Hungry for Life: How the arcuate nucleus and neuropeptide Y may play a critical role in mediating the benefits of calorie restriction

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Abstract

Laboratory studies consistently demonstrate extended lifespan in animals on calorie restriction (CR), where total caloric intake is reduced by 10–40% but adequate nutrition is otherwise maintained. CR has been further shown to delay the onset and severity of chronic diseases associated with aging such as cancer, and to extend the functional health span of important functions including cognition. Less understood are the underlying mechanisms through which CR might act to induce such alterations. One theory postulates that CR's beneficial effects are intimately tied to the neuroendocrine response to low energy availability, of which the arcuate nucleus in the hypothalamus plays a pivotal role. Neuropeptide Y (NPY), a neurotransmitter in the front line of the arcuate response to low energy availability, is the primary hunger signal affected by CR and therefore may be a critical mechanism for lifespan extension.

1. Introduction: Appetite

Deprived of food, an organism becomes hungry. As seemingly straightforward as this relationship appears externally, internally it is mediated by a decidedly complex interaction of numerous alterations both psychological and physiological. For example, hunger may be described in behavioral terms as the state in which an organism is motivated to eat. The feeding response, the most overt outcome subsequent to negative energy balance, incorporates numerous physiological and neurophysiological alterations imperceptible to the naked eye: neural signaling patterns, body temperature, metabolism, and various blood-borne hormones and metabolites are just a few of the many processes responsive to hunger and satiety in animals. As an organism shifts from a fed to a fasted state, its empty stomach ceases signaling fullness and commences to call for refeeding. Circulating metabolites shift from energetic macronutrients to byproducts of metabolism, triggering a compensatory adjustment in pancreatic output. The sum of these signals is tallied by the brain, where the peripheral call to eat is put into action.

Central recipients of the peripheral messages relaying the status of satiety are primarily the hypothalamus and the brainstem (Berthoud, 2004). The brainstem functions in the control of autonomous feeding behavior via the caudal nucleus of the solitary tract (NTS). Gastrointestinal, circulatory and central cues all reach the NTS and influence the determination

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of meal size (Schwartz, 2006). The NTS alone, however, has been shown to be insufficient for a full response to long-term food deprivation (Seeley et al., 1994) as this requires the action of another CNS satiety center: the hypothalamus. This critical difference relates to the primary signal input for these brain regions; the NTS acts as the main port of entry for gastrointestinal signals while the hypothalamus predominately services an inflow of peripheral signals pertaining to metabolic energy stores (Näslund and Hellström, 2007), as depicted in Figure 1. Located above the pituitary and below the thalamus, the hypothalamus is found in all mammalian brains and operates as a central regulator of multiple physiological processes and circadian cycles, with the most salient to this review being its role as the major integration center for peripheral satiety signals.

2. The role of the hypothalamic arcuate nucleus in hunger

Appreciation of the hypothalamus as a regulator of appetite became firmly established in the 1950s when it was demonstrated that lesions of the hypothalamic ventromedial nucleus (VMH) result in hyperphagia and obesity, whereas lesions of the lateral hypothalamus (LHA) result in anorexia and weight loss (Anand and Brobeck, 1951a,b). Thus was born the hypothesis that a relay of humoral signals communicates energy needs through the brain (Stellar, 1954). Ensuing research has continued to demonstrate the importance of the hypothalamus to feeding behavior (Hoebel, 1997), and today the hypothalamus is considered to be an essential component in the regulatory system for energy homeostasis (Berthoud, 2006; Elmquist et al., 2005; Meister, 2007).

Hypothalamic centers associated with the regulation of energy balance include the arcuate (ARC), dorsomedial (DMH), paraventricular (PVN), and ventromedial (VMH) nuclei and the LHA. Of these, the ARC in particular is a critical locus for food intake regulation as it integrates signals from the brainstem and the periphery (Cone et al., 2001; Cowley et al., 2003), and is uniquely accessible to the latter because the blood-brain barrier is semi-permeable here (Broadwell and Brightman, 1976; Peruzzo et al., 2000). Nestled at the base of the third ventricle just above the median eminence in an elongated, 'arc-like' bundle, the first-order neurons of the ARC are in direct contact with peripheral satiety factors which they translate and convey to the second-order neuron centers of the DMH, PVN, VMH and LHA (Heijboer et al., 2006; Schwartz and Porte, 2005). At least two populations of first-order neurons controlling appetite are present in the ARC: (1) neurons coexpressing NPY and agouti-related protein (AgRP), and (2) neurons coexpressing pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART). The former (NPY/AgRP) stimulate food intake (Broberger et al., 1998; Hahn et al., 1998; Shutter et al., 1997) while the latter (POMC/CART) repress it (Elias et al., 1998; Kristensen et al., 1998).

