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COMMENTARY

Manipulation of the endocannabinoid system by a general anaesthetic

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An article appearing in this issue of the *British Journal of Pharmacology* shows for the first time that the general anaesthetic propofol inhibits one of the enzymes catalysing endocannabinoid hydrolysis and inactivation, the fatty acid amide hydrolase, thereby enhancing the brain levels of anandamide and 2-arachidonoylglycerol in mouse brain. The authors provide evidence that this effect of propofol underlies part of the sedative effects of this compound. The importance of these findings in the light of the likely role of the endocannabinoid system in the control of sleep–wake cycles, and of the possibility of developing therapeutic drugs from substances that manipulate endocannabinoid levels, is discussed.
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Abbreviations: 2-AG, 2-arachidonoylglycerol; FAAH, fatty acid amide hydrolase; OBAA, 2-octyl-γ-bromoacetoacetate; oleamide, *cis*-9-octadecenoamide

In an intriguing article in the current issue of the *British Journal of Pharmacology*, Patel and co-workers report data strongly suggesting that the general anaesthetic, propofol, owes part of its sedative properties to the capability of enhancing brain endocannabinoid levels and, subsequently, of activating *indirectly* central cannabinoid CB_1 receptors. That marijuana, as well as its major psychoactive principle and CB_1 receptor agonist, Δ^9-tetrahydrocannabinol, induce sedation has been known for decades (see Adams & Martin, 1996, for a review). However, that tonic stimulation of CB_1 by endocannabinoids could control sleep–wake cycles was suggested only by recent investigations. First, acute blockade of CB_1 with the compound known as SR141716A (rimonabant®) prolongs the time spent awake by rats (Santucci *et al*., 1996). Secondly, the endocannabinoid anandamide was found to induce sleep in these rodents (Mendelson & Basile, 1999). Finally, two endogenous sleep-inducing factors, 9-*cis*-octadecenoamide (oleamide) and 2-octyl-γ-bromoacetoacetate (OBAA), share the capability of significantly inhibiting the enzymatic hydrolysis of the endocannabinoid anandamide by the fatty acid amide hydrolase (FAAH) (see Boger *et al*., 1998, for a review). The sedative activity of these two compounds was thus ascribed, at least in part, to the capability of potentially enhancing brain anandamide levels, thus indirectly activating CB_1 receptors in brain areas deputed to the control of sleep onset and duration (Mechoulam *et al*., 1997; Boger *et al*., 1998). Accordingly, although oleamide binds to CB_1 receptors only at very high concentrations, the sleep-inducing effect of this compound is antagonized by rimonabant® (Mendelson & Basile, 1999). However, neither oleamide nor OBAA were ever shown to enhance endocannabinoid levels *in vivo*. It is this latter possible mechanism of action that Patel *et al*. have chosen to investigate for propofol, based also on other pharmacological properties that this general anaesthetic appears to have in common with CB_1 agonists. First, the authors show that propofol does indeed produce an enhancement of endocannabinoid levels within a time frame compatible with the peak of its sedative action in mice. Next, they provide a likely explanation for this effect by demonstrating that propofol, like oleamide and OBAA, inhibits anandamide hydrolysis by FAAH, but not anandamide cellular uptake. Finally, Patel and co-workers present strong evidence that at least part of the sedative action of propofol is due to the indirect, rather than direct, activation of CB_1 receptors (which would follow the enhancement of anandamide levels produced by this compound *via* inhibition of FAAH). In fact, the authors show that: (1) propofol-induced loss of righting reflex (an index of the sedative action of general anaesthetics in mice) is antagonized by a selective dose of rimonabant®–the antagonist, instead, did not inhibit the sedative effect of another general anaesthetic thiopental, which, accordingly, was unable to enhance mouse brain endocannabinoid levels, and (2) a clear relation exists between the efficacy of the sedative effects of a series of propofol analogues and their potency as FAAH inhibitors.

