Mol Neurobiol (2009) 39:178–184
DOI 10.1007/s12035-009-8061-4

Adaptations of Striatal Endocannabinoid System During Stress

Silvia Rossi · Valentina De Chiara · Alessandra Musella · Giorgia Mataluni · Lucia Sacchetti · Giorgio Bernardi · Alessandro Usiello · Diego Centonze

Received: 10 December 2008 / Accepted: 18 February 2009 / Published online: 7 March 2009

Abstract The endocannabinoid system (ECS) plays a fundamental role in the regulation of synaptic transmission. Exposure to stressful events triggers synaptic adaptations in many brain areas. The activity of the ECS in stress-responsive neural circuits suggests that it may be involved in the behavioral responses and synaptic effects typical of stress. In this review, we discuss evidence demonstrating that striatal ECS is modulated by stress. Chronic stress exposure alters endocannabinoid levels, cannabinoid CB1 receptor binding and cannabinoid CB1 receptor-mediated control of inhibitory synaptic transmission in the striatum. Recent studies have shown that impairment of endocannabinoid signalling is associated with inability to adapt to chronic stress and to the development of maladaptive behaviors. The ECS represents a novel potential pharmacological target to treat stress-associated neuropsychiatric conditions.

Keywords Anxiety · Cocaine · Depression · FAAH · Glucocorticoids · Natural reward

S. Rossi · V. De Chiara · A. Musella · G. Mataluni · G. Bernardi · D. Centonze (✉)
Clinica Neurologica, Dipartimento di Neuroscienze,
Università Tor Vergata,
Via Montpellier 1,
00133 Rome, Italy
e-mail: centonze@uniroma2.it

S. Rossi · V. De Chiara · A. Musella · G. Mataluni · G. Bernardi · D. Centonze
Centro Europeo per la Ricerca sul Cervello (CERC)/Fondazione Santa Lucia,
Rome, Italy

L. Sacchetti
Clinica Psichiatrica, Dipartimento di Neuroscienze,
Università Tor Vergata,
Rome, Italy

A. Usiello
Behavioural Neuroscience Laboratory,
CEINGE-Biotecnologie Avanzate,
Naples, Italy

A. Usiello
Department of Health Science, Università del Molise,
Campobasso, Italy

Introduction

Cannabis sativa is a psychoactive substance used recreationally worldwide for its relaxing and stress alleviating properties. These emotional alterations are mostly mediated by the ability of its constituent Δ9-tetrahydrocannabinol [1] to interact with specific cannabinoid receptors throughout the brain. Two receptors have been characterized and cloned to date, CB1 and CB2 receptors. They are both G-protein-coupled receptors that activate Galpha$_{i/o}$ proteins resulting in inhibition of adenylyl cyclase activity [2, 3]. In addition, they activate mitogen-activated-protein kinases and ion channels as A-type and inwardly rectifying potassium channels and inhibit calcium channels activated by membrane depolarizations [2–4].

The CB1 receptor is the predominant cannabinoid receptor in the central nervous system [5, 6], but, at lower expression levels, it has been found also in the periphery such as blood vessels, immune cells, and reproductive tissues [7–9]. The CB2 receptor is located mainly in immune cells, such as macrophages [7] and microglia [10], but evidence exists that it is also expressed in neurons of the brainstem, cortex, and cerebellum [11, 12]. In addition to these targets, some cannabinoids may exhibit affinity for other receptor subtypes, such as transient receptor potential vanilloid 1 (TRPV1) receptors [13] or transient receptor potential ankjrin 1 receptors [14], peroxisome-proliferator-activated receptors [15] and non-CB1/CB2 G-protein-coupled receptors GPR55 [16].