Hypothalamic ARC circuits are directly responsive to an array of circulating hunger and satiety signals such as hormones (e.g., ghrelin, insulin and leptin), and metabolites (e.g., glucose) and thus monitor input regarding both short-term fuel status as well as long-term energy stores. Registered in concert, these signals convey the current state of energy availability. An array communicating energy sufficiency leads to low ARC NPY/AgRP expression and high POMC/CART expression, which promotes satiety (Ziotopoulou et al., 2000). When the opposite is true and the ARC registers an energy deficit, the resulting neuropeptide balance is shifted to high NPY/AgRP expression and low POMC/CART expression to promote hunger (Pinto et al., 2004). If the energy status of an animal is skewed to the negative end over a long-term period such as during repeated fasting or chronic CR, the prolonged shift in ARC neuropeptide expression could have profound consequences on the organism. In fact, this response could be essential to driving systemic adaptations noted under conditions of reduced energy availability.

2.1. Neuropeptide Y

ARC neuropeptides highly expressed during the hunger response may carry significant responsibility for instigating downstream physiological adaptations with resounding health implications. For one of these neuropeptides to influence aging-related processes, such a peptide would likely respond to a variety of peripheral satiety signals, actively signal to secondary brain appetite centers and continue to respond to negative energy balance over the long term. One such hypothalamic peptide has been identified: NPY.

2.1.1. Distribution—NPY, first isolated from the porcine brain in 1982, is a powerfully orexigenic 36-amino-acid protein in the pancreatic polypeptide family (Tatemoto et al., 1982a; Tatemoto, 1982b), and is one of the most abundant peptides in the mammalian central nervous system (Adrian et al., 1983; Chan-Palay et al., 1985; Chan-Palay et al., 1986; Chronwall et al., 1985). Widely distributed throughout the brain, NPY localization is predominantly hypothalamic wherein immunoreactivity is highest in the neurons of the ARC and the DMH (Allen et al., 1983; Chronwall et al., 1985; Gray and Morley, 1986) because it is within these neurons that NPY is synthesized and stored (Bi et al., 2003). Both ARC and DMH NPY neurons project to the LHA, PVN and VMH (Chronwall et al., 1985; Cripps et al., 2005; Jhanwar-Uniyal et al., 1993), but ARC NPY is the primary responder to both short-term and long-term fasting conditions (Bi, 2007). NPY is also found in the peripheral nervous system in sympathetic nerves (Pernow et al., 1987).

Widespread distribution of NPY extends beyond the nervous system. NPY is released from sympathetic nerves into endocardial endothelial cells (Jacques et al., 2006), the gut (Cox, 2007) and the spleen (Ericsson et al., 1987). Splenic NPY is incorporated by developing blood cells and ultimately circulates in immune cells and platelets (Ericsson et al., 1987; Kuo et al., 2007b). NPY is also released into circulation from sympathetic nerves and the adrenal medulla under stress (Bernet et al., 1998; Han et al., 2005; Kuo et al., 2007b). Recently, adipocytes have been demonstrated to express NPY where it may play a role in mediating adiposity (Kos et al., 2007).

2.1.2. Mechanism of action—NPY signals through G protein-coupled receptors, seven of which have been named (Y_1–Y_7) and five of which have been cloned and described: Y_1, Y_2, Y_4, Y_5, and Y_6 (Dumont et al., 1993; Michel et al., 1998). This is not to say that all receptors are relevant to all species; the existence of Y_3 has been postulated but not demonstrated (Herzog et al., 1993; Jazin et al., 1993), Y_6 is inactive in primates (Matsumoto et al., 1996), and mammals have lost the Y_7 gene altogether (Larhammar and Salaneck, 2004). NPY acts through Y receptors to inhibit adenylyl cyclase (Herzog et al., 1992) and increase intracellular calcium levels (Jacques et al., 2000). In some instances NPY receptor activity has been shown to result in activation of mitogen-activated protein kinase (Nie and Selbie, 1998) and protein kinase C (Mannon and Raymond, 1998). The NPY Y_1 and Y_5 receptors expressed in the hypothalamus are considered to be the most active in the regulation of appetitive behavior and energy balance in mammals (Duhault et al., 2000; Hu et al., 1996; Lecklin et al., 2002; Parker and Herzog, 1999).

2.1.3. Physiological pluripotency—The relative abundance of NPY and its receptors, combined with their widespread distribution, suggests NPY is involved in multiple important physiological roles beyond the regulation of food intake. This is indeed the case, and the gamut of NPY's systemic and central effects is depicted in Table 1. Of particular interest to this review are NPY's involvement in food intake and neuroendocrine coordination, to be elaborated below.

In the broadest terms, NPY's central actions include stimulating hunger, fat storage and weight gain (Beck et al., 1992; Stanley et al., 1986; Zarjevski et al., 1993) while decreasing sex drive, locomotion, energy expenditure and body temperature (Billington et al., 1991; Hwa et al., 1999; Kulkosky et al., 1988; Lopez-Valpuesta et al., 1996; Menendez et al., 1990). These effects contrast the actions of NPY in the periphery, where stress is a major factor influencing the release of NPY (Bernet et al., 1998; Han et al., 2005; Kuo et al., 2007b) and the consequences are strongly registered by the adrenal and cardiovascular systems. It has been hypothesized that in the current Western lifestyle—which agonizes central NPY through leptin resistance and peripheral NPY through stress—NPY could contribute to a number of diseases such as hypertension, diabetes, and obesity where calories are in plentiful supply (Chronwall and Zukowska, 2004; Kuo et al., 2007b).

