

Interactive report

Insulin and leptin: dual adiposity signals to the brain for the regulation of food intake and body weight¹

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Abstract

Insulin and leptin are hypothesized to be ‘adiposity signals’ for the long-term regulation of body weight by the brain. Accordingly, a change in the plasma levels of leptin or insulin indicates a state of altered energy homeostasis and adiposity, and the brain responds by adjusting food intake to restore adipose tissue mass to a regulated level. The candidate site for the brain’s detection of leptin adiposity signaling is the hypothalamic arcuate nucleus, where leptin inhibits expression neuropeptide Y and increases expression of the pro-opiomelanocortin (POMC) precursor of α MSH. Insulin also inhibits arcuate nucleus expression of neuropeptide Y but its effects on other hypothalamic signaling systems are not known. Leptin-responsive neurons in the arcuate nucleus are hypothesized to project to the paraventricular nucleus and lateral hypothalamic area where they are proposed to influence the expression of peptides that regulate food intake. Future development of this model will incorporate brain pathways for integration of leptin and insulin adiposity signaling to the hypothalamus with meal-related signals that act in the caudal brainstem. Recent research showing that leptin and insulin enhance the satiety action of peripheral CCK, thereby causing meals to be terminated earlier and reducing cumulative food intake, suggests that hypothalamic pathways that are sensitive to leptin and insulin adiposity signals have anatomical connections with caudal brainstem neurons that respond to meal-related signals and regulate meal size. The recent findings that insulin alters the expression and function of neural transporters for dopamine and norepinephrine indicate that adiposity signals may influence food intake by acting on non-peptide neurotransmitter systems. © 1999 Elsevier Science B.V. All rights reserved.

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1. Adiposity signals

The prevailing model for the physiological mechanism underlying the long-term regulation of body weight by the brain was proposed two decades ago by Woods and Porte, based on their studies that demonstrated the effect of intracerebroventricular (ICV) insulin to reduce food intake and body weight in baboons [86,128]. According to this model, two classes of feedback signals are generated as a result of ingestion of food [129]. One type is related to the quantity and quality of food ingested; it consists of neural

afferents, psychosocial conditioning factors, and peptide signals that are released from the gastrointestinal tract by specific nutrient intake. These short-term signals operate on a meal-to-meal basis and determine the amount of food ingested in single meals. A second type of feedback signal is also sensitive to nutrient intake but is modulated by adipose tissue mass (i.e., they are ‘adiposity signals’).

Implicit in the concept of adiposity signaling is the existence of hormones whose circulating concentrations are relatively constant and proportional to adipose tissue mass and, furthermore, that act as tonic signals to the brain for regulating food intake and body weight over long time intervals. Insulin, which is secreted by the islets of Langerhans in the pancreas, has a well-established role in regulation of nutrient substrate metabolism by insulin-sensitive

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tissues such as skeletal muscle and fat. In the presence of insulin, substrates derived from ingestion of food are taken up and metabolized by the body's cells, and excess caloric intake is stored as increased adipose tissue, leading to increased adiposity and obesity. One consequence of increased positive energy balance and adiposity (and the associated state of insulin resistance) is increased insulin secretion in proportion to adipose tissue mass. Thus, in contrast to its generalized function to promote anabolic metabolism in peripheral tissues, insulin is hypothesized to have a second important metabolic function of providing a 'feedback' adiposity signal to the CNS. According to the adiposity signaling model, a change in the plasma level of insulin signals a state of altered energy homeostasis and adiposity to the central nervous system (CNS) and the brain responds by adjusting food intake and energy utilization to restore adipose tissue mass to a normal regulated level.

