Peripheral CNR1 antagonists to the fore

By Michael J. Haas, Senior Writer

In the three years following an FDA panel recommendation against approval of **sanofi-aventis Group's** Acomplia rimonabant to treat obesity due to severe neurological side effects, centrally acting inhibitors of cannabinoid CB₁ receptor have all but disappeared from development. Now, researchers at the **NIH** and **Northeastern University** have taken the CNS out of the equation by showing that a peripheral inhibitor of the receptor treated obesity and related metabolic disorders without eliciting neurological side effects in mice even though it could not enter the CNS.¹

The NIH group is now working with **Jenrin Discovery Inc.**, which has a number of peripheral cannabinoid CB₁ receptor (CNR1) inhibitors in preclinical development. The company hopes to select a lead compound to treat diabetes or liver disease.

CNR1 is expressed in the brain, where it regulates appetite, and in peripheral tissues such as the liver, pancreas, skeletal muscle and fat, where it regulates lipogenesis and other metabolic processes. A number of pharma companies developed brain-permeable CNR1 inhibitors for obesity, including rimonabant and **Merck & Co. Inc.'s** taranabant (MK-0364). The problem was that the efficacy of the compounds could not be separated from severe CNS side effects. As a result, all of the inhibitors had been discontinued by 2008.

But also that year, clues began to emerge that CNR1 inhibitors may not need to cross the blood brain barrier to elicit therapeutic effects. Researchers led by George Kunos showed that liver-specific knockout of *Cnr1* protected obese mice from diet-induced insulin resistance, hepatic steatosis (fatty liver) and other metabolic disorders.² Kunos is scientific director and chief of the laboratory of physiologic and pharmacologic studies at the NIH's **National Institute on Alcohol Abuse and Alcoholism** (NIAAA).

Kunos' group reasoned that selective inhibition of peripheral CNR1 could help treat metabolic disorders without inducing psychiatric side effects^{2,3} but lacked molecules with which to test the hypothesis. Then his team heard about a peripherally restricted rimonabant analog (AM6545) from Alexandros Makriyannis, professor of biotechnology and bioorganic chemistry and director of the Center for Drug Discovery at Northeastern.

In its report in *The Journal of Clinical Investigation*, the NIH-Northeastern team has now shown that treatment with AM6545 resulted in at

least 14-fold lower levels of the compound in the brains of normal mice than treatment with comparable doses of rimonabant. AM6545 did not elicit behavioral side effects associated with inhibition of CNR1 in the brain such as catalepsy, hypomotility and hypothermia.

At the same time, compared with rimonabant, AM6545 produced similar improvements in dyslipidemia, insulin resistance and hepatic steatosis in two mouse models of obesity: wild-type mice fed a high-fat diet and leptin-deficient mice fed a high-fat diet.

Peripheral advances

"There was the general perception that 100% of the weight loss induced by rimonabant resulted from the drug's inhibition of CNR1 in the brain and consequent suppression of appetite," said John McElroy, founder, president and CSO of Jenrin. "In fact, many people believed that all benefit in diabetes, lipid profile or liver disease was secondary to CNS-mediated weight loss. George Kunos has definitely blown this belief out of the water by showing that blockade of peripheral CNR1 is sufficient to have therapeutic benefit in diabetes, liver disease and dyslipidemia independent of its effects on weight."

Although the *JCI* findings showed that peripheral CNR1 inhibition induced only about half as much weight loss as rimonabant, McElroy thinks the effect was still sufficient to support treating obesity.

Moreover, he said, "by keeping CNR1 inhibitors out of the brain, you might be able to go to higher doses and see greater efficacy than was possible with rimonabant" due to its dose-limiting CNS toxicity.

McElroy added: "This greater efficacy is exactly what we have seen with our compounds in preclinical models of diabetes" and expect to see in models of weight loss as well.

Over a 28-day course of treatment, equivalent doses of AM6545 and rimonabant induced about 12% and 22% weight loss, respectively, in the wild-type mouse models of obesity compared with vehicle control. In 4 Phase III trials of rimonabant, patients taking 20 mg daily with a hypocaloric diet lost about 14 pounds after 1 year compared with patients who lost about 3.5 pounds with a hypocaloric diet plus placebo.⁴

Like rimonabant, Jenrin's peripherally selective CNR1 inhibitors are inverse agonists, which block a receptor's ligand-binding site and reverse any constitutive activity it might have. Neutral antagonists—such as AM6545—only block the ligand-binding site.

"In-house preclinical results for our compounds are consistent with those reported by Kunos, and we have not observed any side effects from long-term dosing with peripherally selective CB₁ receptor antagonists," McElroy said.

"This paper should certainly generate more interest in the target and thus in our chemistry," said Robert Chorvat, VP of chemistry at Jenrin. "We have lead compounds in three structurally diverse cores and have IP on three additional series."

Christian Elling, VP of biology and development at **7TM Pharma A/S**, agreed that the *JCI* study should renew interest in CNR1 as a target.

"We are a small company, so we will need to partner eventually to develop our peripheral CNR1 inhibitor," he said. "The paper can help us forge meaningful partnerships because it adds to growing evidence that

there is a way to target CB₁ receptors pharmacologically while avoiding the side effects” caused by rimonabant.

7TM's TM38837 has completed a Phase I trial to treat obesity and is in an ongoing Phase I trial designed to demonstrate the peripheral CNR1 inhibitor's lack of CNS exposure. The company expects to have results for the second trial by year end, Elling said.

In July the company announced results of PET imaging studies in macaques showing that TM38837 was restricted to the periphery. 7TM has also conducted preclinical studies in animal models of diabetes.

Elling said 7TM has not decided whether to pursue obesity or diabetes as a lead indication for future clinical trials of TM38837.

He added that the *JCI* study “nicely captured the effects of peripheral CNR1 inhibition on the liver and points to an opportunity to develop these inhibitors to treat liver disease. While this is not of interest to us, it is an important aspect of the findings.”

On the horizon

Kunos said his NIH group is collaborating with Jenrin on preclinical studies of an undisclosed peripheral CNR1 inhibitor from the company. Preliminary results from those studies suggest the compound might be better than AM6545 at inducing weight loss and treating metabolic symptoms.

Unlike AM6545, Kunos added, “Jenrin's compound seems to cause a small but notable reduction in food intake. If the Jenrin compound turns out to be really effective, then I'm personally interested in taking it through IND-enabling toxicology studies and Phase I or Phase II clinical studies here at NIH.”

For the company, McElroy said, “the first clinical indication will likely be diabetes or nonalcoholic hepatic steatosis” because those trials would be shorter and less expensive than obesity or dyslipidemia studies.

Apart from the Jenrin collaboration, Kunos said his team is investigating the molecular mechanisms by which activation of hepatic CNR1 causes insulin resistance in mouse models of diabetes.

Northeastern holds a patent on AM6545 and its uses.

Haas, M.J. *SciBX* 3(32); doi:10.1038/scibx.2010.972

Published online Aug. 19, 2010

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