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The endocannabinoid system as a target for therapeutic drugs

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Cannabinoid receptors, the molecular targets of the cannabis constituent Δ^9-tetrahydrocannabinol, are present throughout the body and are normally bound by a family of endogenous lipids – the endocannabinoids. Release of endocannabinoids is stimulated in a receptor-dependent manner by neurotransmitters and requires the enzymatic cleavage of phospholipid precursors present in the membranes of neurons and other cells. Once released, the endocannabinoids activate cannabinoid receptors on nearby cells and are rapidly inactivated by transport and subsequent enzymatic hydrolysis. These compounds might act near their site of synthesis to serve a variety of regulatory functions, some of which are now beginning to be understood. Recent advances in the biochemistry and pharmacology of the endocannabinoid system in relation to the opportunities that this system offers for the development of novel therapeutic agents will be discussed.

Since the discovery of the first cannabinoid receptor 12 years ago[1,2], important advances have been made in several areas of cannabinoid pharmacology. Endocannabinoid compounds and their pathways of biosynthesis and inactivation have been identified, and the molecular structures and anatomical distribution of cannabinoid receptors have been investigated in detail. Pharmacological agents that interfere with various aspects of the endocannabinoid system have been developed, and pathophysiological circumstances in which this system might be active have begun to emerge. The manner in which these discoveries might impact our understanding of endocannabinoid signaling and help unlock its potential for developing novel therapeutic agents will be discussed.

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Endogenous cannabinoids

The two endocannabinoids isolated so far – anandamide and 2-arachidonylglycerol (2-AG)[3–5] – are lipid in nature but differ from amino acid, amine and peptide transmitters in ways other than just their chemical structures. Classical and peptide transmitters are synthesized in the cytosol of neurons and stored in synaptic vesicles, from where they are secreted by exocytosis following excitation of nerve terminals by action potentials. By contrast, anandamide and 2-AG can be produced upon demand by receptor-stimulated cleavage of membrane lipid precursors and released from cells immediately after their production.

Anandamide can be produced from the hydrolysis of an *N*-acylated species of phosphatidylethanolamine (PE) *N*-arachidonyl PE, a process catalysed by phospholipase D (PLD)[6] (Fig. 1). The stimulation of neurotransmitter receptors appears to play a determinant role in initiating this reaction, as indicated by the finding that anandamide release in the striatum is strongly enhanced by activation of dopamine D2 receptors[7]. Once released, anandamide can act on cannabinoid receptors or accumulate back into cells via an energy- and Na^+-independent transport system[8]. The selectivity of this system for anandamide has been documented[9] but its molecular structure remains uncharacterized. Inside cells, anandamide can be catalytically hydrolysed by an amidohydrolase[10], whose gene has been cloned[11] (Fig. 1).

The most likely route of 2-AG biosynthesis involves the same enzymatic cascade that catalyses the formation of the second messengers inositol (1,4,5)-trisphosphate and 1,2-diacylglycerol (DAG) (Fig. 2). Phospholipase C (PLC), acting on phosphatidylinositol (4,5)-bisphosphate, generates DAG, which is converted to 2-AG by DAG lipase[12]. 2-AG might also be synthesized by the hydrolysis of lysophospholipids or triacylglycerols[6]. Regardless of the mechanism involved, 2-AG formation can be triggered by neural activity[12] or by occupation of membrane receptors[13]. Following its release, 2-AG can be taken up by cells via the anandamide transport system[9] and hydrolysed by an unknown monoacylglycerol lipase activity[14] (Fig. 2).

Thus, anandamide and 2-AG can be released from neuronal and non-neuronal cells when the need arises, utilizing analogous but distinct receptor-dependent pathways. The non-synaptic release mechanisms and short life spans of anandamide and 2-AG suggest that these compounds might act near their site of synthesis to regulate the effects of primary messengers, such as neurotransmitters and hormones.

Inhibitors of anandamide inactivation

Drugs that block the formation or inactivation of anandamide and 2-AG should help identify the physiological functions of these compounds and might be beneficial in disease states in which regulation of endocannabinoid levels might produce more selective responses than those elicited by cannabinoid receptor ligands. Although this area of pharmacology is still largely unexplored, inhibitors of the two main steps of anandamide disposition (membrane transport and intracellular hydrolysis) have recently become available.

