CURRENT OPINION
www.current-opinion.com

Functional interactions between cannabinoid and metabotropic glutamate receptors in the central nervous system

James Doherty* and Raymond Dingledine†

The recent appreciation that two G-protein-coupled receptors, metabotropic glutamate and cannabinoid, are trans-synaptically linked by a small lipid messenger has profound implications, both for control of synaptic transmission and for novel therapeutic strategies. There is much evidence for this assertion and on the significance of this dual receptor cooperation for modulation of synaptic transmission in the central nervous system.

Addresses
*Correspondence: Department of Neuroscience, AstraZeneca Pharmaceuticals, 1800 Concord Pike, Wilmington, DE 19803, USA
e-mail: james.doherty@astrazeneca.com
†Department of Pharmacology, Emory University Medical School, 1510 Clifton Road, Atlanta, GA 30322, USA

Current Opinion in Pharmacology 2003, **3**:46–53

This review comes from a themed issue on
Neurosciences
Edited by Robert S Sloviter and Thomas P Blackburn

1471-4892/03/$ – see front matter
© 2003 Elsevier Science Ltd. All rights reserved.

DOI 10.1016/S1471-4892(02)00014-0

Abbreviations

2-AG	arachidonylglycerol
ACPD	(1*S*,3*R*)-1-aminocyclopentane-1,3-dicarboxylic acid
BG	basal ganglia
CNS	central nervous system
CPCCOEt	7-(hydroxyimino)cyclopropa[b]chromen-1a-carboxylate ethyl ester
DHPG	dihydroxyphenylglycine
DSI	depolarisation-induced suppression of inhibition
eCN	endocannabinoid
EPSC	excitatory postsynaptic current
GABA	γ-n-aminobutyric acid
IPSC	inhibitory postsynaptic current
LTD	long-term depression
LTP	long-term potentiation
mGluR	metabotropic glutamate receptor
MPEP	2-methyl-6-(phenylethynyl)pyridine
PAG	periaqueductal grey
PLC	phospholipase C

Introduction

Metabotropic glutamate receptors (mGluRs) are a family of G-protein-coupled receptors distributed throughout the central nervous system (CNS). Through actions on several signal transduction cascades, mGluRs modulate multiple CNS functions, including neuronal excitability [1,2] and neurotransmitter release [3]. Because of their sensitivity to the ubiquitous neurotransmitter glutamate, molecular diversity, widespread distribution and perisynaptic localisation, it is widely hypothesised that mGluRs serve critical roles in information processing in the brain. Initial studies with recombinant receptor systems expressed in heterologous cells highlighted a linkage of mGluR activation to adenylate cyclase and phospholipid metabolism; however, mGluRs couple to additional signalling cascades *in vivo*. Many mGluR-mediated physiological functions depend on these alternative signal transduction cascades. Despite a widespread recognition that manipulation of mGluR signalling may have therapeutic benefits, a comprehensive understanding of how mGluR activation is coupled to physiological functions does not yet exist.

The mGluRs belong to family three of the G-protein-coupled receptors. Eight different mGluR subtypes have been identified to date, each represented by a single gene. The subtypes are segregated into three groups based on sequence homology, transduction mechanisms and agonist pharmacology [1,4]. In heterologous expression systems, group I mGluRs (mGluR1 and mGluR5) are coupled through Gq to a mechanism that stimulates phospholipase C (PLC) and thereby phosphoinositide hydrolysis. Group II mGluRs (mGluR2 and mGluR3) are negatively coupled by Gi to adenylate cyclase in heterologous expression systems. The group III mGluRs (mGluRs 4, 6, 7 and 8) are also negatively coupled by Gi to adenylate cyclase, but have a pharmacology that is distinct from that of the group II mGluRs [1,4].

Recent data from several investigators have begun to uncover an entirely novel signalling mechanism for mGluRs, namely the production and subsequent release of the signalling molecules known as endocannabinoids (eCNs). Put another way, some of the effects previously attributed directly to mGluR activation are in reality indirectly mediated by signalling through the eCN system. Evidence for this interaction between mGluRs and the eCN system can be found for both short- and long-term forms of synaptic plasticity and may have direct implications for the design of therapeutics for neurological disorders.

The eCN system is a novel G-protein-coupled receptor signalling cascade that participates in numerous CNS functions (for recent reviews see [5–7]). eCNs are endogenously produced, membrane-permeable lipids that activate cannabinoid receptors. The cannabinoid receptors were originally identified based on their responsiveness to Δ^9-tetrahydrocannabinol (Δ^9-THC), the main psychoactive component of *Cannabis sativa*. Two sub-

Table 1

Pharmacological tools for modulating the endocannabinoid system.

Agonists
Δ^9-THC
CP 55,940 (CB1=CB2, partial agonist)
HU-210 (CB1>CB2)
Anandamide
2-AG
WIN55,212-2 (CB2>CB1)
ACEA (CB1)
Antagonists
Cannibidiol
Inverse agonists
SR141416A
AM251 (CB1)
AM281 (CB1)
AM630 (6-Iodopravadoline)
Anandamide transporter inhibitor
AM 404

See [14,57].

Table 2

Inhibition of neurotransmitter release by cannabinoid receptors in the CNS.

Acetylcholine
Cortical synaptosomes [71]
Hippocampus [72]
Dopamine
Retina [73]
GABA
Hippocampus [29,74,75•]
Neocortex [76]
Nucleus accumbens [77]
PAG [69]
Spinal cord [79]
Ventromedial medulla [78]
Ventral tegmental area [88]
Glutamate
Cerebellum [32•,35,80]
Hippocampus [29,75•]
Neocortex [81]
Nucleus accumbens [77,82]
PAG [78]
Prefrontal cortex [83]
Spinal cord [79,84]
Striatum [85,86]
Substantia nigra [80]
Glycine
Spinal cord [79]
Norepinepherine
Hippocampus [87]

types of cannabinoid receptor, CB1 and CB2, have been cloned to date [8,9]. CB1 and CB2 have a 44% amino acid identity. Both genes code for G-protein-coupled receptors that couple through G proteins of the $G_{i/o}$ family to inhibition of adenylyl cyclase (negative coupling) and activation of mitogen-activated protein kinase pathways. In addition, CB1 receptor activation potentiates certain voltage-sensitive potassium channels [10]. CB2 receptors are primarily localised to cells in the immune system, whereas CB1 receptors are found throughout the CNS in addition to expression in the immune and cardiovascular systems [5,11–13].