Several endogenous ligands of the cannabinoid receptors, termed endocannabinoids, have been isolated from brain tissues, anandamide (AEA, [17]) and 2-arachidonoylglycerol (2-AG, [18]) being the best characterized. Both endocannabinoids are synthesized preferentially postsynaptically by cleavage of phospholipidic groups by specific enzymes, such as diacylglycerol lipase (DAGL) for 2-AG, and a Ca^{2+}-dependent N-acyltransferase together with N-acylphosphatidylethanolamine-specific phospholipase D (NAPE-PLD) for AEA [19]. Endocannabinoid levels, therefore, are maintained by catabolic enzymes, and namely by the fatty acid amide hydrolase (FAAH) for AEA and by the monoacylglyceride lipase (MAGL) for 2-AG [20, 21] even if a recent study suggests the involvement of FAAH in controlling 2-AG levels [22].

The endocannabinoids, synthesized “on demand” in response to increased neuronal excitation or increased intracellular calcium, act in a retrograde manner to activate the presynaptic CB1 receptors and to inhibit neurotrasmitter release [23, 24]. Endocannabinoid-mediated retrograde control of synaptic activity has also been recently demonstrated after activation of group I metabotropic glutamate receptors [25, 26] or dopamine D2 receptors [27, 28]. The neurophysiological consequences of the activation of CB1 receptors depend on the localization of these receptors in various brain regions and the excitatory or inhibitory pathways being stimulated. Hence, the clinical potential of cannabinoid drugs is vast.

Alterations in the endocannabinoid system have been found in many neuropsychiatric disorders, such as Huntington’s disease [29, 30], Parkinson’s disease [31–33], Alzheimer disease [34], multiple sclerosis [35, 36], chronic migraine [37], schizophrenia [38], drug addiction [39, 40], and major depression [41]. Furthermore, the presence of the endocannabinoid system in stress-responsive neural circuits, as limbic structures and the striatum [3, 5, 6], suggests that it may play a critical role in regulating behavioral responses to stress and to stress-associated neuropsychiatric conditions. In fact, the activation of the endocannabinoid system (ECS) during stress modulates complex responses, such as stress-induced analgesia [42], escaping behavior [43], suppression of reproductive behavior [44], and sensitivity to natural reward [45]. CB1 receptors are also involved in the extinction of aversive memories through a selective inhibitory effect on the amygdala [46].

The aim of this review is to describe the current state of knowledge concerning the regulation of the ECS by stress in the striatum. The striatum plays a central role in motor, cognitive, and emotional functions modulated by stress [47, 48] and contains high levels of cannabinoid receptors controlling both excitatory and inhibitory synaptic transmission [3, 29, 40, 49, 50].

Furthermore, this review will also briefly discuss the therapeutical implications of stress-induced alterations in endocannabinoid signalling.

Effect of Stress on Striatal Endocannabinoid Levels

In vitro data demonstrated that both AEA and 2-AG contents increase in hypothalamic tissue after application of glucocorticoids [51], suggesting that stress could result in a rapid induction of endocannabinoid signalling. Conversely, acute stress exposure (30 min of restraint stress) failed to alter endocannabinoid levels in the ventral striatum [52] and decreased them in other neural structures [52, 53].

Other studies have addressed the regulation of striatal endocannabinoid levels under conditions of chronic stress. The effects of repeated homotipic stress have been examined in male mice exposed to five to ten daily sessions of restraint stress for 30 min [52]. In this study, an opposite pattern of AEA alteration has been described, since AEA content was significantly elevated in the ventral striatum following 10 but not 7 days of repeated restraint stress, whereas 2-AG content was reduced following 7 but not 10 days of this treatment. Since it has been hypothesized that glutamatergic synapses are primarily controlled by AEA while GABAergic terminals by 2-AG [54, 55] and it has demonstrated that AEA can inhibit 2-AG-mediated control of GABAergic transmission [56], the changes of the two endocannabinoids in opposite direction could result in enhanced GABAergic tone of synaptic transmission. The implications of this change are not clear at this stage, but it could reflect the habituation process of behavioral responses that usually occurs after repeated homotipic stress.