2.1.4. NPY in appetite—Within two years of its discovery, NPY became well known for inducing a robust feeding response in rats (Clark et al., 1984; Levine and Morley, 1984; Stanley and Leibowitz, 1984), and to this day NPY is the most potent endogenous orexigenic stimulant known (Chamorro et al., 2002; Edwards et al., 1999). The feeding effect of NPY appears to be well conserved, as central injection induces food intake in a wide range of species (Clark et al., 1984; Larsen et al., 1999; Miner et al., 1989; Morley et al., 1987; Morris and Crews, 1990; Pau et al., 1988). The only known exception is the baboon, in which intracerebroventricular injection of NPY did not induce feeding (Sipols et al., 1996).

The potency of NPY to provoke feeding extends even to sated animals (Levine and Morley, 1984; Parrott et al., 1986), and chronic administration of NPY results in sustained hyperphagia and ultimately obesity (Beck et al., 1992; Pierroz et al., 1996; Stanley et al., 1986; Zarjevski et al., 1993). Conversely, compounds that lower NPY levels or inhibit its activity reduce feeding and body weight (Akabayashi et al., 1994; Burlet et al., 1995; Hulsey et al., 1995; Lambert et al., 1998; Shimokawa et al., 2002).

Assessment of NPY expression levels over time and during periods of feeding and fasting has formed the basis for a close relationship between hypothalamic NPY and food intake that suggests a critical role for NPY in the long-term control of appetite. For example, rodent NPY levels peak in the dark phase, which is when the majority of their feeding occurs (Jhanwar-Uniyal et al., 1990; McKibbin et al., 1991). Furthermore, hypothalamic NPY levels are increased in several models of hyperphagia, such as after short-term food deprivation (Ahima et al., 1996; Bi et al., 2003; Brady et al., 1990; Grove et al., 2003), long-term CR (Bi et al., 2003; Boswell et al., 1999; Brady et al., 1990; de Rijke et al., 2005; Lewis et al., 1993; Mercer et al., 2001), heavy exercise (Chen et al., 2007; Lewis et al., 1993), and in animals displaying seasonal hyperphagia in preparation for hibernation (Boswell et al., 1993; Lakhdar-Ghazal et al., 1995).

Hypothalamic NPY is also increased in genetic models of obesity involving hyperphagia. These include obese (*ob/ob*) mice (Jang and Romsos, 1998), diabetic (*db/db*) mice (de Luca et al., 2005), Zucker fatty (*fa/fa*) rats (Dryden et al., 1995), and the Koletsky corpulent (*cp/cp*) rat (Williams et al., 1992). Tubby (*tub/tub*) mice are unique in that they show significantly reduced ARC NPY; however, high levels of NPY are found in their VMH and DMH, indicating increased neurotransmission of NPY from the ARC to the VMH and DMH could explain their hyperphagia (Guan et al., 1998). Whether increased NPY is associative or causative to obesity in these models remains to be definitively proven, but in at least one model—*fa/fa* rats—NPY overexpression occurs pre-obesity and is thought to be a driving factor in its weight gain (Bchini-Hooft et al., 1993). The reverse association has also been observed; anorexic (*anx/anx*) mice display reduced NPY signaling concomitant with their reduced food intake (Broberger et al., 1997).

Research investigating the effects of genetic manipulation of NPY expression and feeding behavior underscores the complexity of food intake regulation. For example, mice engineered to overexpress central NPY by 15% did not display increased feeding (Inui et al., 1998), and NPY knockout ($NPY^{-/-}$) mice on a mixed background have normal food intake and body weight and are able to respond to fasting with hyperphagia (Erickson et al., 1996b). C57BL/6 (B6) $NPY^{-/-}$ mice even develop mild obesity when access to food is unrestricted (Segal-Lieberman et al., 2003). Concomitant knockout of NPY and AgRP—mutually expressed by ARC neurons in response to negative energy balance—did not prevent mice from attaining normal body weight or displaying hyperphagia following fasting (Qian et al., 2002). Given that roughly two dozen neurotransmitters have been identified to play a role in regulating feeding behavior (Kalra et al., 1999), overlapping mechanisms have likely developed to ensure the feeding instinct is not easily extinguished and survival jeopardized. Regardless, other data confirm NPY's salience in appetite control. For example, targeted postembryonic ablation of ARC NPY neurons leads to reduced food intake and body weight (Bewick et al., 2005). B6 $NPY^{-/-}$ mice show a 25% (Bannon et al., 2000) to 50% (Segal-Lieberman et al., 2003) reduction in the hyperphagic response to fasting compared with wild-types. $NPY^{-/-}$ mice also exhibit less hyperphagia in streptozotocin-induced diabetes (Sindelar et al., 2002).

2.1.5. NPY in neuroendocrine coordination—The neuroendocrine system consists of hormones, hormone producing and secreting glands, and neurons that regulate these glands' activity. In mammals these neurons are found in the hypothalamus, and they act to ensure coordinated secretion of hormones in response to environmental cues (e.g., food availability). As a primary messenger at the central-peripheral crossroads, NPY is produced by the hypothalamus to translate systemic signals about energy status into the local neurochemical dialect.

