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Fatty Pain Cures

Peter Imming[1,*]
[1]Institut für Pharmazie, Martin-Luther-Universität Halle-Wittenberg, Wolfgang-Langenbeck-Str. 4, 06120 Halle/Saale, Germany
*Correspondence: peter.imming@pharmazie.uni-halle.de
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In this issue, Alvin King, Daniele Piomelli, and colleagues publish another interesting paper on inhibition of monoacylglycerol lipase (MGL). MGL is a hot target for antinociceptive agents, being the chief degrading enzyme of the endocannabinoid 2-arachidonoylglycerol [1].

"The problem of pain" [2] has troubled everybody, often to the verge of despair. Equally troublesome and despairing have been efforts at developing analgesics. Pathways were discovered that simply must have something to do with sensing, transmitting, and realizing pain, and inhibitors were found that worked ever so well in the usual animal models of antinociception—but in humans, they apparently failed to cause or display distinct effects. In humans at least, pain is a very subjective state of perception, and that is probably why linear extrapolations from molecular to clinical effects are rarely possible. Perhaps the same biochemical events will be interpreted differently by the mind when it comes to states of consciousness like pain? To, as it were, chemically detach a patient from feeling his pain, without impairing his emotional and intellectual capacities, remains a major challenge with very likely no satisfactory solution.

Listing all known molecular targets of approved drugs [3], we identified eight whose stimulation or blockade are thought to lead to analgesia or antinociception, not counting the targets of neuroleptics and tranquilizers that have an analgetic by-effect. Against this background, new molecular targets that hold the promise of being relevant for nociception are always welcome. In this context, nociception or hyperalgesia means that even slight touches or pressures (e.g., caused by swellings or inflammation) induce pain, as opposed to pain caused by a fracture or hard blow. The endocannabinoid—or rather eicosanoid—system that has been discovered during the past years is strongly involved in basic sensory physiology including nociception.

Presently, the endocannabinoid system [4, 5] is known to consist mainly of: (1) two receptors of the G protein coupled receptor family, CB1 and CB2; (2) endogeneous ligands that are derived from arachidonic acid, like anandamide and 2-arachidonoyl glycerol (2-AG); (3) a transporter of anandamide that has escaped thorough characterization so far; and (4) hydrolases that catalyze the biosynthesis and inactivation of the ligands. 2-AG is inactivated by two or more monoacylglycerol lipases (MGL, MAGL), while anandamide is hydrolyzed by fatty-acid amide hydrolase (FAAH) and N-acylethanolamine acid amidase (NAAA).

CB receptors are supposed to be more numerous in the CNS than dopamine receptors, and they were also found in other body tissues. Endocannabinoid signaling, which is of the short-range short-term type, is strongly involved in antinociception, anxiolytic action, cell proliferation, reproduction, memory processes, and modulation of feeding [3].

Due to its abuse, it has long been known that cannabis has analgesic effects. At the moment, the following modulators of the endocannabinoid system are thought to lead to analgesic action: agonists at CB1 and/or CB2 receptors, inhibitors of FAAH, and inhibitors of MGL. The latter two interferences would work indirectly by increasing the amount of endocannabinoids.

Cause-and-effect is anything but clear with endocannabinoids. Different literature reports have shown, for instance, the CB2 receptor and 2-AG to be strongly involved in stimulation and in attenuation of inflammation and immune responses [6]. Apart from the consideration on nondeterminedness of psychopharmaceutical action, the intertwining of the CB and other pathways need to be taken

