–75 hr), especially in the telencephalic-preoptic area, hypothalamus, and optic tectum-thalamus regions (Narnaware & Peter, 2001a). The fasting-induced increase in NPY mRNA in these brain areas reverts to non-fasting levels within 1–3 hr of refeeding, suggesting sensitivity to energetics in the central NPY system of this species (Narnaware & Peter, 2001a). Goldfish significantly increase their food intake after icv, but not intraperitoneal (ip) administration of exogenous NPY 2 hr post-injection, an effect completely blocked by a general NPY receptor antagonist (Bodkin *et al.*, 1996; Borer *et al.*, 1985, 1979; Borker & Gogate, 1981; Boss-Williams & Bartness, 1996; Boswell *et al.*, 1998; Boyer *et al.*, 1997; Broberger & Hokfelt, 2001; Browne & Borer,

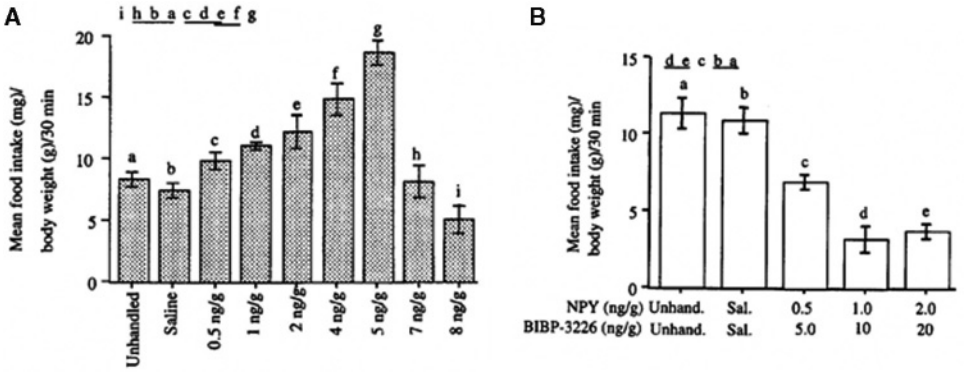


Figure 3. Effects of (A) NPY and (B) NPY + NPY Y1 receptor antagonist (BIBP-3226) on food intake and body weight in goldfish (from Narnaware *et al.*, 2000).

1978; Bungo *et al.*, 1999) suggesting a central site of action and a receptor-mediated effect (Lopez-Patino *et al.*, 1999). Furthermore, NPY-induced feeding is blocked by the NPY Y1-receptor antagonist BIBP-3226 suggesting involvement of this receptor subtype (Narnaware, Peyon, Lin, & Peter, 2000; Figure 3). In support of the role of the NPY Y1-receptor subtype in the NPY-induced increase in food intake by goldfish, icv NPY Y1, but not NPY Y2 receptor agonists, stimulate feeding in goldfish (de Pedro *et al.*, 2000), effects blocked by the general NPY receptor antagonist NPY (de Pedro *et al.*, 2000). Furthermore, as in laboratory rats and mice (e.g., Corp, McQuade, Krasnicki, & Conze, 2001; Iyengar & Simmons, 1999), the NPY Y5 receptor subtype may be involved in food intake by goldfish because a NPY Y5 receptor subtype agonist ([D-32Trp]NPY) increases food intake, but simultaneous stimulation of both receptor subtypes is not additive (Narnaware & Peter, 2001b). Because desensitization of either receptor subtype does not reduce the sensitivity of the other subtype, this suggests that NPY-induced increases in food intake by goldfish may be due to independent stimulation of both the Y1 and Y5 receptor subtypes (Narnaware & Peter, 2001b). The ability to determine the primary NPY receptor subtype responsible for the NPY-induced increases in food intake is not possible at this time for this, or any species, because highly specific receptor subtype agonists or antagonists are not available.

Teleost fish possess NPY in addition to a related neuropeptide, anglerfish peptide YG (aPY), as indicated by their isolation and characterization from brain and the peripheral nerves innervating pancreatic islets of the anglerfish (*Lophius americanus*) (Milgram, Balasubramaniam, Andrews, McDonald, & Noe, 1989; Noe *et al.*, 1989). No attempt has been made, however, to test the stimulatory effects on exogenous NPY on food intake by teleost fish.

### NPY: Effects on Food Intake by Other Species

Nonhuman primates have been tested for the stimulatory effects of NPY on food intake yielding mixed results. NPY potently stimulates food intake in rhesus monkeys (Larsen *et al.*, 1999), but unlike other species, NPY does not increase food intake in baboons (Sipols *et al.*, 1996). Lastly, in the only study conducted on a reptilian species, NPY significantly reduced courtship behavior and stimulated food

intake of male red-sided garter snakes (*Thamnophis sirtalis parietallis*). The NPY-induced increase in food intake occurs with a substantial delay compared with other vertebrates (4–5 hr post-injection, Morris & Crews, 1990).

Collectively, the studies discussed above suggest that NPY acts as a potent orexigenic agent, stimulating food intake in virtually all species studied to date. In several cases, central injections of the hormone are required to elicit increased food intake, whereas peripheral injections are generally ineffective. As with leptin, these data suggest that NPY appears to act on central NPY receptors, likely Y1 receptors and possibly other receptor subtypes, to affect food intake. The precise mechanisms by which activation of NPY receptors triggers increased food intake and whether such mechanisms are conserved across taxonomically distinct species, however, require further research.

### Cholecystokinin (CCK)

CCK is a polypeptide hormone secreted by the gastrointestinal tract that has been demonstrated to exert marked effects of gastric motility, bile secretions from the gall bladder, and exocrine pancreatic secretion, also is synthesized in the brain and appears to be a potent satiety factor. In terms of the latter, intraperitoneally administered CCK inhibits food intake in laboratory rats and, moreover, elicits a sequence of behaviors virtually indistinguishable from those exhibited after naturally occurring satiety or after infusions of food onto pre-gastric and gastric gut surfaces (Gibbs & Smith, 1982). This inhibitory effect of CCK on food intake also occurs after icv administration (Gibbs, Young, & Smith, 1973). The site of action for these effects of CCK is likely both peripheral and central (for review see Reidelberger, 1994).

### CCK: Effects on Food Intake by Syrian and Siberian Hamsters

CCK decreases food intake in both Syrian and Siberian hamsters. For example, icv injections of CCK octapeptide (CCK-8) decrease food intake in a dose-dependent manner in Syrian hamsters (Miceli & Malsbury, 1983). Relatively large peripheral injections of CCK-8 (1.0–4.0 μg/kg) given to Syrian hamsters also decrease food intake, whereas smaller peripheral injections (e.g., 0.5 μg/kg) do not (Miceli & Malsbury, 1983). The site for the central effects of CCK in hamsters is unknown, but potentially could differ from that of laboratory rats in that the distribution of central- and peripheral-type receptor binding sites and peptide immunoreactivity is somewhat different from laboratory rats. Specifically, peripheral-, but not central-type CCK binding sites are found in the magnocellular PVN (Miceli & Steiner, 1989) and CCK-immunoreactivity occurs in the suprachiasmatic nucleus in Syrian and Siberian hamsters compared with laboratory rats that have both central- and peripheral-type binding sites (Miceli, van der, Post, Della-Fera, & Baile, 1987; Reuss, 1991). The receptor binding differences may help explain why CCK-8 injections into the PVN inhibit food intake by laboratory rats (e.g., Blevins *et al.*, 2000), but not by Syrian hamsters (Miceli & Steiner, 1989).

It is important to note that, unlike other peptide hormones (e.g., calcitonin gene-related peptide) that can act as "behavioral bombs" by triggering nonspecific incapacitating or debilitating effects on behavior (e.g., Bartness *et al.*, 1986), the effects of exogenous administration of CCK-8 on behavior appear specific to food intake (Miceli & Malsbury, 1983). In addition, peripheral injections of CCK-8 are as

effective in decreasing food intake during the day and night for female hamsters, but oddly only are effective in doing so during the night for males (Miceli & Malsbury, 1985). Injections of a CCK antagonist, proglumide, does not affect normal food intake or block the effects of CCK-8 administration on food intake by Syrian hamsters (Miceli & Malsbury, 1985). Long-day-housed Siberian hamsters decrease food intake after peripheral injections of CCK-8 administration, but similarly treated Chinese hamsters (*Cricetulus griseus*) do not (Billington *et al.*, 1984). After transfer of long-day-housed Siberian hamsters to short days, the same doses of CCK-8 inhibit food intake to a substantially greater degree than in long days; indeed, several low doses that were ineffective in suppressing food intake in long days readily inhibit food intake in short days suggesting photoperiodic changes in sensitivity to this satiety peptide (Bartness *et al.*, 1986). This enhanced sensitivity to the suppressive effects of CCK on food intake in short days suggests that the naturally occurring decreases in food intake of short-day-housed Siberian hamsters (e.g., Wade & Bartness, 1984a) may be due to an increased role of CCK and perhaps other satiety peptides (Bartness *et al.*, 1986).

### CCK: Effects on Food Intake by Sheep

Consistent with the hypothesis that CCK is a natural satiety signal, its serum concentrations are significantly reduced after prolonged fasting of lambs and conversely increased after 20–50 min after suckling (Nowak *et al.*, 1997). It may not be surprising, therefore, that CCK potently inhibits food intake of adult sheep; thus, continuous application of CCK-8 into the lateral ventricles of sheep reduces feeding by ~40% during their feeding period, and food intake returns to normal levels within 24 hr after treatment stops (Della-Fera & Baile, 1980). A CCK receptor antagonist (L364–718) *increases* food intake of sheep (Dynes, Poppi, Barrell, & Sykes, 1998), as it does in laboratory rats (Reidelberger & Rourke, 1989; Reidelberger, Varga, & Solomon, 1991), but only after central, but not peripheral infusions (Dynes *et al.*, 1998).

### CCK: Effects on Food Intake by Pigs

As with other species, CCK reduces food intake in domestic pigs (*Sus scrofa*). For example, infusions of CCK-8 into the jugular vein and carotid artery reduce food intake by ~65–70% of control values in pigs (Houpt, 1983). Furthermore, CCK appears to affect motivation to eat in addition to food intake *per se*; thus, pigs trained to perform an operant response to obtain food reduce their responding after iv administered CCK in a dose-dependent manner (Baldwin, Cooper, & Parrott, 1983). The CCK-A agonist A-71378, but not the CCK-B agonist pentagastrin, given iv increases food intake in the operant response model, but neither agonist reliably decreases food intake when administered centrally (Parrott, 1993). This latter finding suggests that stimulation of peripheral CCK A receptors underlie the inhibition of food intake by CCK in pigs and that central or peripheral CCK B receptors are not involved with feeding in this species (Parrott, 1993). Conversely, immunization against CCK via application of CCK antibodies (Pekas, 1991; Pekas & Trout, 1990), or administration of the CCK receptor antagonist MK-329 (Ebenezer, de la, & Baldwin, 1990) expectedly increases food intake in swine. Thus, the primary site of action for the inhibitory effects of CCK on food intake in pigs may be of peripheral origin.

### CCK: Effects on Food Intake by Birds

CCK also may act as a satiety peptide in birds. Specifically, iv injections of CCK-8 suppress food intake in broiler and layer chickens (Savory & Gentle, 1983; Savory & Hadgkiss, 1984). This inhibitory effect of CCK on food intake is overcome as the length of the fast preceding CCK injection is increased (Savory & Gentle, 1983). The dual site of action for CCK seen in most other species (but apparently not pigs, see above) also occurs in chickens, although a stronger importance of central sites is suggested. That is, both icv and iv injections of CCK-8 reduce food intake in chickens, but the iv effects are not blocked by iv pretreatment with the peripheral CCK receptor antagonists L-364-718 or L-365-260. Pretreatment with L-364-718 icv, however, blocks the inhibition of food intake by icv CCK-8 (Rodriguez-Sinovas, Fernandez, Manteca, Fernandez, & Gonalons, 1997). In addition, central and peripherally administered CCK antagonists L-365-260 and L-364-718 increase food intake in chickens (Rodriguez-Sinovas *et al.*, 1997).

It is possible that the CCK-induced suppression of food intake is due to malaise, as is always the situation when a treatment decreases food intake. Indeed, conditioned avoidance tests in chickens show that CCK produces a mild aversion (Savory, 1987), perhaps suggesting that CCK is not a naturally occurring satiety signal in chickens. Because two potent stimulators of CCK, soybean trypsin inhibitor and phenylalanine, do not affect food intake by chickens, nor do the CCK-A receptor antagonists, devazepide (Choi, Furuse, Satoh, & Okumura, 1994) or MK-329 (Covasa & Forbes, 1994), the notion that CCK is an illness-inducing agent in this species and not a normal satiety signal seems supported. Alternatively, CCK may act as a natural agent in moderate doses, but cause nausea when administered at higher doses.

CCK dose-dependently decreases food intake when given peripherally to white-crowned sparrows (ip; Richardson, Boswell, Weatherford, Wingfield, & Woods, 1993). This effect was blocked by the CCK-A receptor antagonist L 365-260, suggesting that, as with mammalian species, the effects of CCK on food intake act via this receptor subtype in birds (Richardson *et al.*, 1993).

