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Understanding the Control of Ingestive Behavior in Primates

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Abstract

Ingestive behavior in free-ranging populations of nonhuman primates is influenced by resource availability and social group organization and provides valuable insight on the evolution of ecologically adaptive behaviors and physiological systems. As captive populations were established, questions regarding proximate mechanisms that regulate food intake in these animals could be more easily be addressed. The availability of these captive populations has lead to the use of selected species to understand appetite control or metabolic physiology in humans. Recognizing the difficulty of quantitating food intake in free ranging groups, the use of captive, singly-housed animals provided a distinct advantage though, at the same time, produced a different social ecology from the animals' natural habitat. However, with the recent application of novel technologies to quantitate caloric intake and energy expenditure in free feeding, socially-housed monkeys permits prospective studies that can accurately define how food intake changes in response to any number of interventions in the context of a social environment. This review provides an overview of studies examining food intake using captive nonhuman primates organized into three areas: a) neurochemical regulation of food intake in nonhuman primates; b) whether exposure to specific diets during key developmental periods program differences in diet preferences or changes the expression of feeding related neuropeptides; and c) how psychosocial factors influence appetite regulation. Because feeding patterns are driven by more than just satiety and orexigenic signals, appreciating how the social context influences pattern of feeding in nonhuman primates may be quite informative for understanding the biological complexity of feeding in humans.

Keywords

nonhuman primates; macaques; neuropeptides; estradiol; appetite; programming

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Assessment of food intake or foraging patterns of nonhuman primates has been of interest to investigators for decades wishing to expand knowledge of the natural history of monkeys and apes to gain better insight into the evolution of ecologically adaptive behaviors and physiological systems (Ofstedal, 1991; Sherry, 2006). Feeding behavior in these free-ranging populations is influenced by resource availability and social group organization both of which dictate access to these resources. As is often the case, access to these resources are delayed among group members who are more socially subordinate (Furuichi, 1983; Koenig, 2002). Once captive populations were established and expanded, questions regarding proximate mechanisms that regulate food intake in these animals could be more easily addressed, leading to the use of selected species of nonhuman primates as models to understand appetite control or metabolic physiology in humans. Recognizing the inherent difficulty, or even impossibility, of quantitating food intake in free ranging groups (Berman and Schwartz, 1988; Janson and van Schaik, 1988), the use of captive, caged populations provided a means to address these questions. While this approach provided models to better define the neurobiological causes (Foltin, 2012) and metabolic consequences of food intake (Raman et al., 2005; Tigno et al., 2004), it produced a different social ecology from the animals' natural habitat. Even though experimental precision was increased, the approach somewhat limited applicability to humans, given the significant impact that the social environment has on appetite regulation in people (Brug et al., 2008; Rogers, 1999). Studies of captive, provisioned social groups of nonhuman primates, most notably macaques, created the opportunity to consider the importance of socio-environmental factors. While studies of these populations showed monkeys presented with a range of metabolic phenotypes, including variation in degrees of adiposity (Howard et al., 1989; Schwartz, 1989) and resulting problems with glucose regulation (Schwartz and Kemnitz, 1992), the use of these captive social groups still made the measurement of food intake at best simply estimates (Marriott et al., 1989). However, with the recent application of radiofrequency identification (RFID) technology to precisely quantify caloric consumption (Wilson et al., 2008), patterns of food intake (Moore et al., 2013), and estimates of energy expenditure (Sullivan et al., 2006) in freely feeding individual monkeys housed in social groups can be determined. With these technologies, prospective studies are now possible that can accurately define how food intake changes in response to any number of dietary or pharmacological interventions in the context of a social environment and may provide additional insight into the complex factors that regulate appetite in people.

Regulation of food intake

Studies of food intake using captive nonhuman primates can be classified into three investigative areas. The first addresses the question of whether peptides or steroids that influence food intake in other mammals have similar effects in nonhuman primates and, relatedly, whether potential therapeutic agents for excess calorie consumption are effective in nonhuman primates. Indeed, a number of drugs developed for treating excess food intake and obesity have been evaluated in a variety of nonhuman primate models and has been reviewed elsewhere (Foltin, 2012). The second general area of investigation focuses on whether exposure to specific diets, particularly in utero, programs differences in dietary preferences or alters the expression of neuropeptides known to regulate appetite in offspring.

Finally, given the emerging evidence from rodents (Dallman et al., 2007) and humans (Moore and Cunningham, 2012), studies are aimed at understanding how psychosocial factors influence “comfort food” ingestion and emotional feeding.

