



genic AAPDs—risperidone, ziprasidone, and aripiprazole—did not.

To investigate the mechanism by which orexigenic AAPDs influence AMPK, the scientists assessed the drugs' effects on receptors in the brain. While these agents did not alter binding of molecules such as leptin that are involved in appetite regulation, the AAPDs did block the histamine H1 receptor, which mediates histamine's inflammatory effects during allergic responses. The investigators observed that, like clozapine—an H1 receptor antagonist stimulated AMPK—histamine decreased AMPK stimulation, an effect that could be reversed by clozapine. Furthermore, AMPK activity quadrupled in mice given clozapine, but the drug had no effect on AMPK in knockout mice lacking the H1 receptor.

Although a number of studies have suggested some role for serotonin, nor-

epinephrine, and dopamine in the development of obesity in patients taking medications for psychiatric conditions, the new findings establish that orexigenic AAPDs act via histamine H1 receptors and AMPK, the authors wrote.

NEXT STEPS

Fortunately, AAPDs' weight gain effects are not related to their therapeutic effects and researchers are optimistic that they will find ways to get around the drugs' propensity to stimulate appetite. The drug recognition sites of dopamine and histamine receptors are different, so developing new antipsychotic drugs that do not block H1 receptors is one option. Another potential strategy could involve giving a drug that mimics histamine and stimulates the receptors as an adjunct or antidote, said Snyder. Yet another ap-

proach is targeting other molecules that affect histamine production while simultaneously administering antipsychotics. Pharmaceutical companies are looking into these various strategies, said Snyder.

The study's findings may have implications for other classes of drugs that can cause significant weight gain, such as antidepressants. One obvious question that arises from the study, said Snyder, is the effect on weight of allergy drugs taken specifically to block the histamine receptors. People who take certain antihistamines for a long period do often gain weight, but most individuals only take small doses of these drugs for short periods, he explained.

In future studies, Snyder and colleagues plan to continue exploring drug-related weight gain in animal models and to further investigate AMPK's role in regulating appetite. □

Prescription Drug Abuse Rises Globally

Bridget M. Kuehn

WORLDWIDE ABUSE OF PRESCRIPTION drugs will soon exceed illicit drug use, warned a United Nations panel charged with monitoring global patterns of drug abuse.

In its 2006 report, the International Narcotics Control Board (INCB), based in Vienna, Austria, noted that medications containing narcotic or psychotropic drugs are becoming the drugs of choice for many abusers, and that drug traffickers are responding to the demand through increased diversion and the production of counterfeit drugs (http://www.incb.org/incb/en/annual_report_2006.html).

The problem is particularly acute in the United States, where cannabis is the only illicit drug that is more widely abused than prescription drugs, including analgesics, stimulants, sedatives, and tranquilizers, according to the INCB. Between 1992 and 2003, the

number of US individuals abusing prescription drugs increased from 7.8 million to 15.1 million.

Demand for prescription drugs for the purpose of abuse is fueling the production of counterfeits. In North America, such demand has led to the distribution of counterfeit oxycodone containing illegally produced fentanyl. In developing countries, where poverty and lack of access to health care force many to seek medications on the black market, 25% to 50% of medicines consumed may be counterfeit, according to World Health Organization estimates (*Counterfeit Medicines*. Geneva, Switzerland: World Health Organization; 2006. Fact Sheet 275).

Growing use of the Internet as a global drug market has also made increasing amounts of prescription drugs and their counterfeit counterparts available for abuse, according to the report.

The consequences of such abuse can be serious. Increasing numbers of

deaths associated with abuse of narcotics such as fentanyl and oxycodone are being reported in the United States and Europe, according to the report.

"What abusers do not realize is that abuse of prescription drugs can be more risky than the abuse of illicitly manufactured drugs," said Philip O. Emafo, MD, president of INCB, in a statement. "The very high potency of some of these synthetic narcotic drugs available as prescription drugs presents in fact a higher overdose risk than the abuse of illicit drugs."

Another worrisome trend described in the report is growing abuse of prescription anorectics, stimulants with an appetite-suppressing effect that are used in the treatment of obesity, narcolepsy, or attention deficit disorder. Emafo explained this trend is being driven by an obsession with thinness in some societies. Use of these drugs is highest in the Americas, particularly in Brazil. □