2. Insulin as an adiposity signal

A large body of evidence from our laboratories and those of others has been developed in support of the hypothesis that circulating insulin enters the brain to produce anorexic responses, including reduced food intake. Much of this extensive literature can be found in review articles and is summarized here [85,102,104,129]. Behavioral studies in rats show that insulin infused ICV inhibits food intake and reverses the hyperphagic syndrome of insulin-deficient type 1 diabetes. Insulin rapidly crosses the blood–brain barrier by a receptor-mediated transport mechanism that involves insulin receptors expressed by brain microvessels. Insulin concentrations in cerebrospinal fluid are present in concentrations that are directly proportional to plasma insulin levels, although the relationship is aberrant in obesity. There is abundant evidence that insulin receptors are expressed in the hypothalamus, particularly in the arcuate nucleus (ARC), which plays a key role in regulating food intake and energy homeostasis. Receptor autoradiography studies show that the ARC has a high density of insulin specific binding sites. The ARC has a large population of neurons that have been shown to express insulin receptor mRNA by in situ hybridization. Furthermore, the insulin receptor substrate protein, IRS-1, has been shown to be present in the ARC by in situ hybridization and immunocytochemistry. Significantly, insulin has been shown to inhibit the expression of mRNA levels encoding the orexigenic peptide neuropeptide Y (NPY) that are normally increased in the ARC during fasting.

3. Leptin as an adiposity signal

The hypothesis that circulating endocrine factors act in the brain to influence food intake has been strengthened by

the discovery of a second adiposity signal, the peptide hormone leptin ('ob protein'), the endocrine product of the *ob* gene in fat cells. Numerous studies support the hypothesis that leptin's anorexic effects on energy balance are mediated by the CNS [8,100]. The wealth of research on leptin and its receptors has been extensively reviewed and many of the early papers can be found by referring to the cited reviews [33,43,47,54,60,106,120]. In summary, there is a consensus that an inappropriate decline of leptin signaling results in hyperphagia and obesity. It has been established that leptin's CNS effect produces anorexia, since the obesity and hyperphagia syndromes of the leptin-deficient *ob/ob* mouse are reversed by leptin and ICV administration of leptin to normal fasted animals inhibits food intake. There is agreement that the brain's anorexic response to leptin is mediated by the 'Ob–Rb' splice variant ('long form') of the leptin receptor. Leptin activation of Ob–Rb initiates intracellular signal transduction via JAK-STAT pathways in the hypothalamus. Furthermore, activation of the ObRb receptor by leptin generates expression of an intracellular signal transduction protein, SOCS-3, that is dramatically increased in the ARC following leptin treatment [17].

4. CNS mechanism of adiposity signaling

According to the proposed model, reduced leptin or insulin signaling to the brain during fasting and weight loss activates circuits that increase food intake and body weight until the deficit in hormonal signaling has been corrected. Thus, leptin and insulin exert long-term, sustained inhibition of food intake. While we refer to leptin and insulin collectively as adiposity signals, their anorexic effects may be based on different brain mechanisms. Since insulin's effects on energy balance parallel those of leptin in many respects, we hypothesize that it is likely that insulin induces anorexia by acting on the same ARC neurons that respond to leptin signaling, although studies are needed to evaluate this hypothesis.

The CNS anorexic effects of leptin and insulin are balanced against a variety of other endocrine, neural, nutritional, and behavioral influences that operate to determine body weight over long periods. But since either leptin deficiency (or resistance) alone can cause severe hyperphagia and obesity in rodents (e.g., *ob/ob*, *db/db*, *fa/fa* models) and humans [24,78], CNS pathways for integrating leptin (and presumably insulin) signaling with food intake must be critical to maintenance of normal body weight. Information about the CNS pathways that are specifically responsible for communication between leptin and insulin signaling to the brain and the CNS mechanisms that control the quantity of food ingested is needed to understand the physiology of body weight regulation by the brain. The identity of these pathways is still largely

unknown, but recent studies point to the hypothalamus as being a critical CNS site for the action of adiposity signals.