### CCK: Effects on Food Intake by Fish

CCK appears to be an important satiety factor in goldfish. For example, goldfish brain contains CCK/gastrin-like immunoreactive neurons within the ventral telencephalon and diencephalons including the preoptic hypothalamus, as well as nerve fibers and endocrine cells in the gut (Himick & Peter, 1994). Moreover, centrally (3rd ventricle) or peripherally (ip) administered CCK-8 inhibits food intake by goldfish (Himick & Peter, 1994).

## Food Intake Responses to High Fat Diets (HFDs)

An important experimental model used to discover the mechanisms underlying the role of palatability on food intake, as well as to induce obesity, is the feeding of HFDs (Mickelson, Takahashi, & Craig, 1955). This model has been used successfully for the past ~50 years in traditionally studied animal species such as laboratory rats and mice and has contributed enormously to our understanding of energy balance (for review see West & York, 1998). For example, laboratory rats

(Faust, Johnson, Stern, & Hirsch, 1978; Masek & Fabry, 1959; Mickelson *et al.*, 1955) and mice (Lemonnier, 1972; Lemonnier, Suquet, Aubert, de Gasquet, & Pequignot, 1975; West, Boozer, Moody, & Atkinson, 1995) maintained on a HFD undergo marked increases in total body fat. This diet-induced obesity is due, in part, to increased caloric intake (for review see Kanarek & Hirsch, 1977) and to decreased energy expenditure (e.g., Storlien, James, Burleigh, Chisholm, & Kraegn, 1986; cf., Schwartz, Young, & Landsberg, 1983). As with most other areas of research, however, much less is known about the effects of HFDs on food intake and energy balance in nontraditional animal species. The factors underlying resistance to diet-induced obesity may be revealed by studying inbred laboratory rats selected for susceptibility or resistance to diet-induced obesity (Levin, Dunn-Meynell, Balkan, & Keesey, 1997) or mouse strains that are differentially susceptible/resistant to HFD-induced obesity (West, Waguespack, & McCollister, 1995). As discussed below, however, several species show a natural resistance to HFD-induced obesity, whereas other species are naturally susceptible to HFD-induced obesity. These responses to HFDs are, by definition, shaped by evolutionarily forces rather than artificially selected. The examples of natural resistance to HFD-induced obesity in particular share several striking physiological characteristics that may offer opportunities to uncover evolutionarily based factors altering the consumption and/or obesity-producing effects of HFDs.

### HFDs: Effect on Food Intake by Hamsters, Gerbils, and Jirds

Unlike laboratory rats and mice that maintain relatively constant levels of food intake and adiposity on an annual basis, many non-tropical rodent species undergo marked seasonal cycles of body and lipid mass that are regulated by environmental cues, predominantly the photoperiod (for review see Bartness & Wade, 1985). Interestingly, some of these species, such as Siberian hamsters (McElroy, Mason, Hamilton, & Wade, 1986; Wade & Bartness, 1983) and meadow voles (*Microtus pennsylvanicus*; J. Dark and I. Zucker, unpublished observations), do not increase body fat levels when fed HFDs. Specifically, long photoperiod-exposed Siberian hamsters fed a HFD (i.e., 2:1 ratio of chow:shortening) either do not increase caloric intake (Wade & Bartness, 1983) or slightly overeat this diet (~20%; McElroy *et al.*, 1986). In both cases, body and lipid mass do not increase, nor does HFD feeding block the naturally occurring short-day-induced decreases in body fat (Wade & Bartness, 1983). The resistance to HFD-induced obesity in the study where overeating occurred (McElroy *et al.*, 1986) was associated with an increase in sympathetic drive to brown adipose tissue (i.e., increased norepinephrine turnover) and guanosine diphosphate binding to mitochondria (i.e., a measure of thermogenic activity Rafael & Heldt, 1976) that would tend to mitigate the effects of increased caloric intake. Thus, these animals have a naturally occurring resistance to HFD-induced obesity either due to a lack of HFD-induced hyperphagia or, if the hyperphagia exists, a corresponding increase in energy expenditure.

By contrast to Siberian hamsters, Syrian hamsters also undergo seasonal cycles in body and lipid mass, but the response is opposite to that of Siberian hamsters (i.e., body fat increases in short compared with long days ([Bartness & Wade, 1984; Hoffman, Davidson, & Steinberg, 1982; Wade & Bartness, 1984b]). Syrian hamsters fed HFDs become impressively obese, but do so largely without overeating (Bartness & Wade, 1984; Wade, 1982, 1983) unlike many strains of laboratory rats and mice (e.g., Schemmel & Mickelsen, 1970; West *et al.*, 1995). The HFD-induced

obesity seen in long-day-housed Syrian hamsters is exaggerated by short-day exposure (Bartness & Wade, 1984; Wade, 1983; Wade & Bartness, 1984b) to the extent that these hamsters are unable to right themselves when placed on their backs. This obesity without overeating is accompanied by decreased sympathetic drive on brown fat (i.e., normal norepinephrine turnover), but surprisingly an increase in mitochondrial cytochrome C oxidase activity and guanosine diphosphate binding showing a dissociation of BAT thermogenesis from sympathetic activity (Hamilton, Mason, McElroy, & Wade, 1986).

Why would one hamster species, Siberian hamsters, be resistant to HFD-induced obesity and perhaps somewhat to HFD-induced overeating, whereas another hamster species, Syrian hamsters, be highly susceptible to HFD-induced obesity, but also, perhaps not HFD-induced overeating? In other words, do these two different, species-specific responses confer an adaptive advantage based on these hamsters' seasonal body fat responses? Siberian hamsters (e.g., Wade & Bartness, 1984a), similar to meadow voles (e.g., Dark, Zucker, & Wade, 1983), exhibit a fall (short-day) energetic strategy of decreasing their body mass. Although the more typical fall energetic strategy is to increase lipid deposition for later use when food is scarce in the winter (e.g., Syrian hamsters; Bartness & Wade, 1984; Hoffman *et al.*, 1982; Wade, 1983), it has been argued that the short-day-reduced body mass carries with it a reduction in maintenance energy requirements (e.g., Weiner, 1987). Thus, it is disadvantageous for species that exhibit this adaptive body fat nadir in fall/winter to fatten by eating a HFD in short "winter-like" days, or even in long days given that any lipid excesses here would need to be reduced in the fall (El-Bakry, Plunkett, & Bartness, 1999). Hence, it would be predicted that other species that exhibit short-day-induced body fat decreases also should be relatively resistant to HFD-induced obesity and perhaps HFD-induced increases in food intake. Consistent with this, Shaw's jird (*M. shawi*) is a desert rodent that decreases its body mass (fat) when exposed to short days (El-Bakry *et al.*, 1999) and, as predicted, HFD feeding has no effect on body mass, food intake, carcass lipid content, or WAT pad mass in long- or short-day-housed jirds compared with their standard lab chow-fed counterparts ([El-Bakry *et al.*, 1999]) Figure 4). Similar effects are seen in a closely related species, Mongolian gerbils (*M. unguiculatus*), that decrease their caloric intake in response to HFD-induced increase in caloric density (Kanarek, Ogilby, & Mayer, 1977) as well as in the bank vole (*Clethrionomys glareolus*) (Peacock & Speakman, 2001). Collectively, the mechanisms underlying resistance or susceptibility to HFD-induced obesity in species that exhibit seasonal body fat cycles are unknown. Nevertheless, it may be that the study of those species that are naturally resistant or naturally susceptible HFD-induced obesity and/or HFD-induced 1overeating, and that are studied in the context of their adaptations to their environments, may add new insights into the advantages and disadvantages of becoming obese when fed a HFD. For example, perhaps in these resistant species, HFD are not as reinforcing (i.e., palatable) as in species that do overeat; such differences may reflect differences in sensory processing of lipid-rich food. In terms of resistance to HFD-induced obesity, it may be that in these species, HFD-induced stimulation of thermogenesis in BAT mitigates the obesity-promoting effects of a HFD; indeed, as mentioned above, HFD-fed Siberian hamsters display exaggerated stimulation of BAT thermogenesis, as suggested by increased GDP binding, compared with other species (McElroy *et al.*, 1986). Although these possibilities are intriguing, they remain to be tested.

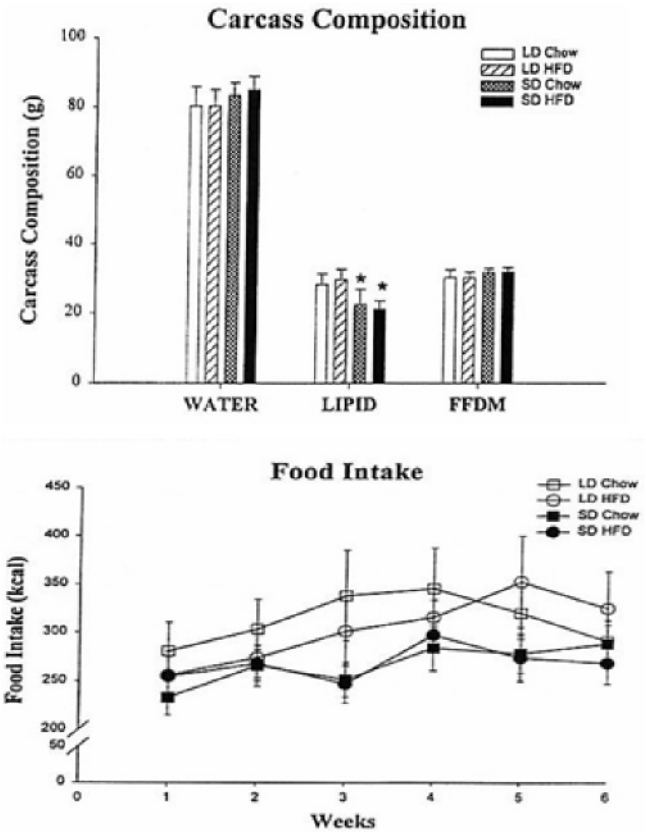


Figure 4. Lack of an effect of high-fat diet (HFD) on food intake and carcass lipid by Shaw's jird (from El-Bakry *et al.*, 1999). FFDM = fat-free dry mass; LD = long day; SD = short day (from El-Bakry *et al.*, 1999).

## Appetitive Ingestive Behaviors

The role of foraging and food hoarding in the ingestive behavioral repertoire of several species, especially hamsters and laboratory rats, has been recently reviewed (Bartness & Day, 2003) and will only be summarized here. The animal behaviorist, Wallace Craig, coined the terms "appetitive" and "consummatory" for the two-part sequence of eating, drinking, and sexual behaviors in 1918 (Craig, 1918). He defined appetitive behaviors as those involved in seeking the goal object (food, water, a mate) and noted that these are flexible and non-stereotyped behaviors drawing animals into physical contact with these goals (Craig, 1918). In terms of food intake, these appetitive behaviors form the initial steps in the ingestive behavior sequence (Craig, 1918), emphasizing that animals must find food before they can eat it. He defined the second part of this sequence as consummatory behaviors (from *consummate* not *consume*), defining them as the final act once the goal object has been contacted and noting that they are reflexive and stereotyped behaviors (Craig, 1918); for food intake, this is the act of eating. The consummatory phase of ingestive behavior has received the most extensive study and several chapters in

this *Handbook* discuss various aspects of it. Foraging and food hoarding, two quintessential appetitive behaviors (for review see Bartness & Day, 2003; Vander Wall, 1990), however, are instructive for comparative analyses. Foraging has been studied extensively at the behavioral rather than the physiological level of analysis, especially in birds and is not reviewed here (for review see Stephens & Krebs, 1986).

Much of the research on the physiological mechanisms underlying food hoarding has been accomplished using laboratory rats that are not natural hoarders. Even their wild counterparts (*Rattus norvegicus*) are not thought to hoard food significantly because no food has been found in their burrows except for occasional observations of food buried near the burrow of lactating rats (Calhoun, 1962; Lore & Flannelly, 1978; Pisano & Storer, 1948; Takahhashi & Lore, 1980; Whishaw & Whishaw, 1996). With that caveat, several points stand out. First, there are species that use hoarding as an integral part of their behavioral energetic repertoire (usually animals possessing specialized anatomical structures to aid in transporting food, such as pouches [Vander Wall, 1990] [e.g., hamster and squirrel species]), where food hoarding serves essentially the same function as does the consequence of food intake—energy storage. Second, some of the peptidergic controls of ingestive behavior revealed through feeding tests with laboratory rats and mice in their home cages (unlimited food, no foraging) may be more directly involved in food acquisition (foraging) and storage (hoarding) than with feeding. Both of these have been assessed in studies of Siberian hamster foraging/hoarding. The ability to separate the appetitive from consummatory ingestive responses in these animals rests on the non-covariance of food intake and food hoarding in Siberian hamsters. With few exceptions, these animals neither overeat *and* "overhoard," nor undereat *and* "underhoard," thereby inferring some degree of separate underlying mechanisms controlling food intake and hoarding. In addition, changes in foraging (pellets earned in a running wheel-based delivery system) do not always covary with changes in food hoarding (Day & Bartness, 2001); thus, it can also be inferred that these two appetitive ingestive behaviors have at least partially separate underlying mechanisms.