A different pattern of ECS-stress interaction has been seen when animals are exposed to chronic unpredictable and varying stress regimens. These protocols are associated with hypersecretion of glucocorticoids and lack of habituation [57]. In the study by Hill and coworkers [58], exposure of rats for 21 days to chronic unpredictable stress (CUS) reduced tissue content of AEA in ventral striatum and in other brain regions. This finding stands in contrast to an earlier study [59], in which CUS failed to affect AEA and 2-AG contents in the ventral striatum (Table 1). It is likely that methodological differences are responsible for this discrepancy.

Reduction of cannabinoid activity could contribute to the development of depression, by promoting maladaptive responses to prolonged stress. In fact, the CUS model is

Table 1 The effects of stress on striatal content of endocannabinoids and CB1 receptors

Stress paradigm	AEA	2-AG	CB1	Reference
Restraint stress (30 min)	–	–	n.d.	Rademacher et al. [52]
CRS (7 days)	–	↓	n.d.	Rademacher et al. [52]
CRS (10 days)	↑	–	–	Rademacher et al. [52]
CUS (21 days)	↓	–	↓	Hill et al. [58]
CUS (21 days)	n.d.	n.d.	↓	Hillard et al. [61]
CUS (70 days)	–	–	–	Bortolato et al. [59]

AEA anandamide, *2-AG* 2-arachidonylglycerol, *CRS* chronic restraint stress, *CUS* chronic unpredictable stress, –no change, ↓ reduction, ↑ increase, *n.d.* not determined

considered as a valid model of depression, eliciting abnormal behavioral and physiological responses reminiscent of those observed in depressed patients: alterations in feeding and body weight, enhanced fearfulness, impaired sleep architecture, and inadequate self-care [60].

Effects of Stress on Striatal Cannabinoid Receptors

The expression of cannabinoid CB1 receptors during conditions of stress has been poorly investigated so far. Rademacher and coworkers [52] reported that exposure to 10 days of repeated stress failed to affect CB1 receptor binding in the ventral striatum. In contrast, exposure to CUS seems to lead to different effects, since CB1 receptor binding site density was reduced by CUS in the ventral striatum [58, 61]. Furthermore, a recent report showed that no change occurred in striatal CB1 mRNA after 70 days of chronic mild unpredictable stress [59]. The differences in the duration of stress regimen could account for these discrepant findings (Table 1).

Because of the diverse methodological approaches, it is difficult to compare the alterations of the ECS that follow chronic homotypic stress and those induced by chronic heterotypic stress. However, the existing data seem to suggest that disruption of the endocannabinoid signalling may prevent adaptive responses and compromise the habituation process during CUS. In line with this, the antagonism of the CB1 receptor has been found to partially reverse the habituation of behavioral activation and neuroendocrine responses in repeatedly stressed mice [43]. Moreover, mice lacking cannabinoid CB1 receptors showed a complete absence of habituation of freezing behaviors when exposed repeatedly to an audiogenic stressor [62]. Thus, deficiencies in the endocannabinoid signalling could prevent the normally occurring adaptation to a repeatedly presented aversive stimulus.

Functional Effects of Stress on Striatal Endocannabinoid Transmission

The biochemical findings reported above suggest an association between stress and endocannabinoid-mediated neurotransmission in the striatum. We have found, by means of neurophysiological recordings from single neurons, a rearrangement of cannabinoid CB1 receptor-mediated control of synaptic transmission in the dorsal striatum of mice exposed to aggression [63]. We have shown, in fact, that a social defeat stress paradigm, able to induce anxiety-like behavior, impaired the sensitivity of GABA synapses to CB1 stimulation. The presynaptic inhibition of GABAergic inhibitory postsynaptic currents, induced by the cannabinoid CB1 receptor agonist HU210, was reduced after a single stressful episode, and fully abolished after 3 and 7 days of stress exposure. We also found that social stress altered the synaptic effects not only of exogenous cannabinoids but also of endocannabinoids mobilized in the striatum in response to mGlu 5 receptor stimulation (Fig. 1). This finding provides support to the notion that stress-induced alteration of cannabinoid transmission may have relevant synaptic consequences during the physiological activity of the striatum, mainly driven by glutamate inputs originating from the cortex and the thalamus.

