Research News

Leptin attenuates heroin craving

A study recently published in the 15 February edition of *The Journal of Neuroscience* suggests that leptin, an adipocyte protein involved in regulating food intake and energy use, also has a role in drug addiction. In people, stressful events such as food deprivation have been associated with drug craving and relapse to drug use. Shalev *et al.* studied this behavior in rats that were trained to self-administer heroin. These rats were deprived of the drug, and then tested for reinstatement of drug-seeking behavior after exposure to various stressful stimuli. The authors found that intracerebroventricular infusions of leptin attenuated the acute relapse to heroin seeking behavior induced by food-deprivation. Conversely, leptin had no effect on reinstatement induced by exposure to intermittent foot-shock or heroin-priming injections. These findings provide mechanistic insight into drug-seeking behavior, and may also help explain the high coincidence of eating disorders and substance abuse in humans.

Iron-eating enzyme

Researchers have identified the first mammalian version of ferric reductase, an enzyme essential for uptake of iron from the diet. In mammals, iron is internalized by cells in the intestinal epithelium. Dietary iron exists in a stable, but insoluble ferric (oxidized) form. In order for cells to internalize iron, they must first convert it to its ferrous (reduced) form. In the 1 February issue of *Science*, McKiet *et al.* report the identification of a mouse gene, *Dcytb*, expressed on the membranes of cells lining the small intestine. The protein catalyzes the conversion of ferric iron to the usable ferrous state, which is then transported into cells by the membrane-bound divalent cation transporter DCT1. As might be expected for a key component of dietary iron uptake, *Dcytb* expression is increased under conditions of dietary iron deficiency. Ferric reductases have been identified in bacteria, yeast and plants, but the sequence of this first mammalian version of the enzyme suggests it may have evolved independently. These findings represent an important advance in our understanding of mammalian iron uptake and may point to future therapies for iron-deficiency diseases.

Chemokines as metastatic agents

Chemokines and their receptors play a well-known role in HIV pathogenesis, but new studies indicate they are also involved in the homing of breast cancer metastases to target organs. In the 1 March issue of *Nature*, Mueller *et al.* report that human malignant breast tumors and metastases express high levels of two chemokine receptors, CXCR4 and CCR7. The authors found that the ligands for these receptors, CXCL12 and CCL21, are highly expressed in lung, lymph nodes, liver and bone—common sites of breast cancer metastasis. Treatment of cultured breast cancer cells with these ligands induced actin polymerization and pseudopodia formation, leading to chemotaxis and invasion. Importantly, antibodies that disrupt CXCR4 signaling dramatically reduced the spread of tumor cells to lung and lymph nodes in a mouse model of breast cancer, indicating that chemokine antagonists might be used to prevent metastasis in patients. Other types of cancers also appear to use the same metastatic mechanism, as Mueller *et al.* observed that melanoma cells express high levels of chemokine receptors.

Fat-busting fragment

Scientists have discovered that the protein fragment gAcrp30 (adipocyte complement-related protein of 30 kD), which is secreted exclusively by fat cells, can cause substantial weight loss in mice fed a high-calorie diet. Importantly, the fragment appears to have a novel pharmacological mechanism of action compared with obesity drugs currently on the market. In the 13 February issue of *PNAS*, Freubis *et al.* report that injection of gAcrp30 into mice fed a diet high in fat and sugar caused substantial weight loss compared with controls. They took post-prandial measurements of plasma triglycerides, glucose and free

fatty acid and showed that gAcrp30 markedly reduced the plasma levels of these substances. Some of the newer anti-obesity drugs, such as Orlistat, block fat absorption from the gut. The team

tested whether gAcrp30 worked in a similar manner by injecting animals with a bolus dose of a fat emulsion, which bypasses the intestine. They found that gAcrp30 accelerates the clearance of free fatty acids by increasing fatty acid oxidation in muscles.

As muscle tissue accounts for 25% of body weight in humans, even moderate increases in free fatty acid oxidation have important consequences for overall energy utilization and therefore weight loss.

Antigen persistence in HIV resistance

A counter-intuitive observation—that prostitutes who were previously resistant to HIV become infected after a reduction in sex work—may have important implications for vaccine design. The study focused on small group of Kenyan sex workers that have been exposed to HIV on a regular basis but remained uninfected for up to 15 years. This ongoing resistance has been associated with the maintenance of a circulating HIV-1-specific cytotoxic T-lymphocyte (CTL) population, which kills infected cells and produces antiviral cytokines. In the February issue of *The Journal of Clinical Investigation*, Kaul *et al.* report that nine of the HIV-resistant women underwent seroconversion after a reduction in sex work over the previous

year. Maintenance of a circulating HIV-1-specific effector CTL population depends on an ongoing antigenic stimulus, and a loss of HIV-specific CTLs was observed in women who either stopped sex work temporarily or reduced the number of clients. HIV-specific effector responses fluctuate, depending on level of antigen exposure, and the authors suggest that ongoing exposure may be necessary to maintain a protective CTL response. The findings point to future strategies for vaccine design, in that the maintenance of HIV immunity may require ongoing antigenic priming.

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