Neurochemical signals and appetite

The neurochemical effects on food intake have been extensively evaluated in rodent models (Gao and Horvath, 2007; Williams and Elmquist, 2012) with the identification of new signals important for appetite regulation emerging frequently (e.g., (Cuomo et al., 2011)). A limited number of these signals have been tested in nonhuman primates (see Table 1). Recent reviews illustrate these pathways and are applicable to framing studies to understand appetite regulation in nonhuman primates and people (Chaudhri et al., 2006; Suzuki et al., 2012). Although the effects of these peptides on food intake are generally similar between nonhuman primates and rodent, differences do emerge, particularly in the central distribution of a ligand or its receptor. For example, an acute fast in adult male rhesus monkeys up regulates neuropeptide Y (NPY) mRNA in the arcuate nucleus and, unlike the rodent, in the paraventricular nucleus of the hypothalamus (Grove et al., 2003; Van Vugt et al., 2006). In addition to an increased expression of NPY, cocaine-amphetamine-regulated transcript (CART), an anorexic neuropeptide that has been shown to be up regulated by leptin in rodent models (Lee et al., 2013), was down-regulated in the arcuate nucleus by fasting in female monkeys (Van Vugt et al., 2006). This fasting-induced decline in CART is similar to what is observed in rodents (Vicentic and Jones, 2007). Furthermore, central administration of NPY dose-dependently stimulates food intake mediated through activation of Y1 receptors in adult male monkeys (Larsen et al., 1999). Activation of Y5 receptors by NPY also stimulates food intake in rodents and people (Duhault et al., 2000) but has yet to be evaluated in monkeys.

Similar to its effects in rodents (Dutia et al., 2013), activation of central melanocortin 3–4 receptors (MCR-3/4) attenuates while administration of agouti-related peptide (AgRP), the endogenous antagonist for the MCR-3/4, stimulates food intake in adult males (Koegler et al., 2001). An acute fast in rhesus monkeys also produced an upregulation of proopiomelanocortin (POMC) expression in the arcuate further supporting the importance of the melanocortin systems for food intake in nonhuman primates (Kievit et al., 2013; Koegler et al., 2001). Indeed, data from rodents indicates brain-derived neurotropic factor (BDNF) and its signaling through its endogenous receptor tyrosine kinase TrkB, is thought to mediate, in part, the anorexic effects of the melanocortin 4 receptor system (Xu et al., 2003). While TrkB agonists administered centrally to adult monkeys acutely attenuated food intake, peripheral administration significantly increased food intake (Lin et al., 2008), a finding opposite to the effects of peripheral administration of TrkB agonists in mice (Tsao et al., 2008). The species differences in peripheral TrkB signaling on food intake are unresolved. Finally, the hypocretins, orexin A or B, are neuropeptides that integrate feeding, wakefulness, and energy expenditure (Sellayah and Sikder, 2012). Consistent with data from rodents (Ida et al., 1999; Sweet et al., 1999), central administration of orexin A to adult male rhesus decreased food intake while orexin B was without effect (Ramsey et al., 2005).

A number of satiety-inducing neuropeptides have also been investigated in macaque monkeys. Acute central, but not peripheral, administration of leptin reduced food intake the day following treatment (Ramsey et al., 1998; Tang-Christensen et al., 1999), suggesting peripherally administered leptin was unable to penetrate the blood brain barrier. This finding is consistent with a large body of data from rodents (Friedman, 2009), underscoring the notion that peripherally administered leptin is not a good therapeutic strategy to attenuate food intake (Considine, 1997; Figlewicz, 2003; Suzuki et al., 2012). Galanin-like peptide (GALP) is one of the several central targets of leptin (Jureus et al., 2000) that may mediate, in part, the anorexic action of leptin. GALP has distribution of expression in the macaque brain similar to that of rodents, notably in the arcuate nucleus, median eminence and posterior pituitary (Cunningham et al., 2002). Fasting significantly reduces GALP mRNA in the arcuate in neurons that co-express NPY Y1 receptors (Cunningham et al., 2004), providing support for the hypothesis that GALP may be an important regulator of food intake in nonhuman primates.

