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Invited review

Insulin signaling and addiction

Lynette C. Daws [a], Malcolm J. Avison [b], Sabrina D. Robertson [c], Kevin D. Niswender [d,e,f], Aurelio Galli [e,g,*], Christine Saunders [h]

[a] Department of Physiology, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA
[b] Institute of Imaging Science, Vanderbilt University School of Medicine, Nashville, TN, USA
[c] Laboratory of Developmental Neurobiology, National Institute of Environmental Health, Research Triangle Park, NC, USA
[d] Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN, USA
[e] Department of Molecular Physiology & Biophysics, Vanderbilt University School of Medicine, Nashville, TN, USA
[f] Tennessee Valley Healthcare System, TN, USA
[g] Center for Molecular Neuroscience, Vanderbilt University, TN, USA
[h] Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, TN, USA

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ABSTRACT

Across species, the brain evolved to respond to natural rewards such as food and sex. These physiological responses are important for survival, reproduction and evolutionary processes. It is no surprise, therefore, that many of the neural circuits and signaling pathways supporting reward processes are conserved from *Caenorhabditis elegans* to *Drosophilae*, to rats, monkeys and humans. The central role of dopamine (DA) in encoding reward and in attaching salience to external environmental cues is well recognized. Less widely recognized is the role of reporters of the "internal environment", particularly insulin, in the modulation of reward. Insulin has traditionally been considered an important signaling molecule in regulating energy homeostasis and feeding behavior rather than a major component of neural reward circuits. However, research over recent decades has revealed that DA and insulin systems do not operate in isolation from each other, but instead, work together to orchestrate both the motivation to engage in consummatory behavior and to calibrate the associated level of reward. Insulin signaling has been found to regulate DA neurotransmission and to affect the ability of drugs that target the DA system to exert their neurochemical and behavioral effects. Given that many abused drugs target the DA system, the elucidation of how dopaminergic, as well as other brain reward systems, are regulated by insulin will create opportunities to develop therapies for drug and potentially food addiction. Moreover, a more complete understanding of the relationship between DA neurotransmission and insulin may help to uncover etiological bases for "food addiction" and the growing epidemic of obesity. This review focuses on the role of insulin signaling in regulating DA homeostasis and DA signaling, and the potential impact of impaired insulin signaling in obesity and psychostimulant abuse.

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1. Insulin signaling in brain

In the periphery, insulin signaling plays a central role in the control of plasma glucose levels, and as a signal relaying the status of body energy stores to central (hypothalamic) regulators of energy homeostasis. Less well recognized is the important role insulin plays in regulating a broad spectrum of cellular and molecular functions within the central nervous system (CNS), including neurodevelopment, cell survival, neurogenesis, receptor trafficking, neurotransmitter release, and neurotransmitter reuptake (Bruning et al., 2000; Owens et al., 2005b; Robertson et al., 2010; Schulingkamp et al., 2000; Siuta et al., 2010; van der Heide et al., 2006; Williams et al., 2007; Woods et al., 1996). Given this diverse array of molecular and cellular targets in the CNS, it is not surprising that insulin signaling has been suggested to impact numerous brain functions, including learning, memory, arousal state, appetite and mood, and that disruptions in insulin signaling might contribute to a wide array of brain-related disorders. While the possibility of endogenous CNS insulin production has been raised, the majority of evidence suggests that insulin enters CNS

* Corresponding author. Department of Molecular Physiology and Biophysics, Center for Molecular Neuroscience, Vanderbilt University, 465 21st Avenue South, Room 7124, Medical Research Building III, Nashville, TN 37232-8548, USA. Tel.: +1 615 936 3891; fax: +1 615 936 3745.
E-mail address: aurelio.galli@vanderbilt.edu (A. Galli).

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from the periphery by active transport across the blood brain barrier (Banks, 2004; Schwartz et al., 1992). Peripheral manipulations of insulin are mirrored by similar alterations in CNS insulin (Schwartz et al., 1990). In a study involving insulin-sensitive *versus* insulin-resistant men, Anthony et al. showed that brain insulin resistance exists in peripheral insulin resistance, especially in brain regions subserving appetite and reward (Anthony et al., 2006). In light of the growing obesity epidemic and its associated disorders stemming from dysregulation of insulin levels and/or sensitivity to insulin in the periphery, the tight correlation between peripheral and central insulin tone raises the possibility that these "disorders of the periphery" may have more far-reaching consequences than previously thought. Thus, they might contribute to "disorders of the brain", particularly those where dysregulation of the DA neurotransmitter system is implicated.

