molecular interventions
pharmacological perspectives from biology, chemistry and genomics

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DEPARTMENTS

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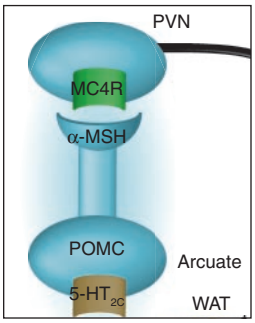
VIEWPOINTS

73 The Role of 5-HT$_{2C}$R in Glucose Homeostasis



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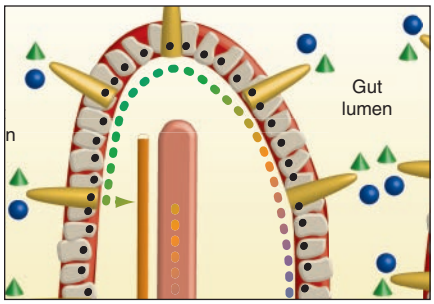
Sugar-coated regulation with 5-HT$_{2C}$?

New findings indicate that the serotonin subtype 2C receptor (5-HT$_{2C}$R) activation results in improved peripheral glucose control in mice. Furthermore, this effect seems to depend on the involvement of the melanocortin system. This appears to be the first demonstration of a link between 5-HT$_{2C}$R activation and glucose regulation, independent of food intake and body weight reductions. These findings may have immediate implications in humans, as there are selective 5-HT$_{2C}$R agonists currently in advanced clinical trials. There is historical utility to these observations as well, putting into perspective past findings from studies utilizing fenfluramine that hinted at links between the serotonin system and glucose control. Recent discoveries linking hypothalamic nutrient-sensing systems and glucose homeostasis are considered, and these underscore the role of the serotonin system in the complicated phenomenon of peripheral glucose regulation.

Keith J. Miller and Anthony V. Azzara

78 Taste-sensing Proteins in the Gut Regulate Glucose Transport



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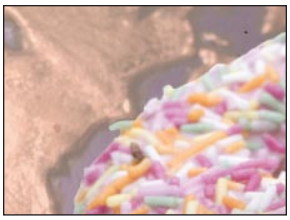
A "gut sense" of glucose transport

Taste receptors, the taste G-protein gustducin, and downstream signaling elements known to underlie the detection and transduction of bitter, sweet, and *umami* (monosodium glutamate–containing) compounds in taste buds of the tongue are present also in specific endocrine cells of the gut: the enteroendocrine K and L cells. Glucose in the gut activates sweet taste receptors and gustducin present in the intestine's enteroendocrine L cells, leading to secretion of glucagon-like peptide-1 (GLP-1) from these cells. GLP-1 and glucose-dependent insulinotropic peptide (GIP) are incretin hormones, which augment insulin release from the beta cells of the pancreas. GLP-1, GIP, and other gut hormones released from the K and L cells affect insulin secretion, glucose homeostasis, nutrient absorption and other gut functions. Glucose transport into enterocytes via Na+,glucose cotransporter 1 (SGLT1) and GLUT2 appears to be regulated by the gustducin- and sweet receptor-expressing enteroendocrine cells. In response to sugar ingestion, knockout mice lacking gustducin show deficits in the release of GLP-1 and insulin, in glucose homeostasis, and in upregulation of SGLT1. Apparently, the gut "tastes" sugars and sweeteners in much the same way as does the tongue and by using many of the same signaling elements. Taste receptors and other taste signaling elements in gut may be contributors to obesity, diabetes, metabolic syndrome and other diet-related disorders. Gut-expressed taste elements are attractive targets for therapeutic intervention.

Josephine M. Egan and Robert F. Margolskee

REVIEWS



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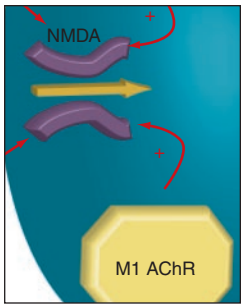
Global obesity

82 The Weight of the World: Drug Researchers Face a Global Epidemic

As obesity claims an increasing number of lives every year, our collective awareness of obesity as a global epidemic has heightened. There are complex origins for this relentless epidemic: easy access to large quantities of inexpensive foods that are calorie-rich; eating habits that have changed to match fast-paced and automated lifestyles; and increasingly sedentary work and recreation. These factors compound inherited tendencies to store excess calories as a defense mechanism for times of famine—the so-called thrifty-gene theory. It is estimated that more than thirty percent of adults, and about fifteen percent of juveniles, are obese. These statistics are accompanied by dramatic increases of diseases such as type 2 diabetes, cardiovascular and respiratory diseases, depression, and some forms of cancer. More than 300,000 obesity-related deaths occur in the US yearly; in fact, the incidence of type 2 diabetes in children has increased by more than tenfold. The urgency of the obesity epidemic has fueled biomedical research into the mechanisms that underlie energy homeostasis and the perturbations of metabolic balances that result in disease. Many of these mechanisms—both peripheral and within the central nervous system—suggest promising avenues for pharmacological intervention into obesity, overweight, and the comorbidities of modern, globalized living. *(I. Laher)*

Stephen R. Bloom, Francis P. Kuhajda, Ismail Laher, Xavier Pi-Sunyer, Gabriele V. Ronnett, Tricia M.M. Tan, and David S. Weigle

99 Novel Molecular Targets in Schizophrenia, New Routes to Rationality



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Beyond dopamine

Schizophrenia is a disabling psychiatric disorder characterized by positive, negative, and cognitive symptoms. The first pharmacological treatments for schizophrenia were discovered by serendipitous, albeit carefully documented, clinical observations. The discovery of chlorpromazine and other dopamine D_2 receptor antagonists as antipsychotic agents set the early course of drug discovery in the context of schizophrenia and other psychiatric disorders, and various monoamine receptors became the prime focus of neuropharmacological studies. Success in treating the positive symptoms nevertheless remained limited by the general lack of efficacy in addressing negative symptoms and cognitive impairment. In recent years, several new experimental approaches have emerged for the identification and treatment of different symptom clusters that do not rely on blockade of monoamine receptors. Muscarinic, nicotinic, and glutamatergic signaling mechanisms have become essential to neuropharmacological and behavioral models of discrete aspects of schizophrenia. And as a consequence of these insights, novel drug entities have become available to study and potentially treat the disabling cognitive and negative symptoms of psychiatric disease. Current attempts to target a new range of receptors entail unprecedented fine-tuning in the pharmacological manipulation of specific receptor subtypes.

P. Jeffrey Conn, Carol Tamminga, Darryle D. Schoepp, and Craig Lindsley

This month marks the Centennial Celebration of ASPET, at EB 2008, in San Diego. The cover of this issue highlights obesity, a topic of the ASPET meeting at EB and a theme that recurs throughout the pages of this month's MI.