A number of gut peptides known to limit food intake in rodent models have also been evaluated in nonhuman primates. Well-established effects of cholecystokinin (CCK) at slowing gastric emptying and reducing subsequent food intake in rodents (Blevins and Baskin, 2010) are also seen in rhesus monkeys (Gibbs et al., 1976; Metzger and Hansen, 1983; Moran and McHugh, 1982). CCK is thought to have these effects by stimulation of vagal receptors that project to the hindbrain to stimulate noradrenergic neurons projecting to hypothalamus (Blevins and Baskin, 2010). Studies in adult male rhesus monkeys, indeed, show similar effects, as peripheral CCK administration activate catecholaminergic neurons in the nucleus of the solitary tract, area postrema and, to a less degree, ventrolateral medulla (Schreihofer et al., 1997). Feeding also causes the release of release peptide-YY (PYY) and generation of its cleavage product, PYY₍₃₋₃₆₎ by intestinal L-cells. This ligand likely reduces gastric emptying by acting through NPY Y2 receptors in the arcuate nucleus (reviewed by (Vincent and le Roux, 2008)). Administration of PYY₍₃₋₃₆₎ to rhesus monkeys produces similar effects on food intake (Moran et al., 2005) but efficacy may vary by time of day and dosage (Koegler et al., 2005). Glucagon-like peptide 1 (GLP-1) is another gut peptide secreted in response to a meal that is also thought to reduce subsequent food intake by slowing gut emptying and reducing meal size (Williams et al., 2009) and, indeed, agonists of GLP-1 dose-dependently attenuate food intake in adult monkeys (Bello et al., 2010). Additionally, amylin, a pancreatic peptide member of the calcitonin family, is co-secreted with insulin. Agonists of amylin, for example salmon calcitonin, attenuates food intake in a number of animal models (Wielinga et al., 2007), including adult male rhesus monkeys (Bello et al., 2008). Co-administration of GLP-1 agonists and salmon calcitonin synergistically attenuate food intake in adult male monkeys, underscoring the potential therapeutic potential of these compounds.

In addition to peptides, gonadal steroids are known to have a significant impact on caloric intake. A large literature from rodent models indicates estradiol has a suppressive effect on food intake in females, notably by reducing the size of meals (Eckel, 2004, 2011; Wade and Gray, 1979). Available data indicate estradiol has this effect by acting through estrogen receptor- α (Santollo et al., 2007) to target hindbrain and hypothalamic regions to alter processing and feedback signals (Roepke, 2009). Such target would include a diminution of

the orexigenic action of NPY (Santollo and Eckel, 2008) and ghrelin (Clegg et al., 2007) and increased sensitivity to the satiating effects of CCK (Eckel and Geary, 1999), serotonin (Eckel, 2004; Simansky, 1996) and glucagon (Geary and Asarian, 2001). Studies show that increased estradiol directs motivation towards mating and away from eating when females are fertile (Schneider et al., 2013). Unlike rodents, humans and other cercopithecine primates have menstrual cycles characterized by a long follicular phase and a prolonged luteal phase following ovulation (Knobil, 1980). In these species, a peri-ovulatory nadir in food intake of a variety of diets is often described in both women (Eck et al., 1997; Fong and Kretsch, 1993; Gong et al., 1989; Hirschberg, 2012; Johnson et al., 1994; Lissner et al., 1988) and nonhuman primates (Bielert and Busse, 1983; Czaja, 1978; Czaja and Goy, 1975; Gilbert and Gillman, 1956; Kemnitz et al., 1989; Rosenblatt et al., 1980). Additional studies show that estradiol administration to ovariectomized rhesus monkeys attenuates cerebrospinal fluid levels of the orexigenic neuropeptide AGRP but the degree of attenuation in the orexigenic neuropeptide was inversely related to body mass index (Xiao et al., 2010).

However, one issue not often systematically considered in evaluating estradiol effects on food intake is the macronutrient content of the diet, as most studies in animal models have used a laboratory diet that is quite unlike the more calorically dense diets consumed by people. Those studies in rodents and humans that have examined estradiol's effect on dietary preference show no consistent effect of estradiol on the selection of particular diet (for review see (Dye and Blundell, 1997)). However, a recent report in adult female rhesus monkeys examined the effect of estradiol on caloric intake when animals were fed the typical low caloric laboratory diet (LCD) or given a choice between this LCD and a more palatable high caloric diet (HCD) containing fat and sugar (Johnson et al., 2013). Females were ovariectomized and were studied in both dietary conditions under either no hormone replacement or during estradiol treatment that mimicked mid-follicular phase concentrations. During the LCD only condition, estradiol significantly reduced food intake compared to the no treatment condition mainly through a reduction in meal size. Animals consumed significantly more calories during the condition when both the LCD and HCD were available compared to the LCD only condition. However, during this dietary choice condition, estradiol had no effect on food intake compared with the no treatment condition. Indeed, estradiol appeared to increase consumption of the HCD compared with the no treatment condition (Johnson et al., 2013). These data suggest that the palatability and macronutrient content of the diet may engage neural circuitry that desensitizes the suppressive effects of estradiol on food intake. Clearly more systematic research is needed to address these questions in female nonhuman primates.