Anandamide transport is inhibited by the compound AM404 (Figs 1,3). This drug potentiates various responses elicited by exogenous anandamide and interacts very poorly with cannabinoid CB_1 receptors[8,15]. For example, AM404 enhances anandamide-induced hypotension without producing

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direct vasodilatory effects[16]. Furthermore, when applied alone, AM404 decreases motor activity[15,17] and elevates the levels of circulating anandamide (A. Giuffrida *et al.*, unpublished). However, AM404 can accumulate in cells where it might reach concentrations that are sufficient to inhibit anandamide amidohydrolase[9] (M. Beltramo and D. Piomelli, unpublished).

Anandamide amidohydrolase is blocked reversibly by transition state analogs such as arachidonyltrifluoromethylketone (ATFMK), which might act by forming a stable intermediate with a serine residue at the enzyme active site[18] (Fig. 3). Moreover, irreversible inhibition can be achieved with a variety of compounds including the fatty acid sulfonyl fluoride AM374 (Ref. 18) (Figs 1,3). AM374, one of the most potent anandamide amidohydrolase inhibitors identified thus far, potentiates anandamide responses *in vitro* and *in vivo*, but its specificity is limited by a relatively high affinity for CB_1 receptors[19].

Cannabinoid receptors

The two cannabinoid receptor subtypes characterized so far, CB_1 and CB_2, belong to the superfamily of G-protein-coupled membrane receptors (GPCRs)[2,20]. Their molecular and pharmacological properties have recently been reviewed[21]. Three issues that might be relevant to the use of cannabinoid agents in medicine will be discussed: (1) the apparently exclusive role of CB_1 receptors in mediating central cannabinoid effects; (2) the rapid tolerance that results from repeated cannabinoid administration; and (3) the possible existence of multiple cannabinoid receptors in peripheral tissues.

Although CB_1 receptors are expressed throughout the body, they are particularly abundant in the CNS where, despite a great deal of effort, no other cannabinoid receptor subtype has yet been found. This unusual situation – most neurotransmitters act on multiple CNS receptors – accords with data that indicate that a single pharmacological site accounts for all central effects of cannabimimetic drugs, whether therapeutically favorable (e.g. analgesia) or harmful (e.g. dysphoria and amnesia). Consequently, although potent CB_1 receptor agonists have been available for some time (Table 1), the therapeutic development of these compounds has been very limited. Given this situation, how might centrally active cannabinoid agents that are more selective than those currently available be developed? One possibility is to target the mechanisms of endocannabinoid inactivation. Blocking such mechanisms might cause an activity-dependent accumulation of anandamide and 2-AG at their sites of release, which might in turn result in a more localized activation of cannabinoid receptors than that elicited by direct receptor agonists.

Another important issue that should be considered in the development of cannabinoid agonists for therapeutic use is receptor desensitization. This process, which might be mediated by the GPCR-kinase–β-arrestin pathway[22,23], causes a pharmacological tolerance that limits the prolonged use of cannabinoid receptor agonists. Partial agonists might offer a clue as to how to circumvent this obstacle. Evidence indicates that the CNS contains a large reserve of CB_1 receptors[24]; thus partial CB_1 receptor agonists, which are expected to cause less receptor desensitization than full agonists, might produce adequate therapeutic responses with diminished tolerance liability.

Although CB_1 receptors are thought to mediate the effects of cannabinoid receptor agonists in the CNS, several peripheral effects of cannabimimetic drugs might only depend partially on CB_1 receptor activation. The high expression of CB_2 receptors in B cells and natural killer cells suggests that this subtype contributes to the potential immunosuppressant and anti-inflammatory effects of cannabinoids[25]. Additional tests of this hypothesis will be facilitated by the recent availability of selective CB_2 receptor agonists and antagonists (Table 1).

