REVIEW: NEUROSCIENCE

Endocannabinoid Signaling in the Brain

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The primary psychoactive ingredient in cannabis, Δ^9-tetrahydrocannabinol (Δ^9-THC), affects the brain mainly by activating a specific receptor (CB1). CB1 is expressed at high levels in many brain regions, and several endogenous brain lipids have been identified as CB1 ligands. In contrast to classical neurotransmitters, endogenous cannabinoids can function as retrograde synaptic messengers: They are released from postsynaptic neurons and travel backward across synapses, activating CB1 on presynaptic axons and suppressing neurotransmitter release. Cannabinoids may affect memory, cognition, and pain perception by means of this cellular mechanism.

Cannabis sativa derivatives (marijuana, hashish, bhang, and so forth) have been used medicinally and recreationally for thousands of years, but our knowledge of the chemistry and physiology of cannabinoids is quite recent. Only in 1964, when the structure of the active ingredient Δ^9-THC was finally determined by Mechoulam's laboratory, was the cannabinoid field placed on a firm footing. Indeed, according to Mechoulam, "our interest in this fascinating field was kindled by the contrast of rich folklore and popular belief with paucity of scientific knowledge" (*1*, p. 36). The identification of Δ^9-THC led to the synthesis of high-affinity cannabinoid ligands, which in turn enabled the identification of a brain cannabinoid receptor (CB1) (*2*). First identified as an "orphan" clone coding for a putative heterotrimeric GTP-binding protein (G protein)–coupled receptor with an unknown ligand, CB1's activation by cannabinoids came as a surprise to its discoverers.

CB1 turns out to be one of the most abundant neuromodulatory receptors in the brain and is expressed at high levels in the hippocampus, cortex, cerebellum, and basal ganglia (*3*–*5*), presumably accounting for the striking effects of Δ^9-THC on memory and cognition (*1*). Most central effects of Δ^9-THC (e.g., catalepsy, tremor, decreased body temperature) are absent in CB1-deficient ($CB1^{-/-}$) mice (*6*, *7*), although Δ^9-THC still inhibits the spinal tail-flick reflex in these mice (*7*). This implies that CB1 mediates most or all supraspinal effects of marijuana, and consistent with this, Δ^9-THC–stimulated [^{3}H]GTPγS binding is abolished in the brains of $CB1^{-/-}$ mice (*8*). A second G protein–coupled cannabinoid receptor (CB2) appears to be absent from the brain but is enriched in immune tissues (*9*).

Finally, new data suggest there may be a third cannabinoid receptor ("CB3"). Brains of $CB1^{-/-}$ mice still show significant (though reduced) binding by the synthetic cannabinoid agonist [^{3}H]WIN55212-2. Moreover, both WIN55212-2 and the endogenous cannabinoid anandamide (but not Δ^9-THC) still stimulate some [^{3}H]GTPγS binding in $CB1^{-/-}$ brain tissue, and this binding is blocked by the cannabinoid antagonist SR141716 (*8*). This suggests the presence of an uncloned cannabinoid receptor in the brain that is sensitive to WIN55212-2, anandamide, and SR141716, but not Δ^9-THC. These results are consistent with data from the cardiovascular system, where anandamide induces mesenteric vasodilation that is blocked by SR141716, but that persists in $CB1^{-/-}$ mice (*10*).

In the hippocampus, immunogold electron microscopy shows CB1 localized exclusively to a subset of presynaptic GABA (γ-aminobutyric acid)–containing boutons (Fig. 1, A and B) (*11*–*13*), suggesting that a major function of hippocampal endocannabinoids is to regulate GABA release. Indeed, the agonist WIN55212-2 causes a presynaptic depression of GABAergic inhibitory postsynaptic currents (IPSCs) in hippocampal slices (*12*, *14*).