Prenatal programming of metabolism and appetite

The fetal origins hypothesis, often referred to as the developmental origins of adult health and disease, was formally proposed in the early 1990s (Barker et al., 1995; Lucas, 1991), asserts that the intrauterine environment may have a significant impact on subsequent offspring metabolic health (Gluckman and Hanson, 2004; Ismail-Beigi et al., 2006). As described in several recent reviews, both prospective studies in rodents and epidemiological analyses of humans indicate that both under – and over nutrition during pregnancy increases

the risk of obesity in offspring through adulthood, including those infants born at lower body weight (Fall, 2011; Langley-Evans et al., 2005; Taylor and Poston, 2007). Thus, a number of research programs, some involving studies of nonhuman primates, have begun to investigate the mechanism by which maternal nutrition affects appetite regulation in offspring.

Several studies have examined the prenatal development of hypothalamic neuropeptide systems in macaque monkeys. Analyses showed that the orexigenic neuropeptides NPY and AgRP and the satiety-related neuropeptide α -melanocyte stimulating hormone (α MSH), systems develop during the second and third trimesters in Japanese macaques compared to the postnatal period in rodents (Grayson et al., 2006; Grove et al., 2005). These observations led to a series of studies investigating the impact of maternal nutrition and metabolic phenotype on the development of these circuits and postnatal physiology. Studies of fetuses during the third trimester of adult Japanese macaques maintained on either a laboratory chow diet or a high fat diet (HFD) throughout pregnancy revealed that NPY expression was unchanged in the arcuate nucleus and paraventricular nucleus but expression of AgRP was reduced. In contrast, the expression of the MCR4 was increased in animals whose mothers were fed a HFD regardless of their resulting adiposity (Grayson et al., 2010). Maternal HFD ingestion also increased POMC expression but measures of α MSH did not differ between groups. In addition, maternal HFD intake was associated with increased cortisol and proinflammatory signals, suggesting that these signals could be a possible mechanism for altered development of the melanocortin system (Grayson et al., 2010). Additional analyses of the same model indicate the maternal consumption of the HFD increases fetal expression of the inhibitory presynaptic serotonin receptor (5HT1A) in the dorsal raphe and increases emotional reactivity in juveniles (Sullivan et al., 2010). Finally, preliminary data from this model suggest that maternal HFD consumption and resulting reprogramming of selected feeding related neural circuits in offspring, predisposes these offspring to prefer diets that are more calorically dense postnatally (Sullivan et al., 2011). Studies have yet determined whether such a feeding phenotype persists into adulthood.

The research conducted with nonhuman primate models thus far suggests that the consequences of maternal HFD consumption and/or obesity during pregnancy generally have an adverse impact on a number of peripheral metabolic systems in both macaque (Fan et al., 2013; Grant et al., 2011; McCurdy et al., 2009; Suter et al., 2012a; Suter et al., 2012b) and baboon offspring (Farley et al., 2009; Maloyan et al., 2013). While the approach used to study diet-induced effects on central neuropeptide regulation and metabolic systems is quite informative, what is understudied is whether the maternal feeding phenotype is transmitted to the offspring. This is particularly relevant given the observation that macaques fed the HFD during pregnancy either were diet sensitive, becoming obese and showing insulin insensitivity, or were diet resistant and did not become obese (McCurdy et al., 2009). Because food intake was not measured in these animals, it is not clear whether the obese monkeys simply ate more of the HFD or were more efficient at storing calories ingested. Although population studies in humans clearly show caloric intake and macronutrient preferences are heritable, perhaps accounting for as much as 30% of the variance (Rankinen and Bouchard, 2006), such studies have yet to be conducted in nonhuman primates, largely due to the lack of pedigreed populations and practical difficulties in quantifying caloric intake in a large number of animals. Of note, studies of pedigreed baboons show significant

heritability for plasma ghrelin (Voruganti et al., 2008), adiponectin (Tejero et al., 2008), as well as plasma CCK, fasting levels of glucose and body weight (Voruganti et al., 2007). How these inherited differences translate to feeding phenotypes under varying dietary conditions is unknown.

