Cannabinoids keep on giving

Endocannabinoids are versatile molecules, regulating a variety of functions in the body. Daniele Piomelli explores how recent clinical trials testing rimonabant, an inhibitor of endocannabinoid signaling, for weight loss emerged from studies of individuals with schizophrenia; such trials have spurred basic research into how endocannabinoids affect both energy use and mood. Beat Lutz and Krisztina Monory examine how rimonabant might prove useful for preventing the development of adult epilepsy in response to fever-induced seizures in infants and young children.

■ BEDSIDE TO BENCH

The element of surprise

Daniele Piomelli

When scientists at French pharmaceutical firm Sanofi-Synthélabo looked at the data from their first clinical trial of rimonabant[1]—a new investigational drug they thought might be effective in the treatment of schizophrenia—they were in for a surprise. They had developed rimonabant with the intent of blocking the receptors activated by Δ^9-tetrahydrocannabinol (THC), the psychoactive constituent of cannabis, thereby neutralizing the activity of endocannabinoids, a recently discovered family of endogenous cannabis-like substances[2]. The researchers suspected that excessive production of these compounds in the brain, or perhaps an increased sensitivity of their attending CB_1 receptors, could explain the delusions, hallucinations and loosening of associations experienced by many people with schizophrenia.

It was a bold idea. Evidence that the brain generates its own cannabis-like neurotransmitters had been provided only a few years before, and still little was known about the function of these substances[2]. The main clues that the investigators could rely on were those supplied by cannabis itself, whose psychoactive properties had long been known. In fact, the first clinical description of such properties had been published in 1845 by psychiatrist Jacques-Joseph Moreau (1804–1884) who, working at a Parisian hospital not far from Sanofi's present headquarters, had identified most hallmark features of cannabis intoxication, including the sensory alterations and hallucinations produced by high doses of the drug[3].

Daniele Piomelli is at the Department of Pharmacology, MedSurge II, University of California, Irvine, California 92697-4625, USA and the Unit of Drug Discovery and Development, Italian Institute of Technology, via Morego 30, Genova I-161631, Italy.
e-mail: piomelli@uci.edu

It was the apparent similarity of these effects to certain symptoms of schizophrenia that caught the attention of scientists at Sanofi. They reasoned that if an overactive endocannabinoid system is involved in psychotic delusions, tempering this activity with rimonabant could provide a novel antipsychotic mechanism—the first in decades—and open up the lucrative schizophrenia market to their company.

It did not work out as anticipated. When the trial's code was broken, the results showed that subjects receiving rimonabant were not doing better than those receiving placebo. This disappointment was tempered, however, by an unexpected result that would spawn a flurry of research, from basic to clinical and back to basic. This research would eventually transform our outlook on the function and therapeutic implications of the endocannabinoid system.

What surprised the investigators was that many subjects taking the drug had lost weight. What caused this unexpected weight loss? No simple answer was available at that time. Surely, the ability of THC to stimulate appetite was already recognized, and evidence from experiments in rats had suggested that rimonabant could reduce food intake[4], pointing to the possibility that endocannabinoid circuits in the brain might be involved in feeding regulation. But the decreased food consumption caused by rimonabant disappeared after a few days of repeated drug administration[4], and such rapid loss of efficacy did not match the persistent weight-reducing effects of the drug observed in rats and people. Despite this discrepancy, the weight loss seen in the schizophrenia trial was strong enough to convince the company (by then, Sanofi-Aventis) to start clinical studies in obesity and eventually launch a series of placebo-controlled trials that involved over 6,600 overweight and obese subjects[5–9]. This clinical program, dubbed RIO (Rimonabant in Obesity) would beget another surprising finding.

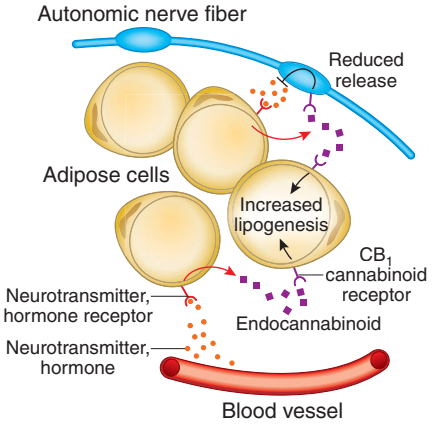

Figure 1 Fatty signals. Hormones derived from blood or neurotransmitters released from autonomic nerve endings activate receptors on the surface of adipose cells in white fat, stimulating the production of endocannabinoids. These lipid-derived mediators act on cannabinoid receptors located on the same cells—to stimulate lipogenesis—or on nerve endings—to regulate autonomic outflow to fat.

The new surprise was that subjects taking a daily 20 mg/kg dose of rimonabant not only lost a significant amount of body weight (the primary efficacy endpoint of the trial) but also showed marked improvements in waist circumference (an indicator of intra-abdominal fat), high-density lipoprotein cholesterol, triglyceride, fasting glucose and insulin levels, and prevalence of metabolic syndrome (which increases risk of cardiovascular disease and type 2 diabetes). Importantly, these effects exceeded those attributable to weight loss alone, suggesting that rimonabant might do more than just counter brain endocannabinoid signals governing food intake.