Furthermore, the stress effect was specific for cannabinoid receptors controlling GABA transmission, while the sensitivity of glutamate synapses to CB1 receptor stimulation was unaltered, indicating a possible differential regulation of distinct cannabinoid receptors. The synaptic alterations found in the dorsal striatum after the stress paradigm were mimicked by corticosterone injections and were prevented by the glucocorticoid receptor antagonist RU486, indicating that corticosteroids released in response to the activation of the hypothalamic-pituitary-adrenal axis play a major role in the synaptic defects of stressed animals [63].

We observed that the recovery of stress-induced synaptic defects were accelerated after exposure to natural rewards and to the psychostimulant cocaine [63], as well as to caffeine [64] (Fig. 1). Enriched environment and novelty exploration has been reported to accelerate the reversal of stress-induced synaptic defects in the hippocampus, as well [65, 66]. Therefore, the synaptic alterations induced by stress in the nervous system are sensitive to the activation of the central reward system. In addition, the integrity of endocannabinoid signalling seems to be important for maintaining reward salience, a phenomenon usually dimin-

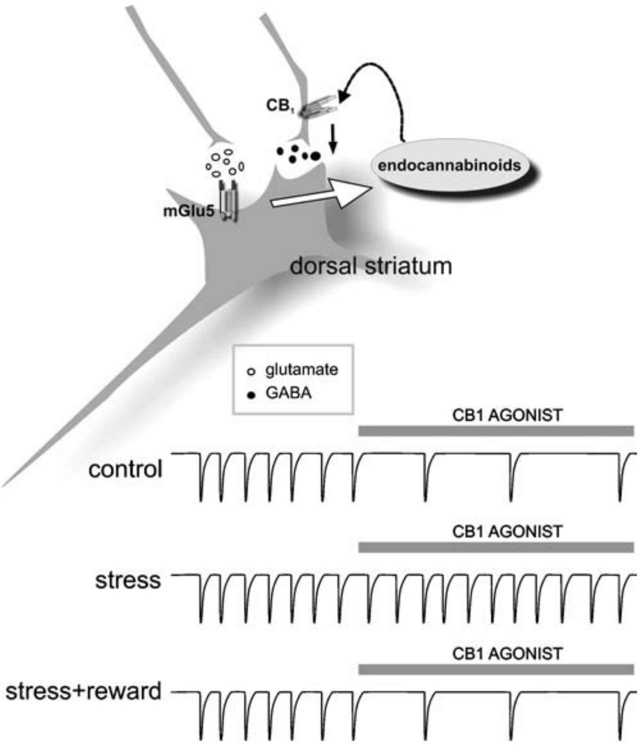

Fig. 1 Overall scheme of the functional effects of stress on striatal endocannabinoid transmission. The endocannabinoids, released in the striatum after stimulation of mGlu 5 receptors by glutamate, act as retrograde signals to limit GABA release through the stimulation of presynaptic CB1 receptors. The *draws on the bottom* are examples of the CB1-mediated inhibition of GABAergic currents (downward deflections) that is present in control condition, abolished after chronic stress exposure, preserved by natural rewards and psychostimulant substances with rewarding properties such as cocaine and caffeine

ished under conditions of protracted stress [67], while a disruption of this neuromodulatory system could prevent this adaptive response. In fact, acute treatment with a CB1 receptor agonist has been found to attenuate stress-induced reduction in sucrose preference, while treatment with the CB1 receptor antagonist rimonabant has been shown to exacerbate it [45].