Consistent with this view, insulin receptors (IRs) are present in brain and are found on midbrain DA neurons (Figlewicz et al., 2003). The downstream effects of insulin include activation of phosphoinositide 3-kinases (PI3K), required for the effects of both insulin (Niswender et al., 2003) and leptin (Niswender et al., 2003) on feeding. This lipid kinase phosphorylates the D-3 position of phosphoinositides to generate PI(3,4,5)P_3(PIP_3) (Taha and Klip, 1999), which activates protein kinase B (Akt) by acting at the plasma membrane as a second messenger. Akt is a central player in insulin and growth factor signaling, and is thought to regulate several cellular functions including cell growth and apoptosis (Hanada et al., 2004). Three isoforms of Akt have been identified (Hanada et al., 2004), and each of them contain a pleckstrin homology (PH) domain that interacts with membrane lipid products of PI3K. This interaction causes phosphorylation of Akt at Thr-308 as well as at Ser-473, and is required for Akt activation (Hanada et al., 2004). In mouse tissue, both Akt1 and Akt2 isoforms are ubiquitously expressed, whereas Akt3 is relatively highly expressed in brain and testis (Hanada et al., 2004). Akt is also involved in the regulation of DA signaling (Beaulieu et al., 2007, 2009) and DA homeostasis (Garcia et al., 2005; Owens et al., 2005b; Wei et al., 2007; Williams et al., 2007). Notably, a human genetic variant of Akt has been found to be associated with schizophrenia and methamphetamine abuse, both disorders in which dysregulation of the DA neurotransmitter system is prominent (Emamian et al., 2004; Ikeda et al., 2006). Consistent with this, we have shown that neuronal genetic alteration of Akt phosphorylation status leads to dysregulation of cortical DA homeostasis in mice (Siuta et al., 2010), underscoring the role of central insulin signaling in regulating DA function.

2. Insulin and DA homeostasis

Very few studies have investigated the relationship between physiological or pathological changes in insulin levels and DA homeostasis. A major regulator of DA homeostasis is the dopamine transporter (DAT). The DAT controls the strength and duration of DA neurotransmission by the high-affinity uptake of DA released into the extracellular space. Patterson and co-workers (Patterson et al., 1998), using food deprivation as a model to decrease levels of plasma insulin in rats, measured uptake of DA by the DAT in striatal synaptosomal suspensions by rotating disk voltammetry. In line with the idea that insulin signaling pathways can regulate DA clearance, they found that the maximal velocity (V_{max}) for DA uptake was decreased in suspensions prepared from fasted rats. Moreover, they were able to restore DA uptake to control levels by addition of a physiological concentration of insulin (1 nM) to the suspension, providing evidence that the decrease in DA uptake observed in fasted rats is a direct consequence of reduced insulin and not other consequences of hypoinsulinemia such as hyperglycemia or elevated free fatty acid levels. Consistent with the fact that food restriction decreases circulating insulin levels (Carr, 1996; Escriva et al., 1992; Koubova and Guarente, 2003) and through this, possibly, DAT activity, Zhen et al. demonstrated that chronic food restriction decreases DAT function in striatal preparations (Zhen et al., 2006). Using chronoamperometry in rats, we extended these findings to show that *in vivo*, food restriction decreased the rate of DA clearance in striatum, and that this effect could be reversed by returning rats to their normal diet (Sevak et al., 2008b), thereby highlighting the plasticity of this system. Our studies in rats made diabetic by a single injection of streptozotocin (STZ) further reinforce this idea. STZ treatment in rats reduces circulating insulin in the periphery and brain. We found that DA clearance in rat striatum, measured *in vivo* by chronoamperometry, was decreased by ~65% in hypoinsulinemic rats (Owens et al., 2005b). Similarly, [^{3}H]DA uptake into striatal synaptosomes prepared from STZ-treated rats was reduced by ~45% relative to control rats (Owens et al., 2005b). These effects were long lasting, persisting for 25 days, but could be reversed by insulin replacement (Williams et al., 2007).