5. Hypothalamic targets of adiposity signals

Research on leptin's effects on food intake have emphasized its actions in the hypothalamus [8,33,44,100,106]. The ARC in the hypothalamus is generally thought to be the most likely CNS site for leptin adiposity signaling to the brain (Fig. 1). The ARC has leptin binding sites [5,25] and appears to be a special CNS location where leptin has access to the brain [3]. The Ob-Rb form of the leptin receptor [120] is expressed by ARC neurons [6,8,10,11,32,37,53,58,74,107]. In the ARC, leptin inhibits the expression of neuropeptide Y (NPY) and the agouti-related protein (AGRP) [6,8,52,99–101,107,108], both potent stimulators of food intake. Conversely, leptin stimulates expression of ARC POMC (the precursor of α MSH) [23,108,121] and 'cocaine and amphetamine regulated transcript' (CART) proteins [29,62], which induce an anorexic response. ObRb mRNA is expressed in both NPY/AGRP and POMC/CART neurons in the ARC [6,10,73]. In addition, evidence indicates that insulin's central anorexic effects are also mediated by the ARC [103,104,129]. Like leptin, insulin inhibits ARC NPY expression and food intake [67,105,109,110,114], but its effects on other hypothalamic signaling systems are not as well described.

Several intracellular proteins involved in signal transduction mechanisms have been shown to be activated by leptin in the hypothalamus. leptin action is associated with

C-fos Activation in Arcuate Nucleus Neurons During Food Intake

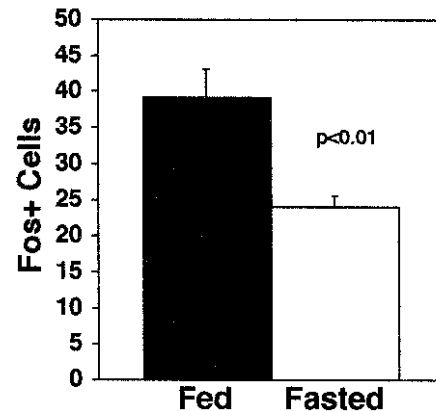


Fig. 2. Activation of c-fos in ARC neurons by food intake. The mean number of c-fos-positive cell bodies (detected by immunostaining of hypothalamic slices) in microscopic fields was counted in fed ($n = 4$) and fasted ($n = 4$) rats. (Baskin and Schwartz, unpublished)

activation of the JAK-STAT cascade of signal transduction proteins in rat and mouse hypothalamus [48,89,130]. ICV or i.p. leptin treatment also induces c-fos expression in the PVN and DMN of the hypothalamus and in the nucleus of the solitary tract (NTS) of the caudal brainstem [31,123,131]. Our studies show that the number of c-fos positive neurons in the ARC and PVN is greater in fed compared to fasted rats, consistent with elevated leptin signaling in fed rats (Fig. 2). However, neurons showing c-fos expression following leptin treatment could represent cells that are acted upon directly by leptin or they could be one or more neurons downstream in a multisynaptic path-