As discussed above, hamsters do not overeat after a fast, but they do overhoard and, depending upon the foraging effort, foraging can increase. Specifically, after a 32-hr fast, food hoarding increases and then decreases as the foraging effort increases, whereas foraging (pellets earned) increases, but only at low foraging efforts. Two approaches have been used to get at the underlying mechanisms. Fasting produces numerous peripheral metabolic changes, and any of these or their combinations might underlie the increased hoarding and foraging. In one report, substances that alter metabolic fuel utilization (i.e., 2DG, MP, and their combination) or storage (i.e., insulin) did not affect hoarding (Bartness & Clein, 1994). These manipulations were acute, with injections occurring just before darkness leaving open the possibility that more chronic metabolic challenges are necessary to trigger increases in food hoarding or foraging such as those that are effective in blocking estrous cycles and reproductive behavior in Syrian hamsters (Schneider, Friedenson, Hall, & Wade, 1993; Schneider & Wade, 1989; Wade *et al.*, 1991).

Alternatively, decreases in lipid fuels *per se* could stimulate food hoarding/foraging. Several studies suggested that whenever body fat is decreased in hamsters, such as after fasts or during pregnancy/lactation, food hoarding increases (Bartness & Clein, 1994; Day *et al.*, 1999; Wood & Bartness, 1996, 1997). This apparent inverse relation between body fat and food hoarding, which has also been hypothesized for laboratory rats (Cabanac & Gosselin, 1996), was explicitly

examined utilizing the lipectomy model for testing body fat regulation (for review see Mauer, Harris, & Bartness, 2001). Removal of both inguinal and epidymal WAT pads triggers increases in food hoarding that are reversed as the remaining unexcised fat pads compensated for the surgical-induced lipid deficit by increasing their lipid stores until no body fat deficit is apparent (Wood & Bartness, 1997). These results contrast with a report of a lack of increased food hoarding in lipectomized rats (Michel & Cabanac, 1999), but interpretation of those findings is complicated because the method used to test food hoarding in the severely lipectomized rats required sequential food restriction to produce a within-animal determination of body mass versus food hoarding (Michel & Cabanac, 1999). Therefore, rats bearing this large lipid deficit were further energetically stressed by repeated restricted feedings. Subsequent studies using the foraging/hoarding system suggest that decreases in gonadal fat (e.g., parametrial fat pads) may be more important for the initial stimulation of food hoarding than overall decreases of body fat (Day & Bartness, 2001). That is, as the foraging effort is increased, parametrial fat mass, but not the mass of other fat pads or total carcass lipid, is decreased and food hoarding is increased (Day & Bartness, 2001). Although not completely established at this time, it seems that normal functioning of the gonads is somewhat dependent on ample lipid fuel stores in the gonadal fat pads (e.g., Srinivasan, Thombre, Lakshmanan, & Chakrabarty, 1986), and it is not surprising that behavioral responses to acquire and store more energy are triggered by decreases in the lipid content of these fat depots. How the brain senses these or other decreases in lipid energy stores is not known, but at least two possible mechanisms exist. First, as stated above, leptin can reflect total lipid stores and this might be one means of conveying that information to the brain; but how decreases in the lipid content of specific fat depots would be communicated by such a general circulating signal does not seem possible. The fasting-induced increases in food hoarding are attenuated by chronically administered leptin given peripherally to Syrian hamsters (Schneider & Buckley, 2003), but similarly administered leptin to Siberian hamsters is without such an effect (C. Rooks, D. Day, and T. Bartness, unpublished observations). Therefore, the role of leptin in appetitive ingestive behaviors is largely unexplored and unclear at present.

Alternatively, changes in lipid content of body fat in general, or of specific fat depots, may be signaled via sensory nerves innervating white fat and transmitting the information to the brain. This possibility is supported by the presence of 'sensory neurotransmitters' (Hill, Ralevic, Crowe, & Burnstock, 1996) in white fat, such as substance P (Fredholm, 1985), and by the labeling of dorsal root ganglia neurons after application of an anterograde tract tracer (true blue) to white fat (Fishman & Dark, 1987) in laboratory rats and FluoroGold in Siberian hamsters (Song, Warren, Youngstrom, & Bartness, 1996). It is not clear what is being sensed. Possibilities range from mechanoception of fat pad expansion and contraction (unlikely) to monitoring of lipolytic rate via chemoception (more likely). Regardless of the exact mechanism, it seems that decreases in body fat either generally or within critical lipid depots (gonadal fat; Day & Bartness, 2001) trigger food hoarding, as do lipid deficits generated surgically (Wood & Bartness, 1997), at least in Siberian hamsters. How and where such sensory information arising in peripheral lipid stores is reflected in neurochemical changes in the CNS is not known, but one possibility would be through changes in neuropeptide systems shown to reflect alterations in energy balance in laboratory rats and mice. For example, fasting induces increases in NPY and AgRP mRNA levels in the arcuate nucleus (i.e., Ebihara *et al.*, 1999; Sanacora, Kershaw, Finkelstein, & White, 1990; Schwartz, Sipols, Grubin, & Baskin,

1993) and also in the arcuate nucleus of Siberian hamsters, the latter showing no changes in orexin, or decreases in proopiomelanocortin gene expression (Mercer, Moar, Ross, Hoggard, & Morgan, 2000; Reddy *et al.*, 1999). Of course changes in gene expression do not necessarily reflect changes in neuropeptide release in the terminal fields, but they are often consistent with such changes (e.g., NPY release in the PVN with fasting; Beck *et al.*, 1990; Jain, Dube, Kalra, & Kalra, 1998; Sahu *et al.*, 1988). In addition, icv- or PVN-injections of NPY causes impressive increases in food intake (Clark *et al.*, 1984; Levine & Morley, 1984; Stanley & Leibowitz, 1984) in rats and other species (Larsen *et al.*, 1999; Moris & Crews, 1990) including Siberian hamsters (Boss-Williams & Bartness, 1996). NPY injected into the PVN of rats also stimulates behaviors suggestive of foraging (Harland, Bennett, & Gardiner, 1988; VanNess, DeMaria, & Overton, 1999). Finally, the failure of icv NPY to stimulate food intake in laboratory rats fed passively via intraoral catheters (Seeley, Payne, & Woods, 1995) has been effectively argued to indicate a role for this traditionally recognized "consummatory neuropeptide" as an "appetitive neuropeptide" (Woods *et al.*, 1998). In Siberian hamsters, 3rd-ventricular injections of NPY stimulate food intake (~100–500% increases), but food hoarding, is increased even more (up to ~1,100%; D. Day and T. Bartness, unpublished observations). The ingestive behavior responses of Siberian hamsters housed in the foraging/hoarding system are even more selective for AgRP. As noted above, AgRP is an intense stimulator of food intake in rats and mice, but in Siberian hamsters 3rd-ventricular AgRP either does not affect or decreases food intake, but it impressively stimulates food hoarding (Day & Bartness, 2004). Thus, many neuropeptides, rather than simply triggering or curtailing food intake *per se*, are likely involved in more subtle, complex regulation of food-related behaviors. Clearly, further studies with these neuropeptide stimulators of ingestive behavior are required for a deeper understanding of their role in responding to changes in peripheral lipid energy stores and in triggering consequent appetitive ingestive behaviors.

## Conclusions

The examples given above across a wide range of species indicate that "experiments of nature" afford scientists of ingestive behavior opportunities to obtain a different, and frequently telling insight into the diversity of this behavior. We selected examples of species that naturally exhibit features of ingestive behavior that are often studied in the laboratory through significant and often highly invasive physiological manipulations performed on more traditional species (rats and mice) or via genetic engineering or selective breeding of these species. We hope that the reader of this trek through the control of food intake across diverse regions of the animal kingdom might more fully appreciate the wide range of feeding strategies and physiological responses of these nontraditionally studied species. Although it is often the view that the ingestive behavior responses of laboratory rats and mice are the "gold standard" by which all others should be compared, it could be just as easily argued that these domesticated and inbred animals are the oddities because of the lack of evolutionary pressures shaping their ingestive and other behaviors/physiology during the last ~100 years of captive breeding. As always, perspective is in the eye of the beholder.

In summary, several points can be drawn from the food intake responses of the species reviewed here in terms of the use of these various species for research on ingestive behaviors: (1) there are naturally occurring fasts of prolonged duration or

more modest reductions in food intake that could offer insight into satiety mechanisms, (2) glucoprivation and lipoprivation are not uniformly stimulators of food intake, (3) there are naturally occurring instances of resistance and susceptibility to HFD-induced obesity that seem to make sense given the animals' behavioral ecology, and (4) perhaps a reason for the ever-expanding list of peptides that stimulate or inhibit food intake is that some may function to draw animals to or away from food (appetitive) (i.e., by affecting foraging and other food-seeking behaviors), rather than affecting ingestive (consummatory) behavior directly. Thus, by studying the differences in physiological responses to the same experimental treatment across a wide range of species, we are able to gain valuable perspective on the organization of energy balance systems, the relative importance of specific sensory input signals, as well as other environmental factors that may modify food ingestion in real-world situations.

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## References

Ahima, R. S., Prabakaran, D., Mantzoros, C. S., Qu, D., Lowell, B. B., Maratos-Flier, E. *et al.* (1996). Role of leptin in the neuroendocrine response to fasting. *Nature, 382*, 250–252.

Alonso-Alvarez, C., & Ferrer, M. (2001). A biochemical study of fasting, subfeeding, and recovery processes in yellow-legged gulls. *Physiological and Biochemical Zoology, 74*, 703–713.

Ambid, L., Castan, I., Atgie, C., & Nibbelink, M. (1990). Food intake and peripheral adrenergic activity in a hibernating rodent, the garden dormouse. *Comparative Biochemistry and Physiology A, 97*, 361–366.

Angel, I., & Taranger, M. A. (1991). Impairment of glucostatic, adrenergic and serotoninergic feeding parallels the lack of glucoprivic signals in the golden hamster. *Brain Research Bulletin, 27*, 353–358.

Atcha, Z., Cagampang, F. R., Stirland, J. A., Morris, I. D., Brooks, A. N., Ebling, F. J. *et al.* (2000). Leptin acts on metabolism in a photoperiod-dependent manner, but has no effect on reproductive function in the seasonally breeding Siberian hamster (Phodopus sungorus). *Endocrinology, 141*, 4128–4135.

Baker, R. A. (1955). The effects of repeated deprivation experiences on feeding behavior. *Journal of Comparative and Physiological Psychology, 48*, 37–42.

Baldwin, B. A., Cooper, T. R., & Parrott, R. F. (1983). Intravenous cholecystokiin octapeptide in pigs reduces operant responding for food, water, sucrose solution or radiant heat. *Physiology and Behavior, 30*, 399–403.

Barnes, D. S., & Mrosovsky, N. (1974). Body weight regulation in ground squirrels and hypothalamically lesioned rats: Slow and sudden set point changes. *Physiology and Behavior, 12*, 251–258.

Bartness, T. J. (1990). Species-specific changes in the metabolic control of food intake: Integrating the animal with its environment. *International Journal of Obesity, 14*, 115–123.

Bartness, T. J. (1997). Food hoarding is increased by pregnancy, lactation and food deprivation in Siberian hamsters. *American Journal of Physiology, 272*, R118–R125.

Bartness, T. J., & Clein, M. R. (1994). Effects of food deprivation and restriction, and metabolic blockers on food hoarding in Siberian hamsters. *American Journal of Physiology, 266*, R1111–R1117.

Bartness, T. J., & Day, D. E. (2003). Food hoarding: A quintessential anticipatory appetitive behavior. In S. J. Fluharty, & H. J. Grill (Eds). New York: Academic Press.

Bartness, T. J., McGriff, W. R., & Maharaj, M. P. (1991). Effect of diabetes and insulin on photoperiodic responses in Siberian hamsters. *Physiology and Behavior, 49*, 613–620.

Bartness, T. J., Morley, J. E., & Levine, A. S. (1986). Photoperiod–peptide interactions in the energy intake of Siberian hamsters. *Peptides, 7*, 1079–1085.

Bartness, T. J., Morley, J. E., & Levine, A. S. (1995). Effects of food deprivation and metabolic fuel utilization on the photoperiodic control of food intake in Siberian hamsters. *Physiology and Behavior, 57*, 61–68.

Bartness, T. J., Ruby, N. F., & Wade, G. N. (1984). Dietary obesity in exercising or cold-exposed Syrian hamsters. *Physiology and Behavior, 32*, 85–90.

Bartness, T. J., & Wade, G. N. (1984). Photoperiodic control of body weight and energy metabolism in Syrian hamsters (Mesocricetus auratus): Role of pineal gland, melatonin, gonads, and diet. *Endocrinology, 114*, 492–498.

Bartness, T. J., & Wade, G. N. (1985). Photoperiodic control of seasonal body weight cycles in hamsters. *Neuroscience and Biobehavioral Reviews, 9*, 599–612.