Psychosocial impact on food intake

Recognizing the importance of gut- and neuropeptide signaling for the regulation of appetite, environmental factors may also have a significant impact on food intake and resulting body composition. As described in a companion paper in this special issue of *Hormones and Behavior*, many species show seasonal changes in food intake and energy utilization that are regulated by thyroid hormone availability (Ebling, 2014). In addition, social-cognitive factors can facilitate or inhibit food intake independent of satiety- or hunger-inducing signals (Cohen, 2008; Zheng and Berthoud, 2007) and these may account for some of the variance in rates of obesity in human populations (Berthoud, 2012; Booth and Booth, 2011). These factors likely operate in nonhuman primates as well, as a recent survey of North American research facilities with captive, socially housed, free-feeding monkeys revealed that obesity is present in a portion of each colony, suggesting social and/or genetic factors increase vulnerability to developing an obese phenotype (Bauer et al., 2011; Bauer et al., 2012).

Because groups of monkeys organize themselves in predictable ways, typically by a dominance hierarchy (Bernstein, 1970), these species provide a unique opportunity to determine the influence of social factors on appetite. Regression analyses of available data from colonies provisioned with standard laboratory chow (a low fat, high fiber fortified diet) suggests dominance status and activity levels are important predictors of body weight with increased rates of obesity and increased time spent feeding observed in more dominant animals (Bauer et al., 2012). Other studies of captive, socially housed monkeys underscore the importance of food distribution and social status, with more subordinate animals developing different strategies of feeding behavior when food is less accessible (see (Bauer et al., 2011) for a review).

These data highlight the notion, often overlooked in traditional studies of the neurobiology of food intake in laboratory animals, including nonhuman primates, that socio-environmental factors can interact with the satiety and orexigenic signaling to shape feeding behavior. The importance of considering these factors for understanding ingestive behavior has been recently described (Schneider et al., 2013), providing a framework to appreciate how a number of appetitive behaviors may take precedence depending on the social context and an individual's metabolic needs. Another factor currently receiving extensive attention in ingestive behavior research is the cognitive salience and the reward value of food (Berridge, 2009). Several studies using rhesus monkeys have shown the involvement of corticolimbic regions in processing the sensory properties of food that likely interacts with satiety-inducing neuropeptides to influence the timing of meal termination (Machado et al., 2010; Pritchard et al., 2008; Rolls, 2007). While similar studies are easily performed in humans (e.g., (Jastreboff et al., 2013; Small et al., 2003; Tomasi and Volkow, 2013)),

nonhuman primates provide an added advantage given the ability to perform systematic interventions not always possible in people.

However, the reward value of food goes beyond its sensory properties particularly given the emerging hypothesis that excess food consumption and resulting obesity is a form of addiction involving the same corticostriatal circuitry engaged by drugs of abuse (Tomasi and Volkow, 2013). Assuming this hypothesis is viable, the question remains what accounts for differential vulnerability to the addictive properties of food. Indeed, diet-induced obesity (DIO) resulting from the persistent consumption of a calorically dense diet is a well-accepted strategy in animal models to study the susceptibility to and consequences of obesity (Hariri and Thibault, 2010; Panchal and Brown, 2011). Nonetheless, some animals do show resistance to developing this phenotype (Levin et al., 1997). Although a number of studies have employed a DIO approach with nonhuman primates to assess the metabolic consequences of obesity (e.g., (Bremer et al., 2011; Hansen et al., 2013), it has not been until recently that studies have begun to investigate this differential susceptibility to diet imposed weight gain in these animals. Analogous to studies of forced exercise in mice (Kawanishi et al., 2013), individual differences in spontaneous activity is a strong determinant of diet-induced weight gain in female rhesus monkeys (Sullivan et al., 2006).

Because chronic stressor exposure has been shown to be a risk factor for psychostimulant abuse in people (Sinha and Jastreboff, 2013) or self administration in animals (Goeders, 2002; Koob and Kreek, 2007), including monkeys (Morgan et al., 2002), a history of psychosocial stress may also explain the variance in susceptibility to DIO. However, it must be noted that the effects of stressor exposure on food intake may be bidirectional with the specific effect dependent on a number of factors such as a stress history and whether the event is acute or chronic (Maniam and Morris, 2012). Macronutrient content of the diet is likely important for the directionality, as a large literature from these rodent models suggests that stressor exposure in animals fed a typical low calorie diet is anorexic (Harris et al., 1998), an effect reversed central administration of a corticotropin releasing factor (CRF) receptor antagonist (Smagin et al., 1999). Indeed, central administration of CRF to adult macaques has an immediate and lasting suppressive effects on food intake (Glowa and Gold, 1991). On the other hand, an extensive literature in rodent models indicates that chronic exposure to stressors is a mitigating factor in the preference for and consumption of excess calories from high caloric, “comfort foods” (Tamashiro et al., 2006; Warne, 2009). Furthermore, studies in rodents show that glucocorticoids dose-dependently increase the intake of diets high in fat and sugar and that consumption of these particular macronutrients reduces the expression of CRF in the hypothalamus (Dallman et al., 2005; Warne, 2009). These data underscore the importance of considering diet when assessing the consequences of stressor exposure or stress hormones on appetite.