The identification of CB-selective compounds (Table 1; for review see [14]) has allowed for investigation of cannabinoid receptor function in the CNS. Thus, several CB1 agonists have now been shown to inhibit the synaptic release of a variety of neurotransmitters, including glutamate and γ-n-aminobutyric acid (GABA), as well as norepinephrine, acetylcholine, dopamine and glycine (Table 2). It is likely that additional uncharacterised cannabinoid receptors exist, including a non-CB1, non-CB2 receptor in the hippocampus that is activated by anandamide (arachidonoyl ethanolamide) and WIN55,212-2, but not CP55,940 [15•].

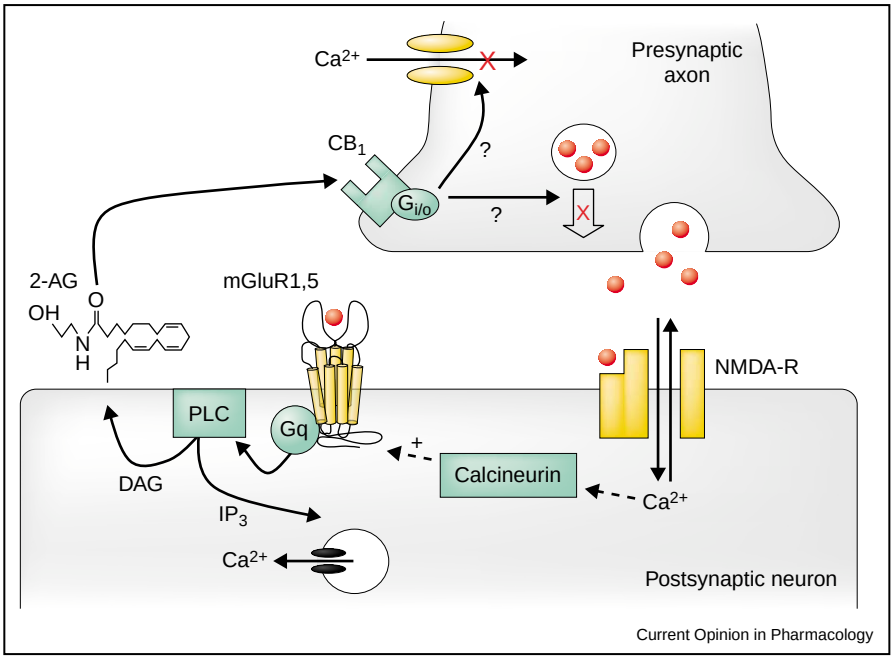
Although the biochemistry of the eCN signalling system is still under investigation, significant components of their synthesis, transport and degradation have recently been elucidated (for recent reviews see [5,16]). The eCNs are produced by hydrolysis of membrane lipids [17] and are released in a non-vesicular fashion either tonically or in response to activating stimuli. Several eCNs have been identified; the major forms include 2-arachidonoylglycine, anandamide and 2-arachidonylglycerol (2-AG). For anandamide, rapid hydrolysis by fatty acid amide hydrolase is thought to mediate termination of signalling [18]. The degradation pathway for 2-AG is currently unresolved.

At this point, the identity of the eCN(s) produced by activation of group I mGluRs is unknown; however, 2-AG is a strong candidate (see Figure 1). High-frequency stimulation-induced long-term potentiation (LTP) increases the release of 2-AG but not anandamide [19]. This high-frequency stimulation-induced production of 2-AG is dependent on an increase in both intracellular Ca^{2+} and PLC activity. Group I mGluRs activate PLC and trigger increases in intracellular calcium levels [1]. Although the biochemistry of stimulation-induced 2-AG production remains to be determined, two major biosynthetic pathways have been proposed [7]. In the first, 1,2-diacylglycerol produced by PLC-mediated hydrolysis of membrane lipids is converted to 2-AG by diacylglycerol lipase. In the second pathway, activation of phospholipase A produces lysophospholipids that are converted to 2-AG by lysophospholipase C.

Regulation of synaptic transmission

One of the functions of mGluRs is the regulation of neurotransmitter release [1,2]. For example, selective

Figure 1



A proposed model for the interaction between postsynaptic mGluRs and retrograde signalling through the endocannabinoid (eCN) system. Synaptic activity triggers the release of glutamate and activation of postsynaptic ionotropic and metabotropic glutamate receptors. Activation of group I mGluRs leads to activation of PLC and the production of diacylglycerol (DAG) and inositol triphosphate (IP_3), and a subsequent release of intracellular calcium. Activation of this transduction pathway triggers the production of eCNs, such as anandamide and 2-AG. eCNs diffuse away from the postsynaptic cell or are transported through the plasma membrane to act as retrograde messengers on the presynaptic cell. eCNs bind to CB1-type cannabinoid receptors at presynaptic terminals. CB1 activation leads to a reduction in neurotransmitter release through an as yet undetermined mechanism: potentially either inhibition of calcium influx or a direct effect on vesicle release machinery. Postsynaptic NMDA receptor activation can relieve mGluR5 desensitisation through the activation of the phosphatase, calcineurin. This mechanism may facilitate the group I mGluR/eCN retrograde signalling pathway, producing a presynaptic inhibition of neurotransmitter release that is dependent on the activity of NMDA, mGluR and CB1 receptors.