While these studies provided preliminary evidence that insulin is capable of altering dopaminergic signaling in the brain, further studies demonstrated specifically the ability of insulin to regulate DAT. For example, tyrosine kinase inhibitors, which block the receptors activated by insulin as well as insulin-like growth factors, were shown to reduce DA clearance due to a decrease in the surface expression levels of DAT (Doolen and Zahniser, 2001). Furthermore, inhibition of downstream components of the insulin signaling pathway, such as PI3K and Akt, also dramatically reduce DA clearance and surface expression of DAT (Carvelli et al., 2002; Garcia et al., 2005). Finally, surface levels and function of DAT are significantly diminished in both STZ models of diabetes (Williams et al., 2007) as well as diet-induced obese states of brain insulin-resistant rats (Speed and Saunders, personal communication). Taken together, insulin signaling in rodents plays a critical role in maintaining appropriate dopaminergic tone by regulating DAT expression at the cell surface.

Early studies in diabetic rodents have also suggested abnormalities in noradrenergic tone. Differences in the types of animals studied and the regions of the nervous system examined, however, failed to offer a consensus on whether deficits in insulin signaling stimulate or depress noradrenergic function. However, initial studies of insulin's regulation of the norepinephrine transporter (NET) function were more consistent. For example, insulin inhibits NE uptake in whole brain neuronal cultures, dissociated brain cells, and whole brain synaptosomes (Boyd et al., 1985, 1986; Masters et al., 1987; Raizada et al., 1988). Furthermore, Figlewicz et al. demonstrated that nanomolar concentrations of acute insulin decrease NE uptake from both hypothalamic and hippocampal rat slices (Figlewicz et al., 1993), and that insulin also inhibits NE uptake in PC12 cells which endogenously synthesize NE and express NET (Figlewicz et al., 1993). Since these original studies in the late 1980's and early 1990's, insulin regulation of noradrenergic signaling and NET function has remained relatively unexplored. Only a single additional study on the topic demonstrated an opposing effect of insulin to increase NE uptake in SK–N–SH cells (Apparsundaram et al., 2001). Recently, Robertson et al. explored the nature of insulin's regulation of NET with particular interest in how disruptions in this regulation have the potential to impact monoamine homeostasis, behavior, and perhaps ultimately mental health (Robertson et al., 2010).

3. Insulin signaling regulates psychostimulant actions

Amphetamine (AMPH)-like stimulants are actively transported by catecholamine carriers such as DAT (Sulzer et al., 2005). As

substrates, AMPHs not only competitively inhibit DA reuptake and thereby increase synaptic DA, but also promote reversal of transport, resulting in efflux of DA *via* the DAT (Sulzer et al., 2005). This efflux results in an increase in extracellular DA and is of major importance for the psychomotor stimulant properties of AMPHs (Sulzer et al., 2005). However, studies of the consequences of reduced insulin signaling for behavioral responses to AMPH are mixed. Some report that decreased insulin status (e.g., STZ treatment) attenuates behavioral responses to AMPH (Galici et al., 2003; Marshall, 1978; Rowland et al., 1985), while others find no or only very modest effects of low insulin on the behavioral responses to AMPH and other DA targeting drugs (Owens et al., 2005a; Sevak et al., 2008a, b). These mixed results are not surprising given differences in experimental design, drug doses, number of drug exposures and the behavioral readout. In contrast, biochemical studies of the consequences for reduced insulin tone and the actions of AMPH have revealed marked effects, described below.