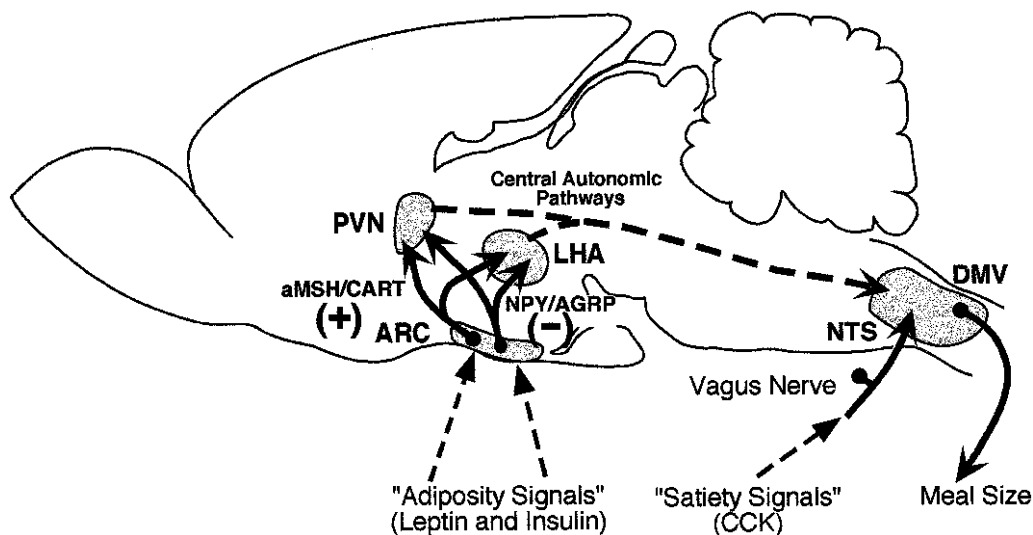


Fig. 1. Diagram showing hypothesized adiposity signaling pathways in the brain. Adiposity signals (leptin and insulin) inhibit (–) and stimulate (+) NPY/AGRP and α MSH/CART neurons, respectively, in the arcuate nucleus (ARC). These neurons are proposed to conduct adiposity signals to the paraventricular nucleus (PVN) and lateral hypothalamic area (LHA), where downstream neurons communicate with the nucleus of the solitary tract (NTS) and dorsomotor nucleus of the vagus (DMV) via central autonomic pathways. These adiposity signaling pathways are hypothesized to integrate adiposity signals that control long-term body weight with meal-related signals (such as CCK action at vagal nerve endings) that influence meal termination, resulting in regulation of meal size and cumulative food intake.

way. Leptin has been discovered to elevate levels of SOCS-3 mRNA in the ARC and DMN of the hypothalamus [18]. SOCS-3, a member of the ‘suppressors of cytokine signaling’ gene family, is induced by activation of cytokine-related receptors. It blocks phosphorylation of the cognate receptor and STAT proteins, resulting in feedback dampening of downstream intracellular signal transduction pathways, although this effect does not necessarily inactivate all signaling pathways or all transcription [118]. Thus, SOCS-3 expression potentially identifies neurons that convey intracellular signals generated by direct leptin activation of the ObRb receptor.

6. The ARC–PVN axis for adiposity signaling

The PVN (paraventricular nucleus) of the hypothalamus receives a rich NPY innervation from the ARC, and the release of NPY in the ARC during fasting and other states of negative energy balance is hypothesized to stimulate refeeding [60,77]. The appetite-promoting effect of NPY in the region of the PVN [59] is believed to be mediated primarily by NPY Y5 receptors [56,97], although other NPY receptor subtypes may participate [81]. Projections of ARC POMC neurons release α MSH in the PVN [20,29,31,34,59,94], where α MSH is hypothesized to exert anorexic effects by acting primarily on MC4R melanocortin receptors [22,36,49,61]. Thus both NPY and α MSH could potentially influence the secretion or action of the numerous neurotransmitters and peptides that are expressed or released in the PVN and influence food intake [127].

An important unanswered question about the mechanism of signaling via an ARC–PVN pathway is: what PVN targets of NPY and α MSH mediate adiposity signaling between the ARC and caudal brainstem? Several neuropeptidergic cell populations in the PVN are possible candidates. TRH (thyrotropin-releasing hormone) neurons may be involved since NPY and α MSH fibers reportedly contact TRH neurons [64,66], and leptin increases TRH mRNA in the PVN, an effect that is blocked by ARC ablation [63]. OXY (oxytocin) neurons are conceivable candidates for mediating adiposity signals from the ARC since OXY has central anorexic effects [82] and many OXY neurons have direct projections to the caudal brainstem [28,93,95]. CRH (corticotropin releasing hormone) neurons are promising candidates since CRH mediates the anorexic effects of leptin [122] and leptin increases CRH expression in the PVN [107]. Furthermore, the preponderance of NPY fibers in the PVN are concentrated in the parvocellular divisions where CRH neuronal perikarya are concentrated [21]. The possibility that other ARC and PVN peptides that influence food intake (such as galanin) participate in adiposity signaling pathways to the caudal brainstem cannot be excluded, although evidence that they are regulated by adiposity signals is not strong [109].