Baskin, D. G., Latteman, D. F., Seeley, R. J., Woods, S. C., Porte, D. Jr., & Schwartz, M. W. (1999). Insulin and leptin: Dual adiposity signals to the brain for the regulation of food intake and body weight. *Brain Research, 848*, 114–123.

Beck, B., Jhanwar-Uniyal, M., Burlet, A., Chapleur-Chateau, M., Leibowitz, S. F., & Burlet, C. (1990). Rapid and localized alterations of neuropeptide Y (NPY) in discrete hypothalamic nuclei with feeding status. *Brain Research, 528*, 245–249.

Bernard, S. F., Mioskowski, E., & Groscolas, R. (2002). Blockade of fatty acid oxidation mimics phase II–phase III transition in a fasting bird, the king penguin. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology, 283*, R144–R152.

Berthoud, H. R. (2002). Multiple neural systems controlling food intake and body weight. *Neuroscience and Biobehavioral Reviews, 26*, 393–428.

Berthoud, H. R., & Mogenson, G. J. (1977). Ingestive behavior after intracerebral and intracerebroventricular infusions of glucose and 2-deoxy-D-glucose. *American Journal of Physiology, 233*, R127–R133.

Billington, C. J., Morley, J. E., Levine, A. S., & Gerritsen, G. C. (1984). Feeding systems in Chinese hamsters. *American Journal of Physiology, 2447*, R405–R411.

Blevins, J. E., Stanley, B. G., & Reidelberger, R. D. (2000). Brain regions where cholecystokinin suppresses feeding in rats. *Brain Research, 860*, 1–10.

Blundell, J. E., Lawton, C. L., Cotton, J. R., & Macdiarmid, J. I. (1996). Control of human appetite: Implications for the intake of dietary fat. *Annual Review of Nutrition, 16*, 285–319.

Bodkin, N. L., Nicolson, M., Ortmeyer, H. K., & Hansen, B. C. (1996). Hyperleptinemia: Relationship to adiposity and insulin resistance in the spontaneously obese rhesus monkey. *Hormone and Metablic Research, 28*, 674–678.

Borer, K. T., Allen, E. R., Smalley, R. E., Lundell, L., & Stockton, J. (1985). Recovery from energy deficit in golden hamsters. *American Journal of Physiology, 248*, R439–R446.

Borer, K. T., Rowland, N. E., Mirow, A., Borer, R. C., Jr., & Kelch, R. P. (1979). Physiological and behavioral responses to starvation in the golden hamster. *American Journal of Physiology, 236*, E105–E112.

Borker, A. S., & Gogate, M. G. (1981). Hunger versus hoarding and body weight in rats. Indian *Journal of Physiology and Pharmacology, 25*, 365–368.

Boss-Williams, K. A., & Bartness, T. J. (1996). NPY stimulation of food intake in Siberian hamsters is not photoperiod dependent. *Physiology and Behavior, 59*, 157–164.

Boswell, T., Millam, J. R., Li, Q., & Dunn, I. C. (1998). Cellular localization of neuropeptide Y mRNA and peptide in the brain of the Japanese quail and domestic chicken. *Cell Tissue Research, 293*, 31–38.

Boyer, B. B., Ormseth, O. A., Buck, L., Nicolson, M., Pelleymounter, M. A., & Barnes, B. M. (1997). Leptin prevents posthibernation weight gain but does not reduce energy expenditure in arctic ground squirrels. *Comparative Biochemistry and Physiology. Part C, Pharmacology Toxicology and Endocrinology, 118*, 405–412.

Broberger, C., & Hokfelt, T. (2001). Hypothalamic and vagal neuropeptide circuitries regulating food intake. *Physiology and Behavior, 74*, 669–682.

Browne, S. A., & Borer, K. T. (1978). Basis for the exercise-induced hyperphagia in adult hamsters. *Physiology and Behavior, 20*, 553–557.

Bungo, T., Shimojo, M., Masuda, Y., Tachibanab, T., Tanaka, S., Sugahara, K. *et al.* (1999). Intracerebroventricular administration of mouse leptin does not reduce food intake in the chicken. *Brain Research, 817*, 196–198.

Cabanac, M., & Gosselin, C. (1996). Ponderostat: Hoarding behavior satisfies the condition for a lipostat in the rat. *Appetite, 27*, 251–261.

Calhoun, J. B. (1962). *The ecology and sociology of the Norway rat.* Washington, DC: US Government Printing Office.

Campfield, L. A., Smith, F. J., Guisez, Y., Devos, R., & Burn, P. (1995). Recombinant mouse OB protein: Evidence for a peripheral signal linking adiposity and central neural networks. *Science, 269*, 546–549.

Castellini, M. A., Costa, D. P., & Huntley, A. C. (1987). Fatty acid metabolism in fasting elephant seal pups. *Journal of Comparative Physiology [B], 157*, 445–449.

Chen, Y., Ono, F., Yoshida, T., & Yoshikawa, Y. (2002). Relationship between body weight and hematological and serum biochemical parameters in female cynomolgus monkeys (Macaca fascicularis). *Experimental Animals, 51*, 125–131.

Cherel, Y., Charrassin, J. B., & Challet, E. (1994). Energy and protein requirement for molt in the king penguin *Aptenodytes patagonicus*. *American Journal of Physiology, 266*, R1182–R1188.

Cherel, Y., Leloup, J., & Le Maho, Y. (1988). Fasting in king penguin. II. Hormonal and metabolic changes during molt. *American Journal of Physiology, 254*, R178–R184.

Cherel, Y., Robin, J. P., Walch, O., Karmann, H., Netchitailo, P., & Le Maho, Y. (1988). Fasting in king penguin. I. Hormonal and metabolic changes during breeding. *American Journal of Physiology, 254*, R170–R177.

Chlouverakis, C., & Hojnicki, D. (1974). Lipectomy in obese hyperglycemic mice (ob/ob). *Metabolism, 23*, 133–137.

Choi, Y. H., Furuse, M., Satoh, S., & Okumura, J. (1994). Endogenous cholesystokinin is not a major regulator of food intake in the chicken. *Journal of Comparative Physiology B, 164*, 425–429.

Clark, J. T., Kalra, P. S., Crowley, W. R., & Kalra, S. P. (1984). Neuropeptide Y and human pancreatic polypeptide stimulate feeding behavior in rats. *Endocrinology, 115*, 427–429.

Clark, J. T., Kalra, P. S., & Kalra, S. P. (1985). Neuropeptide Y stimulates feeding but inhibits sexual behavior in rats. *Endocrinology, 117*, 2435–2442.

Clarke, I. J. (2001). Sex and season are major determinants of voluntary food intake in sheep. *Reproduction, Fertility, and Development, 13*, 577–582.

Clarke, I. J., Rao, A., Chilliard, Y., Delavaud, C., & Lincoln, G. A. (2003). Photoperiod effects on gene expression for hypothalamic appetite-regulating peptides and food intake in the ram. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology, 284*, R101–R115.

Concannon, P., Levac, K., Rawson, R., Tennant, B., & Bensadoun, A. (2001). Seasonal changes in serum leptin, food intake and body weight in photoentrained woodchucks. *American Journal of Physiology, 281*, R951–R959.

Corp, E. S., Greco, B., Powers, J. B., Bivens, C. L., & Wade, G. N. (2001). Neuropeptide Y inhibits estrous behavior and stimulates feeding via separate receptors in Syrian hamsters. *American Journal of Physiology, 280*, R1061–R1068.

Corp, E. S., McQuade, J., Krasnicki, S., & Conze, D. B. (2001). Feeding after fourth ventricular administration of neuropeptide Y receptor agonists in rats. *Peptides, 22*, 493–499.

Covasa, M., & Forbes, J. M. (1994). Effects of the CCK receptor antagonist MK-329 on food intake in broiler chickens. *Pharmacology, Biochemistry, and Behavior, 48*, 479–486.

Craig, W. (1918). Appetites and aversions as constituents of instincts. *The Biological Bulletin, 34*, 91–107.

Cusin, I., Dryden, S., Wang, Q., Rohner-Jeanrenaud, F., Jeanrenaud, B., & Williams, G. (1995). Effect of sustained physiological hyperinsulinaemia on hypothalamic neuropeptide Y and NPY mRNA levels in the rat. *Journal of Neuroendocrinology, 7*, 193–197.

Dark, J., Forger, N. G., Stern, J. S., & Zucker, I. (1985). Recovery of lipid mass after removal of adipose tissue in ground squirrels. *American Journal of Physiology, 249*, R73–R78.

Dark, J., Zucker, I., & Wade, G. N. (1983). Photoperiodic regulation of body mass, food intake, and reproduction in meadow voles. *American Journal of Physiology, 245*, R334–R338.

Davis, D. E. (1976). Hibernation and circannual rhythms of food consumption in marmots and ground squirrels. *The Quarterly Review of Biology, 51*, 477–514.

Davis, D. E., & Finnie, E. P. (1975). Entrainment of circannual rhythm in weight of woodchucks. *Journal of Mammalogy, 56*, 199–203.

Day, D. E., & Bartness, T. J. (2001). Foraging effort alters body fat and food hoarding by Siberian hamsters (*Phodopus sungorus*). *The Journal of Experimental Zoology, 289*, 162–171.

Day, D. E., & Bartness, T. J. (2003). Fasting-induced increases in food hoarding are dependent on the foraging level. *Physiology and Behavior, 78*, 655–668.

Day, D. E., & Bartness, T. J. (2004). AgRP increases food hoarding, but not food intake by Siberian hamsters. *American Journal of Physiology, 286*, R38–R45.

Day, D. E., Mintz, E. M., & Bartness, T. J. (1999). Diet self-selection and food hoarding after food deprivation by Siberian hamsters. *Physiology and Behavior, 68*, 187–194.

de Pedro, N., Lopez-Patino, M. A., Guijarro, A. I., Pinillos, M. L., & Delgado, M. J., & Alonso-Bedate, M. (2000). NPY receptors and opioidergic system are involved in NPY-induced feeding in goldfish. *Peptides, 21*, 1495–1502.

Della-Fera, M. A., & Baile, C. A. (1980). CCK-octapeptide injected in CSF decreases meal size and daily food intake in sheep. *Peptides, 1*, 51–54.

Demas, G. E., & Bartness, T. J. (1999). Effects of food deprivation and metabolic fuel utilization on food hoarding by jirds (*Meriones shawi*). *Physiology and Behavior, 67*, 243–248.

Demas, G. E., Bowers, R. R., Bartness, T. J., & Gettys, T. W. (2002). Photoperiodic regulation of gene expression in brown and white adipose tissue of Siberian hamsters (*Phodopus sungorus*). *American Journal of Physiology, 282*, R114–R121.

Denbow, D. M., Meade, S., Robertson, A., McMurtry, J. P., Richards, M., & Ashwell, C. (2000). Leptin-induced decrease in food intake in chickens. *Physiology and Behavior, 69*, 359–362.

Dewasmes, G., Le Maho, Y., Cornet, A., & Groscolas, R. (1980). Resting metabolic rate and cost of locomotion in long-term fasting emperor penguins. *Journal of Applied Physiology, 49*, 888–896.

DiBattista, D. (1982). Effects of 5-thioglucose on feeding and glycemia in the hamster. *Physiology and Behavior, 29*, 803–806.

DiBattista, D. (1983). Food deprivation and insulin-induced feeding in the hamster. *Physiology and Behavior, 30*, 683–687.

DiBattista, D. (1984). Characteristics of insulin-induced hyperphagia in the golden hamster. *Physiology and Behavior, 32*, 381–387.

DiBattista, D. (1987). Dietary self-selection of golden hamsters in response to acute food deprivation and chronic food restriction. *Behavioral Neuroscience, 101*, 568–575.

DiBona, G. F. (2002) Neuropeptide Y. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology, 282*, R635–R636.

Drazen, D. L., Demas, G. E., & Nelson, R. J. (2001). Leptin effects on immune function and energy balance are photoperiod dependent in Siberian hamsters (*Phodopus sungorus*). *Endocrinology, 142*, 2768–2775.

Drazen, D. L., Kriegsfeld, L. J., Schneider, J. E., Nelson, R. J. (2000) Leptin, but not immune function, is linked to reproductive responsiveness to photoperiod. *American Journal of Physiology, 278*, R1401–R1407.

Dridi, S., Raver, N., Gussakovsky, E. E., Derouet, M., Picard, M., Gertler, A. *et al.* (2000). Biological activities of recombinant chicken leptin C4S analog compared with unmodified leptins. *American Journal of Physiology. Endocrinology and Metabolism, 279*, E116–E123.

Dyer, C. J., Simmons, J. M., Matteri, R. L., & Keisler, D. H. (1997a). Effects of an intravenous injection of NPY on leptin and NPY-Y1 receptor mRNA expression in ovine adipose tissue. *Domestic Animal Endocrinology, 14*, 325–333.

Dyer, C. J., Simmons, J. M., Matteri, R. L., Keisler, & D. H. Leptin (1997b). receptor mRNA is expressed in ewe anterior pituitary and adipose tissues and is differentially expressed in hypothalamic regions of well-fed and feed-restricted ewes. *Domestic Animal Endocrinology, 14*, 119–128.

