CB₁'s peripheral vision

By Tim Fulmer, Senior Writer

In 2007 an FDA panel recommended against approval of **sanofi-aventis Group's** Accomplia rimonabant for obesity. Neurological safety concerns arose due to increased levels of seizures and suicidality in patients taking the cannabinoid CB₁ receptor antagonist.¹ Now, U.S. and European researchers have found that restricting CB₁ receptor antagonists to non-CNS tissue could avoid such side effects.²

Cannabinoid CB₁ receptors occur in higher numbers in the CNS than in peripheral tissues.³ As noted by several FDA panelists at the time, CB₁ receptor antagonists that do not cross the blood-brain barrier may be a solution to their undesirable side effects.

As reported in the *Journal of Clinical Investigation*, George Kunos, a senior investigator at the **National Institute on Alcohol Abuse and Alcoholism**, and colleagues investigated cannabinoid CB₁ receptor signaling in mice exposed to a high-fat diet.

The study shows that wild-type mice on a high-fat diet had greater expression of cannabinoid CB₁ receptor in their livers than wild-type mice fed a normal diet. Fat-fed wild-type mice also developed glucose intolerance and insulin resistance, whereas mice with global or liver-specific CB₁ receptor knockouts were protected from diet-induced metabolic dysregulation.

Although the liver-specific knockouts did not lose weight, they did show decreases in fatty liver, as well as lower serum levels of leptin, insulin, triglycerides and low-density lipoprotein cholesterol compared with what was seen in wild-type mice on a high-fat diet.

The authors concluded that liver-specific knockout of CB₁ receptors "led to a dissociation of obesity from insulin and leptin resistance induced by a high-fat diet."

Thus, Kunos told *SciBX*, "our study suggests that restricting cannabinoid CB₁ receptor antagonists to the peripheral organs by preventing their passage into the CNS could influence leptin and insulin signaling and thus potentially treat some metabolic disorders. Importantly, this would minimize the risk of CNS side effects associated with cannabinoid receptor antagonists used to treat obesity in humans."

Kunos did note that side effects such as diarrhea and GI upset could persist "to the extent those symptoms are due to blockade of CB₁ receptors in the gut that normally act to inhibit GI motility and secretion."

Now, said Scott Friedman, professor of medicine and chief of the Division of Liver Diseases at **Mount Sinai School of Medicine**, "the remaining challenge is to develop CB₁ receptor antagonists that target peripheral

organs like the liver and that don't cross the blood-brain barrier when administered intravenously."

"Pharmaceutical developers could be faced with choosing between global CB₁ receptor antagonists that target both the CNS and periphery and restricted CB₁ receptor antagonists that target only peripheral tissue," said Uberto Pagotto, a professor of medicine at the **Santa Orsola-Malpighi General Hospital** who is studying the role of endocannabinoid signaling in metabolic disease. "Based on the *JCI* findings, the latter approach may hold more promise in at least some metabolic disorders."

Peripherals

Kunos told *SciBX* his group is designing peripherally restricted CB₁ receptor antagonists. "Manipulation of molecular parameters like lipid solubility should allow us to design CB₁ receptor antagonists with minimal tendency to partition into the CNS," he said.

The knockout mouse data in the *JCI* paper suggest that fatty liver is a good starting indication. "Our findings suggest that peripherally restricted CB₁ receptor antagonists could help treat fatty liver disease and thus slow or prevent progression to more serious hepatic conditions like liver fibrosis and cirrhosis," noted Kunos.

Kunos' group already had shown that activation of CB₁ receptors in liver contributed to the development of steatosis (fatty liver) in mice chronically exposed to alcohol.⁴

Current standard of care for fatty liver is typically some combination of weight loss, exercise, avoidance of alcohol and, in more severe cases, corticosteroids to help treat hepatic inflammation.

Beat Lutz, a principal investigator on the *JCI* paper, said work is ongoing to generate mice with CB₁ receptor knockout in adipose and muscle tissue. The goal is to design a repertoire of tissue-specific CB₁ receptor knockout models, with the aim of "getting an idea of the complexity of the CB₁-dependent regulation of cellular processes in different organs and tissues and to see how these tissues and cell types interact with each other," he said.

Lutz is professor of physiological chemistry at **The Johannes Gutenberg University of Mainz**.

Although peripherally acting CB₁ receptor antagonists might have safety advantages over globally acting antagonists, the former are unlikely to entirely replace the latter, said Pagotto.