7. The ARC–LHA axis for adiposity signaling

The LHA (lateral hypothalamic area) and adjacent PFA (perifornical area) have populations of neurons that express hypocretin/orexin (H/O) and melanocyte concentrating hormone (MCH). Both H/O and MCH peptides stimulate food intake and show increased expression under leptin-deficient conditions [87,91], and are inhibited by leptin [13,57,90]. In addition, MCH knockout mice have a lean phenotype [112], suggesting a critical role for MCH in normal weight regulation. However, the effects of leptin on H/O and MCH neurons are likely to be downstream of primary leptin signaling in the ARC because the ObRb receptor is poorly expressed in the LHA [5,25,32,37,107] and SOCS-3 is not detectably elevated in the LHA by leptin [17] or food intake. This conclusion is supported by the abundance of NPY fibers in the LHA and PFA adjacent to H/O and MCH cells [21,55]. Indeed, there is a prominent projection of NPY/AGRP and POMC/CART fibers from the ARC to the vicinity of H/O and MCH neurons in the LHA and PFA [20,21,30], although NPY input to the LHA and PVN could also arise in the medulla where NPY is co-expressed with catecholamines [96]. The origins of the NPY inputs to the specific H/O and MCH cells that respond to adiposity signaling from the ARC need to be identified.

8. Meal size and the caudal brainstem

Ultimately, total cumulative energy intake is based on the sizes of individual meals, which in turn is regulated by diverse ‘meal-related signals’ that are generated when ingested food enters the stomach and intestines. Ingestion of food during a meal elicits a burst of rapid-acting neural, endocrine, and duodenal nutrient signals that converge on the caudal brainstem and result in termination of the meal [76,98,116]. Convincing evidence for the importance of the caudal brainstem in the control of meal size comes from experiments showing that rats are able to respond to intestinal neural and humoral signals and to regulate the size of individual meals when their brainstem is completely transected, severing all connections with the hypothalamus [50,111]. Therefore, since body weight is influenced by the cumulative amount of food eaten in individual meals, the anorexic effects of adiposity signals must interact with brain circuits that regulate meal size. Indeed, Flynn et al. [45] recently found that leptin anorexia is associated with a marked reduction in the size of individual meals. This finding suggests that brain neural circuits that respond to adiposity signals interact with those that respond to meal termination signals.

Meal-related signals are conveyed to the NTS in the caudal brainstem by way of the vagus nerve (Fig. 1) and other routes [98]. One particularly intensely studied meal-

related signal is cholecystokinin (CCK), a peptide released from intestinal endocrine cells during feeding. CCK binds to CCK-A receptors on gut vagal fibers [26,79] that end in the caudal brainstem [46,125], causing termination of the meal [113,116]. The meal-terminating ('satiety') effect of CCK is hypothesized to involve neurons in the NTS and other caudal brainstem regions such as the dorsomotor nucleus of the vagus (DMV) (Fig. 1), and is blocked by vagal deafferentation [117]. Furthermore, ObRb receptor mRNA appears has been identified in the rodent NTS [75], and fourth ventricular ICV injection of leptin slows gastric emptying [115], consistent with the possibility that leptin may act directly in the caudal brainstem to influence meal size. Moreover, the satiety effect of a CCK i.p. injection is retained when all connections from the hypothalamus are severed [51], suggesting that adiposity signaling via the hypothalamus may not be an absolute requisite for CCK to have a satiety effect.