Dynes, R. A., Poppi, D. P., Barrell, G. K., & Sykes, A. R. (1998). Elevation of feed intake in parasite-infected lambs by central administration of a cholecystokinin receptor antagonist. *British Journal of Nutrition, 79*, 47–54.

Ebenezer, I. S., de la, R. C., & Baldwin, B. A. (1990). Effects of the CCK receptor antagonist MK-329 on food intake in pigs. *Physiology and Behavior, 47*, 145–148.

Ebihara, K., Ogawa, Y., Katsuura, G., Numata, Y., Masuzaki, H., Satoh, N. *et al.* (1999). Involvement of agouti-related protein, an endogenous antagonist of hypothalamic melanocortin receptor, in leptin action. *Diabetes, 48*, 2028–2033.

El-Bakry, H. A., Plunkett, S. S., & Bartness, T. J. (1999). Photoperiod, but not a high fat diet, alters body fat in Shaw's jird. *Physiology and Behavior, 68*, 87–91.

Elmquist, J. K. (2001). Hypothalamic pathways underlying the endocrine, autonomic, and behavioral effects of leptin. *International Journal of Obesity and Related Metabolic Disorders, 25*(Suppl. 5), S78–S82.

Even, P., & Nicolaidis, S. (1985). Spontaneous and 2DG induced metabolic changes and feeding: The ischymetric hypothesis. *Brain Research Bulletin, 15*, 429–435.

Faust, I. M., Johnson, P. R., & Hirsch, J. (1977). Adipose tissue regeneration following lipectomy. *Science, 197*, 391–393.

Faust, I. M., Johnson, P. R., Stern, J. S., & Hirsch, J. (1978). Diet-induced adipocyte number increase in adult rats: A new model of obesity. *American Journal of Physiology, 235*, E279–E286.

Fine, J. B., & Bartness, T. J. (1996). Daylength and body mass affect diet self-selection by Siberian hamsters. *Physiology and Behavior, 59*, 1039–1050.

Fishman, R. B., & Dark, J. (1987). Sensory innervation of white adipose tissue. *American Journal of Physiology, 253*, R942–R944.

Florant, G. L., Richardson, R. D., Mahan, S., Singer, L., & Woods, S. C. (1991). Seasonal changes in CSF insulin levels in marmots: Insulin may not be a satiety signal for fasting in winter. *American Journal of Physiology, 260*, R712–R716.

Florant, G. L., Tokuyama, K., & Rintoul, D. A. (1989). Carbohydrate and lipid utilization in hibernators. In A. Malan, & B. Canguilhem (Eds). *Living in the cold, II* (pp. 137–145). London: John Libbey Eurotext.

Flynn, F. W., & Grill, H. J. (1983). Insulin elicits ingestion in decerebrate rats. *Science, 221*, 188–190.

Flynn, F. W., & Grill, H. J. (1985). Fourth ventricular phlorizin dissociates feeding from hyperglycemia in rats. *Brain Research, 341*, 331–336.

Frederich, R. C., Lollmann, B., Hamann, A., Napolitano-Rosen, A., Kahn, B. B., Lowell, B. B. *et al.* (1995). Expression of ob mRNA and its encoded protein in rodents: Impact of nutrition and obesity. *Journal of Clinical Investigation, 96*, 1658–1663.

Fredholm, B. B. (1985). Nervous control of circulation and metabolism in white adipose tissue. In: A. Cryer, & R. L. R. Van (Eds.) *New perspectives in adipose tissue: Structure, function and development* (pp. 45–64). Boston: Butterworth.

Friedman, J. M. (1998). Leptin, leptin receptors, and the control of body weight. *Nutrition Review, 56*, S38–S46.

Friedman, M. I. (1995). Control of energy intake by energy metabolism. *American Journal of Clinical Nutrition, 62*, 1096S–1100S.

Friedman, M. I., Ramirez, I., Bowden, C. R., & Tordoff, M. G. (1990). Fuel partitioning and food intake: Role for mitochondrial fatty acid transport. *American Journal of Physiology, 258*, R216–R221.

Friedman, M. I., & Tordoff, M. G. (1986). Fatty acid oxidation and glucose utilization interact to control food intake in rats. *American Journal of Physiology, 251*, R840–R845.

Galster, W., & Morrison, P. (1976). Seasonal changes in body composition of the arctic ground squirrel, *Citellus undulatus*. *Canadian Journal of Zoology, 54*, 74–78.

Gauthier-Klerc, M., LeMaho, Y., Clerquin, Y., Drault, S., & Handrich, Y. (2000). Penguin fathers preserve food for their chicks. *Nature, 408*, 928–929.

Gavrilova, O., Leon, L. R., Marcus-Samuels, B., Mason, M. M., Castle, A. L., Refetoff, S. *et al.* (1999). Torpor in mice is induced by both leptin-dependent and -independent mechanisms. *Proceedings of the National Academy of Sciences, USA, 96*, 14623–14628.

Gettys, T. W., Schanbacher, B. D., & Taylor, I. L. (1989). An assessment of the interaction between photoperiod and sex phenotype in relation to appetite development in sheep. *Livestock Production Science, 22*, 283–293.

Gibbs, J., & Smith, G. P. (1982). Gut peptides and food in the gut produce similar satiety effects. *Peptides, 3*, 553–557.

Gibbs, J., Young, R. C., & Smith, G. P. (1973). Cholecystokinin decreases food intake in rats. *Journal of Comparative and Physiological Psychology, 84*, 488–495.

Gil, K. M., & Friedman, M. I. (1982). Caloric compensation following insulin administration in rats. *Physiology and Behavior, 29*, 847–855.

Granneman, J., & Wade, G. N. (1982). Effects of photoperiod and castration on post-fast food intake and body weight gain in golden hamsters. *Physiology and Behavior, 28*, 847–850.

Grill, H. J., Schwartz, M. W., Kaplan, J. M., Foxhall, J. S., Breininger, J., & Baskin, D. G. (2002). Evidence that the caudal brainstem is a target for the inhibitory effect of leptin on food intake. *Endocrinology 143*, 239–246.

Groscolas, R., & Cherel, Y. (1992). How to molt while fasting in the cold: The metabolic and hormonal adapations of the emperor and king penguins. *Ornis Scandinavican, 23*, 328–334.

Groscolas, R., & Clement, G. (1976). Utilisation des reserves energetiques au cours due jenune du manchot empereur, *aptenodytes fosteri*. *Comptes rendus de l'Academie des Sciences Paris Serie D, 282*, 297–300.

Groscolas, R., & Robin, J. P. (2001). Long-term fasting and re-feeding in penguins. *Comparative Biochemistry and Physiology. Part A, Molecular and Integrative Physiology, 128*, 645–655.

Halaas, J. L., Gajiwala, K. S., Maffei, M., Cohen, S. L., Chait, B. T., Rabinowitz, D. *et al.* (1995). Weight-reducing effects of the plasma protein encoded by the obese gene. *Science, 269*, 543–546.

Hamilton, J. M., Mason, P. W., McElroy, J. F., & Wade, G. N. (1986). Dissociation of sympathetic and thermogenic activity in brown fat of Syrian hamsters. *American Journal of Physiology, 250*, R389–R395.

Hamilton, J. M., & Wade, G. N. (1988). Lipectomy does not impair fattening induced by short photoperiods or high-fat diets in female Syrian hamsters. *Physiology and Behavior*, 43, 85–92.

Harland, D., Bennett, T., & Gardiner, S. M. (1988). Cardiovascular actions of neuropeptide Y in the hypothalamic paraventricular nucleus of conscious Long Evans and Brattleboro rats. *Neuroscience Letters, 85*, 121–123.

Harris, R. B., Zhou, J., Redmann, S. M., Jr., Smagin, G. N., Smith, S. R., Rodgers, E. *et al.* (1998). A leptin dose-response study in obese (ob/ob) and lean (+/?) mice. *Endocrinology, 139*, 8–19.

Harris, R. B. S. (2000). Leptin—much more than a satiety signal. *Annual Review of Nutrition, 20*, 45–75.

Harris, R. B. S., Hausman, D. B., & Bartness, T. J. (2002). Compensation for partial lipectomy in mice with genetic alterations of leptin and its receptor subtypes. *American Journal of Physiology, 283*, R1094–R1103.

Henry, B. A., Goding, J. W., Alexander, W. S., Tilbrook, A. J., Canny, B. J., Dunshea, F. *et al.* (1999). Central administration of leptin to ovariectomized ewes inhibits food intake without affecting the secretion of hormones from the pituitary gland: Evidence for a dissociation of effects on appetite and neuroendcrine function. *Endocrinology, 140*, 1175–1182.

Henry, B. A., Goding, J. W., Tilbrook, A. J., Dunshea, F. R., & Clarke, I. J. (2001). Intracerebroventricular infusion of leptin elevates the secretion of luteinising hormone without affecting food intake in long-term food-restricted sheep, but increases growth hormone irrespective of bodyweight. *Journal of Endocrinology, 168*, 67–77.

Hiebert, S. M., Thomas, E. M., Lee, T. M., Pelz, K. M., Yellon, S. M., & Zucker, I. (2000). Photic entrainment of circannual rhythms in golden-mantled ground squirrels: Role of the pineal gland. *Journal of Biological Rhythms, 15*, 126–134.

Hill, B., Ralevic, V., Crowe, R., & Burnstock, G. (1996). Innervation and nitric oxide modulation of mesenteric arteries of the Golden hamster. *European Journal of Pharmacology, 317*, 275–283.

Himick, B. A., & Peter, R. E. (1994). CCK/gastrin-like immunoreactivity in brain and gut, and CCK suppression of feeding in goldfish. *American Journal of Physiology, 267*, R841–R851.

Hoffman, R. A., Davidson, K., & Steinberg, K. (1982). Influence of photoperiod and temperature on weight gain, food consumption, fat pads and thyroxine in male golden hamsters. *Growth, 46*, 150–162.

Horton, T. H., Buxton, O. M., Losee-Olson, S., & Turek, F. W. (2000). Twenty-four-hour profiles of serum leptin in Siberian and golden hamsters: Photoperiodic and diurnal variations. *Hormones and Behavior, 37*, 388–398.

Hotta, K., Gustafson, T. A., Ortmeyer, H. K., Bodkin, N. L., Nicolson, M. A., & Hansen, B. C. (1996). Regulation of *obese* (*ob*) mRNA and plasma leptin levels in rhesus monkeys. *Journal of Biological Chemistry, 271*, 25327–25331.

Houpt, T. R. (1983). The sites of action of cholecystokinin in decreasing meal size in pigs. *Physiology and Behavior, 31*, 693–698.

Invartsen, K. L., & Boisclaire, Y. R. (2001). Leptin and the regulation of food intake, energy homeostasis and immunity with special focus on periparturient ruminants. *Domestic Animal Endocrinology, 21*, 215–250.

Iyengar, S., Li, D. L., & Simmons, R. M. (1999). Characterization of neuropeptide Y-induced feeding in mice: Do Y1–Y6 receptor subtypes mediate feeding? *Journal of Pharmacology and Experimental Therapeutics, 289*, 1031–1040.

Jain, M. R., Dube, M. G., Kalra, S. P., & Kalra, P. S. (1998). Neuropeptide Y release in the paraventricular nucleus is decreased during transient hyperphagia induced by microinjection of colchicine into the ventromedial nucleus of rats. *Neuroscience Letters, 256*, 21–24.

Jensen, J. (2001). Regulatory peptides and control of food intake in non-mammalian vertebrates. *Comparative Biochemistry and Physiology. Part A, Molecular and Integrative Physiology, 128*, 471–479.

Kalra, S. P., Clark, J. T., Sahu, A., Kalra, P. S., & Crowley, W. R. (1989). Hypothalamic NPY: A local circuit in the control of reproduction and behavior. In V. Mutt (Ed.), *Neuropeptide Y* (pp. 229–241). New York: Raven Press.

Kanarek, R. B., & Hirsch, E. (1977). Dietary-induced overeating in experimental animals. In R. B. Kanarek, E. Hirsch (Eds), Dietary-induced overeating in experimental animals. *Federation Proceedings*, 36, 154–158.

Kanarek, R. B., Ogilby, J. D., & Mayer, J. (1977). Effects of dietary caloric density on feeding behavior in Mongolian gerbils (*Meriones*). *Physiology and Behavior, 19*, 497–501.

Kanatani, A., Ishihara, A., Asahi, S., Tanaka, T., Ozaki, S., & Ihara, M. (1996). Potent neuropeptide $YY_1$ receptor antagonist, 1229U91: Blockade of neuropeptide Y-induced and physiological food intake. *Endocrinology, 137*, 3177–3182.

Kanatani, A., Ito, J., Ishihara, A., Iwaasa, H., Fukuroda, T., Fukami, T. *et al.* (1998). NPY-induced feeding involves the action of a Y1-like receptor in rodents. *Regulatory Peptides, 75–76*, 409–415.

Keys, A., Brozek, J., Henschel, A., Mickelson, O., & Taylor, H. L. (1950). *The biology of human starvation.* Minneapolis, MN: University of Minnesota Press.