These studies in rodents of stress-induced intake of calorically dense diets are consistent with the notion of comfort food ingestion in people (Adam and Epel, 2007; Epel et al., 2000). With the exception of a few studies (Solomon et al., 2011), the majority of studies in rodent models have used males (Tamashiro et al., 2005; Warne, 2009), despite the growing evidence highlighting significant bias towards stress-eating and obesity in women (Grunberg and Straub, 1992; Kittraki et al., 2004; Soulis et al., 2005; Soulis et al., 2007). Female

macaques provide an opportunity to further define mechanisms for emotional feeding in women. A large body of data show that social subordination in well-established macaque groups produces a number of stress-related phenotypes (Michopoulos et al., 2012a), including a dysregulation of the limbic-hypothalamic-pituitary-adrenal axis (Kaplan et al., 2010; Michopoulos et al., 2012b; Shively et al., 1997). In a dietary environment where a typical low fat, fiber monkey chow diet is available, subordinate female rhesus monkeys consistently show lower body weights than more dominant group mates (Michopoulos and Wilson, 2011). Employing automated feeding stations that detects food intake by individuals in these social groups (Wilson et al., 2008), this reduced body weight in subordinate females is associated with mild inappetence (Michopoulos, 2009) or calorie intake similar to dominant females (Michopoulos et al., 2012c). A very different pattern emerges when animals are maintained in a rich dietary environment and given the choice between the low calorie chow diet and a calorically dense diet (Arce et al., 2010; Michopoulos et al., 2012c). Under these conditions, all animals prefer the high calorie diet. Interestingly, dominant females did not consume significantly more calories in this rich dietary environment compared to the chow only condition. In contrast, subordinates consumed significantly more calories in this choice dietary environment compared with dominant females (Arce et al., 2010; Michopoulos et al., 2012c). While these studies were short term in nature focusing on changes in appetite and not the consequences of consuming these diets on body composition, the data nonetheless suggest that female rhesus provide a model to better understand how psychosocial stressor exposure may account for variance in DIO in females.

Further studies employing rhesus monkeys have begun to investigate what accounts for this stress-induced intake of high caloric diets. One possibility is that subordinate female monkeys may be more sensitive to orexigenic peptides. Although acute ghrelin administration increased intake of the a chow diet in subordinate but not dominant females (Michopoulos et al., 2010), it had no effect on consumption of a high calorie diet. Alternatively, signals from the stress hormone axis may be critical in sustaining intake of these rich diets. However, acute administration of a CRH type 1–2 receptor antagonist, which is unable to penetrate the blood-brain-barrier, does not reduce this emotional feeding phenotype shown by subordinates despite a significant reduction in serum cortisol (Michopoulos et al., 2010). In contrast, peripheral administration of the CRF type 1 receptor antagonist, Antalarmin, that does penetrate the brain significantly reduces daily caloric intake in subordinate female monkeys to amounts comparable to those consumed by dominant group mates in a dietary environment that includes a choice between a chow diet and a high caloric diet (Moore et al., in review). Because this dose and route of administration of Antalarmin does not affect peripheral cortisol secretion (Herod et al., 2011a; Herod et al., 2011b), the data suggest that activation of central CRF type 1 receptors may be important for sustaining this emotional feeding phenotype. These observations are consistent with data from rodents indicate that chronic activation of central CRF type 1 receptors are likely important for stress-induced over consumption of palatable diets. In these rodent models, diet cycling or intermittent dietary restriction of a palatable diet has been shown to function as a mild stressor, and immunohistochemistry reveals elevated CRF positive cells in the central nucleus of the amygdala among diet cycled but not control rats (Cottone et al., 2009; Iemolo et al., 2013). Importantly, microinfusion of the CRF type 1

receptor antagonist, Antalarmin, into the CeA of diet cycled male rats fully blocked hyperphagia of a palatable food with no effect on standard chow intake (Iemolo et al., 2013).

