

Anandamide hydrolysis: a new target for anti-anxiety drugs?

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The major psychoactive constituent of cannabis, Δ^9 -tetrahydrocannabinol, affects emotional states in humans and laboratory animals by activating brain cannabinoid receptors. A primary endogenous ligand of these receptors is anandamide, the amide of arachidonic acid with ethanolamine. Anandamide is released in selected regions of the brain and is deactivated through a two-step process consisting of transport into cells followed by intracellular hydrolysis. Pharmacological blockade of the enzyme fatty acid amide hydrolase (FAAH), which is responsible for intracellular anandamide degradation, produces anxiolytic-like effects in rats without causing the wide spectrum of behavioral responses typical of direct-acting cannabinoid agonists. These findings suggest that anandamide contributes to the regulation of emotion and anxiety, and that FAAH might be the target for a novel class of anxiolytic drugs.

Pharmacological studies of anxiety disorders have been traditionally focused on the γ -aminobutyric acid (GABA)_A-benzodiazepine receptor complex but several additional neurotransmitter systems have recently emerged, which might play important roles in these conditions [1]. A case in point is the endocannabinoid system, which is constituted by the cannabinoid receptors – the molecular target of Δ^9 -tetrahydrocannabinol (Δ^9 -THC) in cannabis – and their attending family of lipid-derived ligands [2].

Retrospective studies in cannabis users [3,4], small clinical trials [5], as well as animal experiments [6] have drawn a complex, often contradictory picture of the impact of cannabis on emotions. In humans, the drug produces a variety of subjective effects, which can range from relaxation and euphoria to anxiety and acute panic attacks [7]. Similarly, in animals, Δ^9 -THC and other cannabinoid agonists can exert both anxiolytic-like and anxiogenic-like actions, depending on a set of variables – such as genetic background [8,9], drug dose [10,11] and environmental context [12] – which remain poorly understood.

How can we explain this contradictory scenario? In part, it might be due to the presence of cannabinoid receptors in brain regions that serve different functions in the regulation of emotions [2,13]. Another reason might be the cellular localization of CB₁, the main cannabinoid receptor subtype in the central nervous system (CNS). In

the forebrain, CB₁ is primarily localized to axon terminals of GABAergic interneurons, where its primary effect is to decrease GABA release [2]. In some of these areas, CB₁ (or a functionally related isoform) is also found on glutamatergic nerve terminals and its activation inhibits glutamate release [14]. As a result of this distribution, CB₁ activation might have dramatically different behavioral consequences, depending on the balance of its effects on GABAergic and glutamatergic transmission within a neural network. Therefore, the question arises as to what, if any, is the role of the endocannabinoid system in the regulation of emotion. The fact that pharmacological blockade or genetic ablation of CB₁ produces anxiety-like states in rats and mice suggests the existence of an intrinsic anxiolytic tone mediated by endogenous cannabinoid (endocannabinoid) ligands [15,16] (but for contrasting results see [17]).

Endogenous cannabinoids

Best studied among the endocannabinoids are the lipid derivatives anandamide (arachidonylethanolamide) and 2-arachidonoylglycerol (2-AG) [2]. The presence of an arachidonic acid chain gives to both compounds a structure that superficially resembles those of the eicosanoids (e.g. prostaglandins, leukotrienes; Figure 1). Yet, the mechanism of endocannabinoid synthesis differs from those of the eicosanoids in that it does not involve metabolism via lipoxygenase, cyclo-oxygenase or cytochrome P450 enzymes. Moreover, anandamide and 2-AG differ from classical and peptide neurotransmitters because

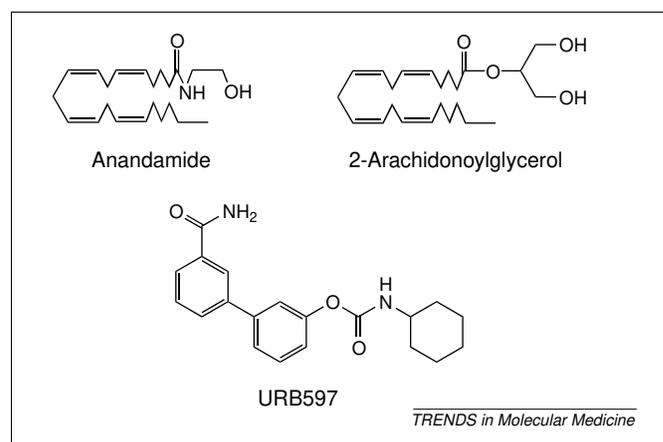


Figure 1. Chemical structures of the endocannabinoids anandamide and 2-arachidonoylglycerol (2-AG), and of the fatty acid amide hydrolase inhibitor URB597.

their release from neurons is not mediated by exocytosis of storage vesicles. Rather, current models suggest that anandamide and 2-AG are produced upon demand through activity-dependent cleavage of membrane lipid precursors and are released from cells immediately after their production [18,19]. These properties underpin the suggested role of anandamide and 2-AG as activity-dependent modulators of synaptic function [20–22].