agonists for all three mGluR subtypes inhibit glutamate release at numerous CNS synapses. For group II and group III mGluRs, this inhibition of glutamate release is mediated by presynaptic autoreceptors, in which mGluRs expressed at presynaptic sites on glutamatergic terminals act either to limit calcium entry through voltage-gated calcium channels or through a direct disruption of vesicle-release machinery. For group I mGluRs, however, the story is more complicated. Although immunohistochemical localisation for mGluR1 and mGluR5 at the electron microscopy level overwhelmingly points to postsynaptic expression [20–24], group I receptor agonists reduce neurotransmitter release at numerous CNS synapses. For example, the group I-selective agonist, dihydroxyphenylglycine (DHPG), reversibly depresses glutamate release onto both principal cells and GABAergic interneurons in the hippocampus [25,26]. At Schaffer collateral inputs to CA1 pyramidal cells, this group-I-mediated reduction of synaptic transmission is mediated by mGluR1 [27]. Thus, despite a postsynaptic localisation at the majority of synaptic connections, activation of group I mGluRs can reduce neurotransmitter release. This disconnection between localisation and physiological action for group I mGluRs has been difficult to reconcile; however, it now seems likely that at least some of the action of both mGluR1 and mGluR5 is mediated by eCN signalling.

One clue to solving this problem was provided by the observation that CB1 receptor immunoreactivity in the hippocampus is found exclusively on presynaptic terminals of GABAergic interneurons [28–30]. The group I mGluR-selective agonist, DHPG, reversibly suppressed inhibitory postsynaptic potentials in paired whole-cell recordings from rat hippocampal neuronal cultures [31]. This effect was blocked by the mGluR5-selective antagonist, 2-methyl-6-(phenylethynyl)pyridine (MPEP), and SR141716A, a CB1 selective inverse agonist, suggesting that mGluR5 activation triggers the production and retrograde transport of eCNs in hippocampal pyramidal cells that presynaptically inhibit GABA release through CB1 receptors. Thus the retrograde eCN link neatly explains the old conundrum that activation of postsynaptic group I mGluR inhibits transmitter release.

Given the widespread expression of postsynaptic group I mGluRs throughout the CNS, and a similarly extensive

expression of CB1 receptors, an obvious question about this surprising interaction is how generalised is the mechanism? The simple answer from the studies that have appeared so far is that mGluR/eCN signalling appears to be a widespread feature of neuronal circuitry.

For example, a similar mechanism operates in the mouse cerebellum. As in the hippocampus, activation of postsynaptic group I mGluRs depresses neurotransmitter release through an eCN-mediated retrograde activation of presynaptic CB1 receptors. In contrast to the hippocampus, however, synaptic depression in the cerebellum has been observed at glutamatergic rather than GABAergic synapses. The CB1-selective antagonists, AM281 and SR141716, block group-I-mediated depression of glutamate release at climbing fiber inputs to Purkinje cells [32•]. This effect is very likely to be mediated by mGluR1, as group I agonist-induced depression of glutamate release was impaired at climbing fiber synapses in mGluR1 (-/-) mice [32•]. Climbing fiber input was also transiently depressed when mGluR1 was activated by parallel fiber stimulation rather than by exogenously applied DHPG. Thus, synaptic activation of mGluR1 also causes the production of eCNs, which in turn diffuse to presynaptic climbing fiber terminals and mediate the observed depression of synaptic glutamate release.

Parallel fiber input to Purkinje cells is also inhibited by activation of group I mGluRs [33,34] as well as presynaptic cannabinoid receptors [35]. Cannabinoid receptor activation depresses presynaptic calcium influx by activating presynaptic potassium channels [36]. Whether cannabinoid antagonists can block mGluR-mediated synaptic depression at parallel fiber synapses has yet to be determined; however, interestingly, 1*S*,3*R*-ACPD-mediated inhibition of glutamate release at these synapses is abolished in mGluR1 (-/-) mice, but is intact in mGluR5 (-/-) mice [33]. It is therefore quite plausible that a similar mGluR/eCNs mechanism occurs at both climbing fiber and parallel fiber inputs to Purkinje cells.

eCNs regulate synaptic release of several neurotransmitters (Table 2; for review see [17]), as do mGluRs (for review see [2]). It is quite possible that the described mechanism linking mGluRs and eCNs in regulating glutamate and GABA release will also be relevant to the regulation of these other transmitters.

Short-term plasticity

The studies described above demonstrate a functional linkage between mGluRs and cannabinoid receptors, but do not directly reveal how this interaction is relevant to CNS function; however, several recent studies indicate that mGluR/eCN signalling is involved in several well-studied forms of synaptic plasticity. Depolarisation-induced suppression of inhibition (DSI) is a phenomenon described in several synaptic networks throughout the CNS, including hippocampal neurons [37,38] and cerebellum [38,39]. Brief (1–3 s) depolarisation of principal glutamatergic neurons transiently suppresses inhibitory postsynaptic potentials through the generation of a retrograde messenger, a signal that diffuses to the synaptic terminals of nearby GABAergic interneurons and transiently depresses GABA release. DSI is thus a form of activity-dependent short-term plasticity that results in transient disinhibition of excitatory inputs to the depolarised neuron and can thus facilitate long-term plasticity [40]. The retrograde messenger was recently identified as an eCN in both hippocampal slices [41] and hippocampal culture [42], and subsequently confirmed in cerebellar slices [43]. Given the evidence presented above, regarding the linkage of mGluR and CB1 signalling, a simple hypothesis would be that DSI is mediated by activation of postsynaptic group I receptors. There is some data to support such an assertion. The group I/II mGluR antagonist, α-methyl-4-carboxyphenylglycine, blocked the induction of DSI in the hippocampus [44]; however, other results indicate mGluR antagonists do not block DSI in hippocampal cultures [42], hippocampal slices [41] or cerebellar slices [43,45]. Negative results with mGluR antagonists indicate that mGluR signalling may not be absolutely required for DSI; postsynaptic depolarisation may lead to elevation of intracellular calcium and subsequent eCN production through more than one signal transduction cascade. However, as described above, activation of group I mGluRs can produce eCNs that act through presynaptic CB1 receptors to inhibit transmitter release. Furthermore, DSI is significantly potentiated by co-activation of group I mGluRs [31,46•]. The CB1 receptor antagonist, AM-251, blocks DHPG-mediated suppression of inhibitory postsynaptic currents (IPSCs) in the hippocampus [46•]. Finally, mGluR agonists were not able to suppress IPSCs onto CA1 pyramidals in CB1 (-/-) mice [46•]. These observations strongly support the notion that group I mGluR activation strongly modulates the activity of the eCN system in DSI. It should be noted that small rises in $[Ca^{2+}]_i$ caused by moderate activation of NMDA receptors can allosterically potentiate mGluR5 by a calcineurin-dependent pathway (Figure 1; [47,48]), further enriching the opportunities for synaptic modulation at glutamatergic synapses.