Two endogenous lipids present in brain tissue (anandamide and 2-arachidonylglycerol) have been identified as CB1 agonists (*15*, *16*). These ligands are not stored, as classical neurotransmitters are. Instead, they are rapidly synthesized by neurons in re-

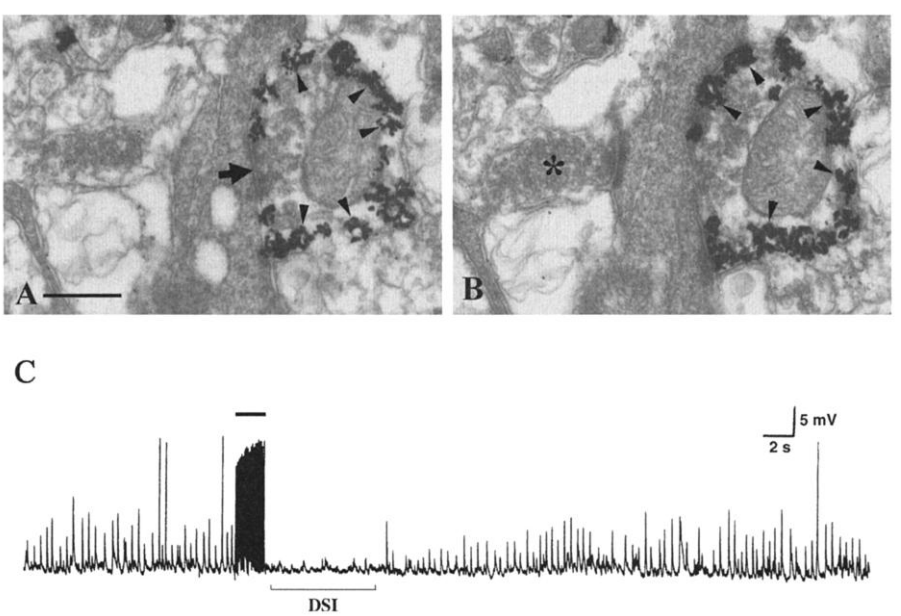

Fig. 1. (**A** and **B**) The subcellular localization of hippocampal CB1 by immunogold electron microscopy. (A) and (B) are serial sections. Arrowheads, silver/gold-enhanced colloidal gold particles indicating CB1 receptors in the axon terminal membrane. Arrow in (A) points to a symmetrical (GABAergic) synapse formed by the CB1-positive bouton. Boutons that form asymmetric synapses [asterisk in (B)] are always negative for CB1. Bar, 0.2 μm. [Adapted from Katona *et al.* (*13*).] (**C**) An example of depolarization-induced suppression of inhibition (DSI). Intracellular recording from a CA1 pyramidal cell (in the presence of ionotropic glutamate receptor antagonists) shows spontaneous GABAergic synaptic activity. Following a brief train of postsynaptic action potentials (thick horizontal bar), spontaneous events are transiently suppressed (thin bracket). [Adapted from Pitler and Alger (*23*).]

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sponse to depolarization and consequent Ca^{2+} influx (*17*, *18*). Because the biosynthetic enzymes that produce endocannabinoids are still being characterized, it is not yet possible to localize endocannabinoid production to a particular subcellular compartment. It has been suggested, however, that endocannabinoids might be released from neuronal somata and dendrites (*19*, *20*).

This review will focus on recent studies clarifying the synaptic mechanisms of endocannabinoid signaling, and discuss the functional implications of these new developments. Other aspects of this field are reviewed elsewhere (*1*, *17*, *18*, *21*).

Synaptic Mechanisms

How do endocannabinoids function at the synapse? Some answers have recently come from the study of a curious synaptic phenomenon first described a decade ago by Marty (*22*) and Alger (*23*). Marty, studying cerebellar Purkinje cells, and Alger, studying hippocampal pyramidal cells, showed that brief depolarization of a neuron can transiently suppress inhibitory GABAergic synaptic events in that cell. They dubbed this phenomenon "depolarization-induced suppression of inhibition," or DSI (Fig. 1C). Alger and Marty's results were exciting because they showed that DSI has a presynaptic locus, although it is postsynaptic in origin. In other words, postsynaptic depolarization must release a retrograde messenger that travels backward across synapses to suppress release of neurotransmitter from axons. DSI is arguably the most convincing example of rapid retrograde signaling in the brain, and as such, it clearly contradicts the textbook description of the synapse as a "one-way street" of information transfer. The mysterious retrograde messenger in hippocampal DSI appeared to be highly specific: It does not affect hippocampal glutamatergic synapses (*24*), which are excitatory. In the cerebellum, by contrast, the retrograde messenger in DSI affects glutamatergic synapses in an analogous phenomenon termed DSE (depolarization-induced suppression of excitation) (*25*).