Effects of Stress on ECS in Other Brain Areas

The major system involved in the neuroendocrine stress response is the hypothalamic-pituitary-adrenocortical (HPA) axis. This system is critically regulated by ECS. According to the "gatekeeper" hypothesis [53], endocannabinoid signalling negatively modulates stress-induced activation of HPA axis. Under basal conditions, endocannabinoids within the paraventricular nucleus of the hypothalamus inhibit excitatory inputs to HPA. Their rapid decline after stress exposure leads to an increased release of corticotropin-releasing hormone into the portal blood, as well as of adrenocorticotropic hormone from the anterior pituitary and of corticosterone from the adrenals [53].

In line with the proposed role of ECS in the adaptation to a repeated aversive stimulus, evidence exists that chronic stress-induced deficits in cognitive flexibility are related to impaired endocannabinoid signalling in the hippocampus [68], another brain region involved in stress effects.

Of note, the ECS often cross-talks with the endovanilloid system in stress-related brain areas [69]. AEA, in fact, is also an important modulator of TRPV1 receptors [13], leading to opposite effects via CB1 stimulation and TRPV1 stimulation on the control of glutamatergic signalling [55]. It also exerts an indirect control on GABAergic signalling by counteracting metabolism and physiological effects of 2-AG [56]. TRPV1 antagonism or genetic inactivation seems to produce anxiolytic effects in rodents [70, 71]. By contrast, TRPV1 channel has been proposed as a potential target to facilitate LTP and suppress LTD, in turn protecting hippocampal synaptic plasticity and spatial memory retrieval from the influence of acute stress [72]. Much research is still needed to understand the exact role to ECS-endovanilloid system in both physiology of the central nervous system and in stress-related pathologic conditions.

Therapeutical Implication of Stress-induced Alterations of the ECS

Since the ECS seems to be important for the maintenance of stress adaptation and impaired endocannabinoid activity is associated with maladaptive responses to stress, the enhancement of endocannabinoid-mediated neurotransmission could be a pharmacological mean to induce and preserve adaptive responses to stress. A poor stress adaptation is related to the development of depression. Thus, targeting cannabinoid CB1 receptors or endocannabinoid metabolism might be a valuable option to treat stress-associated neuropsychiatric conditions and mood disorders.

Several preclinical studies have suggested that agents facilitating the endocannabinoid signalling exhibit antidepressant potential. Specifically, URB597, a FAAH activity inhibitor, increased the amount of time spent by animals in the open arms of an elevated maze [73], decreased plasma corticosterone levels in restrained mice [53], enhanced stress-coping behaviors in the forced swim test in rats, and in the tail suspension test in mice [74]. This pharmacological agent also attenuated the development of anhedonia after repeated restraint stress [45] and normalized body weight gain and sucrose intake in rats exposed to chronic heterotypic mild stress [59]. Of note, indirect modulation of ECS seems to have a more beneficial profile than direct CB1 receptor agonism. In particular, FAAH inhibition does not cause hypothermia, catalepsy, or hyperphagia, three typical signs of CB1 receptor activation [73].

Furthermore, several treatments which are beneficial to depression, such as electroconvulsive shock and tricyclic antidepressant consumption, increased CB1 receptor activity in subcortical neural structures [75, 76]. In addition, CB1 receptors are required for the behavioral effects of noradrenergic antidepressants [77]. Not surprisingly, therefore, recent clinical trials for obesity with rimonabant, a CB1 receptor antagonist, have revealed a significant increase in the percentage of patients reporting symptoms of anxiety and depression [78, 79].

Conclusions

The ECS has an essential role in the regulation of synaptic transmission. Dysregulation of the endocannabinoid signalling in the striatum is associated with the effects of chronic stress exposure and, in particular, with poor adaptation to repeated adversive stimuli. A compromised habituation to stress can contribute to the development of maladaptive behaviors such as anhedonia and enhancement of endocannabinoid activity by targeting uptake and metabolic enzyme inhibitors might be a valuable option to treat stress-associated neuropsychiatric conditions.