Diverse circulating factors influence NPY expression, including leptin (Ahima et al., 1996; Baskin et al., 1999; Schwartz et al., 1996; Stephens et al., 1995; Tang-Christensen et al., 1999), insulin (Schwartz et al., 1992) and glucocorticoids (Higuchi et al., 1988b). Various gut hormones such as ghrelin, pancreatic polypeptide (PP) and peptide YY (PYY) are also known to modulate NPY expression (Asakwa et al., 2003; Batterham et al., 2002; Challis et al., 2003; Kamegai et al., 2001; Nakazato et al., 2001; Shintani et al., 2001). NPY expression is also directly responsive to energy availability via circulating glucose (Mizuno et al., 1999).

NPY's relationship with leptin has been a popular focal point in appetite research. Leptin, a hormone produced in adipocytes in proportion to fat mass, acts as a feedback signal to the hypothalamus and plays a fundamental role in maintaining energy homeostasis (Jequier, 2002). Not only is ARC NPY gene expression downregulated by leptin administration (Ahima et al., 1996; Schwartz et al., 1996; Stephens et al., 1995), leptin also hyperpolarizes NPY neurons and inhibits their signaling activity (Spanswick et al., 1997). In the ideal model, an increase in fat mass would lead to an increase in leptin, thereby decreasing NPY levels and signaling, which would in turn reduce feeding and restore body mass to the appropriate set point. Evidence from *ob*/*ob* mice (which lack leptin and grow into obese adults) supports the importance of the ARC NPY response in this model, as these mice display increased hypothalamic NPY and hyperphagia, which can be reduced by either leptin administration (Ahima et al., 1996; Schwartz et al., 1996; Stephens et al., 1995) or NPY ablation (Erickson et al., 1996a). Furthermore, leptin therapy is ineffective in reversing weight gain in *ob*/*ob* mice when the ARC is rendered dysfunctional by lesioning (Takeda et al., 2002).

Anorexigenic (appetite-suppressing) signals other than leptin have a similar influence on NPY. Insulin hyperpolarizes and inactivates ARC NPY (Spanswick et al., 1997), and the high NPY levels observed in streptozotocin-induced diabetes models (which underproduce insulin) can be normalized by insulin therapy (Jones et al., 1992; Sahu et al., 1997; White et al., 1990;

Williams et al., 1989). The gut hormones pancreatic polypeptide (PP) and peptide YY (PYY) are released postprandially and induce a reduction in hypothalamic NPY (Asakawa et al., 2003; Batterham et al., 2002; Challis et al., 2003). Glucagon-like peptide 1 (GLP-1), a cleavage product of preproglucagon released postprandially by the small intestine (Herrmann et al., 1995), has been observed to block the NPY-induced feeding response in chicks (Furuse et al., 1997). Oxyntomodulin, another cleavage product of preproglucagon released postprandially by intestinal endocrine cells, also inhibits food intake (Dakin et al., 2001) and may do so by inhibiting ARC NPY neurons through GLP-1 receptors (Wynne and Bloom, 2006).

Orexigenic (appetite-stimulating) signals activate ARC NPY neurons. Ghrelin, secreted primarily by the stomach in increasing amounts with fasting (Ariyasu et al., 2001), raises NPY levels (Cowley et al., 2003; Kamegai et al., 2001; Nakazato et al., 2001; Shintani et al., 2001). Orexin, which influences the ARC via neuronal innervation from the LHA, stimulates NPY neurons (Burdakov et al., 2003).

Once released, NPY has multiple downstream effects (Fig. 2). Central administration of NPY, for example, has been shown to induce the release of glucoregulatory hormones including adrenocorticotropic hormone (ACTH), corticosterone and insulin (Akabayashi et al., 1994; Leibowitz et al., 1988; Moltz and McDonald, 1985; Wahlestedt et al., 1987; Zarjevski et al., 1994). Central NPY administration also leads to reduced growth hormone (GH) and insulin-like growth factor 1 (IGF-1) release (Catzeflis et al., 1993). As ARC NPY neurons also express GH receptor (Chan et al., 1996a), they have been hypothesized to mediate feedback control of this important pituitary hormone (Chan et al., 1996b).

3. Aging

Aging, most simply defined as the temporal process of growing older, is not in itself a deleterious process. Furthermore, while it may be said that the greatest risk factor for all natural causes of death is old age, aging is not a disease either. Maximum lifespan, defined as the average lifespan of the longest-lived decile of a cohort (Holloszy, 2000), is often used as the gold standard in gerontology research because valid biomarkers of physiological aging have not yet been identified (Johnson, 2006). The oldest documented person in recent history, Jean Louise Calment, died in 1997 at the age of 122, representing what has been considered the near-maximum lifespan for humans (Coles and LA-GRG, 2004). Despite concerted effort, the mechanisms underlying the aging process that set the maximum lifespan of species have not been completely elucidated. It is likely that multiple mechanisms impact lifespan, and many potential contributors have been nominated based on commonly observed consequences of aging. These include oxidative damage (Beckman and Ames, 1998; Muller et al., 2007), aggravation of inflammatory processes (Chung et al., 2001), increased fat mass (Enzi et al., 1986; Shimokata et al., 1989), decreased muscle mass (Morley, 2001), insulin resistance (Fraze et al., 1987; Ma et al., 2002), and shifting hormonal profiles (Bartke, 2005). Subsequently, a number of theories have been developed to explain aging within the context of these phenomena.