Recent studies have now shown that hippocampal DSI and cerebellar DSI and DSE are blocked by CB1 antagonists, as well as being mimicked and occluded by a CB1 agonist (*25*–*30*). This indicates that the retrograde messenger in DSI and DSE is an endogenous cannabinoid.

Postsynaptic mechanisms. Postsynaptic depolarization will open voltage-gated Ca^{2+} channels, and three pieces of evidence link this Ca^{2+} influx to DSI and DSE. First, cytoplasmic Ca^{2+} increases after postsynaptic depolarizations that induce hippocampal DSI (*27*). Second, DSI and DSE induction require postsynaptic Ca^{2+}; Ca^{2+} chelators in the postsynaptic cell block DSI and DSE (*23*, *25*). Third, postsynaptic Ca^{2+} is sufficient to induce hippocampal DSI, because flash photolysis–induced release of caged Ca^{2+} in a single postsynaptic cell mimics the DSI induced by postsynaptic depolarization (*29*). These results agree with biochemical studies showing that endocannabinoid synthesis is largely Ca^{2+} dependent (*31*, *32*). Postsynaptic synthesis and release of endocannabinoids by this pathway must be fairly rapid. At hippocampal synapses, the latency between postsynaptic depolarization and presynaptic inhibition is, on average, about 1.2 s (*33*).

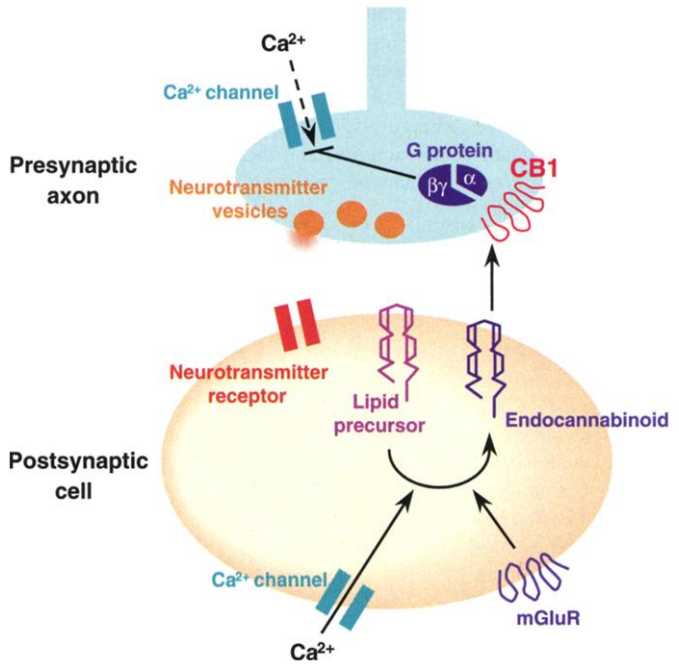

Fig. 2. Retrograde signaling by endocannabinoids. Postsynaptic depolarization opens voltage-dependent Ca^{2+} channels; postsynaptic Ca^{2+} then activates enzymes that synthesize endocannabinoids from lipid precursors. Activation of postsynaptic mGluRs can also generate endocannabinoids, possibly by activation of phospholipase C, generating diacylglycerol, which is then cleaved by diacylglycerol lipase to yield 2-arachidonylglycerol. Endocannabinoids then leave the postsynaptic cell and activate presynaptic CB1 receptors. G-protein activation liberates $G_{\beta\gamma}$, which then directly inhibits presynaptic Ca^{2+} influx. This decreases the probability of release of a vesicle of neurotransmitter.