Despite their similarities in chemical structure, anandamide and 2-AG are synthesized through different biochemical pathways. The former is produced via the hydrolysis of an N-acylated species of phosphatidylethanolamine (PtdEtn), N-arachidonoyl-PtdEtn, which requires the activity of an unknown phospholipase D [18]. 2-AG is probably generated via an enzymatic cascade similar to the one that catalyzes the formation of the second messengers inositol-(1,4,5)-trisphosphate and 1,2-diacylglycerol (1,2-DAG): a phospholipase acting on membrane phosphoinositides generates 1,2-DAG, which is then converted to 2-AG by a DAG-lipase activity [19].

After release, anandamide and 2-AG are rapidly eliminated through two separate mechanisms, which resemble those involved in the deactivation of other neurotransmitters, namely transport into cells and intracellular hydrolysis. Even though anandamide and 2-AG are highly hydrophobic molecules, their penetration into neurons is likely to occur via a carrier-mediated transport system, rather than through passive diffusion. Thus, endocannabinoid accumulation in neurons is structurally specific, displays classical saturation kinetics and is selectively inhibited by drugs such as AM404 [18,23,24]. However, this putative transport system does not require cellular energy or external Na⁺, implying that it might be mediated through a mechanism of facilitated diffusion [23,24].

Although anandamide and 2-AG share a functionally similar uptake mechanism, they follow two distinct routes of intracellular breakdown. Anandamide is metabolized by fatty acid amide hydrolase (FAAH), a membrane-bound intracellular serine hydrolase that also cleaves oleoylethanolamide, an endogenous satiety factor [25,26], and other lipid amides. By contrast, the hydrolysis of 2-AG is probably catalyzed by monoglyceride lipase (MGL), a cytosolic serine hydrolase that converts 2- and 1-monoglycerides into fatty acid and glycerol [27].

FAAH as a drug target

In the rat brain, neurons that express FAAH are often found in the proximity of axon terminals containing CB₁ receptors, providing important evidence for a role of FAAH in anandamide deactivation [28]. Moreover, mutant mice lacking the gene encoding FAAH (*Faah*) cannot metabolize anandamide and show various signs of an exaggerated anandamide tone (for example, reduced pain sensation) [29]. These findings suggest that selective inhibitors of intracellular FAAH activity could enhance the actions of anandamide in brain areas where synthesis and release of this compound occur under physiological conditions. The increased anandamide tone produced by blocking FAAH might result in a more restricted spectrum of pharmacological effects than those produced by a direct-acting CB₁ agonist and, possibly, in fewer side effects. A similar paradigm has already been successful in pharmaceutical discovery: for example, inhibitors of serotonin reuptake and intracellular monoamine oxidase, which are clinically used in the treatment of depression, act by protecting biogenic amines from degradation and making them more available for receptor activation.

Can this concept be applied to the endocannabinoid system? To answer this question, appropriate pharmacological tools are needed. Although several FAAH inhibitors have been described, most of these do not meet the necessary criteria of potency, bioavailability or target selectivity (Table 1). Recently, however, a new class of small-molecule FAAH inhibitors was identified, which might obviate many of these limitations [30,31]. Lead compounds in this class, such as the substituted biphenyl carbamate URB597 (Figure 1), produce a rapid and persistent inhibition of brain FAAH activity both *in vitro* and *in vivo*. For example, URB597 inhibits FAAH activity with a half-maximal inhibitory concentration (IC₅₀) of 0.5 nM in primary cultures of rat brain neurons, and a half-maximal inhibitory dose (ID₅₀) of 0.15 mg kg⁻¹ after parenteral administration in the rat. Importantly, URB597 is 7500 to 25 000 times more selective for FAAH than any other cannabinoid-related targets, including CB₁ and CB₂ receptors, endocannabinoid transport and MGL [30].

Although URB597 increases brain anandamide levels, it does not mimic the spectrum of pharmacological responses produced by typical CB₁ agonists. For example, parenteral doses of URB597 (0.3–1 mg kg⁻¹) that

