In This Issue

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A brief summary of the articles appearing in this issue of *Biological Psychiatry*.

Serotonin-Dopamine Circuitry Regulates Binge Eating

Impaired serotonin signaling and the dopamine system have both been linked to binge eating in humans. **Xu *et al.*** (737–747) used a multipronged approach to assess these systems in the regulation of binge-eating behavior in mice. They demonstrate that serotonin compounds fluoxetine, d-fenfluramine, and lorcaserin suppress binge eating in mice and that these effects are mediated by 5-HT_{2C} receptors expressed by dopamine neurons. These findings suggest that the serotonin-dopamine neural circuit exerts inhibitory effects on binge-eating behavior in mice and that 5-HT_{2C} receptors in dopamine neurons may be a viable target for the development of binge-eating therapies.

Review: The Hippocampus and Food Intake Control

The hippocampus plays a vital role in memory processes. Emerging findings suggest that the hippocampus also controls higher-order aspects of feeding behavior. This review by **Kanoski and Grill** (pages 748–756) proposes a model whereby the hippocampus controls feeding behavior by integrating memory processes with external environmental and internal physiological cues. The authors also highlight recent findings showing that hormones secreted from peripheral organs act on hippocampal neurons to control food intake and regulate body weight.

Novel Mouse Models of Eating Disorder Behaviors

Eating disorders and associated behaviors, such as binge eating, are highly heritable and comorbid with mood and addictive disorders, yet the underlying genetic factors are not known. Here, **Kirkpatrick *et al.*** (pages 757–769) assessed multiple mouse strains and identified *Cyfip2* as a potential genetic factor of binge-eating susceptibility. They then developed and characterized a genetic model, with *Cyfip2* knockout mice showing reduced binge eating. Transcriptome analysis also revealed differentially expressed genes between the strains. Together, these data identify *Cyfip2* as a genetic factor underlying binge eating that may have implications for treating eating disorders in humans.

A mutation in *HDAC4* has recently been linked to the risk for eating disorders in humans. **Lutter *et al.*** (pages 770–777) created and characterized a new transgenic mouse model carrying the *Hdac4* mutation at the corresponding site. They found that heterozygous female mice, but not male mice, carrying this mutation display several feeding and behavioral phenotypes related to human eating disorders, but these phenotypes differed based on housing condition. They also identified mitochondrial biogenesis as a potential molecular pathway contributing to the observed behavioral deficits. The results suggest that this *Hdac4* mutant model may contribute toward a better understanding of human eating disorders.

Striatal Mechanisms of Drug and Food Addiction

Mu opioid receptors (MORs) mediate the rewarding effects of drugs, but the underlying circuit mechanisms remain unclear. **Charbogne *et al.*** (pages 778–788) generated and characterized a conditional mouse model by using a targeted *Oprm1* knockout strategy in gamma-aminobutyric acidergic forebrain neurons. They found that striatal MORs are not necessary for opiate reward, a finding consistent with the model that implicates ventral tegmental area neurons in this process. However, they did identify a novel role for striatal MORs in motivated behaviors for both drug and food reward. These data reveal dissociable MOR functions in the rewarding and motivational components of addiction across brain networks.

The food addiction model posits that obesity is associated with neural adaptations in the striatum and within striatal networks, similar to those observed with drugs of abuse. Using functional imaging in excess- and normal-weight participants, **Contreras-Rodríguez *et al.*** (pages 789–796) found that obesity is associated with increased connectivity between the ventral striatum and the medial prefrontal cortex, and between the dorsal striatum and the somatosensory cortex. Dorsal striatum connectivity correlated with food craving and longitudinally predicted future weight gain. These findings link striatal alterations to obesity, food craving, and persistent food intake and provide further support for the food addiction model.

Addiction-like Synaptic Impairments in Obesity

Using a rat model, **Brown *et al.*** (pages 797–806) investigated whether diet-induced obesity is associated with addictive-like behavior and synaptic impairments, two hallmark features of drug addiction. Compared with obesity-resistant rats, obesity-prone rats showed addictive-like food behaviors, including increased motivation for palatable food, excessive intake, and increased food seeking. The obesity-prone rats also showed impairments at excitatory synapses in the nucleus accumbens core. These data provide neurophysiological evidence linking obesity and addiction, supporting the concept of a shared endophenotype underlying these two disorders.

Leptin Dysregulation in Depression

Leptin dysregulation may be a mechanism underlying the link between obesity and depression, but findings have been mixed, which may be due to the clinical heterogeneity of major depressive disorder. Using data from a well-characterized cohort, **Milaneschi *et al***. (pages 807–814) report that high leptin concentrations, relative to leptin levels in healthy subjects, are associated with the atypical subtype, but not the typical subtype, of major depressive disorder. Higher leptin was also associated with hyperphagia, increased weight, and reduced energy, symptoms that are core features of the atypical major depressive disorder subtype. Thus, leptin mechanisms may be a promising target for the development of therapies to benefit patients with depression characterized by obesity-related metabolic alterations.

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