Acknowledgements This study was supported by grants from the Italian Ministero dell'Università e della Ricerca, the Italian Ministero della Salute, and Italian Ministero della Difesa to DC.

References

1. Isbell H, Gorodetzsky CW, Jasinski D, Claussen U, von Spulak F, Korte F (1967) Effects of (–)delta-9-trans-tetrahydrocannabinol in man. Psychopharmacologia 11:184–188
2. Felder CC, Glass M (1998) Cannabinoid receptors and their endogenous agonists. Annu Rev Pharmacol Toxicol 38:179–200
3. Piomelli D (2003) The molecular logic of endocannabinoid signalling. Nat Rev Neurosci 4:873–884
4. Van der Stelt M, Di Marzo V (2003) The endocannabinoid system in the basal ganglia and in the mesolimbic reward system: implications for neurological and psychiatric disorders. Eur J Pharmacol 480:133–150
5. Herkenham M, Lynn AB, Johnson MR, Melvin LS, de Costa BR, Rice KC (1991) Characterization and localization of cannabinoid receptors in rat brain: a quantitative in vitro autoradiographic study. J Neurosci 11:563–583
6. Moldrich G, Wenger T (2000) Localization of the CB1 cannabinoid receptor in the rat brain. An immunohistochemical study. Peptides 21:1735–1742
7. Parolaro D (1999) Presence and functional regulation of cannabinoid receptors in immune cells. Life Sci 65:637–644
8. Hillard CJ (2000) Endocannabinoids and vascular function. J Pharmacol Exp Ther 294:27–32
9. Habayeb OM, Taylor AH, Bell SC, Taylor DJ, Konje JC (2008) Expression of the endocannabinoid system in human first trimester placenta and its role in trophoblast proliferation. Endocrinology 149:5052–5060
10. Cabral GA, Marciano-Cabral F (2005) Cannabinoid receptors in microglia of the central nervous system: immune functional relevance. J Leukoc Biol 78:1192–1197
11. Van Sickle MD, Duncan M, Kingsley PJ, Mouihate A, Urbani P, Mackie K, Stella N, Makriyannis A, Piomelli D, Davison JS, Marnett LJ, Di Marzo V, Pittman QJ, Patel KD, Sharkey KA (2005) Identification and functional characterization of brainstem cannabinoid CB2 receptors. Science 310:329–332
12. Gong JP, Onaivi ES, Ishiguro H, Liu QR, Tagliaferro PA, Brusco A, Uhl GR (2006) Cannabinoid CB2 receptors: immunohistochemical localization in rat brain. Brain Res 1071:10–23
13. Ross RA (2003) Anandamide and vanilloid TRPV1 receptors. Br J Pharmacol 140:790–801
14. De Petrocellis L, Vellani V, Schiano-Moriello A, Marini P, Magherini PC, Orlando P, Di Marzo V (2008) Plant-derived cannabinoids modulate the activity of transient receptor potential channels of ankyrin type-1 and melastatin type-8. J Pharmacol Exp Ther 325:1007–1115
15. Sun Y, Alexander SP, Kendall DA, Bennett AJ (2006) Cannabinoids and PPARalpha signalling. Biochem Soc Trans 34:1095–1097
16. Ryberg E, Larsson N, Sjögren S, Hjorth S, Hermansson NO, Leonova J, Elebring T, Nilsson K, Drmota T, Greasley PJ (2007) The orphan receptor GPR55 is a novel cannabinoid receptor. Br J Pharmacol 152:1092–1101
17. Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, Gibson D, Mandelbaum A, Etinger A, Mechoulam R (1992) Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science 258:1946–1949
18. Sugiura T, Kondo S, Sukagawa A, Nakane S, Shinoda A, Itoh K, Yamashita A, Waku K (1995) 2-Arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain. Biochem Biophys Res Commun 215:89–97
19. Di Marzo V, Deutsch DG (1998) Biochemistry of the endogenous ligands of cannabinoid receptors. Neurobiol. Dis 5:386–404
20. Ueda N (2002) Endocannabinoid hydrolases. Prostaglandins Other Lipid Mediat 68–69:521–534
21. Dinh TP, Freund TF, Piomelli D (2002) A role for monoglyceride lipase in 2-arachidonoylglycerol inactivation. Chem Phys Lipids 121:149–158
22. Di Marzo V, Maccarrone M (2008) FAAH and anandamide: is 2-AG really the odd one out? TiPS 29:229–233
23. Bisogno T, Ligresti A, Di Marzo V (2005) The endocannabinoid signalling system: biochemical aspects. Pharmacol Biochem Behav 81:224–238
24. Basavarajappa BS (2007) Neuropharmacology of the endocannabinoid signaling system—molecular mechanisms, biological actions and synaptic plasticity. Curr Neuropharmacol 5:81–97
25. Jung KM, Mangieri R, Stapleton C, Kim J, Fegley D, Wallace M, Mackie K, Piomelli D (2005) Stimulation of endocannabinoid formation in brain slice cultures through activation of group I metabotropic glutamate receptors. Mol Pharmacol 68:1196–1202
26. Centonze D, Rossi S, Prosperetti C, Gasperi V, De Chiara V, Bari M, Tscherter A, Febbraro F, Bernardi G, Maccarrone M (2007) Endocannabinoids limit metabotropic glutamate 5 receptor-mediated synaptic inhibition of striatal principal neurons. Mol Cell Neurosci 35:302–310
27. Centonze D, Battista N, Rossi S, Mercuri NB, Finazzi-Agrò A, Bernardi G, Calabresi P, Maccarrone M (2004) A critical interaction between dopamine D2 receptors and endocannabinoids mediates the effects of cocaine on striatal gabaergic transmission. Neuropsychopharmacology 29:1488–1497
28. Melis M, Pistis M, Perra S, Muntoni AL, Pillolla G, Gessa GL (2004) Endocannabinoids mediate presynaptic inhibition of