The eCN/mGluR interaction may also be active in other portions of the CNS. For example, an activity-dependent retrograde inhibition of GABAergic IPSCs has been reported in neocortical pyramidal neurons [49]. This retrograde inhibition is dependent on mGluRs as well as elevations in postsynaptic intracellular calcium. Because mGluR antagonists blocked retrograde inhibition, it was concluded that glutamate is the retrograde messenger; however, in light of the mGluR/eCN pathway described here, it would be interesting to determine whether blockade of the eCN system would abolish the retrograde signal in the neocortex.

Long-term plasticity

In addition to various mechanisms of short-term plasticity, mGluR/CB1 interactions also contribute to long-lasting synaptic plasticity. In the mouse nucleus accumbens, tetanic stimulation of glutamatergic afferents induces long-term depression (LTD). Several lines of evidence link mGluR5-mediated eCN production to tetanus-induced LTD [50•]. First, the CB1 agonist, WIN55,212-2 occluded LTD induction, whereas the CB1-selective antagonist, SR141716A, blocked induction. WIN55,212-2 reduced spontaneous excitatory postsynaptic current (EPSC) frequency without changing EPSC amplitude, strongly suggesting a presynaptic action site of action for CB1 receptors. Second, an eCN transport inhibitor, AM-404, attenuated tetanus-induced LTD, whereas tetanic stimulation did not produce LTD in the CB1 (-/-) mouse. This eCN-mediated form of LTD was dependent on postsynaptic activation of mGluR5 and a subsequent rise in intracellular calcium. The mGluR5 selective antagonist, MPEP, completely blocked the eCN-dependent LTD. The LTD was also blocked by high (50 μM), but not low (200 nM) concentrations of the mGluR antagonist, LY341495, which is consistent with activation of group I mGluR. Finally, the group I agonist DHPG induced LTD in wild type, but not CB1 (-/-), mice.

In the striatum, a similar form of LTD also appears to depend on both group I mGluRs and eCNs. The induction of striatal LTD is group I mGluR-dependent, as both mGluR1 and mGluR5 selective antagonists block LTD induction [51]. Striatal LTD is blocked by SR141716A and abolished in CB1 (-/-) mice [52], indicating a requirement for CB1 receptors in the induction of striatal LTD. However, experiments that directly establish the link between mGluR5 and eCNs in striatal LTD have not yet been reported.

Recently, it has been reported that eCN-mediated DSI enabled a normally subthreshold tetanus to induce LTP in hippocampal CA1 pyramidal cells [40]. This result seemingly contradicts a large body of work indicating that cannabinoid receptor activation impairs LTP induction (for review see [6]), but is consistent with the reduced LTP threshold observed with reduced GABAergic inhibition [53,54].

Therapeutic implications

The potential for cannabinoid (for review see [5,55–57]) and metabotropic glutamate (for review see [58–61]) receptors as targets for the development of novel pharmacotherapies has been extensively reviewed. Given the novel interaction between these two receptor signalling systems, it is relevant to speculate on how this newly discovered interaction between mGluRs and eCNs may be important in drug development. Although there are numerous therapeutic areas where these two receptor systems overlap, we briefly highlight the potential relevance of mGluR/eCN signalling in the treatment of movement disorders, cognitive impairment and pain.

Reciprocal feedback regulation of neocortical activity by the basal ganglia (BG), a highly interconnected group of sub-thalamic nuclei, is critical for the control of motor behaviour. Disorders in BG function are associated with a number of movement disorders, including Parkinson's disease, Huntington's disease and Tourette's syndrome. Both CB1 receptors [62] and group I mGluRs [24,63] are highly expressed within BG circuitry and the roles of mGluRs in regulating the circuitry of the BG have been intensively investigated (for review see [60]). In a similar sense, the eCNs system also participates in regulating BG function (for review see [55]). Are any effects of group I mGluRs in the BG indirectly mediated by CB1 receptors? Although this has not yet been tested, one strong candidate is group-I-mediated regulation of glutamatergic neurotransmission. Activation of mGluR1 presynaptically inhibits synaptic glutamate release onto neurons in the subthalamic nucleus [64] and substantia nigra pars reticulata [24]. Glutamatergic input to the substantia nigra pars reticulata is also presynaptically regulated by CB1 receptors [65]. eCN signalling becomes overactive in Parkinson's disease (for review see [55]), implying that a reduction in mGluR/eCN signalling may have therapeutic value. In support of this possibility, chronic treatment with mGluR5-selective antagonist, MPEP, produced a significant improvement in motor performance in a rodent model of Parkinson's disease [66•].

Systemic activation of cannabinoid receptors leads to cognitive deficits in rodents and man (for review see [6]); however, local eCN release following DSI facilitates the induction of LTP [40]. The likeliest explanation for this disparity is that the relatively focal disinhibition produced by eCN signalling during DSI allows induction of LTP, whereas a more global disinhibition produces disruption of plasticity. Perhaps this localised disinhibition produced by mGluR/eCN-mediated DSI can be exploited as a cognitive enhancing strategy, either by potentiating the activation of group I mGluRs (for review see [67]) or by inhibiting reuptake of eCNs (for review see [5]).