Klingenspor, M., Dickopp, A., Heldmaier, G., & Klaus, S. (1997). Short photoperiod reduces leptin gene expression in white and brown adipose tissue of Djungarian hamsters. *FEBS Letters, 399*, 290–294.

Klingenspor, M., Niggemann, H., & Heldmaier, G. (2000). Modulation of leptin sensitivity by short photoperiod acclimation in the Djungarian hamster, *Phodopus sungorus. Journal Comparative Physiology B, 170*, 37–43.

Korner, J., Savontaus, E., Chua, S. C., Jr., Leibel, R. L., & Wardlaw, S. L. (2001). Leptin regulation of Agrp and Npy mRNA in the rat hypothalamus. *Journal of Neuroendocrinology, 13*, 959–966.

Kortner, G., & Heldmaier, G. (1995). Body weight cycles and energy balance in the alpine marmot (*Marmota marmota*). *Physiological Zoology, 68*, 149–163.

Kristensen, P., Judge, M. E., Thim, L., Ribel, U., Christjansen, K. N., Wulff, B. S. *et al.* (1998). Hypothalamic CART is a new anorectic peptide regulated by leptin. *Nature, 393*, 72–76.

Kuenzel, W. J., Douglass, L. W., & Davison, B. A. (1987). Robust feeding following central administration of neuropeptide Y or peptide YY in chicks, Gallus domesticus. *Peptides, 8*, 823–828.

Kulkosky, P. J., Glazner, G. W., Moore, H. D., Low, C. A., & Woods, S. C. (1988). Neuropeptide Y: Behavioral effects in the golden hamster. *Peptides, 9*, 1389–1393.

Lambert, P. D., Couceyro, P. R., McGirr, K. M., Dall Vechia, S. E., Smith, Y., & Kuhar, M. J. (1998). CART peptides in the central control of feeding and interactions with neuropeptide Y. *Synapse, 29*, 293–298.

Larsen, P. J., Tang-Christensen, M., Stidsen, C. E., Madsen, K., Smith, M. S., & Cameron, J. L. (1999). Activation of central neuropeptide Y Y1 receptors potently stimulates food intake in male rhesus monkeys. *Journal Clinical Endocrinology and Metabolism, 84*, 3781–3791.

Lawrence, D. H., & Mason, W. A. (1955). Food intake in the rat as a function of deprivation intervals and feeding rhythms. *Journal of Comparative and Physiological Psychology, 48*, 267–271.

Lazzarini, S. J., Schneider, J. E., & Wade, G. N. (1988). Inhibition of fatty acid oxidation and glucose metabolism does not affect food intake or hunger motivation in Syrian hamsters. *Physiology and Behavior, 44*, 209–213.

Le Maho, Y. (1989). Utilization of proteins vs. lipid reserves in spontaneous fasting and hibernation. In A. Malan, & B. Canguilhem (Eds.), *Living in the cold II* (pp. 147–152). London: John Libbey Eurotext.

Le Maho, Y., Delclitte, P., & Chatonnet, J. (1976). Thermoregulation in fasting emperor penguins under natural conditions. *American Journal of Physiology, 231*, 913–922.

Lea, S. E. G., & Tarpy, R. M. (1986). Hamsters' demand for food to eat and hoard as a function of deprivation and cost. *Animal Behaviour, 34*, 1759–1768.

LeMagnen, J. (1984). Is regulation of body weight elucidated? *Neuroscience and Biobehavioral Reviews, 8*, 515–522.

Lemonnier, D. (1972). Effect of age, sex, and site on the cellularity of the adipose tissue in mice and rats rendered obese by a high-fat diet. *Journal of Clinical Investigation, 51*, 2907–2915.

Lemonnier, D., Suquet, J. P., Aubert, R., de Gasquet, P., & Pequignot, E. (1975). Metabolism of the mouse made obese by a high-fat diet. *Diabete and Metabolisme, 1*, 77–85.

Levin, B. E., Dunn-Meynell, A. A., Balkan, B., & Keesey, R. E. (1997). Selective breeding for diet-induced obesity and resistance in Sprague-Dawley rats. *Amercian Journal of Physiology, 273*, R725–R730.

Levine, A. S., & Morley, J. E. (1984). Neuropeptide Y: A potent inducer of consummatory behavior in rats. *Peptides 5*, 1025–1029.

Liebelt, R. A., Ichinoe, S., & Nicholson, N. (1965). Regulatory influences of adipose tissue on food intake and body weight. *Annals of the New York Academy Sciences, 131*, 559–582.

Lopez-Patino, M. A., Guijarro, A. I., Isorna, E., Delgado, M. J., Alonso-Bedate, M., & de Pedro, N. (1999). Neuropeptide Y has a stimulatory action on feeding behavior in goldfish (*Carassius auratus*). *European Journal of Pharmacology, 377*, 147–153.

Lopez-Valpuesta, F. J., Nyce, J. W., Griffin-Biggs, T. A., Ice, J. C., & Myers, R. D. (1996). Antisense to NPY-Y1 demonstrates that Y1 receptors in the hypothalamus underlie NPY hypothermia and feeding in rats. *Proceedings of the Royal Society of London [Biol.], 263*, 881–886.

Lore, R. K., & Flannelly, D. J. (1978). Comparative studies of wild and domestic rats: Some difficulties in solating the effects of geneotype and environment. *Aggressive Behavior, 7*, 253–257.

Marie, M., Findlay, P. A., Thomas, L., & Adam, C. L. (2001). Daily patterns of plasma leptin in sheep: Effects of photoperiod and food intake. *Journal of Endocrinology, 170*, 277–286.

Masek, J., & Fabry, P. (1959). High-fat diet and the development of obesity in albino rats. *Experientia, 15*, 444–446.

Mauer, M. M., & Bartness, T. J. (1994). Body fat regulation following partial lipectomy in Siberian hamsters is photoperiod-dependent and fat pad-specific. *American Journal of Physiology, 266*, R870–R878.

Mauer, M. M., & Bartness, T. J. (1996). Photoperiod-dependent fat pad mass and cellularity changes following partial lipectomy in Siberian hamsters. *American Journal of Physiology, 270*, R383–R392.

Mauer, M. M., & Bartness, T. J. (1997). Fat pad-specific compensatory mass increases after varying degrees of partial lipectomy in Siberian hamsters. *American Journal of Physiology, 273*, 2117–2123.

Mauer, M. M., Harris, R. B. S., & Bartness, T. J. (2001). The regulation of total body fat: Lessons learned from lipectomy studies. *Neuroscience and Biobehavioral Reviews, 25*, 15–28.

Mayer, J. (1953). Glucostatic mechanism of regulation of food intake. *New England Journal of Medicine, 249*, 13–16.

McElroy, J. F., Mason, P. W., Hamilton, J. M., & Wade, G. N. (1986). Effects of diet and photoperiod on NE turnover and GDP binding in Siberian hamster brown adipose tissue. *American Journal of Physiology, 250*, R383–R388.

Melchoir, J. C., Rigaud, D., Rozen, R., Malon, M., & Apfelbaum, M. (1989). Energy expenditure economy induced by decrease in lean body mass in anorexia nervosa. *European Journal of Clinical Nutrition, 43*, 793–799.

Mercer, J. G. (1998). Regulation of appetite and body weight in seasonal mammals. *Comparative Biochemistry and Physiology. Part C, Pharmacology, Toxicology and Endocrinology, 119*, 295–303.

Mercer, J. G., Lawrence, B., Beck, B., Burlet, A., Atkinson, T., & Barrett, P. (1995). Hypothalamic NPY and preproNPY mRNA in Djungarian hamsters: Effects of food deprivation and photoperiod. *American Journal of Physiology, 269*, R1099–R1106.

Mercer, J. G., Lawrence, C. B., & Atkinson, T. (1996). Hypothalamic NPY and CRF gene expression in the food-deprived Syrian hamster. *Physiology and Behavior, 60*, 121–127.

Mercer, J. G., Lawrence, C. B., Moar, K. M., Atkinson, T., & Barrett, P. (1997). Short day weight loss and effect on hypothalamic NPY and CRF mRNA of food deprivation in Djungarian hamsters. *American Journal of Physiology, 273*, R768–R776.

Mercer, J. G., Moar, K. M., Logie, T. J., Findlay, P. A., Adam, C. L., & Morgan, P. J. (2001). Seasonally inappropriate body weight induced by food restriction: Effect on hypothalamic gene expression in male siberian hamsters. *Endocrinology, 142*, 4173–4181.

Mercer, J. G., Moar, K. M., Ross, A. W., Hoggard, N., & Morgan, P. J. (2000). Photoperiod regulates arcuate nucleus POMC, AGRP, and leptin receptor mRNA in Siberian hamster hypothalamus. *American Journal of Physiology, 278*, R271–R281.

Mercer, J. G., Moar, K. M., Ross, A. W., & Morgan, P. J. (2000). Regulation of leptin receptor, POMC and AGRP gene expression by photoperiod and food deprivation in the hypothalamic arcuate nucleus of the male Siberian hamster (*Phodopus sungorus*). *Appetite, 34*, 109–111.

Miceli, M. O., & Malsbury, C. W. (1983). Feeding and drinking responses in the golden hamster following treatment with cholecystokinin and angiotensin II. *Peptides, 4*, 103–106.

Miceli, M. O., & Malsbury, C. W. (1985). Effects of putative satiety peptides on feeding and drinking behavior in golden hamsters (*Mesocricetus auratus*). *Behavioral Neuroscience, 99*, 1192–1207.

Miceli, M. O., & Steiner, M. (1989). Novel localizations of central- and peripheral-type cholecystokinin binding sites in Syrian hamster brain as determined by autoradiography. *European Journal of Pharmacology, 169*, 215–224.

Miceli, M. O., van der, K. D., Post, C. A., Della-Fera, M. A., & Baile, C. A. (1987). Differential distributions of cholecystokinin in hamster and rat forebrain. *Brain Research, 402*, 318–330.

Michel, C., & Cabanac, M. (1999). Lipectomy, body weight, and body weight set point in rats. *Physiology and Behavior, 66*, 473–479.

Mickelsen, O., Takahashi, S., & Craig, C. (1955). Experimental obesity. I. Production of obesity in rats by feeding high-fat diets. *Journal of Nutrition, 57*, 541–554.

Milgram, S. L., Balasubramaniam, A., Andrews, P. C., McDonald, J. K., & Noe, B. D. (1989). Characterization of aPY-like peptides in anglerfish brain using a novel radioimmunoassay for aPY-Gly. *Peptides, 10*, 1013–1017.

Miner, J. L., Della-Fera, M. A., Paterson, J. A., & Baile, C. A. (1989). Lateral cerebroventricular injection of neuropeptide Y stimulates feeding in sheep. *American Journal of Physiology, 257*, R383–R387.

Moinat, M., Deng, C., Muzzin, P., Assimacopoulos-Jeannet, F., Seydoux, J., Dulloo, A. G. *et al.* (1995). Modulation of obese gene expression in rat brown and white adipose tissues. *FEBS Letters, 373*, 131–134.

Morley, J. E., Levine, A. S., Bartness, T. J., Nizielski, S. E., Shaw, M. J., & Hughes, J. J. (1985). Species differences in the response to cholecystokinin. *Annals of the New York Academy of Sciences, 448*, 413–416.

Morris, Y. A., & Crews, D. (1990). The effects of exogenous neuropeptide Y on feeding and sexual behavior in the red-sided garter snake (*Thamnophis sirtalis parietallis). Brain Research, 530*, 339–341.

Morton, M. L. (1975). Seasonal cycles of body weights and lipids in Belding ground squirrels. *Bulletin of the Southern California Academy of Science, 4*, 128–143.

Mrosovsky, N., & Sherry, D. F. (1980). Animal anorexias. *Science, 207*, 837–842.

Naito, C., Yoshitoshi, Y., Higo, K., & Ookawa, H. (1973). Effects of long-term administration of 2-deoxy-D-glucose on food intake and weight gain in rats. *Journal of Nutrition, 103*, 730–737.

Narnaware, Y. K., & Peter, R. E. (2001a). Effects of food deprivation and refeeding on neuropeptide Y (NPY) mRNA levels in goldfish. *Comparative Biochemistry and Physiology. Part B, Biochemistry and Molecular Biology, 129*, 633–637.

Narnaware, Y. K., & Peter, R. E. (2001b). Neuropeptide Y stimulates food consumption through multiple receptors in goldfish. *Physiology and Behavior, 74*, 185–190.

Narnaware, Y. K., Peyon, P. P., Lin, X., & Peter, R. E. (2000). Regulation of food intake by neuropeptide Y in goldfish. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology, 279*, R1025–R1034.

Newsholme, E. A., & Leech, A. R. (1983). *Biochemistry for the medical sciences*. Chichester UK: John Wiley.

Niijima, A. (1998). Afferent signals from leptin sensors in the white adipose tissue of the epididymis, and their reflex effect in the rat. *Journal of the Autonomic Nervous System, 73*, 19–25.