Cannabinoid CB₁ receptors in the hypothalamus modulate appetite,⁵ whereas the receptors in peripheral tissues are thought to modulate metabolism. Thus, restricting cannabinoid CB₁ receptor inhibition to the periphery is likely to have diminished efficacy in obesity.

"These two groups of antagonists would not be exactly competitive," said Pagotto. "This is because peripherally acting CB₁ receptor antagonists do not have a clear antiobesity effect, at least at the doses studied in the *JCI* paper. Thus, globally acting CB₁ antagonists could still be the primary option for reducing weight, while peripherally acting antagonists might be ideal for treating metabolic syndromes like dyslipidemia and insulin resistance, as well as fatty liver."

sanofi-aventis declined to comment, but the company is clearly looking to broaden the use of rimonabant into multiple metabolic indications.

Table 1. Targeting CB₁ receptor. Selected compounds targeting the cannabinoid CB₁ receptor to treat metabolic disorders, including diabetes and obesity.

Company	Compound	Description	Status (indication)
sanofi-aventis Group (Euronext:SAN; NYSE:SNY)	Acomplia rimonabant	CB ₁ receptor antagonist	Marketed in Europe (obesity); Phase III (diabetes)
Merck & Co. Inc. (NYSE:MRK)	Taranabant (MK-0364)	CB ₁ receptor inverse agonist	Phase III (obesity)
Pfizer Inc. (NYSE:PFE)	CP-945,598	CB ₁ receptor antagonist	Phase III (obesity)
sanofi-aventis	AVE1625	CB ₁ receptor antagonist	Phase II (diabetes)
Solvay S.A. (Euronext:SOLB)/ Bristol-Myers Squibb Co. (NYSE:BMJ)	SLV319 (BMS-646256)	CB ₁ receptor antagonist	Phase II (obesity)
GW Pharmaceuticals plc (LSE:GWP)	THCV	CB ₁ and CB ₂ receptor antagonist	Phase I (dyslipidemia)
Vernalis plc (LSE:VER)	V24343	CB ₁ receptor antagonist	Phase I (obesity)
Acadia Pharmaceuticals Inc. (NASDAQ:ACAD)	CB ₁ program	CB ₁ receptor antagonist	Preclinical (obesity)
7TM Pharma A/S	TM38837	CB ₁ receptor antagonist	Preclinical (obesity and diabetes)

Despite the FDA panel snub, rimonabant is approved for obesity in more than 35 countries. The company also has two ongoing Phase III trials of rimonabant to treat nonalcoholic steatohepatitis in patients with and without type 2 diabetes.

In rat models of obesity, the drug minimized hepatic steatosis compared with what was seen in rats that received vehicle control.⁶

There are at least six globally acting cannabinoid CB₁ receptor antagonists or inverse agonists in clinical development (see Table 1, “Targeting CB₁ receptor”).

Other indications

The JCI findings could also be of interest to companies developing cannabinoid CB₁ receptor agonists for pain and cachexia. Indeed, a key question, said Steven Heymsfield, global director of scientific affairs at Merck & Co. Inc.’s Merck Research Laboratories, is whether agonists like tetrahydrocannabinol (THC) in fact lead to hepatic steatosis or insulin resistance.

The labels of two marketed cannabinoid receptor agonists—Sativex sublingual cannabis extract spray from GW Pharmaceuticals plc and Cesamet nabilone from Valeant Pharmaceuticals International—make no mention of liver-related side effects.

Merck’s taranabant (MK-0364), a centrally acting cannabinoid CB₁ receptor inverse agonist, is in Phase III trials to treat obesity.

In a 12-week Phase II trial in 533 patients with a body mass index

between 30 and 43, taranabant increased weight loss compared with the effect of placebo at all doses studied.⁷

Patients with a history of psychiatric illness were excluded from the trial. Nevertheless, researchers observed a dose-related trend in psychiatric-related side effects, with about 27% of patients at the highest dose reporting symptoms including anxiety, depression and insomnia.

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COMPANIES AND INSTITUTIONS MENTIONED

GW Pharmaceuticals plc (LSE:GWP), Salisbury, U.K.
The Johannes Gutenberg University of Mainz, Mainz, Germany
Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.
Mount Sinai School of Medicine, New York, N.Y.
National Institute on Alcohol Abuse and Alcoholism, Rockville, Md.
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