Both mGluRs and cannabinoid receptors have been implicated in the neurobiology of pain (for review see [5,68]). One potential point of convergence is in the periaqueductal grey area (PAG): a midbrain region that participates in the central processing of nociception. Activation of CB1 receptors inhibits the release of both glutamate and GABA in the PAG through a presynaptic mechanism [69]. mGluR5 has been recently demonstrated to participate in cannabinoid-mediated antinociception in the PAG. Microinjections of MPEP, but not CPCCOEt, into the PAG blocked the antinociceptive

effects of WIN55,212-2 [70]. It is unlikely, therefore, that the mechanism of this mGluR/eCN interaction is the one described throughout this review. In this case, a mGluR5-selective antagonist blocked the effects of a directly administered CB agonist. Because CB1 activation is downstream of mGluR signalling in the proposed cascade (see Figure 1), these results imply a more complicated mechanism. Furthermore, the antinociceptive effects of direct injection of (*RS*)-2-chloro-5-hydroxyphenylglycine, a mGluR5-selective agonist, into the PAG were not blocked by SR141716A [70]. Thus, defining the interaction between mGluR- and cannabinoid-induced analgesia in the PAG will require a more detailed understanding of PAG circuitry.

Conclusions

Data reviewed here link the inhibition of glutamate and GABA release mediated by cannabinoid agonists to mGluR activation. The picture emerges that activation of postsynaptic group I mGluRs (both mGluR1 and mGluR5) causes the postsynaptic production of eCNs, which in turn diffuse out of the postsynaptic neuron in a retrograde fashion to presynaptic terminals, where they bind to CB1 receptors and mediate the observed depression of transmission by reducing transmitter release. This linkage has been demonstrated in the hippocampus and cerebellum, but evidence suggests that it may occur in other brain regions, including the ventral tegmentum and BG. New experiments will be required to confirm an interaction between mGluRs and the eCN system in these brain regions.

Acknowledgements

The authors would like to thank Amy Doherty for assistance with preparation of the manuscript and the NINDS for research support at Emory University (RD).

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Conn PJ, Pin J-P: **Pharmacology and functions of metabotropic glutamate receptors**. *Annu Rev Pharmacol Toxicol* 1997, **37**:205-237.

2. Anwyl R: **Metabotropic glutamate receptors: electrophysiological properties and role in plasticity**. *Brain Res Rev* 1999, **29**:83-120.

3. Cartmell J, Schoepp DD: **Regulation of neurotransmitter release by metabotropic glutamate receptors**. *J Neurochem* 2000, **75**:889-907.

4. Schoepp DD, Jane DE, Monn JA: **Pharmacological agents acting at subtypes of metabotropic glutamate receptors**. *Neuropharmacol* 1999, **38**:1431-1476.

5. Goutopoulos A, Makriyannis A: **From cannabis to cannabinergics: new therapeutic opportunities**. *Pharm Ther* 2002, **95**:103-117.

6. Davies SN, Pertwee RG, Riedel G: **Functions of cannabinoid receptors in the hippocampus**. *Neuropharmacol* 2002, **42**:993-1007.

7. Piomelli D, Beltramo M, Guiffrida A, Stella N: **Endogenous cannabinoid signaling**. *Neurobiol Dis* 1998, **5**:462-473.

8. Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI: **Structure of a cannabinoid receptor and functional expression of the cloned cDNA**. *Nature* 1990, **346**:561-564.

9. Munro S, Thomas KL, Abu-Shaar M: **Molecular characterization of a peripheral receptor for cannabinoids**. *Nature* 1993, **365**:61-65.

10. Deadwyler S, Hampson RE, Childers SR: **Functional significance of cannabinoid receptors in brain.** In *Cannabinoid Receptors*. Edited by Pertwee R. London: Academic press; 1995:206-227.

11. Tsou K, Brown S, Sanudo-Pena MC, Mackie K, Walker JM: **Immunohistochemical distribution of cannabinoid CB1 receptors in the rat central nervous system**. *Neurosci* 1998, **83**:393-411.

12. Marsicano G, Lutz B: **Expression of the cannabinoid receptor CB1 in distinct neuronal subpopulations in the adult mouse forebrain**. *Eur J Neurosci* 1999, **11**:4213-4225.

13. Egertova M, Elphick MR: **Localisation of cannabinoid receptors in the rat brain using antibodies to the intracellular c-terminal tail of CB1**. *J Comp Neurol* 2000, **422**:159-171.

14. Howlett AC, Barth F, Bonner TI, Cabral G, Casellas P, Devane WA, Felder CC, Herkenham M, Mackie K, Martin BR *et al.*: **International Union of Pharmacology. XXVII. Classification of cannabinoid receptors**. *Pharmacol Rev* 2002, **54**:161-202.

15. • Breivogel CS, Griffin G, DiMarzo V, Martin BR: **Evidence for a new G protein-coupled cannabinoid receptor in mouse brain**. *Mol Pharm* 2001, **60**:155-163.
Study of a variety of CB1 agonists and antagonists in wild-type and CB1 receptor null mice provides strong inferential evidence for a third CB receptor.

16. Kumar RN, Chambers WA, Pertwee RG: **Pharmacological actions and therapeutic uses of cannabis and cannabinoids**. *Anaesthesia* 2002, **56**:1059-1068.

17. DiMarzo V, Melck D, Bisogno T, DePetrocellis L: **Endocannabinoids: endogenous cannabinoid receptor ligands with neuromodulatory action**. *Trends Neurosci* 1998, **21**:521-528.

18. Thomas EA, Cravatt BF, Danielson PE, Gilula NB, Sutcliffe JG: **Fatty acid amide hydrolase, the degenerative enzyme for anandamine and oleamide, has selective distribution in neurons within the rat central nervous system**. *J Neurosci Res* 1997, **50**:1047-1052.