Theories of aging can be divided into two major categories: 'programmed aging' theories and 'wear and tear' theories. Programmed aging theories view aging as the result of an innate genetic program that dictates the rate of aging and maximum lifespan (Butler et al., 2003). In contrast, wear and tear theories envision aging as the result of spontaneous events (Muller et al., 2007). They hypothesize an organism is subject to continual stress (especially oxidative stress) from the environment and metabolism, and that the ability to repair damage declines with age such that mutated DNA, proteins and lipids accumulate and lead to impaired function of cells and tissues.

Within the aging field, there is great interest in the aging field to identify a unifying theory that can singly account for the myriad symptoms of senescence. One that continues to garner proponents is the neuroendocrine theory of aging (Bishop and Guarente, 2007; Speakman and Hambly, 2007). Because the neuroendocrine system manages the general homeostatic tone of the body and mediates its response to stress, the neuroendocrine theory of aging hypothesizes these activities set the pace of aging. For example, menopause and andropause are associated with neurodegeneration (Atwood et al., 2005), reduced GH/IGF-1 in elderly humans is associated with decreased muscle strength and frailty (Ceda et al., 2005), and removal of the pituitary gland with corticosterone replacement has been shown to extend lifespan in rats (Everitt et al., 1980).

3.1. Calorie restriction

Few environmental manipulations have been reported to consistently extend the lifespan of multiple species. CR, the reduction of macronutrient intake while maintaining sufficient micronutrient intake, is one notable exception. Early studies by McCay and colleagues at Cornell University established the effectiveness of CR for extending the lifespan of rats in the 1930s (McCay et al., 1935; McCay et al., 1939; McCay and Crowell, 1934). Subsequent studies have demonstrated that reducing calorie intake from 30–60% can increase maximum lifespan in a wide range of species, and to date CR remains the most robust dietary intervention in aging research (Ingram, 2006).

3.2. CR mechanisms of action

The earliest documented effect of CR was its potent antitumor activity (reviewed in Kritchevsky, 2002). Since then CR has been demonstrated to affect nearly every physiological process (reviewed in Sinclair, 2005). From an evolutionary viewpoint, the effect of CR seems to be explained by organisms having evolved mechanisms to maximize survival when faced with food scarcity (Holliday, 1989). These mechanisms remain to be definitively identified, but may include reduced adiposity, metabolic rate, body temperature, oxidative stress and insulin/IGF-1 signaling, and increased antioxidant protection, damage repair and protein turnover rates (Masoro, 2007).

Given that several of CR's effects pertain to neuroendocrine adaptations, the neuroendocrine system has been hypothesized to be a critical mediator of the beneficial effects secondary to negative energy balance (Bishop and Guarente, 2007; Lamberts et al., 1997; Meites, 1989; Nelson et al., 1995; Rehman and Masson, 2001; Speakman and Hambly, 2007). Fuel sensing systems are likely to play an important role in the initial response to altered caloric intake, since the organism must first recognize reduced caloric intake in order to respond to it. Sensation of food withdrawal occurs primarily within the gastrointestinal tract and the central nervous system. It is unlikely that the coordinated systemic response is mediated by the gastrointestinal system alone, and that the gut communicates with the brain both directly and humorally further suggests systemic control mediated by neural and endocrine factors. Neuroendocrine-related effects of CR include frequent periods of moderate hyperadrenocorticism (Ahima et al., 1996; Masoro, 2007), reduced serum thyroid hormones (Ahima et al., 1996; Herlihy et al., 1990) and inhibition of gonadal axes (Ahima et al., 1996). In fact, removal of the pituitary gland with corticosterone replacement leads to lifespan extension in rats similar to that seen with CR (Everitt et al., 1980).

3.3. Neuropeptide Y: How and Y calorie restriction extends lifespan?

It is well established that CR raises ARC NPY levels (Bi et al., 2003; Brady et al., 1990; de Rijke et al., 2005; Kim et al., 1988; Mercer et al., 2001; Widdowson et al., 1997). Because the normal response to increased NPY levels is hyperphagia and a return to normal energy balance, animals on CR must be maintained on a strict regimen and fed periodically their restricted

meals. Similar to reducing calorie intake, restricting intake of the amino acid methionine also extends lifespan (Miller et al., 2005; Orentreich et al., 1993) with a concomitant increase in hypothalamic NPY (White et al., 1994). Whether the increased NPY is a necessary precursor to the functional benefits associated with dietary restriction is not known, but considering NPY's unique long-term response to CR compared with other neuropeptides (Bi et al., 2003) and its plethora of physiological actions, a causal relationship is certainly plausible.