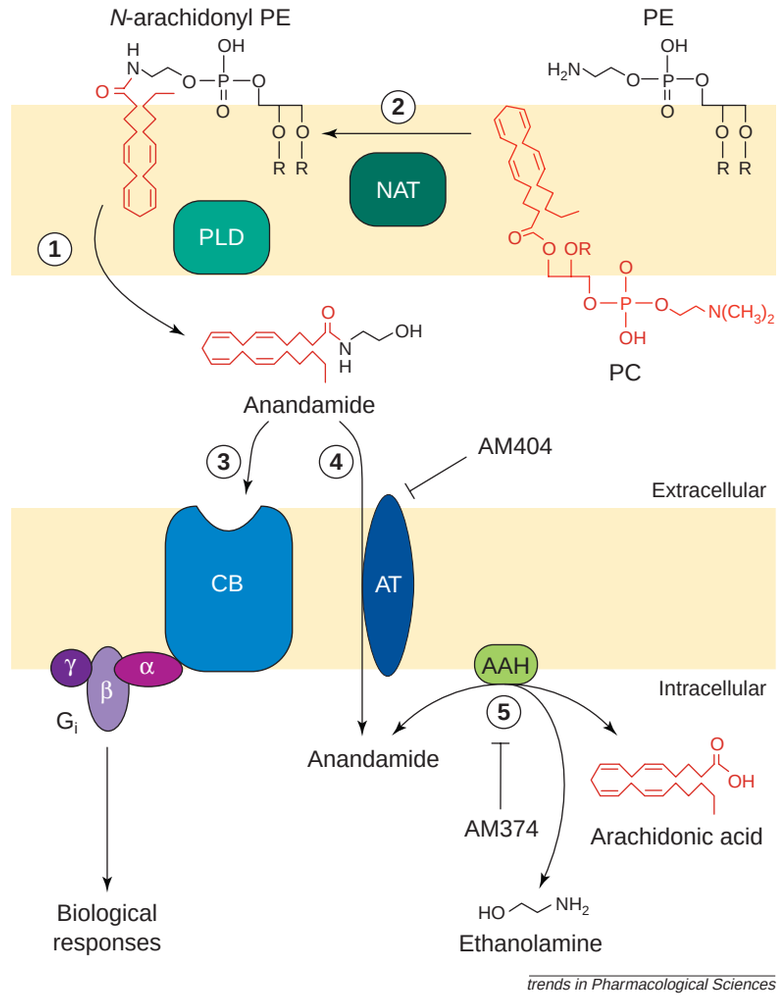


Fig. 1. Formation and inactivation of anandamide. Anandamide can be generated by hydrolysis of *N*-arachidonyl phosphatidylethanolamine (*N*-arachidonyl PE), which is catalysed by phospholipase D (PLD) (1)[6]. The synthesis of *N*-arachidonyl PE, depleted during anandamide formation, might be mediated by *N*-acyl transferase activity (NAT) (2), which detaches an arachidonate moiety (red) from the *sn*-1 position of phospholipids such as phosphatidylcholine (PC) and transfers it to the primary amino group of PE. The membrane localizations of PLD and NAT are speculative. Newly formed anandamide can be released into the extracellular space, where it can activate G-protein-coupled cannabinoid (CB) receptors located on neighboring cells (3) or on the same cells that produce anandamide (not shown). Anandamide release in the external milieu has been demonstrated both *in vitro* and *in vivo*[6,7]. Anandamide can be removed from its sites of action by carrier-mediated transport (anandamide transport, AT) (4)[8,9], which can be inhibited by AM404. Transport into cells can be followed by hydrolysis catalysed by a membrane-bound anandamide amidohydrolase (AAH, also called fatty acid amide hydrolase) (5)[10,11], which can be inhibited by AM374. Arachidonic acid produced during the AAH reaction can be rapidly reincorporated into phospholipid and is unlikely to undergo further metabolism. *In vitro*, AAH can also act in reverse, catalysing the formation of anandamide from arachidonic acid and ethanolamine. The physiological significance of this reaction in anandamide formation is unclear. Abbreviation: R, fatty acid group.