9. Model for interaction between adiposity signals and meal-related signals

Figlewicz and Woods first showed that ICV infusion of insulin enhances the satiety response to CCK in rats [88] and primates [42]. Leptin has a similar effect when given i.p. in mice [4,69,124] and rats [35,68]. Conversely, fasting reduces the satiety effect of CCK in primates and rats [2,119], consistent with the hypothesis that reduced signaling by insulin and leptin attenuates the brain's response to meal-related signals and increases meal size. Furthermore, both obese *ob/ob* mice and *fa/fa* Zucker rats are relatively insensitive to the meal-terminating effect of CCK, confirming that reduced leptin signaling attenuates the satiety action of CCK [2,71,72]. These findings suggest the hypothesis that communication between hypothalamic circuits that respond to changes in adiposity signals and those in the caudal brainstem that respond to meal-generated signals are essential for long-term regulation of energy homeostasis and adipose tissue mass.

Seminal investigations demonstrate that the satiety action of CCK is enhanced by leptin and insulin [4,41,42,68,69,88,125], resulting in smaller meals that have the cumulative effect of reducing body weight. This suggests the existence of central autonomic pathways between the hypothalamus and the caudal brainstem that specifically integrate the reception of insulin and leptin adiposity signals in the ARC with the processing of vagally mediated meal-related signals to the caudal brainstem. We hypothesize that the mechanism of this interaction involves the primary action of leptin and insulin on subsets of ARC NPY and POMC neurons that project to the PVN and the LHA, which have direct descending connections to caudal brainstem centers that regulate meal size (Fig. 1). Candidate neurons for serving this adiposity signaling function have been identified in the PVN and LHA, which have

direct descending connections to caudal brainstem regions involved in food intake [28,93,95]. These include populations of OXY and CRH neurons that project directly from the PVN to the NTS [95]. H/O and MCH neurons in the LHA also project directly to the caudal brainstem [16,33,84].

10. Insulin and leptin signaling to other brain regions

The ventromedial nucleus (VMN) and dorsomedial nucleus (DMN) of the hypothalamus express leptin receptors and the DMN has an abundance of insulin receptors, and both regions are well known to be involved in regulation of food intake behavior [14,15,60]. The VMN has multisynaptic and indirect projections to the caudal brainstem [14], which could be involved in relaying adiposity signals from the hypothalamus although this hypothesis has received little attention. The DMN has direct connections with the LHA and PVN, expresses NPY [60] and ObRb receptors [5,8,32,37], and shows increased SOCS-3 mRNA levels with leptin treatment [17]. Furthermore, leptin binding sites and ObRb receptor mRNA and protein are found in the cerebral cortex, pyriform cortex, and thalamus in rats [5], although the phenotypes of cells expressing ObRb receptors in those areas are not known. Similarly, insulin receptors are widely expressed in non-hypothalamic brain regions including the olfactory bulb, hippocampus and dentate gyrus, cerebral cortex, cerebellum, and brainstem [7,9,12]. The physiological roles of insulin and leptin in these non-hypothalamic regions are largely unknown, and it is not certain that the actions of these peptides in those regions has any relationship to food intake and body weight. Studies are critically needed to determine whether the insulin-sensitive and leptin-sensitive neurons in these regions interact with hypothalamic or brainstem pathways that respond to changes in food intake and adiposity signals.

11. Insulin and catecholamine transporters

Insulin may potentially influence food intake by actions on brain catecholaminergic pathways [70]. Recent studies have focused upon the effect of insulin on the presynaptic re-uptake transporters for norepinephrine (NE) and dopamine (DA). These proteins are localized in the plasma membrane of NE and DA neurons lateral to the synaptic specializations associated with transmitter exocytosis [80]. They terminate NE and DA signaling by taking up the transmitters from the synaptic cleft into pre-synaptic nerve terminal [1]. Both the NE transporter (NET) and DA transporter (DAT) are members of a family of transporter proteins that includes uptake transporters for gamma aminobutyric acid (GABA), glutamate, and serotonin.