One way CR may act to extend lifespan through NPY is by prolonging youthful expression levels of NPY. Aging is associated with reduced levels of NPY in the brain in general (Gruenewald et al., 1994; Higuchi et al., 1988a; Sohn et al., 2002; Vela et al., 2003) and in response to fasting (Gruenewald et al., 1996). Reduced NPY has been associated with Alzheimer's disease (Alom et al., 1995; Edvinsson et al., 1993) and the development of a condition termed 'anorexia of aging', thought to be responsible for aging-associated undernutrition and consequent physical deterioration such as osteoporosis, sarcopenia, impaired immunity and parenchymatous organ failure (Matsumoto et al., 2000; Morley, 2001). Evidence from the rat showing NPY loss with age is progressive and independent of testosterone levels has been interpreted to suggest an active role for NPY in the anorexia of aging (Gruenewald et al., 1994).

The increase in NPY under CR conditions can lead to a wide array of physiological modifications. Among these, there exist a number of parallels between the observed effects of CR and NPY that extend beyond their obvious influence on hunger (Fig. 3). For example, CR is well known for lowering core body temperature in mammals (Walford and Spindler, 1997), as does central administration of NPY (Billington et al., 1991;Kotz et al., 2000), both of which may act through an increase in ghrelin emission from the stomach (Gluck et al., 2006). While the extent to which reduced core body temperature mediates lifespan extension by CR is still debated, work by Koizumi et al. (1996) has suggested that reduced body temperature may account for up to 50% of lifespan extension in mice.

Altered metabolism is another hallmark of CR, manifest in part by reduced levels of circulating blood glucose (Harris et al., 1994). Likewise, acute administration of NPY has been shown to lower blood glucose in both rats and humans (Ahlborg and Lundberg, 1994; Bischoff and Michel, 1998; Marks and Waite, 1997). The effects of CR and NPY on blood glucose mirror their effects on corticosterone in rodents, which is to say they both induce increased circulating levels of this glucocorticoid (Harris et al., 1994; Leibowitz et al., 1988; Wahlestedt et al., 1987).

Delayed puberty and reduced fertility are consequences of CR (Holehan and Merry, 1985) that are thought to contribute to longevity under CR in the disposable soma theory of aging (Kirkwood et al., 2000). In this theory, reduced fecundity in response to CR evolved to maximize long-term reproductive success during periods of food shortage. Because NPY modulates the secretion of gonadotropin-releasing hormone and luteinizing hormone (LH) in response to energy availability, it is thought to be a key relay signal integrating metabolism and reproduction centrally (reviewed in Crown et al., 2007).

In the end, the relationship between ARC NPY levels and lifespan will be the ultimate litmus test for the extent to which NPY mediates CR *in vivo*. Interestingly, transgenic rats that overexpress NPY have been found to have improved stress resistance as demonstrated through reduced blood pressure in response to novelty stress and increased mean (but not maximum) lifespan (Michalkiewicz et al., 2003). Lifespan benefits with increased NPY may be reflected in humans as well, as long-lived female centenarians have high plasma NPY levels compared with younger women (Baranowska et al., 2006). More studies are needed to show whether the

increase in NPY under CR is necessary for lifespan extension, and whether NPY can be manipulated as a CR mimetic.

4. Conclusion

Because CR is so successful in multiple species, there is increasing interest in the therapeutic potential for CR to extend maximum lifespan in humans (Ingram, 2006). In fact, the prospect of CR in humans is already a reality, and there are societies, books and internet sites devoted to CR in humans (see http://www.calorierestriction.org/). Despite the willful adherence by this CRonie minority, the current hunch of gerontologists is that most humans will prefer not to strictly regimen their diet in the presence of an abundant food supply if alternatives, or mimetics, to CR may be found. Indeed, candidate CR mimetics are already under investigation (Ingram, 2006) with the hopes of rendering CR's benefits attainable to the overeating masses. This movement presupposes one critical notion: that CR's beneficial effects can be separated from those imposed on appetite. Taking into account the profound effects of CR on the appetite-regulating machinery of the hypothalamus and NPY—the key central hunger signal that may play a critical role in transducing CR's benefits—it may be that the very effectiveness of CR stems from the same hunger-inducing phenomena that CR mimetic research seeks to repress.