These findings are extremely important for several reasons. First, they indicate for the first time that a general anaesthetic might work through the increase of endocannabinoid levels and indirect stimulation of 'central' CB_1 cannabinoid receptors. Secondly, they provide further support to the hypothesis that manipulation of the endocannabinoid system with substances that inhibit the inactivation of endocannabinoids, and hence enhance the levels of endocannabinoids, can be used to induce some therapeutically useful, cannabimimetic effects, instead of 'direct' cannabinoid CB_1 receptor agonists with

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stronger and undesired psychotropic actions. Indeed, one of these possible therapeutic uses might be the development of novel anaesthetics. Finally, the data presented by Patel and co-workers substantiate the proposed role of the endocannabinoid system in the control of sleep, and relaunch the hypothesis that part of the sedative effects of oleamide might be due to inhibition of FAAH and enhancement of anandamide levels (Mechoulam *et al*., 1997). This hypothesis, while supported by the similar profiles of pharmacological actions exhibited by the two fatty acid amides, had to be revisited recently, after the finding that other cannabimimetic actions of oleamide were strengthened, rather than being decreased, in FAAH-deficient mice (Lichtman *et al*., 2002). Although also the conclusions of the study by Patel *et al*. should be challenged in the future by examining the sedative effects of propofol in these 'FAAH-knockout' mutants, it must be emphasized that congenital deletion of FAAH might produce adaptive mechanisms through which oleamide, propofol and other substances manipulating endocannabinoid inactivation might then act preferentially at other targets (i.e. GABA and/or 5-HT receptors). Following in the same line of thought, the findings of the authors should not be seen as being in contrast with the lack of apparent alterations in the sleep–wake cycle of $FAAH^{-/-}$ or $CB_1^{-/-}$ mutants.

The possibility that substances selectively manipulating the inactivation of endocannabinoids might induce cannabimimetic, and, particularly, therapeutically useful actions looks certainly very attractive, and has gained already some support from experimental facts. Inhibitors of FAAH and of endocannabinoid cellular uptake were shown to counteract spasticity in a mouse model of multiple sclerosis (Baker *et al*., 2001), as well as excitotoxic glutamatergic signalling in a rat model of Parkinson's disease (Gubellini *et al*., 2002). FAAH inhibitors were very recently found to inhibit anxiety in mice (Kathuria *et al*., 2003), while enhancing at the same time the levels of anandamide, but not 2-AG, in the brain. This latter finding, and the previous report that only anandamide levels are enhanced in $FAAH^{-/-}$ mice, are, in fact, somehow in contrast with the data presented by Patel *et al*., who show that the levels of *both* anandamide *and* 2-AG are increased by propofol. At this stage, it cannot be excluded that propofol also inhibits other enzymes (i.e. monoacylglycerol lipase, cyclooxygenase-2, lipoxygenases, acylCoA-dependent acyltransferases) that appear to control 2-AG levels (see Di Marzo *et al*., 200l, for review). It is also possible that, under certain physiological or pathological conditions, FAAH, which easily accepts 2-AG as a substrate, does play a, possibly brain region-specific, role in 2-AG inactivation, differently from what can be inferred from studies examining only the overall basal levels of the compound, with or without acute or congenital inactivation of the enzyme. Finally, propofol was recently found (Tsutsumi *et al*., 2001) to activate the vanilloid VR1 (or TRPV1) receptor, an inward cation channel activated by capsaicin, heat and protons, and expressed not only in sensory neurons, but also in the brain, including areas involved in the control of sleep. Since VR1 stimulation, by causing calcium influx into neurons, leads to endocannabinoid formation (Ahluwalia *et al*., 2003), it would be interesting to investigate if part of the effects of propofol on endocannabinoid levels, and on sedation, are exerted also through this mechanism.

In conclusion, the article by Patel and co-workers indicates that there is hope to develop in the future substances that, by manipulating endocannabinoid levels, cause anaesthetic effects. The possibility that, thanks to other beneficial actions exerted *via* indirect activation of CB_1 receptors, these substances might also reduce pain, anxiety and emesis, makes of this issue a particularly appealing subject of investigation from both the pharmacological and pharmaceutical points of view.

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