Interaction of Raclopride and Insulin: 5-min Sucrose Lick Rate

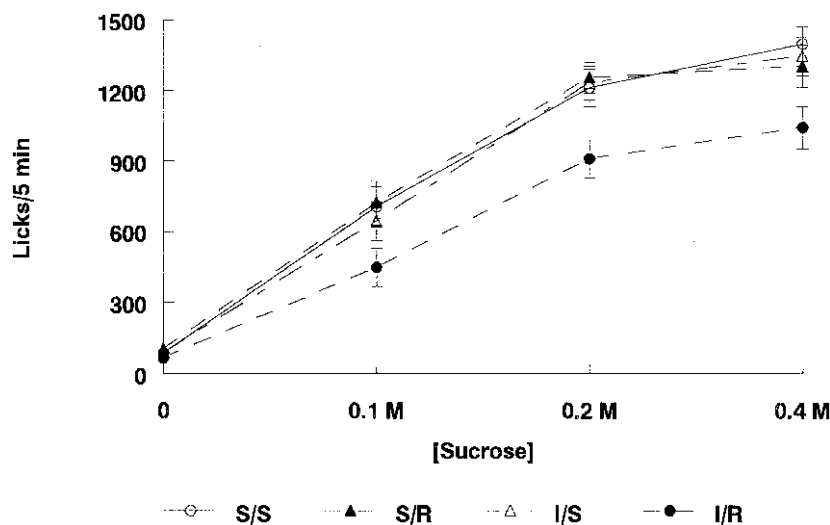


Fig. 3. Intraventricular injection of a subthreshold dose of insulin (5 mU at $t-4$ h) interacts with the dopamine receptor antagonist raclopride at a subthreshold dose (50 $\mu\text{g}/\text{kg}$ at $t-15$ min) to decrease sucrose lick rate (Stuber, Sipols, and Figlewicz Lattemann, unpublished results). S/S, ivt saline/ip saline, $n = 12$; S/R, ivt saline, ip raclopride, $n = 12$; I/S, ivt insulin/ip saline, $n = 12$; I/R, ivt insulin/ip raclopride, $n = 14$.

It has been proposed that the neurotransmitter transporters might be regulated by endocrine factors [39,40]. Insulin appears to have opposing effects on NET and DAT mRNA levels: chronic intraventricular infusions of small amounts of insulin result in decreases of NET mRNA but increases of DAT mRNA. When rats are made acutely insulinopenic (diabetic) with the administration of streptozotocin, the changes are reversed: NET mRNA levels are elevated, whereas DAT mRNA levels are reduced [38]. In addition to its chronic effects on their mRNA levels, insulin has acute effects on NET and DAT function, decreasing NE uptake and facilitating DA uptake [19,83]. Although these actions of insulin on NE and DA neurons are no doubt of importance for brain catecholaminergic signaling, specific effects of NE or DA on the physiological regulation of body weight and adiposity have not been identified, although effects of manipulation of these transmitter systems on food intake have been described [65]. Furthermore, DA transmission is important in the rat for the rewarding and motivational components of food intake [27,92,126]. For example, a behavioral paradigm that assesses hedonic aspects of food, where rats have very short-term access to palatable solutions (e.g., sucrose), administration of dopamine receptor antagonists results in decreased lick rate of the palatable solutions. Because insulin acutely and directly stimulates uptake of DA into striatal DA nerve terminals [83] and presumptively decreases synaptic concentrations of DA through this action, we hypothesized that it would synergize with DA receptor antagonists which act post-synaptically. Consistent with this hypothesis, we have recently observed that co-administration of subthreshold doses of insulin (intraventricular)

and the DA antagonist raclopride (intraperitoneal) results in a significant decrease in 5-min lick rates of palatable sucrose solutions (Fig. 3). These data, although preliminary, suggest that in addition to direct effects of insulin on the neural circuitry that regulates food intake, insulin may also influence ingestive behavior by decreasing the brain's perception of the hedonic qualities of food.

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