What is unclear from these studies in rodent or monkeys is how signals that result from chronic stressor exposure compromise gut- and neuropeptide signals that would otherwise define feeding behavior in the absence of stress. Furthermore, is not fully known how chronic stressor exposure increases susceptibility to DIO. However, evidence from rodents and humans suggests that changes in dopamine (DA) activity are at least part of the mechanism linking stress to comfort food ingestion (Bassareo and Di Chiara, 1999; Martel and Fantino, 1996a, b; Pelchat, 2002; Rada et al., 2005). Based on studies in rodents, it is well established that signals from the stress axis, including glucocorticoids and CRF target DA neurons in mesolimbic regions (Ambroggi et al., 2009; Burke and Miczek, 2013; Koob et al., 2014) producing a dysregulation of DA neurotransmission (Izzo et al., 2005) that increases the expression of anhedonia and the risk for developing an addictive phenotype (Anisman and Matheson, 2005; Koob and Kreek, 2007; Koob and Le Moal, 2001). This stress-induced DA dysfunction has been referred to as a “reward deficiency syndrome”, characterized by reduced DA activity (Blum et al., 1996) that is both predictive of an addictive phenotype (Volkow et al., 2003; Volkow and Wise, 2005) and observed in human obesity (Wang et al., 2001). Whether the imposition of chronic stress in the monkey model of social subordination lead to this reward deficiency syndrome that predicts stress-induced consumption of calorically dense diets remains to be determined.

Gaps in understanding feeding behavior in nonhuman primates

Nonhuman primates are of value to test the efficacy of drugs that target gut- and neuropeptide systems for the treatment of eating disorders in people and, in some cases, may be required for preclinical evaluation. Furthermore, a number of studies have used captive nonhuman primates to investigate basic metabolic processes (Cai et al., 2004; Comuzzie et al., 2003; Hansen et al., 2013); the physiological consequences of the consumption of a particular diet (Adams et al., 2008; Bremer et al., 2011; Brozinick et al., 2013; Fabbrini et al., 2013; Kaplan et al., 2002; Nygaard et al., 2013; Stanhope et al., 2013; Sullivan et al., 2005); and the potential benefits of caloric restriction (Mattison et al., 2005; Mattison et al., 2003) on metabolic health or on changes in biomarkers that are predictive of adverse health outcomes in people. These studies are particularly informative when measures of actual calories consumed are reported (e.g., (Sullivan et al., 2005)). Otherwise it is difficult to determine whether variability in calorie intake among subjects accounts for variability in outcomes. Any assessment of an impact of an intervention on body composition must monitor caloric intake.

Based on available data, it appears that the specific effects of gut- and neuropeptides that generally regulate feeding similarly in non-primate animals and nonhuman primates. While some differences do exist, what may differ more between species is how these system develop. Understanding these species differences may be intrinsically important but these empirical interests may be trumped by deciding what is the best model to address specific questions that are translatable to human metabolic health. Like rodents (Zorrilla et al., 2005), free feeding monkeys eat in distinct meals interspersed with snacking (Moore et al., 2013).

Thus, either model could be used effectively to assess how an intervention affects meal patterns. However, because old world monkeys, like macaques, are diurnal, they provide an opportunity to determine how nighttime feeding is affected and its consequences on body composition (Sullivan et al., 2005). Indeed, stress eating by subordinate female rhesus monkeys is associated with an increase in nocturnal feeding (Wilson et al., 2008), a significant risk factor for obesity risk in people (Milano et al., 2012). Importantly, with the exception of a few studies (Sullivan and Cameron, 2010; Sullivan et al., 2006), missing from the analysis of appetite and resulting body composition in nonhuman primates is a consideration of activity and energy expenditure. Thus, studies must consider both sides of the energy balance equation to appreciate how changes in appetite affect body composition.