Acknowledgments

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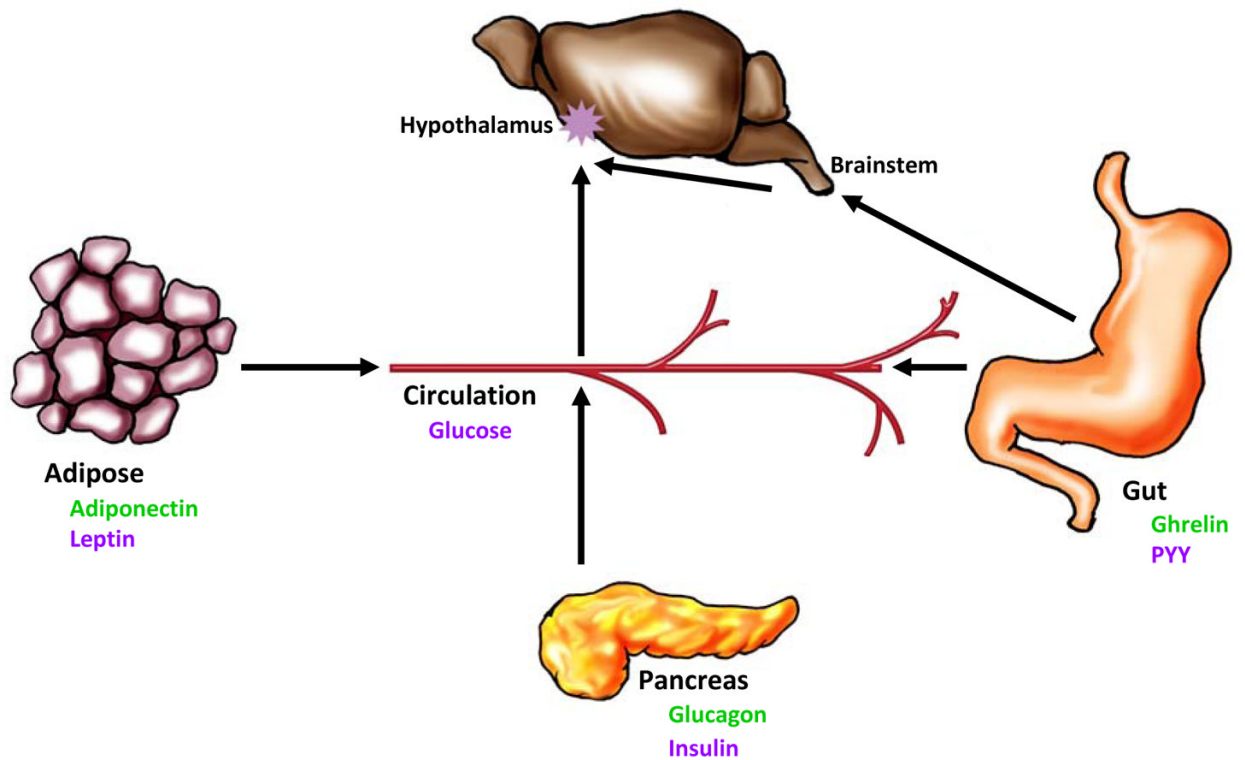
Fig. 1.
Central integration of satiety signals. The two main central targets of peripheral cues regarding energy status are the brainstem and the hypothalamus. Afferent nerves carry sensory information about feeding status directly from the gut to the brainstem while circulating factors derived from metabolism, adipose tissue, the pancreas and the gut signal through the hypothalamus. The appetitive state is determined by the balance of hunger- versus satiety-inducing cues, depicted above in green (pro-hunger) and purple (pro-satiety). PYY, peptide YY.
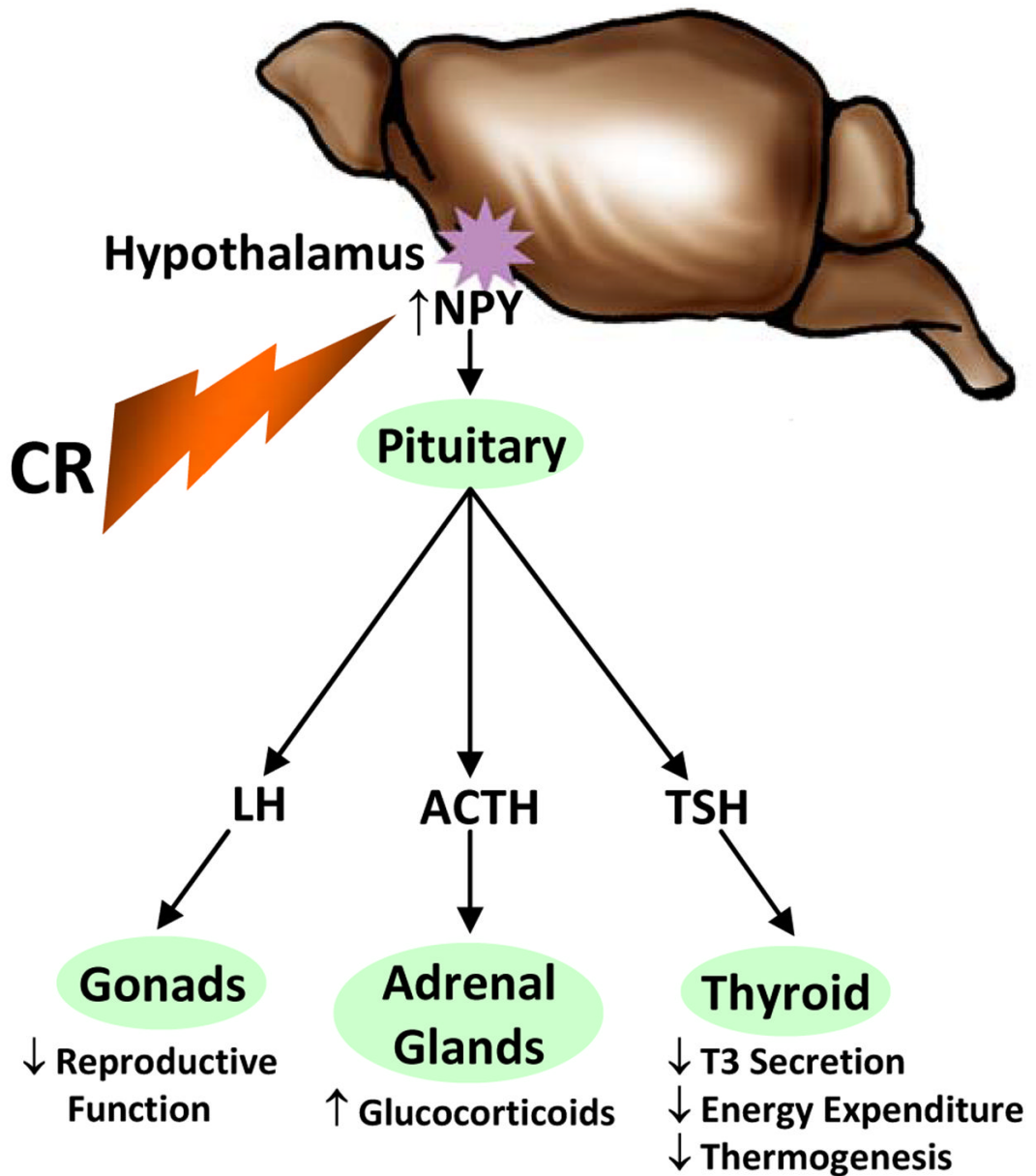
Fig. 2.
Neuroendocrine manifestations of CR through the hypothalamic-pituitary axes. CR increases NPY expression which alters hypothalamic output to the pituitary and ultimately leads to decreased reproductive function, increased glucocorticoid expression, and reduced energy expenditure. ACTH, adrenocorticotrophin hormone; LH, luteinizing hormone; T3, triiodothyronine; TSH, thyroid-stimulating hormone.
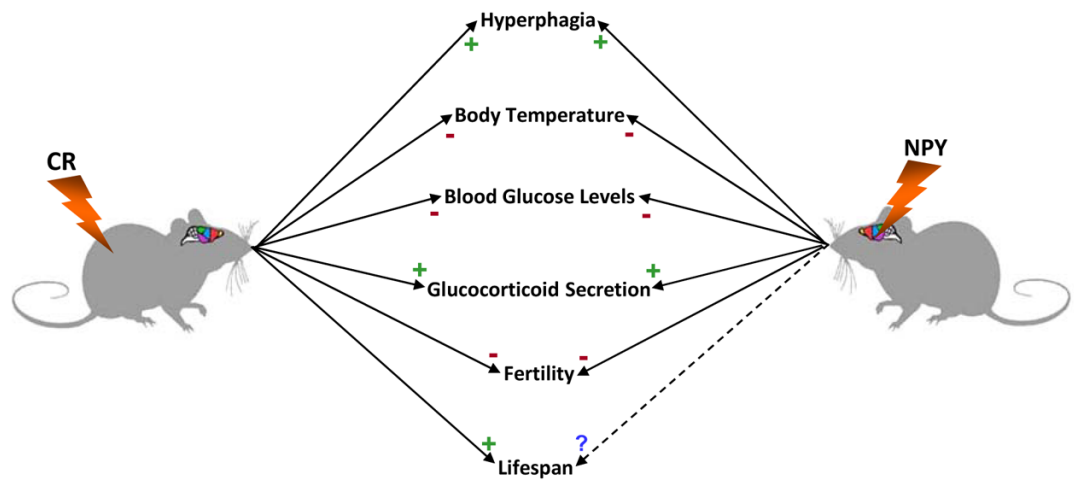
Fig. 3.