Endocannabinoid synthesis can also be triggered by activation of group I metabotropic glutamate receptors (mGluRs). It was previously known that activation of group I mGluRs can suppress neurotransmitter release by acting at a presynaptic locus, even though group I mGluRs are localized almost exclusively to postsynaptic structures (*34*). This paradox has been resolved with findings of two new studies—one focusing on hippocampal GABAergic synapses (*28*) and the other on cerebellar climbing fiber synapses (*35*)—in which a CB1 antagonist was shown to block the effects of group I mGluR activation. Furthermore, inhibition of hippocampal GABA release by group I mGluRs is absent in $CB1^{-/-}$ mice (*28*). Ca^{2+} does not seem to be required for endocannabinoid synthesis mediated by this pathway, because a postsynaptic Ca^{2+} chelator does not block the effects of a group I mGluR agonist (*35*). Thus, mGluRs and depolarization appear to be two independent pathways to endocannabinoid synthesis (Fig. 2) which, together, can additively increase the magnitude of DSI (*28*).

Presynaptic mechanisms. Because hippocampal DSI is completely absent in CB1 knockout mice (*28*, *33*), it is likely that CB1 is the presynaptic target for hippocampal DSI. Consistent with this notion, hippocampal CB1 is expressed exclusively by inhibitory interneurons (*11*–*13*, *36*, *37*); hippocampal pyramidal neurons neither express CB1 nor show sensitivity to the ligands released during DSI. Because CB1 is present at both excitatory and inhibitory synapses onto Purkinje cells (*5*, *37*), it is a plausible target of both DSE and DSI in the cerebellum.

CB1 activation suppresses neurotransmitter release by decreasing the local release probability of synaptic vesicles (*14*, *19*, *25*, *27*, *29*, *38*) by inhibiting a Ca^{2+}-dependent step in vesicle release (*14*). In principle, CB1 could either decrease Ca^{2+} entry or else inhibit some subsequent Ca^{2+}-dependent step in exocytosis. Measurements from cerebellar climbing fiber synapses, which have large presynaptic arbors and are well suited to Ca^{2+} imaging, show a clear decrease in presynaptic Ca^{2+} entry associated with DSE (*25*). Ca^{2+} channels themselves appear to be inhibited by CB1, because a Ca^{2+}-channel antagonist, but not a cocktail of K^+-channel antagonists, blocks effects of CB1 activation (*14*). The rapid-onset kinetics of DSI (*33*) suggest that CB1 inhibits presynaptic Ca^{2+} channels by the direct pathway, whereby $G_{\beta\gamma}$ directly inhibits the channel, rather than by an indirect second messenger cascade. These results are consistent with previous work showing that cannabinoid receptors inhibit Ca^{2+} channels in CB1+ cell lines (*39*) and in cultured hip-

pocampal pyramidal neurons that express CB1 (unlike pyramidal neurons in situ) (*40*–*42*).

The putative "CB3" receptor may also have a presynaptic role in the hippocampus. The CB1 agonist WIN55212-2 suppresses glutamate release at excitatory synapses (*43*) even though these synapses do not contain CB1 (*11*–*13*, *36*, *37*). This effect persists in CB1 knockout mice (*44*), suggesting that "CB3" may be involved. Presynaptic inhibition by "CB3" seems mechanistically similar to hippocampal DSI and cerebellar DSE/DSI, involving a decrease in the probability of vesicular release (*43*). More work is needed to determine when and how "CB3" might be activated by endogenous ligands. Hippocampal DSE, for example, might require different patterns of postsynaptic excitation, and different modes of postsynaptic Ca^{2+} entry (*45*), compared with DSI. Because group I mGluRs, which are localized postsynaptically (*34*), inhibit release of glutamate as well as GABA at hippocampal synapses (*46*), this pathway may also produce a "CB3" ligand.

