Endogenous cannabinoids: a new target in the treatment of obesity

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THE RECENT DISCOVERY OF CANNABINOID receptors and their natural ligands, the endocannabinoids, within the central nervous system (3, 4, 14, 15) has provoked an accelerating program of research to uncover the physiological roles of these systems. An important tool in that effort has been the Sanofi compound SR141716, a selective antagonist of the CB1 cannabinoid receptor that is widely expressed throughout the brain (18).

Clues as to the possible normal roles of endocannabinoids are present in the well-documented pharmacological actions of marijuana-derived exogenous cannabinoids, such as Δ⁹-tetrahydrocannabinol (Δ⁹-THC). Among the established behavioral actions of Δ⁹-THC is the stimulation of eating (12), an effect that has been exploited in the treatment of appetite and body weight loss in AIDS and cancer patients (16). Following that lead, two seminal studies by Sanofi scientists investigated the consequences of CB1 receptor blockade on feeding behavior (1, 19). Those studies demonstrated that SR141716 can reliably suppress food intake in laboratory species, indicating for the first time that tonic endocannabinoid activity may be a key component in the neurochemical regulation of appetite. That role has since been supported by the demonstration that the endocannabinoids anandamide and 2-arachidonoyl glycerol (2-AG) will, like Δ⁹-THC, stimulate feeding via agonist actions at CB1 receptors (9, 10, 13, 21). Additionally, brain levels of anandamide and 2-AG have been found to change in relation to fasting or the expression of feeding behavior (13) and to be upregulated in genetically obese, hyperphagic rodents with defective leptin signaling (5).

Studies using a variety of behavioral paradigms indicate that endocannabinoids may play a very specific role in appetite control. In particular, there is strong evidence that they are linked to the reward processes that mediate the incentive or hedonic value of food. Indeed, Sanofi’s original studies reported that SR141716 preferentially attenuated ingestion of highly palatable foods (1, 19). Subsequently, CB1 agonists or antagonists have been shown to, respectively, increase or decrease the motivation to work for palatable ingesta (6–8). Cannabinoids appear to directly stimulate eating by actions on appetitive processes, making food stimuli more salient and can rapidly induce eating even in satiated animals (23). Importantly, cannabinoid activity may also modulate consummatory aspects of eating motivation to enhance food palatability, possibly via interactions with endogenous opioid peptides (11, 22).

The behavioral actions of CB1 receptor ligands are thus unusual in the field of feeding research, and drugs such as SR141716 may offer a unique opportunity to develop new pharmaceutical approaches to the management of obesity, supported by a previous report that SR141716 can reduce body weight gain (2). Traditionally, antiobesity compounds have attempted to limit food consumption by targeting satiation mechanisms. The efficacy of that approach in sustaining weight loss can be undermined by people’s natural sensitivity to the appetizing properties of an enormous variety of readily available, highly palatable and energy-dense snack foods. Blockade of systems that actively instigate feeding and that regulate the appeal and palatability of such foods could thus be a highly effective alternative strategy in preventing overconsumption, reducing body weight and maintaining weight loss. It is in this context that the studies reported in this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology by Ravinet-Trillou and colleagues (17) have particular significance. This group has previously shown that SR141716 suppresses food intake in genetically obese Zucker rats (1), but in this latest study they assessed the antagonist’s effect in a model—diet-induced obesity—that more realistically reflects the most common cause of human obesity.

In the study, mice that were made obese simply through the provision of a high-fat diet were treated chronically with a daily oral dose of SR141716 over 5 wk. Compared with control animals fed the same high-calorie diet, the drug produced an initial, profound suppression of energy intake, with a concomitant re-
duction in body weight. Although the anorectic potency of the drug declined somewhat after the first week of treatment, an impressive 20% weight loss (and 50% reduction of adiposity) was maintained throughout the course of the experiment. Importantly, the persistent weight loss was accompanied by a restoration of plasma leptin, insulin, and free fatty acid toward the levels found in lean mice fed a normal diet. Additionally, in fasted, antagonist-treated animals, weight loss was accentuated, insulin resistance was corrected, and hyperglycemia was restored to levels observed in lean mice.

These data indicate that SR141716 not only targets the motivational mechanisms that regulate food intake, but can also induce advantageous metabolic changes to potentiate and sustain weight loss, even in animals maintained on a caloricly dense high-fat diet. The implications of these findings are obvious, both for understanding the role of endocannabinoids in appetite control and for the development of cannabinoid-based antiobesity applications. The results of clinical trials with SR141716 are eagerly awaited.

REFERENCES