Physiological parallels between the effects of CR and centrally-administered NPY. CR and intracerebroventricular injection of NPY both result in reduced body temperature and increased glucocorticoid secretion, for example, but only CR has been shown to extend the lifespan of mammals.

Table 1

The diverse effects of central and systemic NPY.

	Reviewed by[*]:
Central Effects	
Alcohol Intake	Carvajal et al. (2006), Thorsell (2007)
Circadian Rhythms	Kallingal and Mintz (2007), Yannielli and Harrington (2001)
Emotion	Carvajal et al. (2006), Heilig (2004)
Feeding Behavior	Arora and Anubhuti (2006), Beck (2006)
Learning	Redrobe et al. (1999)
Locomotion	Karlsson et al. (2005)
Neuroendocrine Coordination	Magni (2003), Plant and Shahab (2002)
Reproductive Function	Kalra and Kalra (2004), Wójcik-G adysz and Polkowska (2006)
Seizures	Dubé (2007), Redrobe et al. (1999)
Systemic Effects	
Adipose Function	Kos et al. (2007)
Adrenal Function	Spinazzi et al. (2005)
Cardiovascular Function	Zukowska et al. (2003)
Gastrointestinal Function	Cox (2007)
Pancreatic Function	Imai et al. (2007)

[*] See review by Thorsell and Heilig (2002) for an overview of many of NPY's actions