It would seem that understanding the socio-ecology of feeding behavior in free-ranging groups may have little applicability to human metabolic health. However, because feeding patterns are driven by factors other than just satiety and orexigenic signals, appreciating how the social context and dietary environment influence pattern of feeding in monkeys may be quite informative for understanding the complexity of feeding in people. Data are accumulating on how early exposure to a particular diet may program feeding behavior later in life (Grove et al., 2005; Vucetic et al., 2010). To augment these studies, emphasis should also be placed on how early social experience or maternal care influence appetite regulation through adulthood. For example, results from rodents clearly show that prenatal stress increases risk for obesity later in life (Tamashiro et al., 2009). Although data from humans are limited, emotional eating in children is associated with reports of stress (Mazur et al., 2011) and children from families reporting more distress have higher rates of obesity (Anderson et al., 2012; Anderson and Whitaker, 2011; Gundersen et al., 2011; Koch et al., 2008; Moens et al., 2009), particularly for girls (Noll et al., 2007; Schneiderman et al., 2012; Suglia et al., 2012). Together, these data support the hypothesis that exposure to social stress during development may be an aggravating factor for DIO during childhood (Evans et al., 2012). Indeed, bonnet macaques that were exposed to a stressor postnatally show an increased prevalence of obesity (Kaufman et al., 2007). In addition, other experiential factors such as age at weaning are likely important, as data from marmoset monkeys indicate a earlier age at weaning predicts increased feeding behavior and an obese phenotype as juveniles (Ross et al., 2013). Because monkeys, like humans, have a relatively long gestation, more often have a single birth, and a protracted lactational period, they provide a unique opportunity to better define how maternal nutritional status affects offspring metabolic health

Finally, recent advances in technology now permit quantification of food intake in these social contexts in response to a number of environmental manipulations with or without pharmacological interventions. Studies employing this methodology can help determine how the resulting metabolic phenotype is altered by changes in feeding behavior and preference for particular diets (Michopoulos et al., 2012c) as well as alterations in signals that influence adiposity (Kaufman et al., 2005) and energy expenditure (Sullivan et al., 2006) in the context of a social environment that people face. Furthermore, the use of pedigreed populations of monkeys can determine the heritability of various parameters of ingestive behavior, leading to studies to identify critical genes that interact with these socio-environmental factors to influence energy balance.

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Highlights

- Review provides an overview of studies examining food intake using captive NHPs
- Exposure to specific diets programs differences in feeding related neuropeptides
- Effects of feeding related neurochemicals are conserved in NHPs
- Psychosocial factors influence appetite regulation

Table 1

Summary of gut and neuropeptide effects on feeding behavior using nonhuman primate models

Intervention	Effect on gut or neuropeptide or known mode of action	Effect on feeding	Reference for nonhuman primates
Fasting	Increased expression of hypothalamic NPY	Not measured	Grove et al 2003 Van Vugt et al 2006
	Down regulation of hypothalamic CART	Not measured	Van Vugt et al 2006
	Upregulation of hypothalamic POMC	Not measured	Koegler et al 2001
	Down regulation of GALP	Not measured	Cunningham et al 2004
Central NPY administration	Activation of Y1 receptors	Increase	Larsen et al 1999
Central α MSH analog administration	Activation of MCR-3/4 receptors	Increase	Koegler et al 2001
Central TrkB agonist administration	Endogenous receptor for BDNF thought to mediate anorexic effect activation MCR 4 (sXu et al 2003)	Decrease	Lin et al 2008
Peripheral TrkB agonist administration		Increased	
Central Orexin A administration	Neuropeptides that integrate feeding, wakefulness, and energy expenditure (Selayah & Sikder 2013)	Decreased	Ramsey et al 2005
Central Orexin B administration		No effect	
Central leptin administration	Anorexic adipokine (Suzuki et al 2012; Figlewicz 2003; Considine 1997)	Decreased	Ramsey et al 1998 Tang-Christensen et al 1999
Peripheral leptin administration		No effect	
Peripheral CCK or its analog administration	Slows gastric emptying and reduces food intake (Blevins & Baskin 2010)	Decreased	Gibbs et al 1976 Metzger & Hansen 1983 Moran & McHugh 1982
	Activation of catecholamine neurons in NTS	Not measured	Schreihof et al 1997
Peripheral PPY analog administration	Activates hypothalamic NPY 2 receptors (Vincent & Le Roux 2008)	Decreased but dose and time of day dependent	Moran et al 2005 Koegler et al 2005
Peripheral GLP-1 agonist administration	Gut peptide shown to slow gut emptying and reduce meal size (Williams et al 2009)	Decreased	Bello et al 2010
Peripheral amylin administration	Pancreatic peptide co-secreted with insulin	Decreased	Bello et al 2008
Estradiol	Acts through estrogen receptor α (Santollo et al 2007) in hindbrain and hypothalamus (see text)	Decreased when laboratory chow available	Bielert & Busse 1983; Czaja 1978; Czaja & Goy 1975; Gilbert & Gillman 1956; Kemnitz et al 1989; Rosenblatt et al 1980; Johnson et al 2013
		No effect when high caloric diet available	Johnson et al 2013