Because insulin and PI3K signaling have been shown to fine-tune DAT cell surface expression (Garcia et al., 2005; Wei et al., 2007), it is possible that inhibition of PI3K signaling *in vivo*, by reducing DAT cell surface expression, inhibits AMPH-induced DA efflux. Selective inhibition of PI3K *via* LY294002 results in a dramatic reduction in AMPH's ability to elicit DAT-mediated DA efflux in heterologous cells, dopaminergic neurons, and *in vivo* within the striatum of rats as measured by both *in vivo* voltammetry and fMRI (Lute et al., 2008; Williams et al., 2007). These data suggest that kinases linked to both glucose homeostasis and food intake are also capable of regulating reward pathways in the brain that are targeted by psychostimulants such as AMPH. Repeated systemic administration of AMPH reverses the effect of food restriction or STZ-induced diabetes to reduce DA clearance *via* a DA D2 receptor (D2R)-dependent mechanism (Owens et al., 2005a; Sevak et al., 2007). Mechanistically, this suggests that insulin signaling *via* IRs and PI3K, and DA signaling *via* D2R, work in tandem to regulate DAT plasma membrane expression and function. This interplay between insulin signaling and drug-induced increases in extracellular DA may contribute to the high co-morbidity of eating disorders and drug abuse. For example, caloric restriction or deprivation, as occurs in anorexia and bulimia, decreases insulin and augments reward-related behaviors (Davis et al., 2010). Furthermore, Ricca et al. have shown that AMPH users reported a high rate of childhood obesity and higher body mass index (BMI). The consumption of AMPH-like agents is associated with higher levels of eating psychopathology and more severe obesity (Ricca et al., 2009). These studies reinforce the need to explore and better understand the clinical implications of the co-morbid nature of psychostimulant abuse and eating disorders (Herzog et al., 2006).

4. Brain insulin resistance and impaired DA neurotransmission: A pathway to obesity

DA is important in modulating several behaviors, ranging from movement to cognition to motivation and pleasure, including our motivation to eat and the pleasure we receive from it (Palmiter, 2007, 2008). A role for DA in feeding behavior is demonstrated by studies showing improper DA signaling in obesity. For example, in humans, upon eating a palatable meal, dopamine rich regions in the brain, such as the striatum, increase in activity (Stice et al., 2008). In subjects with a BMI in the obese range, this increase in activity is dampened in a BMI-dependent manner. This effect appears to be particularly significant in individuals with a genetic polymorphism in the Taq1A1 allele, which is associated with reduced D2R expression (Stice et al., 2008). These data suggest that dysregulation of DA neurotransmission occurs in obese individuals, and raise the possibility of traits in DA signaling that may predispose to obesity. However, the precise relationship between this polymorphism and BMI remains to be elucidated. In obese rats, mesolimbic DA turnover is impaired (Davis et al., 2008), and mRNA expression for the DAT, DA receptors (DRs), and tyrosine hydroxylase (TH), key elements controlling DA neurotransmission, are reduced (Huang et al., 2005, 2006). In humans, D2R availability, as measured by PET, decreases with increasing BMI (Wang et al., 2001). Similar results were found for DAT, where high BMI was correlated with low DAT availability (Chen et al., 2008). Taken together, DA neurotransmission may not only play an important role in determining eating patterns, but may be perturbed by excessive food consumption. However, the molecular mechanism(s) underlying these phenomena remain to be discovered.

DA has several roles in determining the amount and type of food consumed, but prominent among them, DA drives the motivation for seeking food (Palmiter, 2007, 2008), and the reward and satiety felt after eating (Berthoud and Morrison, 2008; Volkow and Wise, 2005). The DA reward system originates in the ventral tegmental area (VTA) and substantia nigra, with projections ending in the nucleus accumbens and striatum. Several inputs feed into this system, including cannabinoid and opiate systems, as well as signaling molecules that are regulated by food consumption: insulin and leptin (Palmiter, 2007). DA is well known for its role as a major signaling molecule for our endogenous reward system. Activation of DRs in the reward system are thought to give rise to the pleasant (rewarding) feelings associated with food consumption and conversely when not stimulated, motivates food seeking behavior. Drugs are known to highjack this system, leading to highs when consuming the "drug" and cravings and anhedonia when the "drug" is no longer onboard.

Food may work in a similar way to drugs. Comparisons between drug addiction and obesity have been made (Volkow and Wise, 2005). This is but one example of how prolonged drug use can change the responsivity of DA systems. Such long term changes in DA signaling are thought to form the biological basis for addiction: these changes can cause individuals to crave the drug more, as well as create the need for greater quantities of drug to obtain a similar "high". Researchers have presented a similar hypothesis for food consumption and obesity. Compared to normal subjects, fMRI scans of obese subjects show a reduction in striatal activation when consuming a highly palatable food (Stice et al., 2008), a finding strikingly similar to that for drug effects in addicts as just described. It is hypothesized that impaired DA signaling overrides metabolic signals regulating homeostatic food consumption, thereby beginning a vicious cycle of over-eating (or non-homeostatic consumption), worsening obesity in affected individuals.