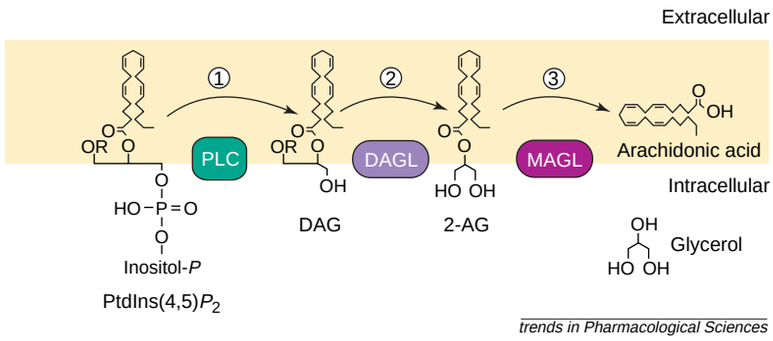


Fig. 2. Formation and inactivation of 2-arachidonylglycerol (2-AG). Hydrolysis of phosphatidylinositol (4,5)-bisphosphate [PtdIns(4,5)P_2] by phospholipase C (PLC) produces the second messengers 1,2-diacylglycerol (DAG) and inositol (1,4,5)-trisphosphate [Ins(1,4,5)P_3] (1). DAG serves as a substrate for DAG lipase (DAGL), which catalyses the production of 2-AG (2). This pathway also gives rise to free arachidonic acid. 2-AG can be released into the external milieu, measured *in vitro*, allowing it to interact with cannabinoid receptors, and its effects can be terminated by uptake into cells[9] (not shown). However, extracellular release of 2-AG has not yet been reported *in vivo*[7]. Intracellular 2-AG can be hydrolysed to arachidonic acid and glycerol by an uncharacterized esterase such as monoacylglycerol lipase (MAGL) (3)[12,14].

Furthermore, cannabinoid-like receptors that are distinct from the CB_1 and CB_2 subtypes might participate in the vasodilatatory and analgesic effects of cannabinoids. Although the hypotensive actions of anandamide are mostly mediated by CB_1 receptors, the endothelium-dependent vasorelaxation produced by this compound in mesenteric arteries appears to require a receptor that is pharmacologically distinct from CB_1 and CB_2 (Ref. 26). Furthermore, the peripheral analgesic effects exerted by the endogenous anandamide analog palmitylethanolamide might also involve a novel cannabinoid-like receptor (see below).

In addition to acting on cannabinoid receptors, anandamide has been suggested to act on a variety of other targets, including capsaicin (vanilloid) receptors[27]. The concentrations required to attain these effects are, however, too high to be considered physiologically relevant and claims that vascular effects of anandamide might be mediated by vanilloid receptors appear unwarranted[28].

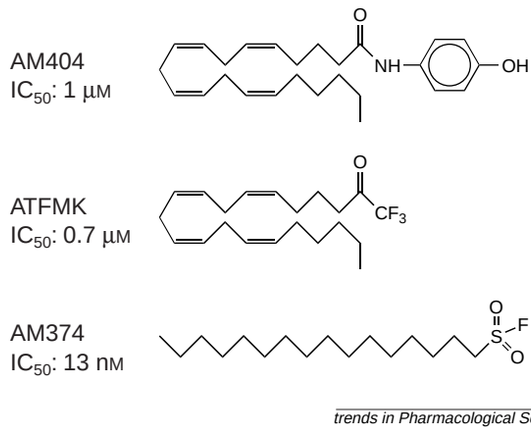


Fig. 3. Inhibitors of anandamide inactivation. The anandamide transport inhibitor AM404 (Ref. 8) and the anandamide amidohydrolase inhibitors arachidonyl trifluoromethylketone (ATFMK) and AM374 (Ref. 18) are shown. Abbreviation: IC_{50}, concentration required to produce half-maximal inhibition of anandamide transport or hydrolysis.

Functions and strategies

The endocannabinoid system might serve important regulatory functions in physiological processes; thus, cannabinoid agents might prove useful in the treatment of pathological conditions that are associated with such processes. Exhaustive evaluations of the medicinal potential of cannabis and its derivatives in other therapeutic areas can be found elsewhere[29].

Modulation of pain

Cannabinoid drugs strongly reduce pain responses by interacting with CB_1 receptors in brain, spinal cord and peripheral sensory neurons (Fig. 4). Brain sites that participate in cannabinoid-induced analgesia include the amygdala, thalamus, superior colliculus, periaqueductal gray and rostral ventromedial medulla[30]. In the spinal cord, CB_1 receptors are found in the dorsal horn and lamina X (Ref. 21), where they are located on intrinsic spinal neurons, nerve terminals of afferent sensory neurons and terminals of efferent supraspinal neurons[31] (Fig. 4). CB_1 receptors are also expressed in the dorsal root ganglia by a subset of small- and large-diameter sensory neurons that contain the pain-stimulating peptides, substance P and α-calcitonin gene-related peptide (CGRP)[32]. Although quantitatively small, the presence of CB_1 receptors on CGRP-containing neurons appears to be functionally significant because CB_1 receptor agonists effectively reduce CGRP release from dorsal horn tissue[33]. Immunohistochemical experiments suggest that CB_1 receptors are present not only on central terminals of primary sensory afferents, but also on their peripheral counterparts[34] (Fig. 4). In agreement with these findings, local applications of CB_1 receptor agonists to skin reduce the responses to formalin and other irritants[35,36].