Table 1. Fatty acid amide hydrolase (FAAH) inhibitors

Name	Description	Refs
Arachidonoyl trifluoromethyl ketone (ATFMK)	Reversible electrophilic carbonyl inhibitor. It belongs to the trifluoromethyl ketones, which, together with α -keto esters and α -keto amides, represent the three classes of anandamide-analog putative 'transition-state inhibitors'. ATFMK not only inhibits FAAH (IC ₅₀ \approx 7.5 μ M) but also inhibits cytosolic phospholipase A2 (cPLA2) and binds to CB ₁ receptors.	[42,43]
1-oxazolo[4,5-b]pyridin-2-phenylpentyl ketone	The most potent reversible FAAH inhibitor, tested <i>in vitro</i> , among several α -keto-oxazolopyridine derivatives (IC ₅₀ \approx 0.2 nM). Although the potency of this class of compounds is very high, their target selectivity and bioavailability have not been determined.	[44,45]
Palmitylsulfonyl fluoride (AM374)	This compound belongs to a family of sulfonyl fluorides, irreversible inhibitors of FAAH (IC ₅₀ \approx 13 nM) that also bind to the CB ₁ receptor. It also inhibits <i>Escherichia coli</i> phospholipase A.	[46–48]
Hydro(pero)xy-anandamides URB532 and URB597	FAAH inhibitors of natural origin. These compounds belong to a series of alkylcarbamic acid aryl esters, designed as inhibitors of FAAH by progressive modification of the structure of the anti-cholinesterase agent carbaryl.	[49] [30,31]

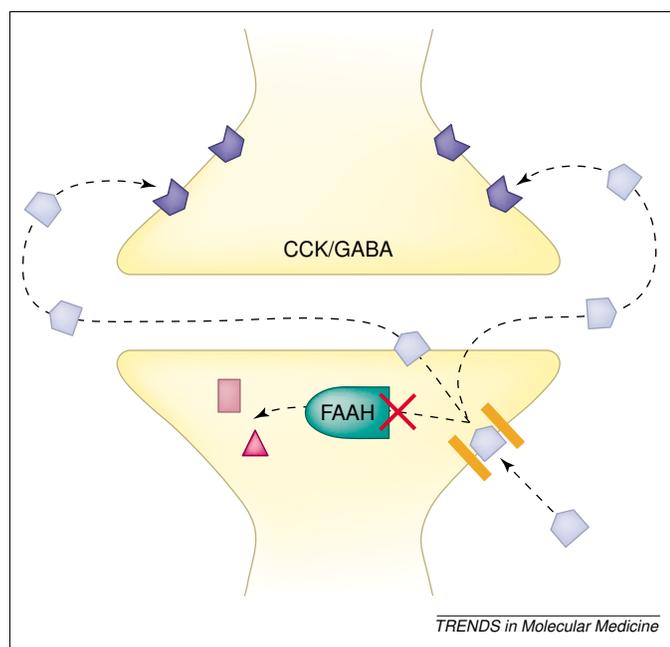


Figure 2. Effects of fatty acid amide hydrolase (FAAH) inhibitors on brain anandamide signaling. Anandamide is deactivated through a two-step process of transmembrane transport and intracellular hydrolysis. Transport is mediated by a hypothetical facilitated diffusion carrier system (endocannabinoid transporter; orange bars). Hydrolysis is catalyzed by a membrane-bound FAAH, which cleaves anandamide (light blue) to produce arachidonic acid (rose rectangle) and ethanolamine (pink triangle). According to this hypothetical model, pharmacological blockade of FAAH might cause unmetabolized anandamide to accumulate in and, eventually, leak out of neurons. This could result in the extracellular accumulation of anandamide and the increased local activation of CB₁ receptors (dark blue).

virtually eliminate brain FAAH activity do not produce catalepsy (rigid immobility), hypothermia or hyperphagia (increased food intake), three cardinal signs of cannabinoid intoxication in the rodent [2]. The compound exerts some degree of anti-nociception in the mouse hot plate test but this effect is very modest when compared with those of CB₁ agonists [30].

Despite its lack of typical cannabimimetic actions, URB597 elicits marked anxiolytic-like responses, which have been documented in two models of anxiety: the elevated zero maze test in adult rats and the isolation-induced ultrasonic vocalization test in rat pups [30].

The zero maze consists of an elevated annular platform divided into four quadrants, two open and two closed. The test is based on the conflict between an animal's instinct to explore its environment and its fear of open spaces, where it might be attacked by predators [32,33]. Anxiolytic agents such as the benzodiazepines increase the proportion of time spent in, and the number of entries made into, the open compartments. The FAAH inhibitor URB597 produces similar anxiolytic-like responses, with a maximal effect at a dose of 0.1 mg kg⁻¹, which inhibits brain FAAH activity by ~50%. As expected of an anandamide-mediated response, this effect is attenuated by the CB₁ antagonist rimonabant (SR141716A) at a dose at which the compound has no anxiogenic effect.

The ultrasonic vocalization emission test measures the number of stress-induced vocalizations emitted by rat pups removed from their nest [34–36]. URB597 markedly reduces these vocalizations at a dose of 0.1 mg kg⁻¹, as observed with clinically used anxiolytic

and antidepressant drugs. The anxiolytic-like actions of URB597 are accompanied by a modest decrease in movement, which is observed, however, at doses that are ten times higher than those causing anxiolysis. Even at these high doses, URB597 exerts no overt cannabimimetic effects such as catalepsy or hypothermia [30].

