Gift of the MAGL

By Lev Osherovich, Senior Writer

A team at **The Scripps Research Institute** has developed the first specific monoacylglyceride lipase (MAGL) inhibitor, which should help determine whether this enzyme is a better pain target than the closely related fatty acid amide dehydrogenase (FAAH).¹ Although the compound, JZL184, is not yet optimized to be a therapeutic candidate, the researchers think it could be a good research tool for further animal studies of endocannabinoid-mediated analgesia.

FAAH and MAGL are responsible for degrading the two major endocannabinoids: FAAH breaks down anandamide and MAGL catabolizes 2-arachidonylglycerol (2-AG). Compounds that block FAAH and MAGL allow the endocannabinoids to activate the cannabinoid receptors (CB receptors), which can promote analgesia and lower inflammation but can also lead to undesirable effects such as catalepsy and cognitive impairment.

Directly targeting CB receptors to treat pain has been complicated by the complex psychoactive effects of CB agonists such as tetrahydrocannabinol as well as by the distinct functions and expression patterns of the two CB receptor subtypes, CB₁ and CB₂.

An open question is what effects—either good or bad—each endocannabinoid elicits when it binds to the CB receptor in a given tissue type.² Previous efforts to answer this question have encountered specificity problems, as most compounds that inhibit MAGL also inhibit FAAH.

The development of JZL184 now enables researchers to compare the effects of inhibiting 2-AG degradation with those of blocking the degradation of anandamide. In a paper in *Nature Chemical Biology*, researchers showed that JZL184 had an IC₅₀ of 6–8 nM for MAGL *in vitro* compared with an IC₅₀ of 4 μM for FAAH.

In mice, a 5 mg/kg dose of the compound inhibited MAGL by 75% compared with what was seen in untreated controls, but it decreased FAAH activity by only about 20%. JZL184-treated mice consequently had higher, longer-lasting spikes in 2-AG levels after neuronal stimulus than mock-treated controls.

“The main novelty is that this is the first MAGL inhibitor that is sufficiently selective and efficacious to be used in living animals,” said Benjamin Cravatt, professor of chemical physiology at Scripps and lead author of the study.

“Inhibiting the MAGL enzyme gives a rapid, dramatic increase in 2-AG but not anandamide.”

“The compounds we created aren’t drugs, but they’re a proof of principle.”
—Benjamin Cravatt,
The Scripps Research Institute

Cravatt’s team has previously published a series of studies describing increasingly selective FAAH inhibitors,³ but MAGL inhibitors have thus far been elusive.

According to Cravatt, the effects of JZL184 in pain and behavior assays show that MAGL inhibition may be a better path to developing pain drugs than hitting CB₁. Indeed, mice treated with JZL184 showed less sensitivity in several pain assays compared with untreated controls. The treated animals also showed no signs of catalepsy.

These results suggest that 2-AG, which is much more abundant than anandamide, mediates the key features of endocannabinoid signaling.

“By targeting MAGL, the authors demonstrate that, similarly to anandamide, elevated levels of 2-AG are also sufficient to produce CB₁/CB₂-mediated analgesia,” said Vito Palombella, VP of drug discovery at **Infinity Pharmaceuticals Inc.**

Infinity is developing FAAH inhibitors to treat neuropathic pain and hopes to select a clinical candidate for a Phase I trial in early 2009.

Despite the potent analgesic effects that come from hitting MAGL, localized inhibition of FAAH may be a better therapeutic strategy, according to Palombella. For example, systemic JZL184 treatment induced hypomotility and hypothermia, which are undesired effects of endocannabinoid signaling.

Cravatt acknowledged the concerns about side effects outside of the CNS, noting that “some serine esterases in the periphery could be affected” by the compound. The question, he said, is whether this is due to inhibition of MAGL in the periphery or off-target effects of JZL184.

In any event, for now Cravatt sees JZL184 as a research tool for studying the role of MAGL in cannabinoid signaling. “The compounds we created aren’t drugs, but they’re a proof of principle,” he said.

The team’s next steps are to characterize the effects of JZL184 in cognitive assays and to solve the structure of MAGL complexed with JZL184 to understand how the compound achieves selectivity.

At least two other companies—**Evotec AG** and **Pfizer Inc.**—have preclinical FAAH inhibitors for pain. Meanwhile, **Pharmos Corp.**, **Cara Therapeutics Inc.** and **Glenmark Pharmaceuticals Ltd.** have preclinical CB₂ agonists to treat pain. **GlaxoSmithKline plc**’s compound 842166, a CB₂ agonist, has completed Phase II trials for dental pain. **Sativex**, a *Cannabis sativa*-derived CB₁ and CB₂ agonist from **GW Pharmaceuticals plc.**, is marketed for cancer pain in Canada and is in Phase II and III trials for neuropathic pain.

Cravatt said JZL184 is the subject of a pending patent. Scripps declined to comment on the licensing status of the compound. The institute licensed Cravatt’s previous FAAH inhibitors to Pfizer.

Osherovich, L. *SciBX* 2(2); doi:10.1038/scibx.2009.39
Published online Jan. 15, 2009

REFERENCES

- Long J. *et al. Nat. Chem. Biol.*; published online Nov. 23, 2008; doi:10.1038/nchembio.129

Contact: Benjamin F. Cravatt, The Scripps Research Institute, La Jolla, Calif.

e-mail: cravatt@scripps.edu

2. Osherovich, L. *SciBX* **1**(17); doi:10.1038/scibx.2008.399

3. Cravatt, B.F. & Lichtman, A.H. *Curr. Opin. Chem. Biol.* **7**, 469–475 (2003)

COMPANIES AND INSTITUTIONS MENTIONED

Cara Therapeutics Inc., Shelton, Conn.

Evotec AG (Xetra:EVT; NASDAQ:EVTC), Hamburg, Germany

GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.

Glenmark Pharmaceuticals Ltd. (NSE:GLENMARK; BSE:532296), Mumbai, India

GW Pharmaceuticals plc (LSE:GWP), Salisbury, U.K.

Infinity Pharmaceuticals Inc. (NASDAQ:INFI), Cambridge, Mass.

Pfizer Inc. (NYSE:PFE), New York, N.Y.

Pharmos Corp. (NASDAQ:PARS), Iselin, N.J.

The Scripps Research Institute, La Jolla, Calif.