Intrigued by this possibility, scientists in Italy and Germany used mutant mice lacking CB_1 receptors to examine the functions served by the endocannabinoids in energy balance[10]. The

researchers quickly noticed that CB_1-null mice ate less than wild-type controls, thus confirming the importance of CB_1-mediated signals in the control of feeding[10]. However, closer analyses revealed that adult CB_1-null mutants gained less weight than did their wild-type littermates, irrespectively of the quantity of food they ate. This was consistent with the mismatch previously observed between the anorexic and weight-reducing effects of rimonabant[4], implying that the lean CB_1-null phenotype could be explained by a deficit in a feeding-independent mechanism that normally stimulates energy storage.

What mechanism? We still don't know for sure, but experiments have shown that adipose cells generate endocannabinoids, express CB_1 receptors and respond to CB_1-receptor activation with enhanced lipogenesis[10]. Thus, a plausible scenario is that endocannabinoid substances produced by adipocytes under the influence of autonomic or hormonal activity act as paracrine messengers within white fat to promote lipid storage (**Fig. 1**). It's this localized anabolic response, which appears to be overactive in obese subjects[11], that may be the primary target of rimonabant's antiobesity actions. Notably, a similar endocannabinoid-mediated mechanism may also participate in alcohol-induced hepatic steatosis[12]. These new data, along with the clinical effectiveness of rimonabant, have encouraged pharmaceutical firms to follow in Sanofi's steps and develop their own CB_1 antagonists.

In the RIO trials, rimonabant was generally well tolerated, and most of its side effects—nausea, back pain and arthralgia[5–9]—were anticipated from its anticannabinoid activity[2]. Nevertheless, some subjects complained about mood deterioration, and many quit the trials because they felt anxious or depressed[5–9].

These psychiatric events are probably linked to what seems to be a basic function of the endocannabinoid system in the brain—the control of emotional responses to stress. We still don't understand how the different components of the endocannabinoid system—the cannabinoid receptors and their two main ligands, anandamide and 2-arachidonoylglycerol—cooperate to regulate emotion. What seems to be reasonably well documented, however, is that drugs that selectively stop anandamide deactivation and boost its activity enhance stress-coping behavior in animals[13,14]. Do rimonabant's blues arise from its blocking action on an antistress mechanism mediated by anandamide? It's not known, but clinical trials of anandamide deactivation inhibitors in pain and anxiety, which were recently started, may soon provide an answer.

Concerns about the side effects of rimonabant have halted the approval of the drug in the United States and hindered its clinical success in countries where it is approved. Such difficulties underscore the risk of pursuing first-in-class drugs—that is, drugs that are aimed at new targets and uncharted disease mechanisms. Nonetheless, the remarkable impact that rimonabant has had on both basic research and drug development reminds us that the pursuit of such drugs is the true *raison d'être* of the pharmaceutical industry, without which the industry would lose its soul[15].

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■ BENCH TO BEDSIDE

Soothing the seizures of children

Beat Lutz & Krisztina Monory

Seizures induced by fever affect 3–5% of infants, with potential long-term consequences[1]. Evidence is accumulating that prolonged or focal febrile seizures in children between the ages of six months and five years are associated with the development of intractable temporal lobe epilepsy. Understanding how febrile seizures induce long-term changes that lead to decreases in seizure threshold has remained a central issue for the development of treatment strategies for epilepsy.

Several lines of evidence, including a recent study in the *Journal of Neuroscience*[2], have pointed to the involvement of endocannabinoids in this process.

The rodent model presented in this study suggests that the endocannabinoid system gets activated at times of high fever in the brain. Such acute activation leads to a decreased release of the inhibitory neurotransmitter, γ-aminoburyric acid (GABA), in a prolonged manner. This change in GABA transmission in turn increases the excitability of neurons, which in the long run may lead to the development of epilepsy. The findings suggest that drugs that counteract endocannabinoid signaling, such as rimonabant, an antagonist of the CB1 cannabinoid receptor, may thwart the development of longer-term complications in response to febrile seizures.

This conclusion did not seem intuitively obvious at first. That's because previous work has suggested that in a model of temporal lobe epilepsy, endocannabinoids decrease neuronal excitability[3].

Endocannabinoids act as retrograde signaling molecules at synapses, suppressing the transmission of both GABA and glutamate[4]. This discovery has drawn considerable attention from researchers who study epilepsy, given that seizures are caused by a loss of balance between the stimulatory glutamate and the inhibitory GABA. The origins of seizures, from mutations to head injury, might be diverse, but the results are similar—uncontrolled neuronal firing resulting from excess stimulation (through glutamate) and reduced inhibition (through GABA).

The effects of endocannabinoids are mediated by presynaptically localized CB_1 cannabinoid receptors; these receptors suppress

Beat Lutz and Krisztina Monory are in the Department of Physiological Chemistry, Johannes Gutenberg University Mainz, Duesbergweg 6, 55099 Mainz, Germany.
e-mail: blutz@uni-mainz.de