Niijima, A. (1999). Reflex effects from leptin sensors in the white adipose tissue of the epididymis to the efferent activity of the sympathetic and vagus nerve in the rat. *Neuroscience Letters, 262*, 125–128.

Noe, B. D., Milgram, S. L., Balasubramaniam, A., Andrews, P. C., Calka, J., & McDonald, J. K. (1989). Localization and characterization of neuropeptide Y-like peptides in the brain and islet organ of the anglerfish (*Lophius americanus*). *Cell Tissue Research, 257*, 303–311.

Nordoy, E. S., & Blix, A. S. (1991). Glucose and ketone body turnover in fasting grey seal pups. *Acta Physiologica Scandinavica, 141*, 565–571.

Nowak, R., Orgeur, P., Piketty, V., Alster, P., Andersson, R., & Uvnas-Moberg, K. (1997). Plasma cholecystokinin concentrations in 3-day-old lambs: Effect of the duration of fasting preceding a sucking bout. *Reproduction, Nutrition, Development, 37*, 551–558.

Ormseth, O. A., Nicolson, M., Pelleymounter, M. A., & Boyer, B. B. (1996). Leptin inhibits prehibernation hyperphagia and reduces body weight in arctic ground squirrels. *American Journal of Physiology, 271*, R1775–R1779.

Owens, J. L., Thompson, D., Shah, N., & DiGirolamo, M. (1979). Effects of fasting and refeeding in the rat on adipocyte metabolic functions and response to insulin. *Journal of Nutrition, 109*, 1584–1591.

Parrott, R. F. (1993). Peripheral and central effects of CCK receptor agonists on operant feeding in pigs. *Physiology and Behavior, 53*, 367–372.

Peacock, W. L., & Speakman, J. R. (2001). Effect of high-fat diet on body mass and energy balance in the bank vole. *Physiology and Behavior, 74*, 65–70.

Pekas, J. C. (1991). Effect of cholecystokinin immunization, enhanced food intake and growth of swine on lean yield and carcass composition. *Journal of Nutrition, 121*, 563–567.

Pekas, J. C., & Trout, W. E. (1990). Stimulation of food intake and growth of swine by cholecystokinin immunization. *Growth Development, and Aging, 54*, 51–56.

Pelleymounter, M. A., Cullen, M. J., Baker, M. B., Hecht, R., Winters, D., Boone, T. *et al.* (1995). Effects of the obese gene product on body weight regulation in ob/ob mice. *Science, 269*, 540–543.

Pinshow, B., Fedak, M. A., Battles, D. R., & Schmidt-Nielsen, K. (1976). Energy expenditure for thermoregulation and locomotion in emperor penguins. *American Journal of Physiology, 231*, 903–912.

Pisano, R. G., & Storer, T. I. (1948). Burrows and feeding of the Norway rat. *Journal of Mammalogy, 29*, 374–383.

Plunkett, S. S. (2002). The influence of a 24 hour fast on the food intake patterns of free-living individuals. Doctoral Dissertation, Georgia State University.

Prevost, J. (1962). *Ecologie du manchot empereur*. Paris: Hermann.

Rafael, J., & Heldt, H. W. (1976). Binding of guanine nucleotides to the outer surface of the inner membrane of guinea-pig brown fat mitochondria in correlation with the thermogenic capacity of the tissue. *FEBS Letters, 63*, 304–308.

Ramirez, I., & Friedman, M. I. (1990). Dietary hyperphagia in rats: Role of fat, carbohydrate, and energy content. *Physiology and Behavior, 47*, 1157–1163.

Ramsey, J. J., Kemnitz, J. W., Colman, R. J., Cunningham, D., & Swick, A. G. (1998). Different central and peripheral responses to leptin in rhesus monkeys: Brain transport may be limited. *Journal of Clinical Endocrinology and Metabolism, 83*, 3230–3235.

Rawson, N. E., Blum, H., Osbakken, M. D., & Friedman, M. I. (1994). Hepatic phosphate trapping, decreased ATP, and increased feeding after 2,5-anhydro-D-mannitol. *American Journal of Physiology, 266*, R112–R117.

Rawson, N. E., & Friedman, M. I. (1994). Phosphate loading prevents the decrease in ATP and increase in food intake produced by 2,5-anhydro-D-mannitol. *American Journal of Physiology, 266*, R1792–R1796.

Rawson, N. E., Ulrich, P. M., & Friedman, M. I. (1994). L-Ethionine, an amino acid analogue, stimulates eating in rats. *American Journal of Physiology, 267*, R612–R615.

Rawson, N. E., Ulrich, P. M., & Friedman, M. I. (1996). Fatty acid oxidation modulates the eating response to the fructose analogue 2,5-anhydro-D-mannitol. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology, 271*, R144–R148.

Reddy, A. B., Cronin, A. S., Ford, H., & Ebling, F. J. (1999). Seasonal regulation of food intake and body weight in the male Siberian hamster: Studies of hypothalamic orexin (hypocretin), neuropeptide Y (NPY) and pro-opiomelanocortin (POMC). *European Journal of Neuroscience, 11*, 3255–3264.

Reidelberger, R. D. (1994). Cholecystokinin and control of food intake. *Journal of Nutrition, 124*, 1327S–1333S.

Reidelberger, R. D., & O'Rourke, M. F. (1989). Potent cholecystokinin antagonist L 364718 stimulates food intake in rats. *American Journal of Physiology, 257*, R1512–R1518.

Reidelberger, R. D., Varga, G., & Solomon, T. E. (1991). Effects of selective cholecystokinin antagonists L 364718 and L 365260 on food intake in rats. *Peptides, 12*, 1215–1221.

Reuss, S. (1991). Photoperiod effects on bombesin- and cholecystokinin-like immunoreactivity in the suprachiasmatic nuclei of the Djungarian hamster (*Phodopus sungorus*). *Neuroscience Letters, 128*, 13–16.

Richardson, R. D., Boswell, T., Raffety, B. D., Seeley, R. J., Wingfield, J. C., & Woods, S. C. (1995). NPY increases food intake in white-crowned sparrows: Effect in short and long photoperiods. *American Journal of Physiology, 268*, R1418–R1422.

Richardson, R. D., Boswell, T., Weatherford, S. C., Wingfield, J. C., & Woods, S. C. (1993). Cholecystokinin octapeptide decreases food intake in white-crowned sparrows. *American Journal of Physiology, 264*, R852–R856.

Rigaud, D., Hassid, J., Meulemans, A., Poupard, A. T., & Boulier, A. (2000). A paradoxical increase in resting energy expenditure in malnourished patients near death: The king penguin syndrome. *American Journal of Clinical Nutrition, 72*, 355–360.

Ritter, R. C., & Balch, O. K. (1978). Feeding in response to insulin but not to 2-deoxy-D-glucose in the hamster. *American Journal of Physiology, 234*, E20–24.

Ritter, R. C., & Slusser, P. G. (1980). 5-Thio-D-glucose causes increased feeding and hyperglycemia in the rat. *American Journal of Physiology, 238*, E141–E144.

Ritter, S., & Taylor, J. S. (1989). Capsaicin abolishes lipoprivic but not glucoprivic feeding in rats. *American Journal of Physiology, 256*, R1232–R1239.

Rodriguez-Sinovas, A., Fernandez, E., Manteca, X., Fernandez, A. G., & Gonalons, E. (1997). CCK is involved in both peripheral and central mechanisms controlling food intake in chickens. *American Journal of Physiology, 272*, R334–R340.

Ross, I., & Smith, W. I. (1953). The hoarding behavior of the mouse II. The role of deprivation, satiation and stress. *The Journal of General Psychology, 82*, 279–297.

Rousseau, K., Atcha, Z., Cagampang, F. R., Le Rouzic, P., Stirland, J. A., Ivanov, T. R. *et al.* (2002). Photoperiodic regulation of leptin resistance in the seasonally breeding Siberian hamster (*Phodopus sungorus*). *Endocrinology, 143*, 3083–3095.

Rousseau, K., Atcha, Z., & Loudon, A. S. (2003). Leptin and seasonal mammals. *Journal of Neuroendocrinology, 15*, 409–414.

Rowland, N., & Bartness, T. J. (1982). Naloxone suppresses insulin-induced food intake in novel and familiar environments, but does not affect hypoglycemia. *Pharmacology, Biochemistry, and Behavior, 16*, 1001–1003.

Rowland, N. E. (1978). Effects of insulin and 2-deoxy-D-glucose on feeding in hamsters and gerbils. *Physiology and Behavior, 21*, 291–294.

Rowland, N. E. (1982). Failure by deprived hamsters to increase food intake: Some behavioral and physiological determinants. *Journal of Comparative and Physiological Psychology, 96*, 591–603.

Rowland, N. E. (1983). Physiology and Behavior, responses to glucoprivation in the golden hamster. *Physiology and Behavior, 30*, 743–747.

Rowland, N. E. (1984). Metabolic fuel homeostasis in golden hamsters: Effects of fasting, refeeding, glucose, and insulin. *American Journal of Physiology, 247*, R57–R62.

Rowland, N. E., Miceli, M. O., Malsbury, C. W., Baile, C. A., Della-Fera, M. A., Gingerich, R. L. *et al.* (1986). Medial hypothalamic lesions in Syrian hamsters: Characterization of hyperphagia and weight gain. *Physiology and Behavior, 36*, 513–521.

Rowland, N. E., Watkins, L., & Carlton, J. (1985). Failure of 2-deoxy-D-glucose to stimulate feeding in deermice. *Physiology and Behavior, 34*, 155–157.

Sahu, A., Kalra, P. S., & Kalra, S. P. (1988). Food deprivation and ingestion induce reciprocal changes in neuropeptide Y concentrations in the paraventricular nucleus. *Peptides, 9*, 83–86.

Sanacora, G., Kershaw, M., Finkelstein, J. A., & White, J. D. (1990). Increased hypothalamic content of preproneuropeptide Y messenger ribonucleic acid in genetically obese Zucker rats and its regulation by food deprivation. *Endocrinology, 127*, 730–737.

Satcher, D. (2001). Overweight and obesity threaten U.S. health gains. (pp. 1–3) Retrieved from www.surgeongeneral.gov/topics/obesity

Savory, C. J. (1987). An alternative explanation for apparent satiating properties of peripherally administered bombesin and cholecystokinin in domestic fowls. *Physiology and Behavior, 39*, 191–202.

Savory, C. J., & Gentle, M. J. (1983). Effects of food deprivation, strain, diet and age on feeding responses of fowls to intravenous injections of cholecystokinin. *Appetite, 4*, 165–176.

Savory, C. J., & Hadgkiss, J. P. (1984). Influence of vagotomy in domestic fowls on feeding activity, food passage, digestibility and satiety effect of two peptides. *Physiology and Behavior, 33*, 937–944.

Scharrer, E., & Langhans, W. (1986). Control of food intake by fatty acid oxidation. *American Journal of Physiology, 250*, R1003–R1006.

Schemmel, R., & Mickelsen, O. (1970). Dietary obesity in rats: Body weight and body fat accretion in seven strains of rats. *Journal of Nutrition, 100*, 1041–1048.

Schemmel, R., Mickelsen, O., Pierce, S. A., Johnson, J. T., & Schirmer, R. G. (1971). Fat depot removal, food intake, body fat, and fat depot weights in obese rats. *Proceedings of the Society for Experimental Biology and Medicine, 136*, 1269–1273.

Scheurink, A. J. W., & Nolan, L. J. (1996). Food intake, fuel homeostasis, and the autonomic nervous system. *Appetite, 26*, 304.

Schneider, J. E., Blum, R. M., & Wade, G. N. (2000). Metabolic control of food intake and estrous cycles in syrian hamsters. I. Plasma insulin and leptin. *American Journal of Physiology, 278*, R476–R485.

Schneider, J. E., & Buckley, C. A. (2003). Food hoarding is increased by food deprivation and decreased by leptin treatment in Syrian hamsters. *American Journal of Physiology, 285*, R1021–R1029.

Schneider, J. E., Friedenson, D. G., Hall, A. J., & Wade, G. N. (1993). Glucoprivation induces anestrus and lipoprivation may induce hibernation in Syrian hamsters. *American Journal of Physiology, 264*, R573–R577.

Schneider, J. E., Goldman, M. D., Tang, S., Bean, B., Ji, H., & Friedman, M. I. (1998). Leptin indirectly affects estrous cycles by increasing metabolic fuel oxidation. *Hormones and Behavior, 33*, 217–228.

Schneider, J. E., Lazzarini, S. J., Friedman, M. I., & Wade, G. N. (1988). Role of fatty acid oxidation in food intake and hunger motivation in Syrian hamsters. *Physiology and Behavior, 43*, 617–623.

Schneider, J. E., & Wade, G. N. (1989). Availability of metabolic fuels controls estrous cyclicity of Syrian hamsters. *Science, 244*, 1326–1328.

Schneider, J. E., & Wade, G. N. (1999). Inhibition of reproduction in service of energy balance. In K. Wallen, & J. E. Schneider (Eds.), *Reproduction in context: Environmental and social influences on reproductive physiology and behavior* (pp. 35–82). Cambridge: MIT Press.