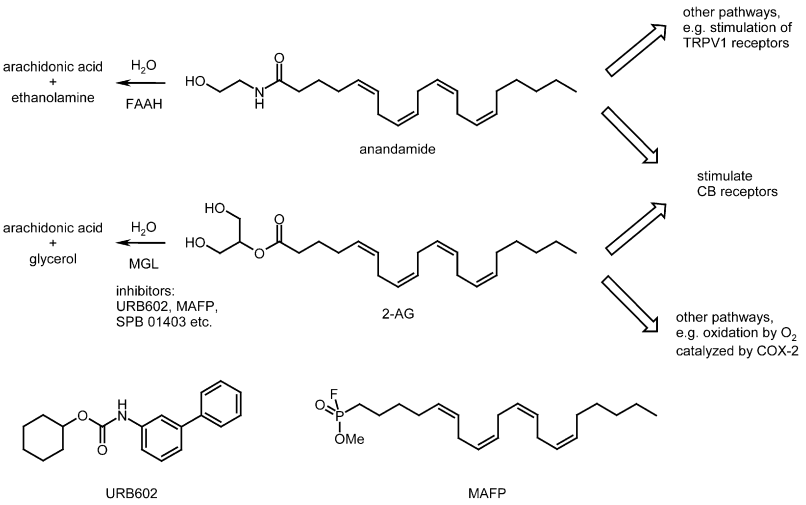

Figure 1. A Few Endogeneous and Synthetic Players of the Endocannabinoid System and a Few Hints at the Extensive Connectivity of the Arachidonates

into account (Figure 1). Receptors and enzymes should be likened to switchboards rather than switches, or to junctions rather than stops of a pathway. Blocking MGL or FAAH will, for instance, deplete the cyclooxygenase isoenzymes of some of their substrate, leading to the diminished production of prostaglandins, leukotriens, hydroxyperoxyacids, and other eicosanoids. Anandamide has also been shown to act agonistically at the vanilloid receptor, an ion channel now known as TRPV1 [7]. Whether this is of quantitative importance remains to be investigated; however, it highlights two of many biochemical "ripples" away from the simple increase of 2-AG levels through MGL inhibition.

FAAH inhibition has been studied much more intensively than MGL inhibition because MGL was characterized later than FAAH and because specific inhibitors of MGL were harder to find. MGL was found in 1976 [8], cloned in 1997 [9], and is considered as the main enzyme catalyzing the hydrolysis of 2-AG. In rats it was shown to be ubiquitous [7], in rat brain it is mainly present in axons, and in the amygdala MGL is localized presynaptically [10].

In 2007, the MGL inhibitor URB602 (biphenyl-3-ylcarbamic acid cyclohexyl ester) was shown to induce antinociception in the mouse paw and enhance the antinociceptive effects of exogenously applied 2-AG, thereby demonstrating the efficacy of an MGL inhibitor in suppressing inflammatory nociception [11]. The effect seems to be due to CB2 stimulation [12].

In this issue, King et al. [1] investigated two inhibitors of cytosolic MGL, viz. URB602 and MAFP (methylarachidonylfluorophosphonate). Both were previously shown to lead to elevated 2-AG levels and enhanced 2-AG-mediated signaling in neurons [13, 14]. However, reports on the details of the action and mechanism of URB602 and MAFP are not unequivocal, and MGL awaits thorough validation as a therapeutic target. The results of King et al. take us a step forward in showing that URB602 indeed does lead to elevated 2-AG levels in rat brain. With an IC_{50} of ~220 μM against recombinant MGL, URB602 is not effective enough to qualify as a drug, but as King et al. also showed that it is a noncovalent inhibitor, the N-arylcarbamate scaffold of URB602 makes it an attractive starting point for further pharmaceutical chemical development. The evidence that it inhibits MGL noncompetitively, however, adds a note of caution since target organisms can easier evade noncompetitive inhibitors by increasing the expression of or developing a nonbinding active mutation than to deal with competitive inhibitors.

Nonetheless, with previous work that provided some proof of concept for MGL inhibition in antihyperalgesia, the current work by King et al. that clarified mechanistic details, and with the discovery of another, more potent carbamate inhibitor of MGL (SPB 01403, n-butylcarbamic acid 4-(4,5-dihydrothiazol-2-yl)phenyl ester) [15], a hopeful new road to analgesic agents is wide open. It will involve keeping a reserve of the right fatty acid derivatives to soothe the pain. So, we better let our fat do its pharmacological work rather than consider it just a burden.

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