19. Stella N, Schweitzer P, Piomelli D: **A second endogenous cannabinoid that modulates long-term potentiation**. *Nature* 1997, **388**:773-778.

20. Baude A, Nusser Z, Roberts JD, Mulvihill E, McIlhinney RA, Somogyi P: **The metabotropic glutamate receptor (mGluR1α) is concentrated at perisynaptic membrane of neuronal subpopulations as detected by immunogold reaction**. *Neuron* 1993, **11**:771-787.

21. Luján R, Nusser Z, Roberts JDB, Shigemoto R, Somogyi P: **Perisynaptic location of metabotropic glutamate receptors mGluR1 and mGluR5 on dendrites and dendritic spines in the rat hippocampus**. *Eur J Neurosci* 1996, **8**:1488-1500.

22. Shigemoto R, Kinoshita A, Wada E, Nomura S, Ohishi H, Takada M, Flor PJ, Neki A, Abe T, Nakanishi S *et al.*: **Differential presynaptic localization of metabotropic glutamate receptor subtypes in the rat hippocampus**. *J Neurosci* 1997, **17**:7503-7522.

23. Testa CM, Friberg IK, Weiss SW, Standaert DG: **Immunohistochemical localization of metabotropic glutamate receptors mGluR1a and mGluR2/3 in the rat basal ganglia**. *J Comp Neurol* 1998, **390**:5-19.

24. Wittmann M, Hubert GW, Smith Y, Conn PJ: **Activation of metabotropic glutamate receptor 1 inhibits glutamatertic transmission in the substantia nigra pars reticulata**. *Neurosci* 2001, **105**:881-889.

25. Gereau RW, Conn PJ: **Multiple presynaptic metabotropic glutamate receptors modulate excitatory and inhibitory synaptic transmission in hippocampal area CA1**. *J Neurosci* 1995, **15**:6879-6889.

26. Doherty J, Dingledine R: **Differential regulation of excitatory synaptic inputs to hilar border interneurons in the dentate gyrus by metabotropic glutamate receptors**. *J Neurophysiol* 1998, **79**:2903-2910.

27. Mannaioni G, Marino M, Valenti O, Traynelis SF, Conn PJ: **Metabotropic glutamate receptors 1 and 5 differentially regulate CA1 pyramidal cell function**. *J Neurosci* 2001, **21**:5925-5934.

28. Irving AJ, Coutts AA, Harvey J, Rae MG, Mackie K, Bewick GS, Pertwee RG: **Functional expression of cell surface cannabinoid CB1 receptors on presynaptic inhibitory terminals in cultured rat hippocampal neurons**. *Neuroscience* 2000, **98**:253-262.

29. Katona I, Sperlágh B, Sík A, Käfalvi A, Vizi ES, Mackie K, Freund T: **Presynaptically located CB1 cannabinoid receptors regulate GABA release from axon terminals of specific hippocampal interneurons**. *J Neurosci* 1999, **19**:4544-4558.

30. Tsou K, Mackie K, Sanudo-Pena MC, Walker JM: **Cannabinoid CB1 receptors are localized primarily on cholecystokinin-containing GABAergic interneurons in the rat hippocampal formation**. *Neurosci* 1999, **93**:969-975.

31. Ohno-Shosaku T, Shosaku J, Tsubokawa H, Kano M: **Cooperative endocannabinoid production by neuronal depolarization and group I metabotropic glutamate receptor activation**. *Eur J Neurosci* 2002, **15**:953-961.

32. • Maejima T, Hashimoto K, Yoshida T, Aiba A, Kano M: **Presynaptic inhibition caused by retrograde signal from metabotropic glutamate to cannabinoid receptors**. *Neuron* 2001, **31**:463-475.
Evidence is presented for two distinct mechanisms for cannabinoid-mediated inhibition of excitatory transmitter release from climbing fibers onto cerebellar Purkinje cells. One mechanism involves activation of postsynaptic mGluR1 receptors; the other involves postsynaptic Ca^{2+} entry through voltage-gated Ca^{2+} channels.

33. Levenes C, Daniel H, Crepel F: **Retrograde modulation of transmitter release by postsynaptic subtype 1 metabotropic glutamate receptors in the rat cerebellum**. *J Physiol* 2001, **537**:125-140.

34. Neale SA, Garthwaite J, Batchelor AM: **Metabotropic glutamate receptor subtypes modulating neurotransmision at parallel fibre-Purkinje cell synapses in rat cerebellum**. *Neuropharmacol* 2001, **41**:42-49.

35. Levenes C, Daniel H, Soubrié P, Crepel F: **Cannabinoids decrease excitatory synaptic transmission and impair long-term depression in rat cerebellar Purkinje cells**. *J Physiol* 1998, **510**:867-879.

36. Daniel H, Crepel F: **Control of Ca^{2+} influx by cannabinoid and metabotropic glutamate receptors in rat cerebellar cortex requires K^+ channels**. *J Physiol* 2001, **537**:793-800.

37. Alger BE, Pitler TA, Wagner JJ, Martin LA, Morishita W, Kirov SA, Lenz RA: **Retrograde signalling in depolarization-induced suppression of inhibition in rat hippocampal CA1 cells**. *J Physiol* 1996, **496**:197-209.

38. Ohno-Shosaku T, Sawada S, Yamamoto C: **Properties of depolarization-induced suppression of inhibitory transmission in cultured rat hippocampal neurons**. *Pflugers Arch* 1998, **435**:273-279.

39. Llano I, Leresche N, Marty A: **Calcium entry increases the sensitivity of cerebellar Purkinje cells to applied GABA and decreases inhibitory synaptic currents**. *Neuron* 1991, **6**:565-574.

40. Carlson G, Wang Y, Alger BE: **Endocannabinoids facilitate the induction of LTP in the hippocampus**. *Nat Neurosci* 2002, **5**:723-724.

