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METABOLIC DISORDERS

Safe cannabinoid receptor modulators in sight?

The endocannabinoid system is involved in the regulation of appetite and is overactive in obesity. Although pharmacological blockade of cannabinoid receptor 1 (CB1R) has emerged as an effective anti-obesity strategy, the risk of adverse neuropsychiatric effects has halted development of agents in this class. Now, writing in *Cell Metabolism*, Tam and colleagues identify a peripherally selective CB1R inverse agonist that safely and effectively reduces body weight in a mouse model of obesity without affecting behaviour.

The endocannabinoids anandamide and 2-arachidonoylglycerol are lipid mediators that elicit a broad range of effects via G protein-coupled CB1Rs and CB2Rs. CB2Rs are found in the immune system and haematopoietic cells, whereas CB1Rs are most densely expressed in the central nervous system but are also located in the peripheral nervous system and peripheral organs. It is generally thought that the hyperphagic actions of endocannabinoids are mediated by CB1Rs located in the brain. However, recent studies have suggested that peripherally located CB1Rs are also likely to be involved. The authors therefore set out to explore the metabolic effects of specific modulation of peripheral CB1R.

To do this, they modified the structure of the CB1R inverse agonist SLV139 (ibipinabant), the development of which was discontinued in 2008, to reduce its brain penetrance. The resulting compound, JD5037, exhibited high affinity and specificity for peripheral CB1Rs, was unable to cross the blood–brain barrier in amounts sufficient to occupy CB1R in the brain, and had no effects on behaviour of mice.

Next, the authors investigated the anti-obesity effects of their agent. Daily oral dosing of diet-induced obese (DIO) mice with JD5037 or SLV139 for 28 days resulted in equal reductions in food intake, body weight and adiposity compared to control mice. The two compounds were also equally effective in reversing hepatic steatosis, normalizing blood glucose and insulin levels, attenuating glucose intolerance and insulin resistance and improving plasma lipid profiles.

However, although JD5037 improved metabolic parameters in two additional mouse models of obesity — *ob/ob* mice, which are deficient in leptin (an adipocyte-secreted hormone that acts on hypothalamic receptors to reduce food intake), and leptin receptor-defective *db/db* mice — the agent had no effect on food intake, body weight or adiposity, suggesting that these effects are leptin-dependent. Indeed, similar effects were seen in DIO mice that were treated with a leptin antagonist prior to JD5037.

DIO mice characteristically exhibit hyperleptinaemia and associated leptin resistance — features that commonly accompany obesity in humans. Interestingly, further experiments revealed that JD5037 normalized leptin levels in DIO mice by decreasing adipocyte secretion and increasing kidney clearance of leptin. This reversal of hyperleptinaemia positively correlated with the reduction in food intake and body weight in DIO mice, and resulted in full restoration of their leptin sensitivity.

Together, these findings suggest that peripherally restricted CB1R inverse agonism may represent a safe and effective anti-obesity strategy. Given the ability of JD5037 to reverse leptin resistance, this approach may not only promote but also maintain weight loss, which is a key challenge in obesity therapy.

Sarah Crunkhorn

ORIGINAL RESEARCH PAPER Tam, J. *et al.* Peripheral cannabinoid-1 receptor inverse agonism reduces obesity by reversing leptin resistance. *Cell Metab.* **16**, 167–179 (2012)