The clinical impact of these advances is still modest but worth noting. Since a previous literature review[37], new studies have documented the analgesic effects of CB_1 receptor agonists in humans (for example, Ref. 38), providing additional impetus for a re-evaluation of the endocannabinoid system as a target for analgesic drugs.

Neuropathic pain

Cannabinoids are potent in alleviating two hallmarks of neuropathic pain: allodynia (pain from non-noxious stimuli) and hyperalgesia (increased sensitivity to noxious stimuli)[36,39–41]. Indeed, in a rat model of neuropathic pain (constriction injury of the sciatic nerve), the CB_1 receptor agonist WIN552122 attenuates such responses at doses that do not cause overt side-effects[39]. In this model, the CB_1 receptor antagonist SR141716A reverses the analgesic response to WIN552122 and exacerbates pain behaviors when administered alone[39]. One possible explanation for the pain-inducing effects of SR141716A is that nerve injury might be associated with an increase in endocannabinoid levels and/or a sensitization of CB_1 receptors.

Plastic modifications in endocannabinoid signaling during persistent pain can also be inferred from experiments conducted in a rat model of inflammation (injection of Freund's adjuvant into the paw)[41]. In this model, SR141716A enhances the sensitivity to mechanical stimuli applied to the paw contralateral to the inflammatory focus, which suggests that

inflammation can be accompanied by an increased cannabinergic activity that can be unmasked by the CB_1 receptor antagonist[41]. Furthermore, the peripheral administration of formalin stimulates anandamide release in the periaqueductal gray, a brain region involved in pain control[42].

Whether CB_1 receptor function and/or endocannabinoid levels are changed in neuropathic pain is unknown. If this syndrome is accompanied by a hypersensitivity of CB_1 receptors in injured tissues, partial CB_1 receptor agonists could alleviate pain at doses that might exert few undesirable effects and produce little tolerance. By contrast, if neuropathic pain is associated with elevated endocannabinoid release, drugs that interfere with the inactivation of these substances might offer an alternative to direct CB_1 receptor agonists. Elucidating the alterations in endocannabinoid function associated with neuropathic pain should be instrumental to define the value of these strategies.

Peripheral pain

The finding that cannabinoid receptor agonists can alleviate pain by acting at peripheral CB_1 receptors[35,36] has both theoretical and practical ramifications. Theoretically, this observation emphasizes the notion that nociceptive signals can be modulated at the first stage of neural processing by a peripheral 'gate' mechanism in which endogenous cannabinoid lipids can act in concert with opioid peptides[43]. Practically, it points to the possibility of achieving an effective control of peripheral pain without causing the psychotropic effects that follow the recruitment of brain CB_1 receptors.

The antinociceptive effects of palmitylethanolamide add a new dimension to this hypothesis[35]. Palmitylethanolamide is produced in tissues through an enzymatic route similar to that of anandamide synthesis[6]. When administered as a drug, palmitylethanolamide potently reduces peripheral pain through a mechanism that is synergistic with anandamide and is blocked by the CB_2 receptor antagonist SR144528 (Ref. 35). However, palmitylethanolamide does not interact with the CB_2 receptor (whose gene has been cloned), which suggests that the compound might produce its analgesic effects by activating an as-yet uncharacterized CB_2-like receptor[35].

Regulation of glutamate transmission

CB_1 receptor agonists inhibit both glutamatergic neurotransmission and long-term potentiation (LTP)[44], a model of glutamate-dependent synaptic plasticity. These effects, which can be triggered by activation of presynaptic CB_1 receptors and mediated by inhibition of glutamate release, might reflect a fundamental role of the endocannabinoid system in the regulation of excitatory neurotransmission (Box 1). Two lines of evidence suggest that this might be the case. In hippocampal slices, electrical stimulation of glutamate-releasing fibers enhances 2-AG formation, a response that might depend on the activation of NMDA receptors[12] (N. Stella and D. Piomelli, unpublished). In the same preparation, exogenous 2-AG prevents the induction of LTP by activating CB_1 receptors[12], which indicates that neurally released 2-AG might act as a negative feedback signal regulating transmission at glutamate synapses (Box 1). Whether or not this hypothesis turns out to be correct, the interaction between cannabinoid and glutamate-mediated signaling opens important perspectives for therapy.