41. Wilson RI, Nicoll RA: **Endogenous cannabinoids mediate retrograde signalling at hippocampal synapses**. *Nature* 2001, **410**:588-592.

42. Ohno-Shosaku T, Maejima T, Kano M: **Endogenous cannabinoids mediate retrograde signals from depolarized postsynaptic neurons to presynaptic terminals**. *Neuron* 2001, **29**:729-738.

43. Kreitzer AC, Regehr WG: **Cerebellar depolarization-induced suppression of inhibition is mediated by endogenous cannabinoids**. *J Neurosci* 2001, **21**:RC174-RC178.

44. Morishita W, Alger BE: **Evidence for endogenous excitatory amino acids as mediators in DSI of $GABA_A$ergic transmission in hippocampal CA1**. *J Neurophysiol* 1999, **82**:2556-2564.

45. Yoshida T, Hashimoto K, Zimmer A, Maejima T, Araishi K, Kano M: **The cannabinoid CB1 receptor mediates retrograde signals for depolarization-induced suppression of inhibition in cerebellar purkinje cells**. *J Neurosci* 2002, **22**:1690-1697.

46. • Varma N, Carlson GC, Ledent C, Alger BE: **Metabotropic glutamate receptors drive the endocannabinoid system in hippocampus**. *J Neurosci* 2001, **21**:RC188.
Depolarization-mediated inhibition in the hippocampus is shown to be enhanced by mGluR activation and blocked in CB1 receptor null mice.

47. Alagarsamy S, Marino MJ, Rouse ST, Gereau RW IV, Heinemann SF, Conn PJ: **Activation of NMDA receptors reverses desensitization of mGluR5 in native and recombinant systems**. *Nat Neurosci* 1999, **2**:234-240.

48. Alagarsamy S, Mansuy I, Gereau RW IV, Conn PJ: **NMDA-induced reversal of mGluR5 desensitization is mediated by activation of protein phosphatase 2B/calcineurin**. *Soc Neurosci Abstr* 2000, **26**:910.

49. Zilberter Y: **Dendritic release of glutamate suppresses synaptic inhibition of pyramidal neurons in rat neocortex**. *J Physiol* 2000, **528**:489-496.

50. • Robbe D, Kopf M, Remaury A, Bockaert J, Manzoni OJ: **Endogenous cannabinoids mediate long-term synaptic depression in the nucleus accumbens**. *Proc Natl Acad Sci USA* 2002, **99**:8384-8388.
eCNs produce activity-dependent long-term synaptic depression in the nucleus accumbens. This study demonstrates that postsynaptic mGluR5 signalling allows glutamatergic neurotransmission to induce synaptic plasticity by coupling to retrograde eCN signalling.

51. Sung K-W, Choi S, Lovinger DM: **Activation of group I mGluRs is necessary for induction of long-term depression at striatal synapses**. *J Neurophysiol* 2001, **86**:2405-2412.

52. Gerdeman G, Lovinger D: **Postsynaptic endocannabinoid release is critical to long-term depression in the striatum**. *Nat Neurosci* 2002, **5**:446-451.

53. Yasui M, Kawasaki K, Matsushita A, Satoh M: **Benzodiazepine inverse agonists augment long-term potentiation in CA1 and CA3 of guinea pig hippocampal slices**. *Neuropharmacol* 1993, **32**:127-131.

54. Hsu KS, Ho WC, Huang CC, Tsai JJ: **Prior short-term synaptic disinhibition facilitates long-term potentiation and suppresses long-term depression at CA1 hippocampal synapses**. *Eur J Neurosci* 1999, **11**:4059-4069.

55. Romero J, Lastres-Becker I, de Miguel R, Berrendero F, Ramos JA, Fernandez-Ruiz: **The endogenous cannabinoid system and the basal ganglia: biochemical, pharmacological, and therapeutic aspects**. *Pharmacol Ther* 2002, **95**:137-152.

56. Pertwee RG: **Cannabinoids and multiple sclerosis**. *Pharmacol Ther* 1998, **95**:165-174.

57. Consroe P: **Brain cannabinoid systems as targets for the therapy of neurological disorders**. *Neurobiol Dis* 2002, **5**:534-551.

58. Chavez-Noriega LE, Schaffhauser H, Campbell U: **Metabotropic glutamate receptors: potential drug targets for the treatment of schizophrenia**. *Current Drug Targets-CNS & Neurological Disorders* 2002, **1**:261-281.

59. Doherty J, Dingledine R: **The roles of metabotropic glutamate receptors in seizures and epilepsy**. *Current Drug Targets-CNS & Neurological Disorders* 2002, **1**:251-260.

60. Marino MJ, Conn PJ: **Modulation of basal ganglia by metabotropic glutamate receptors: potential for novel therapeutics**. *Current Drug Targets-CNS & Neurological Disorders* 2002, **1**:239-250.

61. Varney MA, Gereau RW IV: **Metabotropic glutamate receptor involvement in models of acute and persistent pain: prospects for the development of novel analgesics**. *Current Drug Targets-CNS & Neurological Disorders* 2002, **1**:283-296.

62. Herkenham M, Lynn AB, de Costa BR, Richfield EK: **Neuronal localization of cannabinoid receptors in the basal ganglia of the rat**. *Brain Res* 1991, **547**:267-274.

63. Testa CM, Standaert DG, Young AB, Penney JB Jr: **Metabotropic glutamate receptor mRNA expression in the basal ganglia of the rat**. *J Neurosci* 1994, **14**:3005-3018.

64. Awad-Granko H, Conn PJ: **Activation of group I or III metabotropic glutamate receptors inhibits excitatory transmission in the rat subthalamic nucleus**. *Neuropharmacol* 2001, **41**:32-41.