Schneider, J. E., & Watts, A. G. (2002). Energy balance, ingestive behavior and reproductive success. In D. Pfaff (Ed.), *Hormones brain and behavior* (pp. 435–523). New York: Academic Press.

Schwartz, J. H., Young, J. B., & Landsberg, L. (1983). Effect of dietary fat on sympathetic nervous system activity in the rat. *Journal of Clinical Investigation, 72*, 361–370.

Schwartz, M. W., Seeley, R. J., Woods, S. C., Weigle, D. S., Campfield, L. A., Burn, P. *et al.* (1997). Leptin increases hypothalamic pro-opiomelanocortin mRNA expression in the rostral arcuate nucleus. *Diabetes, 46*, 2119–2123.

Schwartz, M. W., Sipols, A. J., Grubin, C. E., & Baskin, D. G. (1993). Differential effects of fasting on hypothalamic expression of genes encoding neuropeptide Y, galanin and glutamic acid decarboxylase. *Brain Research Bulletin, 31*, 361–367.

Sclafani, A., & Eisenstadt, D. (1980). 2-Deoxy-D-glucose fails to induce feeding in hamsters fed a preferred diet. *Physiology and Behavior, 24*, 641–643.

Seeley, R., Payne, C. J., & Woods, S. C. (1995). Neuropeptide Y fails to increase intraoral intake in rats. *American Journal of Physiology, 268*, R423–R427.

Shapiro, B., Borer, K. T., Fig, L. M., & Vinik, A. I. (1987). Exercise-induced hyperphagia in the hamster is associated with elevated plasma somatostatin-like immunoreactivity. *Regulatory Peptides, 18*, 85–92.

Silverman, H. J., & Zucker, I. (1976). Absence of post-fast food compensation in the golden hamster (*Mesocricetus auratus*). *Physiology and Behavior, 17*, 271–285.

Simek, V. (1974). Energy metabolism of golden hamsters adapted to intermittent fasting: Influence of season and sex. *Physiologia Bohemoslovaca, 23*, 437–446.

Simek, V. (1975). Effect of sex and season on the production and deposition of lipid and glycid reserves in the intermittently starving golden hamster. *Physiologia Bohemoslovaca, 24*, 183–190.

Simek, V. (1980). Effect of intermittent fasting followed by cold on growth, formation of reserves and energy metabolism in the golden hamster. *Physiologia Bohemoslovaca, 29*, 167.

Simek, V., & Petrasek, R. (1974). The effects of two time-different feeding regimens on food intake, growth rate and lipid metabolism in golden hamster (Rodentia). *Vest. Csek. Spol. Zool. 38*, 152–159.

Sipols, A. J., Figelwicz, D. P., Seeley, R. J., Chavez, M., Woods, S. C., & Porte, D., Jr. (1996). Intraventricular neuropeptide Y does not stimulate food intake in the baboon. *Physiology and Behavior, 60*, 717–719.

Slusser, P. G., & Ritter, R. C. (1980). Increased feeding and hyperglycemia elicited by intracerebroventricular 5-thioglucose. *Brain Research, 202*, 474–478.

Smith, G. P. (1996). The direct and indirect controls of meal size. *Neuroscience and Biobehavioral Reviews, 20*, 41–46.

Smith, G. P., & Epstein, A. N. (1969). Increased feeding in response to decreased glucose utilization in the rat and monkey. *American Journal of Physiology, 217*, 1083–1087.

Song, C. K., Warren, W. S., Youngstrom, T. G., & Bartness, T. J. (1996). Sensory and motor innervation of white adipose tissue. *Society for the study of ingestive behavior.*

Srinivasan, V., Thombre, D. P., Lakshmanan, S., & Chakrabarty, A. S. (1986). Effect of removal of epididymal fat on spermatogenesis in albino rats. *Indian Journal of Experimental Biology, 24*, 487–488.

Stamper, J. L., & Dark, J. (1997). Metabolic fuel availability influences thermoregulation in deer mice (*Peromyscus maniculatus*). *Physiology and Behavior, 61*, 521–524.

Stamper, J. L., Dark, J., & Zucker, I. (1999). Photoperiod modulates torpor and food intake in Siberian hamsters challenged with metabolic inhibitors. *Physiology and Behavior, 66*, 113–118.

Stanley, B. G., & Leibowitz, S. F. (1984). Neuropeptide Y: Stimulation of feeding and drinking by injection into the paraventricular nucleus. *Life Sciences, 35*, 2635–2642.

Stanley, B. G., Magdalin, W., Seirafi, A., Nguyen, M. M., & Leibowitz, S. F. (1992). Evidence for neuropeptide Y mediation of eating produced by food deprivation and for a variant of the Y1 receptor mediating this peptide's effect. *Peptides, 13*, 581–587.

Steinlechner, S., Heldmaier, G., & Becker, H. (1983). The seasonal cycle of body weight in the Djungarian hamster: Photoperiodic control and the influence of starvation and melatonin. *Oecologia, 60*, 401–405.

Steinman, J. L., Fujikawa, D. G., Wasterlain, C. G., Cherkin, A., & Morley, J. E. (1987). The effects of adrenergic, opioid and pancreatic polypeptidergic compounds on feeding and other behavior in neonatal leghorn chicks. *Peptides, 8*, 585–592.

Stephens, D. W., & Krebs, J. R. (1986). *Foraging theory.* Princeton, NJ: Princeton University Press.

Storlien, L., James, D. E., Burleigh, K. M., Chisholm, D. J., & Kraegn, E. W. (1986). Fat feeding causes widespread in vivo insulin resistance, decreased energy expenditure, and obesity in rats. *American Journal of Physiology, 251*, E576–E583.

Strader, A. D., & Buntin, J. D. (2001). Neuropeptide-Y: A possible mediator of prolactin-induced feeding and regulator of energy balance in the ring dove (*Streptopelia risoria*). *Journal of Neuroendocrinology, 13*, 386–392.

Stricker, E. M., & Rowland, N. E. (1978). Hepatic versus cerebral origin of stimulus for feeding induced by 2-deoxy-D-glucose in rats. *Journal of Comparative and Physiological Psychology, 92*, 126–132.

Stricker, E. M., Rowland, N. E., Saller, C. F., & Friedman, M. I. (1977). Homeostasis during hypoglycemia: Central control of adrenal secretion and peripheral control of feeding. *Science, 196*, 79–81.

Takahhashi, L. K., & Lore, R. K. (1980). Foraging and food hoarding of wild *Rattus norvegicus* in an urban environment. *Behavioral and Neural Biology, 29*, 537–541.

Tang-Christensen, M., Havel, P. J., Jacobs, R. R., Larsen, P. J., & Cameron, J. L. (1999). Central administration of leptin inhibits food intake and activates the sympathetic nervous system in rhesus macaques. *Journal of Clinical Endocrinology and Metabolism, 84*, 711–717.

Taouis, M., Dridi, S., Cassy, S., Benomar, Y., Raver, N., Rideau, N. *et al.* (2001). Chicken leptin: Properties and actions. *Domestic Animal Endocrinology, 21*, 319–327.

Thouzeau, C., Duchamp, C., & Handrich, Y. (1999). Energy metabolism and body temperature of barn owls fasting in the cold. *Physiological and Biochemical Zoology, 72*, 170–178.

Tsai, A. C., Bach, J., & Borer, K. T. (1981). Somatic, endocrine, and serum lipid changes during detraining in adult hamsters. *American Journal of Clinical Nutrition, 34*, 373–376.

Tsai, A. C., Rosenberg, R., & Borer, K. T. (1982). Metabolic alterations induced by voluntary exercise and discontinuation of exercise in hamsters. *American Journal of Clinical Nutrition, 35*, 943–949.

Vander Wall, S. B. (1990). *Food hoarding in animals.* Chicago: University of Chicago Press.

VanNess, J. M., DeMaria, J. E., & Overton, J. M. (1999). Increased NPY activity in the PVN contributes to food-restriction induced reductions in blood pressure in aortic coarctation hypertensive rats. *Brain Research, 821*, 263–269.

Vaughan, T. A. (1978). *Mammalogy.* Philadelphia: W. B. Saunders.

Wade, G. N. (1982). Obesity without overeating in golden hamsters. *Physiology and Behavior, 29*, 701–707.

Wade, G. N. (1983). Dietary obesity in golden hamsters: Reversibility and effects of sex and photoperiod. *Physiology and Behavior, 30*, 131–137.

Wade, G. N., & Bartness, T. J. (1983). Dietary obesity in hamsters: Effects of age, fat source and species. *Nutrition and Behavior, 1*, 169–177.

Wade, G. N., & Bartness, T. J. (1984a). Effects of photoperiod and gonadectomy on food intake, body weight and body composition in Siberian hamsters. *American Journal of Physiology, 246*, R26–R30.

Wade, G. N., & Bartness, T. J. (1984b). Seasonal obesity in Syrian hamsters: Effects of age, diet, photoperiod, and melatonin. *American Journal of Physiology, 247*, R328–R334.

Wade, G. N., Schneider, J. E., & Friedman, M. I. (1991). Insulin-induced anestrus in Syrian hamsters. *American Journal of Physiology, 260*, R148–R152.

Waldbillig, R. J., & Bartness, T. J. (1982). The suppression of sucrose intake by cholecystokinin is scaled according to the magnitude of the orosensory control over feeding. *Physiology and Behavior, 28*, 591–595.

Wang, Q., Bing, C., Al-Barazanji, K., Mossakowaska, D. E., Wang, X. M., McBay, D. L. *et al.* (1997). Interactions between leptin and hypothalamic neuropeptide Y neurons in the control of food intake and energy homeostasis in the rat. *Diabetes, 46*, 335–341.

Webb, G. P., Jagot, S. A., & Jakobson, M. E. (1982). Fasting-induced torpor in *Mus musculus* and its implications in the use of murine models for human obesity studies. *Comparative Biochemistry and Physiology, A, 72A*, 211–219.

Webb, P. I., & Skinner, J. D. (1996). Summer torpor in African woodland dormice *Graphiurus murinus* (Myoxidae: Graphiurinae). *Journal of Comparative Physiology B, 166*, 325–330.

Weigle, D. S., Bukowsk, T., Foster, D., Holderman, S., Kramer, J., Lasser, G. *et al.* (1995). Recombinant ob protein reduces feeding and body weight in the ob/ob mouse. *Journal of Clinical Investigation, 96*, 2065–2070.

Weiner, J. (1987). Limits to energy budget and tactics in energy investments during reproduction in the Djungarian hamster (*Phodopus sungorus sungorus* Pallas, *1770*). *Symposium Zoological Society London, 57*, 167–187.

West, D. B., Boozer, C. N., Moody, D. L., & Atkinson, R. L. (1995). Dietary obesity in nine inbred mouse strains. *American Journal of Physiology, 262*, R1025–R1032.

West, D. B., Waguespack, J., & McCollister, S. (1995). Dietary obesity in the mouse: Interaction of strain with diet composition. *American Journal of Physiology, 268*, R658–R665.

West, D. B., & York, B. (1998). Dietary fat, genetic predisposition, and obesity: Lessons from animal models. *American Journal of Clinical Nutrition, 67*, 505S–512S.

Whishaw, I. Q., & Whishaw, G. E. (1996). Conspecific aggression influences food carrying: Studies on a wild population of *Rattus norvegicus. Aggressive Behavior, 22*, 47–66.

White, J. D., & Kershaw, M. (1989). Increased hypothalamic neuropeptide Y expression following food deprivation. *Molecular and Cellular Neurosciences, 1*, 41–48.

Williams, A. J., Siegfried, W. R., Burger, A. E., & Berruti, A. (1977). Body composition and energy metabolism of moulting eudyptid penguins. *Comparative Biochemistry and Physiology A, 56*, 27–30.

Williams, T. D. (1995). *The penguins.* Oxford: Oxford University Press.

Wingfield, J. C., Hahn, T. P., Wada, M., & Schoech, S. J. (1997). Effects of day length and temperature on gonadal development, body mass, and fat depots in white-crowned sparrows, *Zonotrichia leucophrys pugetensis. General and Comparative Endocrinology, 107*, 44–62.

Wong, R., & Jones, C. H. (1985). A comparative analysis of feeding and hoarding in hamsters and gerbils. *Behavioral Processes, 11*, 301–308.

Wood, A. D., & Bartness, T. J. (1996). Food deprivation-induced increases in food hoarding in Siberian hamsters is not photoperiod-dependent. *Physiology and Behavior, 60*, 1137–1145.

Wood, A. D., & Bartness, T. J. (1997). Partial lipectomy, but not PVN lesions, increases food hoarding by Siberian hamsters. *American Journal of Physiology, 272*, R783–R792.

Woods, S. C., Figlewicz, D. P., Madden, L., Porte, D., Jr., Sipols, A. J., & Seeley, R. J. (1998). NPY and food intake: Discrepancies in the model. *Regulatory Peptides, 75–76*, 403–408.

Zucker, I., & Boshes, M. (1982). Circannual body weight rhythms of ground squirrels: Role of gonadal hormones. *American Journal of Physiology, 243*, R546–R551.