Table 1. Cannabinoid receptor ligands

	Receptor subtype[a]		
	CB_1	CB_2	Refs
Nonselective agonists	HU210 (tricyclic cannabinoid)		54
	CP55940 (bicyclic cannabinoid)		54
	WIN552122 (aminoalkylindole)		54
Selective agonists	Methanandamide	JWH015	55,56
	ACPA	L759633	57,58
	ACEA	L759656	57,58
		HU308	59
Selective antagonists	SR141716A	SR144528	60,61

[a]Abbreviations: ACPA, arachidonylcyclopropylamide; ACEA, arachidonyl-2-chloroethylamide.

Brain ischaemia

A primary pharmacological approach to ischaemic brain injury aims to arrest excitoxicity, the neuronal death triggered by glutamate via activation of Ca^{2+}-permeable ionotropic receptors[45]. On the basis of their ability to reduce excitoxicity

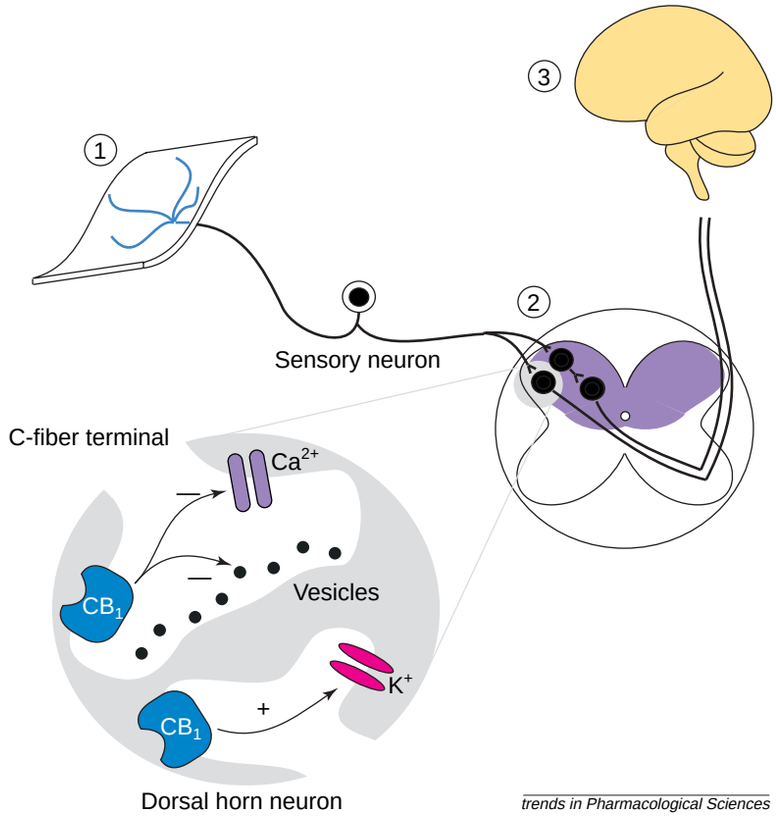
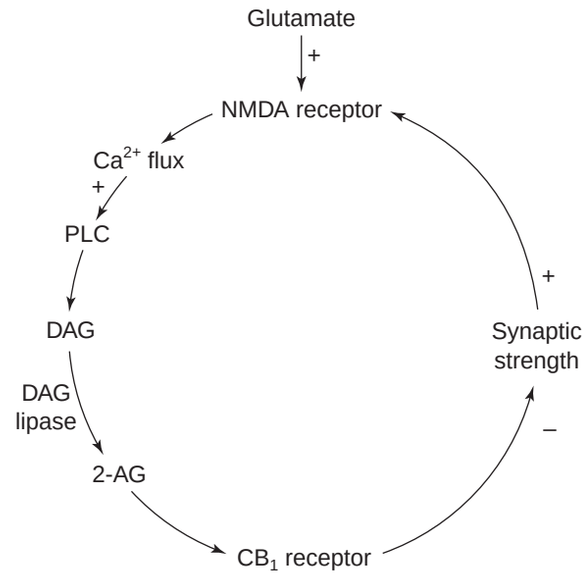


Fig. 4. Localization and functional roles of cannabinoid CB_1 receptors in pain-processing pathways. CB_1 receptors are present in peripheral terminals of primary sensory neurons (1), at synapses in the spinal cord (2), and in pain-processing areas of the brain (3). At spinal synapses (2), CB_1 receptors might be located on nerve terminals of afferent neurons, on intrinsic spinal neurons, and/or on terminals of efferent neurons originating in supraspinal structures (not shown). Thus, CB_1 receptors might modulate the transmission of nociceptive information presynaptically (by inhibiting the release of excitatory neurotransmitters) and/or postsynaptically (by reducing neuronal excitability).