Diffusion and uptake. On the basis of biochemical data, it has been suggested that endocannabinoids might diffuse widely though brain tissue and affect brain regions remote from their site of release (*47*). Recently, this question has been addressed directly with electrophysiological techniques in the hippocampal slice. When simultaneous recordings were performed from two postsynaptic cells, and one cell was depolarized to elicit DSI, a simultaneous suppression of GABAergic events was often observed in the nondepolarized cell, likely reflecting diffusion of endocannabinoids across the distance separating the two postsynaptic neurons. However, spread of DSI was only seen across distances $\leq$20 μm (*29*). The degree of diffusion may vary with the architecture of different brain regions: In cerebellar slices, mGluR-dependent endocannabinoid synthesis was not observed to have any heterosynaptic effects (*35*). Together, these results indicate that endocannabinoids are quite local signals.

It is still unclear how newly synthesized endocannabinoids are induced to leave the postsynaptic plasma membrane. They may be secreted by simple diffusion; alternatively, passive (energy-independent) carrier proteins may be required to extrude endocannabinoids (*18*, *31*). After endocannabinoids have been released into the extracellular space, a specific transport protein on both neurons and glia appears to participate in endocannabinoid uptake (*18*, *31*). An antagonist of this transporter, AM404, potentiates the effect of exogenous anandamide on cultured neurons (*48*). In vivo, AM404 increases the effects of anandamide on blood pressure (*49*) and elevates circulating levels of anandamide in plasma (*50*). Similarly, in hippocampal slices, AM404 causes a progressive suppression of GABA release and decreases DSI (*29*). This suggests that blocking uptake causes endocannabinoids to accumulate in the slice, resulting in tonic CB1 activation and DSI occlusion.

After endocannabinoids are removed from the extracellular space, they are degraded by intracellular enzymes. Anandamide is destroyed by fatty acid amide hydrolase (FAAH) (*17*, *18*), and mice deficient in FAAH show significantly increased levels of brain anandamide, implying that FAAH helps regulate endogenous cannabinoid tone (*51*).

Together, these new results suggest that endocannabinoids are unusual neural signals (Fig. 2): These neuromodulatory ligands are rapidly synthesized in response to postsynaptic activity, and then move backward across synapses, violating the traffic rules of the brain. Given the wide, apparently exclusively presynaptic, distribution of CB1, it is likely that this phenomenon will be observed at other synapses in the brain. Future work should indicate whether retrograde synaptic movement represents the major mode of endocannabinoid signaling or whether other cellular mechanisms will emerge as equally fundamental.

Systems Effects

Endocannabinoids have been implicated in the function of many brain regions, including the hippocampus, neocortex, brainstem, basal ganglia, cerebellum, and olfactory bulb (*21*). We focus here on two systems—the hippocampus/neocortex, and nociceptive pathways of the brainstem and spinal cord—that are the subject of much recent work linking anatomy, cellular physiology, and behavior.

Hippocampus and neocortex. The hippocampus and neocortex probably use endocannabinoids to subserve the same functions, on the basis of the similarities in CB1 localization in these two regions. In both the hippocampus and neocortex, CB1 is only expressed by a morphologically and histochemically defined subpopulation of GABAergic interneurons (*11*, *36*, *52*) (Fig. 3). A striking property of CB1+ interneurons in the hippocampus and neocortex is that these cells generally express the neuromodulatory peptide cholecystokinin (CCK) (*11*, *36*, *52*). Consistent with this, CB1 activation suppresses CCK release in addition to GABA release (*53*). CCK generally antagonizes the neural and behavioral effects of opioids; thus, colocalization of CB1 and CCK might be one reason why cannabinoids and opioids have synergistic effects on the brain (*54*). CB1+ interneurons may also mediate cross talk between other neuromodulatory systems, because endocannabinoid-sensitive interneurons are selectively depolarized by acetylcholine (*55*) and substance P (*12*).

