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COMMENTARY

Oleamide: a member of the endocannabinoid family?

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The fatty acid amide class of compounds, which include the endocannabinoid anandamide and the sleep-inducing compound oleamide, have been shown *in vitro* to have a multiplicity of actions upon different neurochemical systems. In the present issue of this journal, Leggett *et al* present data indicating that oleamide functionally activates CB_1 cannabinoid receptors *in vitro*. The significance of their finding is discussed in this commentary.
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Abbreviations: CB, cannabinoid

Among the fatty acid amide chemical class of compounds are a number of important endogenous biologically active agents including palmitoylethanolamide (an anti-inflammatory agent), anandamide (arachidonoylethanolamide, an antinociceptive and possibly neuroprotective agent, among other actions) and oleamide (a sleep-inducing agent) (see Bezuglov *et al*, 1998; Rice, 2001). Despite the obvious chemical similarity of the compounds (see Figure 1), they show widely divergent pharmacological profiles. Thus, for example, anandamide activates cannabinoid receptors but is devoid of activity at the nuclear receptor PPAR-α, whereas the reverse is true for its homologue oleoylethanolamide (Fu *et al*, 2003). A second important feature of the compounds is their multiplicity of actions. The most well studied of these, anandamide, has in addition to its cannabimimetic activity effects upon other molecular targets, of which the vanilloid receptors have received the most attention, not the least in this journal (for a review, see Ross, 2003). When it is considered that the ethanolamine subgroup of fatty acid amides are synthesised on demand and released together, and that they can affect the actions of one another (see e.g. Smart *et al*, 2002 and references cited therein), it is clear that dissection of the predominant mechanisms of *in vivo* action of individual compounds becomes rather difficult. Even for a well-investigated compound like anandamide, there is debate at present as to whether this compound is both an endocannabinoid and an 'endovanilloid', or alternatively whether its vanilloid effects are pharmacologically possible but physiologically irrelevant (see Di Marzo *et al*, 2001).

Oleamide is no exception to the rule of 'single compound, multiple actions', producing effects *in vitro* upon a variety of targets including gap junction communication, serotonin 5-HT_{1A}, 5-$HT_{2A/2C}$, 5-HT_7 and $GABA_A$ receptors (see Leggett *et al*, 2003). The ability of oleamide to interact with cannabinoid receptors has, however, been a matter of controversy. In this issue, Leggett *et al* present data indicating that oleamide functionally activates CB_1 cannabinoid receptors *in vitro*. Thus, the authors demonstrate among other findings that oleamide is able to: (a) inhibit agonist and antagonist ligand binding to CB_1 receptors; (b) increase *via* CB_1 receptors the binding of [^{35}S]GTPγS to membranes, an effect associated with G-protein coupled receptors; and (c) inhibit forskolin-stimulated cyclic AMP production in a manner blocked by a CB_1 cannabinoid receptor antagonist and by pertussis toxin. *In vitro* potencies of lipophilic compounds like anandamide and oleamide are notoriously variable between laboratories, a point well made by Leggett *et al*. However, relative potencies between compounds with similar physicochemical properties determined in the same laboratory have value, and their finding that oleamide inhibits agonist binding to CB_1 receptors with a potency only three-fold lower than seen for anandamide may be of potential importance in neurons, at least on the basis of the relative levels of the two compounds in neuroblastoma cells (Bisogno *et al*, 1997). This assumes, of course, that the concentrations of the compounds at the biophase under the assay conditions used reflect the situation *in vivo*, a rather large assumption given that factors such as metabolic processes may occur

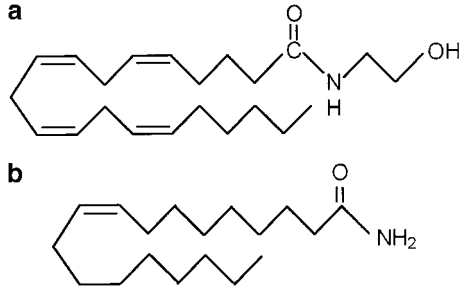

Figure 1 Chemical structures of (a) anandamide and (b) oleamide. The simplest nomenclature of these compounds is to annotate the length of the acyl chain and the number of bonds together with a note as to whether the compound is an amide or an ethanolamide. Thus, anandamide is C20:4 ethanolamide and oleamide is C18:1 amide. Other related endogenous compounds with biological activity include palmitoylethanolamide (C16:0 ethanolamide), stearoylethanolamide (C18:0 ethanolamide), oleoylethanolamide (C18:1 ethanolamide) and erucamide (C22:1 amide) (see Bezuglov *et al*, 1998).

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during the incubation times used. Both anandamide and oleamide are avidly metabolised by fatty acid amide hydrolase present in membrane fractions, and the relative potencies of the two compounds in binding assays may be entirely different under conditions where FAAH is inhibited, or absent, than in its presence (Lichtman *et al*, 2002).

While the data presented here by Leggett *et al* convincingly demonstrate that in their hands oleamide is capable of interacting with and activating CB_1 receptors *in vitro*, their conclusion that this compound 'is a directly acting endogenous cannabinoid with selectivity for the CB_1 receptor' can be interpreted in many ways. Certainly, the compound is endogenous, and certainly it shows *in vitro* selectivity for the CB_1 receptor over the CB_2 receptor. A wider interpretation that the compound acts as an *endo*cannabinoid *in vivo* is perhaps premature. The *in vivo* data so far reported in the literature give conflicting information regarding the contribution of CB_1 receptors at least for some of the actions of exogenously applied oleamide (see Leggett *et al*, 2003) and there is, to my knowledge, no evidence to indicate that the compound is involved in the endocannabinoid tone that is believed to modulate neurotransmitter release, neuroprotection and other important physiological events (see Wilson & Nicoll, 2002; Marsicano *et al*, 2003). Nevertheless, the study of Leggett *et al* raises important issues that can but stimulate further research into an exciting area of pharmacology.

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