Box 1. A hypothetical model of the role of endocannabinoid signaling in glutamate neurotransmission

Flux of external Ca^{2+} through activated NMDA receptor channels can stimulate phospholipase C (PLC) (Fig. I), which initiates 2-arachidonylglycerol (2-AG) formation via diacylglycerol (DAG) lipase[a] (N. Stella and D. Piomelli, unpublished). Newly formed 2-AG can activate cannabinoid CB_1 receptors on presynaptic nerve terminals, which might in turn reduce glutamate release and decrease synaptic strength[b]. It is important to note that in several regions of the CNS, CB_1 receptors are localized on axon terminals of GABA-containing neurons, where they might be linked to inhibition of GABA release[c,d]. Moreover, excitatory effects of cannabinoids mediated by changes in postsynaptic ion conductances have also been reported[e]. Thus, the net effect of CB_1 receptor activation might be more to produce a functional reconfiguration of neuronal networks than just to blunt glutamate-mediated transmission.

Fig. I



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in vitro and *in vivo*, CB_1 receptor agonists show promise as potential neuroprotective agents[46,47]. In cultures of rat hippocampal neurons, repetitive synaptic activity stimulates glutamate release and causes neuronal death. The CB_1 receptor agonist WIN552122 prevents this response but does not protect the neurons against exposure to exogenous glutamate, which suggests that WIN552122 might reduce excitotoxicity by activating presynaptic CB_1 receptors coupled to the inhibition of glutamate release[46]. Indeed, *in vivo* pharmacological studies support this idea. WIN552122 potently increases neuronal survival in two different animal models of ischaemia, an effect that is dose-dependent and prevented by the CB_1 receptor antagonist SR141716A (Ref. 47). Thus, inhibition of glutamate release is likely to play a primary role in the neuroprotective actions of CB_1 receptor agonists although additional protection might be provided by the anti-inflammatory and hypothermic[21] properties of these compounds.

Regulation of dopamine transmission

CB_1 receptors are densely expressed in the basal ganglia and cortex, CNS regions that are critical for movement control[21]. This distribution provides an anatomical substrate for functional interactions between the endocannabinoid system and ascending dopaminergic pathways. Several observations suggest that these interactions might indeed occur. First, in the striatum of freely moving rats anandamide release is stimulated by activation of dopamine D2 receptors[7]. Second, the CB_1 receptor antagonist SR141716A, which has little effect on motor activity when administered alone, potentiates the motor hyperactivity produced by the D2 receptor agonist quinpirole[7]. Third, D2 and CB_1 receptor agonists produce opposing behavioral responses after injection into the basal ganglia[48]. These and other findings suggest that anandamide might modulate dopamine-induced facilitation of psychomotor activity. In further support of this hypothesis, disruption of the gene encoding the CB_1 receptor profoundly affects motor control, decreasing locomotor activity[49].

Movement disorders

The recommendation by the Institute of Medicine that studies be conducted 'to test the hypothesis that cannabinoids play an important role in movement disorders'[29] is justified by a significant body of experimental and clinical evidence. Preclinical studies have focused on the possible application of CB_1 receptor agonists in the management of dyskinesias that accompany the treatment of Parkinson's disease with L-dihydroxyphenylalanine (L-DOPA)[50]. Clinical investigations have been primarly concerned with the ability of CB_1 receptor agonists to alleviate spasticity in various conditions[29] and tics in Tourette's syndrome[51]. In particular, a recent double-blind trial has demonstrated significant improvements in tics and obsessive compulsive behaviors following administration of the oral constituent Δ^9-tetrahydrocannabinol (Δ^9-THC) to 12 Tourette patients (K. Müller-Vahl *et al.*, unpublished). However, these improvements were accompanied in five patients by mild side-effects that included fatigue, dizziness and euphoria.