As we continue to explore DA signaling in feeding behavior, this view becomes overly simplistic. One study examined the effects of DA on feeding by creating mice that are DA deficient in the brain (Sotak et al., 2005). These DA-deficient mice do not eat and die shortly after birth, having no motivation to seek and consume food. Restoration of DA synthesis by viral technology to the dorsal striatum rescued the phenotype and the animals ate and survived. This study highlights the dorsal striatum, and therefore the nigrostriatal system, in feeding behavior. While the hypothalamus has long been considered the "central controller" of feeding behavior, these authors suggest that the dorsal striatum may be the brain region critical for driving the motivation to eat; defining our basic need for food. Without DA signaling in this region, the animals did not eat. Restoration of DA signaling to the ventral striatum did not rescue the phenotype, leading to the hypothesis that the dorsal striatum is necessary to ensure food intake, while the ventral striatum may serve to fine-tune feeding behavior (Palmiter, 2007, 2008; Sotak et al., 2005).

These studies highlight the importance of DA systems, in particular the dorsal striatum, for feeding behaviors. Not surprisingly, in this era of fast-food and increasing health issues related to obesity, the effects of high fat diets on DA systems have become the focus of intense research. Geiger and colleagues examined the effects of diet-induced obesity on DA systems in rats (Geiger et al., 2009). Rats were made obese by being maintained on a "cafeteria style" diet, consisting of access to several different highly palatable, highly caloric foods such as meats, cheeses, cookies, sweetened condensed milk, etc., for 15 weeks (Geiger et al., 2009). They found that DA release after electrical stimulation *ex vivo* was dramatically reduced in slices from both the ventral and dorsal striatum of obese rats compared to controls (Geiger et al., 2009), suggesting that obese rats have reduced DA neurotransmission in these striatal regions. In an elegant paper by Johnson and Kenny (Johnson and Kenny, 2010), striatal D2R were downregulated in obese rats which led to reward hypofunction, akin to that of substance-abuse addicts. Interestingly, these investigators found that lentivirus-mediated knockdown of striatal D2Rs in rats mimicked the drug addiction-like reward hyposensitivity, leading to the development of compulsive eating (Johnson and Kenny, 2010), suggesting that obesity and drug addiction fascinatingly share a common neuronal hedonic etiology. While the exact role of these striatal regions in regulating feeding behavior remains to be elucidated, it is clear that both regions are sensitive to diet. The mechanism underlying this sensitivity needs to be further studied in order to gain a complete understanding of the role of striatal DA systems in obesity.

We and others have uncovered the molecular mechanism by which CNS monoaminergic systems are regulated by insulin (Robertson et al., 2010; Williams et al., 2007). Neuronal insulin signaling is exquisitely sensitive to dietary macronutrient intake (Posey et al., 2009). We suggest a link between dysregulated brain insulin signaling and altered monoamine-related behaviors including food intake. In this model, food-induced disruption of brain insulin action (insulin resistance) may confer risk for and/or underlie "food-use" by altering DA reward pathways, since these pathways are insulin-sensitive. This molecular model, thus, explains how even short term exposure to "the fast-food lifestyle" creates a vicious cycle of disordered eating that cements pathological changes in DA signaling leading to weight gain, and obesity.

While the focus of this review has been on DA neurotransmission in striatum as it relates to insulin, feeding and reward, an array of molecular targets and complex neurocircuitries mediating feeding and reward should be discussed. These include the interplay of neural pathways connecting hypothalamic nuclei to the ventral tegmental area, nucleus accumbens and striatum (e.g., GABA, serotonin, orexin and melanocortin pathways) and a plethora of regulatory molecules, including, but not limited to, CREB, delta-FosB, α-MSH, NPY, ghrelin and leptin. In addition, limbic brain regions, such as the hippocampus and amygdala, are involved in the emotional response to food reward and learned behavioral responding (Dagher, 2009). Furthermore, the literature supports a role for insulin in mediating cognition and hippocampal plasticity (Chiu et al., 2008; Huang et al., 2003). These topics have been comprehensively reviewed elsewhere (Blumenthal and Gold, 2010; Figlewicz and Siplos, 2010; Lutter and Nestler, 2009; Sanchez-Lasheras et al., 2010; van der Heide et al., 2006). The key focus of this review is on the expanding evidence that modest perturbations in insulin signaling can produce dramatic changes in DAT trafficking, function and DA neurotransmission. As a major regulator of reward pathways, and a primary target for abused drugs (e.g. cocaine, AMPH), this connection between insulin and DAT warrants further investigation as to how it might mechanistically play a role in the "pathway to obesity".

