signaling is increasingly of interest in obesity with findings that dopamine D2 receptor binding is reduced in a BMI-dependent manner (Wang *et al*, 2001). Building on this observation, current models of obesity pathogenesis posit that dopaminergic dysfunction, referred to as hypodopaminergic reward deficiency syndrome (HRDS), has a predisposing and/or causative role (Wang *et al*, 2001). HRDS shares features of impaired striatal dopamine neurotransmission with substance use disorders (Wang *et al*, 2001).

Insulin is a glucoregulatory hormone in the periphery that functions in the CNS to regulate both homeostatic and reward-based high-fat feeding (Figlewicz and Benoit, 2009). 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, cognition, and others. We, and others, have hypothesized that identification of a molecular link between brain insulin signaling and dopaminergic-related behaviors would have the potential to explain susceptibility to 'food-use' disorders. Therefore, strategies aimed at improving brain dopamine function in obesity may be a possible solution.

We and others have distilled the molecular mechanism by which CNS monoaminergic systems are regulated by insulin (Robertson *et al*, 2010; Williams *et al*, 2007). That neuronal insulin signaling is exquisitely sensitive to dietary macronutrient intake (Posey *et al*, 2009) (fat and sugar) allows us to propose a transformative potential molecular mechanism for the pathogenesis of obesity. These observations, and similar findings from others, suggest a link between brain insulin signaling and monoamine-related behaviors. Disruption of brain insulin action (genetic or acquired) may, therefore, confer risk for and/or underlie 'food-use'—as well as a range of neurocognitive and psychiatric—disorders. 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 dopamine signaling leading to weight gain, and obesity.

We propose that intact insulin signaling in dopamine-rich brain regions supports dopamine homeostasis and normal reward for food. In our modern, energy-dense food environment, reward drives poor dietary decisions where reward-driven overconsumption of high-fat, high-sugar, energy-dense foods quickly leads to neuronal insulin resistance, dysregulation of dopamine homeostasis, and HRDS. In this stage of pathogenesis, HRDS, described in obese humans, is established (Wang *et al*, 2001). This 'syndrome' results in chronically increased intake of fat and sugar to achieve a normal level of reward in the setting of decreased dopamine tone.

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Extinction Learning and Adult Neurogenesis

Extinction of maladaptive conditioned responses or behaviors is a process of new and active learning, and requires the organism to learn new stimulus–response and action–outcome relationships, and to form new associations between previously hypersalient stimuli (ie, trauma-related cues and contexts) and appropriate cognitive and/or behavioral responses. Much of our knowledge about the neural substrates that underlie extinction processes comes from studies of fear conditioning (Myers and Davis, 2007), but an increasing number of studies have begun to examine the mechanisms underlying extinction of drug-seeking behavior (Cleva and Gass, 2010).

Adult neurogenesis is an ongoing process that occurs in most mammalian species, including humans. This phenomenon occurs primarily in two brain regions: the subgranular layer of the dentate gyrus region of the hippocampus, which gives rise to neurons that migrate and integrate into the granule cell layer (GCL), and the subventricular layer of the lateral ventricles, which supplies newborn neurons to the olfactory system through the rostral migratory stream. Factors that contribute to the birth, differentiation, maturation, migration, and survival of adult-born neurons, as well as the specific function of surviving neurons, are poorly understood. However,

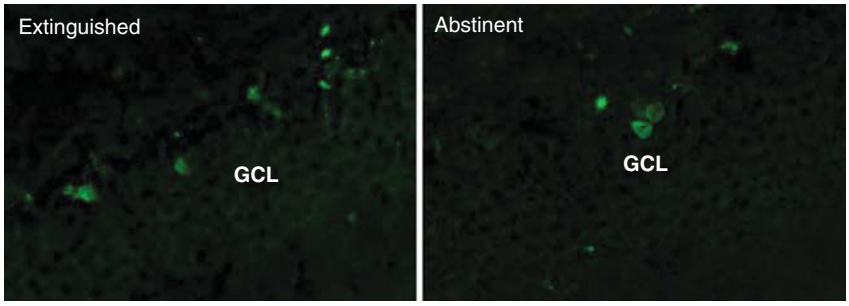

Figure 1. Rats self-administered heroin 3 h daily for 12 days and were then administered 2-bromodeoxyuridine (BrdU) immediately after the first five extinction training sessions or the on first 5 days of forced abstinence. Extinction-trained animals (left) showed approximately twice as many BrdU-labeled cells in the subgranular layer as those that underwent forced abstinence (right). GCL, granule cell layer.

adult-born neurons may be involved in certain learning and memory processes.

As extinction is a form of learning, it would follow that adult hippocampal neurogenesis (AHN) might have a role in extinction processes. An initial study showed that ablation of AHN in mice by γ-irradiation or anti-mitotic agent administration failed to affect the extinction of contextual fear memory (Ko *et al*, 2009). However, it was subsequently showed that conditional ablation of AHN in a nestin-thymidine kinase transgenic mouse line indeed impaired extinction of a contextual fear memory (Deng *et al*, 2009). In agreement with these latter findings, disruption of AHN by irradiation impaired the extinction of cocaine-seeking behavior in rats following intravenous cocaine self-administration (Noonan *et al*, 2010).

Performance of various learning and memory tasks can increase AHN, further supporting a role for these neurons in experience-dependent neural plasticity. To this end, extinction training following intravenous heroin self-administration increases cell proliferation in the hippocampus (Figure 1; see also Wischerath *et al*, 2009), and in agreement with the observations of Noonan *et al* (2010), conditional ablation of AHN in mice impairs extinction learning following heroin self-administration (unpublished observations). Together, these data suggest that in most instances, AHN is involved in extinction learning, and future studies are needed to determine the precise environmental conditions as well as the chemical and molecular regulators of AHN. As a result, AHN could potentially be targeted as an adjunct to extinction-based therapies, such as cue exposure therapy, that are used in the treatment of anxiety and substance use disorders.

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Transcriptional Control of Serotonin-Modulated Behavior and Physiology

Altered levels of serotonergic activity have been linked to the pathogenesis of numerous neurological and psychiatric disorders such as autism, sudden infant death syndrome (SIDS), depression, and anxiety. These alterations are thought to cause abnormal formation of neural circuitry responsible for the development and expression of adaptive behaviors and physiological processes. How might these alterations be brought about? Genetic variation in or near genes encoding the serotonin (5-HT) reuptake transporter, *5-HT$_{1A}$* receptor, and the rate-limiting synthetic enzyme tryptophan hydroxylase 2 is associated with risk for behavioral pathogenesis (Holmes, 2008). Functional studies in cell culture suggest that some of the identified variants alter levels of gene transcription.

These findings raise an alternative potential mechanism underlying behavioral pathogenesis in which variation in serotonergic gene transcription causes altered levels of serotonergic activity. As many of the disorders in which serotonergic dysfunction has been implicated are neurodevelopmental in origin, altered function of the transcriptional programs that control 5-HT neuron generation may establish a vulnerability for pathogenesis by directing abnormal levels of serotonergic signaling that in turn disrupt neural circuit formation during critical periods in early life.

Over the past decade, transcriptional cascades that program the generation of 5-HT neurons have been identified. Gene targeting of individual cascade factors has created specific deficiencies in serotonergic transcription at a stage when CNS neural circuitry has not yet formed (Hendricks *et al*, 2003; Zhao *et al*, 2006). These studies show that all of the cascade factors are necessary for the initiation of 5-HT synthesis.