Psychoses

There is a general consensus that heavy cannabis abuse can precipitate psychotic episodes in individuals with an underlying schizophrenic condition. This idea, which is supported

by substantial epidemiological evidence[52], instigated an ongoing clinical trial of the CB_1 receptor antagonist SR141716A in schizophrenic patients. Yet, on examining the basis of cannabis-precipitated psychosis, consideration should also be given to CB_1 receptor desensitization and to the fact that this process can have repercussions that go beyond behavioral tolerance. One such repercussion is an exacerbated response to the psychostimulant, D-amphetamine. In animals, D-amphetamine increases motor activity and stereotypies, an effect that depends on dopamine receptor activation and is blocked by D2 receptor antagonists. Because D-amphetamine can also trigger psychotic episodes in schizophrenics, the behavioral response to D-amphetamine in animals is often used as a screening test for antipsychotic medications. The stimulation of stereotyped movements elicited by D-amphetamine is blocked by acute administration of Δ^9-THC, but this same stimulation is increased in animals that have been made tolerant to cannabinoids by repeated injections of Δ^9-THC (Ref. 53). Thus, CB_1 receptor activation might counterbalance stimulation of dopamine-containing neurons, whereas CB_1 receptor inactivation might enhance such stimulation. In this framework, cannabis use by schizophrenics might be interpreted as a misguided attempt to obtain relief from psychotic symptoms[29], which might in turn facilitate a psychotic episode when CB_1 receptors become desensitized.

The ability of Δ^9-THC to reduce tics in Tourette's syndrome and to inhibit D-amphetamine-induced stereotypy suggests that CB_1 receptor agonists might be therapeutically useful to alleviate the symptoms of dopamine hyperactivity associated with many neuropsychiatric conditions. However, the psychotropic effects produced even by low doses of Δ^9-THC in Tourette patients and the possible impact of CB_1 receptor desensitization underscore the need to investigate a wider variety of cannabinoid agents (e.g. inhibitors of endocannabinoid inactivation) in animal models of motor disorders and psychosis. For example, evidence suggests that the anandamide transport inhibitor AM404 can normalize motor activity in genetically hyperactive rats without causing overt cannabimimetic effects[15].

Concluding remarks

The image of the endocannabinoid system that gleams through the studies summarized in this review is that of a modulatory complex that is parallel, in its varied functional roles, to the opioid system but analogous, for its biochemical properties, to other lipid mediators such as the eicosanoids. It would be surprising if such a prominent signaling system, which gives every indication of serving key physiological functions in the CNS and in peripheral tissues, will fail to prompt the development of new medicines in the not too distant future.

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Chemical names

CP55940: (2)-3-[2-hydroxy-4-(1,1,-dimethylheptyl)phenyl]-4-(3-hydroxypropyl)cyclohexane-1-ol

HU210: (6*aR*)-*trans*-3-(1,1-dimethylheptyl)-6*a*,7,10,10*a*-tetrahydro-1-hydroxy-6,6-dimethyl-6*H*-dibenzo[*b*,*d*]pyran-9-methanol

HU308: bicyclo[3.1.1]hept-2-ene-2-methanol,4-[4-(1,1-dimethylheptyl)-2-6-dimethoxyphenyl]-6,6-dimethyl-(1*R*,4*R*,5*R*)

JWH015: 2-methyl-1-propyl-3-(1-naphthoyl)indole

L759633: (6*aR*,10*aR*)-3-(1,1-dimethyl-heptyl)-1-methoxy-6,6,9-trimethyl-6*a*,7,10,10*a*-tetrahydro-6*H*-benzo[*c*]chromene

L759656: (6*aR*,10*aR*)-3-(1,1-dimethyl-heptyl)-1-methoxy-6,6-dimethyl-9-methylene-6*a*,7,8,9,10,10*a*-hexahydro-6*H*-benzo[*c*]chromene

SR141716A: *N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide hydrochloride

SR144528: *N*-([1*s*]-endo-1.3.3-trimethylbicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-3-methylphenyl)-1-(4-methylbenzyl)-pyrazole-3-carboxamide

WIN552122: (*R*)-(1)[2,3-dihydro-5-methyl-3-[4-morpholino)methyl]pyrrolo-[1,2,3-*de*]-1,4-benzoxazin-6-yl](1-naphthyl)methanone