CB1+ interneurons are also distinctive in that they form GABAergic synapses with

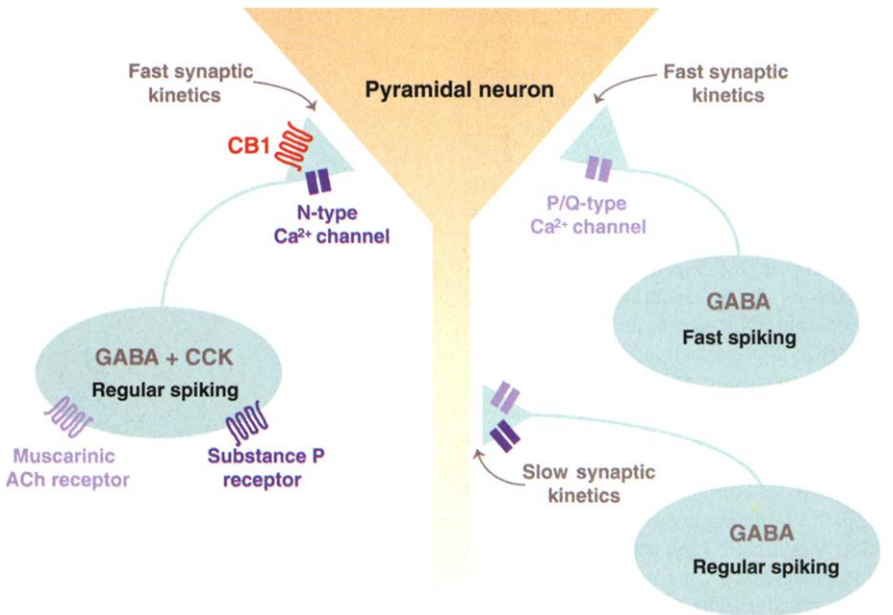

Fig. 3. Endocannabinoids and the inhibitory hippocampal network. Endocannabinoids selectively inhibit GABA release from regular-spiking basket cells. These cells also release the neuromodulatory peptide CCK and are depolarized by acetylcholine and substance P. CB1+ interneurons use only N-type Ca^{2+} channels at the presynaptic bouton; the function of this presynaptic specialization is unknown, but may confer supersensitivity to presynaptic inhibition because N-type channels are strongly inhibited by $G_{\beta\gamma}$. Another class of basket cells is negative for CB1 and CCK, fast-spiking, and uses only P/Q-type Ca^{2+} channels for GABA release. Finally, regular-spiking cells forming synapses with slow kinetics on distal dendrites use both N- and P/Q-type channels for GABA release and are endocannabinoid insensitive.

particularly fast kinetics (*33*, *55*). Single inhibitory neurons contact hundreds of principal neurons in the hippocampus, and this widespread connectivity is important in synchronizing the firing of principal neurons. Interneurons forming fast synapses are thought to orchestrate fast synchronous oscillations in the gamma range (20 to 80 Hz) (*56*). Gamma oscillations are synchronized over long distances in the brain and are hypothesized to bind together sensory perceptions and to play a role in cognition (*57*). Because endocannabinoid-sensitive synapses are of this fast type, endocannabinoids would be predicted to selectively suppress gamma oscillations in vivo, an idea supported by recent in vitro data (*12*).

An equally important function of inhibitory interneurons is to control plasticity at excitatory synapses. Blocking inhibition generally promotes long-term potentiation (LTP) at excitatory synapses. Consistent with this notion, hippocampal DSI also promotes LTP. This interaction of DSI and LTP is blocked by antagonists of CB1 or $GABA_A$ receptors, implying that DSI indeed facilitates LTP by endocannabinoid-mediated disinhibition (*58*). It would be premature, however, to conclude that endocannabinoids promote learning: $CB1^{-/-}$ mice reportedly exhibit both impaired (*6*) and enhanced (*59*) memory, and locomotor deficits in these mice (*7*) make it difficult to design meaningful behavioral tests. Also, the CB1/"CB3" antagonist SR141716 has no effect (*60*, *61*) or has even a positive effect (*62*) on memory—although, again, hyperlocomotive effects of SR141716 (*63*) potentially complicate this picture.