5. Summarizing remarks

The exploding obesity epidemic provides compelling support for the idea that feeding behaviors depend heavily - often negatively – on factors beyond the simple need to maintain energy homeostasis. Indeed, emotions provide positive (or negative) feedback toward certain behaviors, and reward has increasingly become a large part of human consummatory behavior. Thus, there is growing recognition that this epidemic is fueled in large part by a transformational shift in the mechanisms – molecular, neural, behavioral and societal – that dominate feeding behavior when low-cost, energy dense, highly palatable foods are readily available, and their ubiquity is reinforced by a barrage of salient cues. Motivation for consuming food has shifted from simple homeostatic necessity, to more complex "habits" that, when dysregulated, appear to share many of the features, as well as molecular and neural substrates, of addiction/substance use disorders.

Brain circuits comprising dopaminergic midbrain nuclei (VTA, substantia nigra), and their subcortical (nucleus accumbens, striatum) and cortical projection fields are key substrates of non-homeostatic feeding. While DA has long been recognized as an important mediator of feeding behavior, the findings of reduced striatal D2R availability in obese subjects (Wang et al., 2001), and reduced feeding-associated striatal activation in obese subjects with a gene polymorphism associated with reduced D2R expression (Stice et al., 2008) have heightened interest in the role of dysregulated dopamine signaling in obesity. Current models posit that dopaminergic dysfunction, which share features of impaired striatal dopamine neurotransmission that are characteristic of substance use disorders (Palmiter, 2007; Wang et al., 2001), plays a predisposing and/or causative role (Johnson and Kenny, 2010; Niswender et al., 2011; Wang et al., 2001).

Insulin acts in the CNS to regulate food intake. Insulin receptors are abundant in CNS, including striatum and hypothalamus, where insulin action serves functions ranging from signaling peripheral metabolic status, to regulation of reward, development, and cognition (Figlewicz and Benoit, 2009; Figlewicz and Siplos, 2010). Our own studies have demonstrated that insulin signaling plays a critical role in maintaining monoamine neurotransmission. Impaired insulin signaling drastically modifies brain function at the molecular, cellular and circuit level as well as dopamine homeostasis and DAT trafficking (Carvelli et al., 2002; Garcia et al., 2005; Owens et al., 2005b; Robertson et al., 2010; Wei et al., 2007; Williams et al., 2005). Furthermore, neuronal insulin signaling is exquisitely sensitive to dietary fat and sugar intake (Posey et al., 2009). These observations, and similar findings from other groups, suggest a link between brain insulin signaling and monoamine-related behaviors, disruption of which may confer risk for and/or underlie "substance-use-disorders", as well as a wide range of neurocognitive and psychiatric disorders. A very recently released and elegant study from Schoffelmeer et al. showed that insulin presynaptically enhances cocaine-sensitive monoamine transporters, both DAT and NET, and reduces impulsive behavior in the rat nucleus accumbens (Schoffelmeer et al., 2011). Impulsivity has been linked to not only drug abuse (Coffey et al., 2003), but obesity as well (Nederkoorn et al., 2006). Thus, insulin displays brain specificity in its effects on monoamine transporter function, and thereby may provide a novel therapeutic target for inhibitory control of disorders such as drug addiction and obesity (Schoffelmeer et al., 2011). Confirmation of such a link would argue strongly that strategies aimed at improving brain DA function, whether by normalizing or bypassing disruptions in insulin signaling, might be effective in treating substance use disorders. Moreover, revealing this link between neuronal insulin signaling and monoamine homeostasis will additionally lay the foundation

for understanding the molecular mechanisms behind obesity and food addiction, and could thereby yield new interventional targets for these diseases.

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