Gambling Rats: Insight into Impulsive and Addictive Behavior

Although nothing more than a harmless recreation for most, gambling can become a 'behavioural addiction' comparable to drug dependency (Potenza, 2008). The incidence of such pathological gambling (PG) in the USA is estimated at 1–5%, yet current treatments are limited and often ineffective. Animal models of substance use have made a significant contribution to our understanding of drug addiction. Modeling gambling processes in non-human subjects could likewise facilitate our understanding of the drive to gamble, and stimulate the development of pharmacotherapies.

Clinically, one of the most common tests of gambling-related decision-making is the Iowa Gambling Task (IGT), in which subjects choose from four decks of cards to win money or points (Bechara *et al*, 1994). Two of the decks are associated with bigger immediate rewards but disproportionately large losses. The correct approach is therefore to favour decks which deliver smaller amounts but also lower penalties, thereby leading to greater long-term gain. Using the IGT as a template, novel rodent models of gambling behaviour have been developed in which rats play against the clock to earn as many sugar pellets as possible by sampling between four different options. The amount of reward available on each option varies in size (1–4 pellets). On a given trial, the animal receives either the set reward or a punishing 'time-out' during which reward cannot be earned. The reinforcement schedules are fixed such that the larger pellet options are associated with a greater frequency or duration of time-outs, decreasing their net worth. Rats must therefore learn to avoid risky options associated with larger rewards, analogous to the optimal strategy on the IGT. Recent data indicate that rats are capable of 'playing the odds' in this way. Furthermore, such choice behaviour can be modulated by drugs which target the serotonin and dopamine systems, with a D_2 receptor antagonist enhancing performance, while amphetamine and a serotonin 1A receptor agonist impair choice (Zeeb *et al*, 2009). Animals which prefer the maladaptive 'high-risk high-reward' options also show elevated preference for exposed or novel environments, indicating this choice pattern may be a valid marker for risk-prone behaviour (Rivalan *et al*, 2009).

Human and animal studies indicate that highly impulsive individuals, particularly those showing elevated levels of motor impulsivity, are more vulnerable to both cocaine dependency and PG (Verdejo-Garcia *et al*, 2008). Whether this form of impulsivity represents an endophenotype for chemical and behavioural addictions remains an interesting hypothesis now open to empirical verification. Demonstrating that rodents can engage in a decision-making process reminiscent of gambling, and that such decision-making can be pharmacologically modified, is certainly a step forward. As with research into substance abuse, however, it will be important to dissociate the act of performing a potentially-addictive behaviour and actually exhibiting symptoms of dependence. Some of the DSM-IV criteria for drug dependency have been translated into behavioural measurements applied to rats self-administering cocaine, theoretically demarcating dependent subjects (Belin *et al*, 2008). A future challenge for the field will be to create a similar standard for gambling models to help identify subjects exhibiting a PG-like phenotype.

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DISCLOSURE

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Insulin Regulation of Monoamine Signaling: Pathway to Obesity

The prevalence of obesity and related disorders such as diabetes has skyrocketed worldwide despite efforts to therapeutically target homeostatic mechanisms that regulate appetite, energy expenditure, and weight gain. The failure of these efforts points to the existence of additional, nonhomeostatic mechanisms that mediate feeding behavior (Palmiter, 2007). Indeed, redundancy in these systems makes obesity therapy difficult as further evidenced by the failure of newer drugs targeting distinct aspects of these systems. Thus, the epidemic of obesity begs for novel concepts and therapeutic targets that ideally treat 'food-use' disorders and related comorbidities such as drug addiction and neuropsychiatric disorders.

Nonhomeostatic or 'reward' circuits originating in dopamine-rich brain structures, which provide motivation and reward stimuli for feeding, are increasingly understood at the cellular and molecular levels (Palmiter, 2007). Long recognized as an important mediator of feeding behavior, dopamine

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,