In addition, ligands that bind "CB3" (anandamide, WIN55212-2), and that inhibit hippocampal glutamate release, also inhibit LTP (*43*, *64*, *65*). This effect of "CB3" ligands has a straightforward mechanism: Decreased glutamate release means that postsynaptic depolarization is insufficient to remove the Mg^{2+} block of *N*-methyl-D-aspartate (NMDA) receptors (*43*). Future experiments should indicate whether the endogenous ligands of "CB3" also inhibit LTP in the context of physiological release, and if so, how this process might interact with DSI to regulate plasticity up or down.

Because Δ^9-THC is apparently not an effective ligand for "CB3" (*8*), marijuana's effects on memory may be mediated entirely by CB1. This implies that Δ^9-THC in the hippocampus acts mainly on GABAergic synapses. If marijuana suppresses many hippocampal inhibitory synapses, this might permit promiscuous plasticity and possibly cause deficits in cognition and recall. However, Δ^9-THC does not increase basal firing rates of hippocampal neurons and in fact inhibits firing elicited by certain sensory stimuli during a learning task (*61*). This implies that marijuana does not produce a global disinhibition—consistent with the observation that many GABAergic synapses are insensitive to cannabinoids (*27*, *33*, *55*)—and suggests that a more complex model may be required to explain how marijuana impairs learning and memory.

Pain pathways. Analgesic properties have been ascribed to *Cannabis sativa* since ancient times (*1*), and endocannabinoids are now thought to participate in a natural analgesic system. Administration of the CB1 antagonist SR141716 causes hyperalgesia (*66*, *67*), implying that endocannabinoids tonically regulate nociception by way of CB1. Furthermore, in vivo microdialysis reveals elevated levels of brainstem endocannabinoids after noxious stimuli (*68*). Although receptors on primary afferents probably play a role in cannabinoid analgesia (*69*, *70*), the most important mechanism of analgesia seems to be modulation of descending inhibitory inputs from the brainstem to spinal nociceptive neurons (*67*, *71*). This brainstem circuit comprises the midbrain periaqueductal gray (PAG) and the rostral ventromedial medulla (RVM), both of which contain CB1 (*5*). Stimulation of either the PAG or the RVM produces analgesia (*72*), as does microinjection of CB1 agonists into either site (*73*, *74*). This suggests that cannabinoids might disinhibit both the PAG and RVM.

Recent in vitro experiments recording from brainstem slices provide a cellular basis for this hypothesis. The CB1 agonist WIN55212-2 reduces GABA release from the presynaptic boutons of local interneurons in the RVM (*75*). This should increase activity in a class of RVM neurons that suppress nociception. Similarly, WIN55212-2 inhibits GABA release from the boutons of interneurons in the PAG (*76*), again with predicted analgesic effects. In these brainstem sites, as in the hippocampus, CB1 appears to be exclusively presynaptic, and its effects are generally disinhibitory (*75*, *76*). More work will be necessary to determine which molecules in the endocannabinoid signaling cascade represent the best targets for analgesic drugs. Because $FAAH^{-/-}$ mice exhibit reduced pain sensitivity, blocking endocannabinoid degradation may prove to be a useful strategy (*51*).

Future directions. The recent developments described here pose some broad functional questions for the cannabinoid field. Why do there seem to be two cannabinoid systems in the brain—a CB1 system and a "CB3" system? When might these systems be differentially activated? Do constitutively active cannabinoid receptors tonically regulate these circuits, or are particularly strong stimuli required to generate sufficient levels of endocannabinoids? Do endogenous cannabinoids and marijuana generally affect the brain in the same way? Or could it be that, whereas endocannabinoids are involved in local control of neuronal activity, Δ^9-THC activates CB1 receptors widely and tonically and disrupts rather than mimics this local system? More selective pharmacological and genetic tools may soon permit advances in the neurophysiology of endocannabinoids and may allow us to pose—and ultimately test—these questions in more concrete form.

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