Concluding remarks

How do FAAH inhibitors affect behavior? Moreover, why do they only produce a limited set of all possible cannabimimetic effects? Experiments *in vitro* show that URB597 causes unmetabolized anandamide to accumulate and, eventually, to leak out of brain neurons [30]. *In vivo*, this would result in an extracellular accumulation of anandamide at its sites of synthesis and, consequently, in an increased local activation of CB₁ receptors (Figure 2). If anandamide release in brain areas engaged in the processing of emotional information occurs at higher levels than in other structures, this might explain the restricted spectrum of action of URB597. That this might be the case is suggested by a recent study, which shows that anandamide content in the mouse amygdala rises when

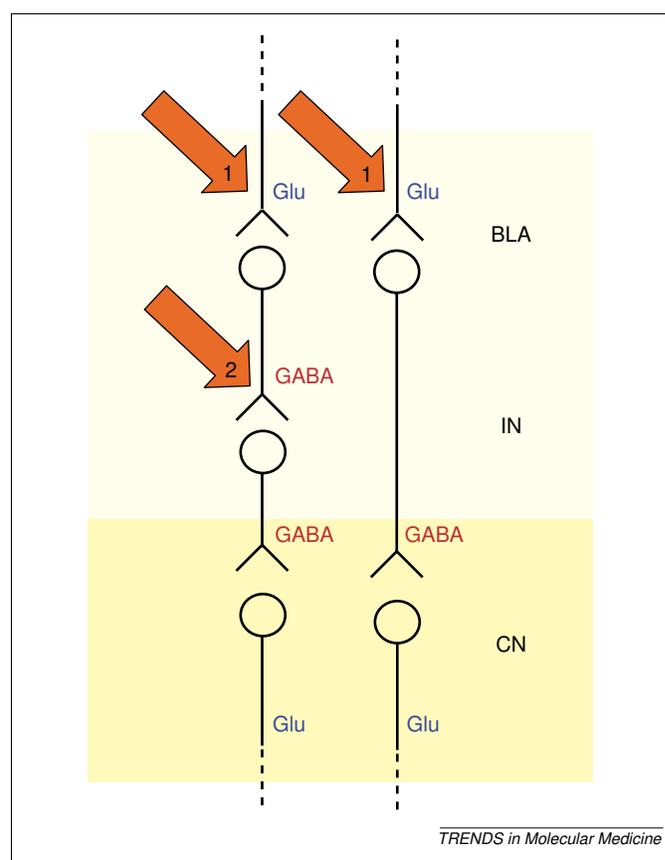


Figure 3. Possible sites of action of fatty acid amide hydrolase (FAAH) inhibitors in the amygdala. The enhanced anxiety that accompanies CB₁ receptor blockade and the anti-anxiety properties of FAAH inhibitors suggest that endocannabinoid substances could be generated in the amygdala during anxiety and that they might regulate emotional states by influencing amygdala outputs. This could be accomplished in several ways. By reducing γ -aminobutyric acid (GABA) release from CB₁-positive interneurons (arrow 2) in the basolateral amygdala (BLA), the endocannabinoids might disinhibit GABAergic cells in the adjacent intercalated nuclei (IN) and consequently inhibit pyramidal neurons in the central nucleus (CN), the primary efferent structure of the amygdala. In addition, the endocannabinoids might inhibit glutamate (Glu) release from cortically derived axon terminals (arrow 1) [50], which richly innervate the basolateral complex (for review, see [2]).

the animal is conditioned to expect a foot shock after hearing a tone [37]. This implies that the endocannabinoid system, and anandamide in particular, might be activated in response to anxiogenic situations such as that generated by a tone preceding a painful stimulus. The evidence reviewed above would further suggest that this activation could be part of a negative feedback system that limits anxiety.

The basolateral amygdala, the anterior cingulate cortex, the prefrontal cortex and the hippocampus are some of the possible brain structures implicated in these effects because they are directly involved in the regulation of emotional behavior [38] and contain high densities of CB₁ receptors [13,39]. Cannabinoid agonists have a profound impact on GABAergic and glutamatergic transmission in these regions [2], suggesting that both neurotransmitter systems could be involved in the anxiolytic effects of FAAH inhibitors (Figure 3). However, they need not be the only ones. Throughout the forebrain, CB₁-positive GABAergic interneurons express the neuropeptide cholecystokinin-8 (CCK-8) [2], the anxiogenic roles of which are well documented [40]. CB₁ agonists inhibit K⁺-evoked CCK-8 release in the hippocampus [41], suggesting that interactions between anandamide and CCK-8 might also contribute to the regulation of emotional states.

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