65. Szabo B, Wallmichrath I, Mathonia P, Pfreundtner C: **Cannabinoids inhibit excitatory neurotransmission in the substantia nigra pars reticulata**. *Neurosci* 2000, **97**:89-97.

66. • Breysse N, Baunez C, Spooren W, Gasparini F, Amalric M: **Chronic but not acute treatment with a metabotropic glutamate 5 receptor antagonist reverses the akinetic deficits in a rat model of parkinsonism**. *J Neurosci* 2002, **22**:5669-5678.
Chronic, but not acute, treatment with the mGluR5-selective antagonist MPEP attenuated specific akinetic motor deficits in an animal model of Parkinson's disease.

67. Pin J-P, DeColle C, Bessis A-S, Acher F: **New perspectives for the development of selective metabotropic glutamate receptor ligands**. *Eur J Pharmacol* 1999, **375**:277-294.

68. Neugebauer V: **Metabotropic glutamate receptors-important modulators of nociception and pain behavior**. *Pain* 2002, **98**:1-8.

69. Vaughn CW, Connor M, Bagley EE, Cristie MJ: **Actions of cannabinoids on membrane properties and synaptic transmission in rat periaqueductal gray neurons *in vitro***. *Mol Pharm* 2000, **57**:288-295.

70. Palazzo E, Marabese I, de Novellis V, Oliva P, Rossi F, Berrino L, Rossi F, Maione S: **Metabotropic and NMDA glutamate receptors participate in the cannabinoid-induced antinociception**. *Neuropharmacology* 2001, **40**:319-326.

71. Gifford AN, Bruneus M, Gatley SJ, Volkow ND: **Cannabinoid receptor-mediated inhibition of acetylcholine release from hippocampal and cortical synaptosomes**. *Br J Pharmacol* 2000, **131**:645-650.

72. Gifford AN, Ashby JRCR: **Electrically evoked acetylcholine release from hippocampal slices is inhibited by the cannabinoid receptor agonist, WIN 55212-2, and is potentiated by the cannabinoid antagonist, SR 141716A**. *J Pharmacol Exp Ther* 1996, **277**:1431-1436.

73. Schlicker E, Timm J, Göthert M: **Cannabinoid receptor-mediated inhibition of dopamine release in the retina**. *Naunyn Schmiedebergs Arch Pharmacol* 1996, **354**:791-795.

74. Hoffman AF, Lupica CR: **Mechanisms of cannabinoid inhibition of $GABA_A$ synaptic transmission in the hippocampus**. *J Neurosci* 2000, **20**:2470-2479.

75. • Hájos N, Freund T: **Pharmacological separation of cannabinoid sensitive receptors on hippocampal excitatory and inhibitory fibers**. *Neuropharmacol* 2002, **43**:503-510.
Evidence is presented that a novel G-protein-coupled receptor sensitive to cannabinoid and vanilloid receptor ligands regulates excitatory, but not inhibitory, synaptic transmission in the hippocampus.

76. Trettel J, Levine ES: **Cannabinoids depress inhibitory synaptic inputs received by layer 2/3 pyramidal neurons of the neocortex**. *J Neurophysiol* 2002, **88**:534-539.

77. Hoffman AF, Lupica CR: **Direct actions of cannabinoids on synaptic transmission in the nucleus accumbens: a comparison with opoids**. *J Neurophysiol* 2001, **85**:72-83.

78. Vaughn CW, McGregor IS, Christie MJ: **Cannabinoid receptor activation inhibits GABAergic neurotransmission in rostral ventromedial medulla neurons *in vitro***. *Br J Pharmacol* 1999, **127**:935-940.

79. Jennings EA, Vaughn CW, Christie MJ: **Cannabinoid actions on rat superficial medullary dorsal horn neurons *in vitro***. *J Physiol* 2001, **534**:805-812.

80. Kreitzer AC, Regehr WG: **Retrograde inhibition of presynaptic calcium influx by endogenous cannabinoids at excitatory synapses onto Purkinje cells**. *Neuron* 2001, **29**:717-727.

81. Ferraro L, Tomasini MC, Gessa GL, Bebe BW, Tanganelli S, Antonelli T: **The cannabinoid receptor agonist WIN 55,212-2 regulates glutamate transmission in rat cerebral cortex: and *in vivo* and *in vitro* study**. *Cereb Cortex* 2001, **11**:728-733.

82. Robbe D, Alonso G, Duchamp F, Bockaert J, Manzoni OJ: **Localization and mechanisms of cannabinoid receptors at the glutamatergic synapses of the mouse nucleus accumbens**. *J Neurosci* 2001, **21**:109-116.

83. Auclair N, Otani S, Soubrie P, Crepel F: **Cannabinoids modulate synaptic strength and plasticity at glutamatergic synapses of rat prefrontal cortex pyramidal neurons**. *J Neurophysiol* 2000, **83**:3287-3293.

84. Morisset V, Urban L: **Cannabinoid-induced presynaptic inhibition of glutamatergic EPSCs in substantia gelatinosa neurons of the rat spinal cord**. *J Neurophysiol* 2001, **86**:40-48.

85. Gerdeman G, Lovinger D: **CB1 cannabinoid receptor inhibits synaptic release of glutamate in rat dorsolateral striatum**. *J Neurophysiol* 2001, **85**:468-471.

86. Huang C-C, Lo S-W, Hsu K-S: **Presynaptic mechanisms underlying cannabinoid inhibition of excitatory synaptic transmission in rat striatal neurons**. *J Physiol* 2001, **532**:731-748.

87. Schlicker E, Timm J, Zentner J, Göthert M: **Cannabinoid CB1 receptor-mediated inhibition of noradrenaline release in the human and guinea-pig hippocampus**. *Naunyn Schmiedebergs Arch Pharmacol* 1997, **356**:583-589.

88. Szabo B, Siemes S, Wallmichrath I: **Inhibition of GABAergic neurotransmission in the ventral tegmental area by cannabinoids**. *Eur J Neurosci* 2002, **15**:2057-2061.