glutamatergic transmission in rat ventral tegmental area dopamine neurons through activation of CB1 receptors. J Neurosci 24:53–62
29. Lastres-Becker I, Fezza F, Cebeira M, Bisogno T, Ramos JA, Milone A, Fernández-Ruiz J, Di Marzo V (2001) Changes in endocannabinoid transmission in the basal ganglia in a rat model of Huntington's disease. Neuroreport 12:2125–2129
30. Centonze D, Rossi S, Prosperetti C, Tscherter A, Bernardi G, Maccarrone M, Calabresi P (2005) Abnormal sensitivity to cannabinoid receptor stimulation might contribute to altered gamma-aminobutyric acid transmission in the striatum of R6/2 Huntington's disease mice. Biol Psychiatry 57:1583–1589
31. Di Marzo V, Hill MP, Bisogno T, Crossman AR, Brotchie JM (2002) Enhanced levels of endogenous cannabinoids in the globus pallidus are associated with a reduction in movement in an animal model of Parkinson's disease. FASEB J 14:1432–1438
32. Lastres-Becker I, Cebeira M, de Ceballos ML, Zeng BY, Jenner P, Ramos JA, Fernández-Ruiz JJ (2001) Increased cannabinoid CB1 receptor binding and activation of GTP-binding proteins in the basal ganglia of patients with Parkinson's syndrome and of MPTP-treated marmosets. Eur J Neurosci 14:1827–1832
33. Pisani A, Fezza F, Galati S, Battista N, Napolitano S, Finazzi-Agrò A, Bernardi G, Brusa L, Pierantozzi M, Stanzione P, Maccarrone M (2005) High endogenous cannabinoid levels in the cerebrospinal fluid of untreated Parkinson's disease patients. Ann Neurol 57:777–779
34. van der Stelt M, Mazzola C, Esposito G, Matias I, Petrosino S, De Filippis D, Micale V, Steardo L, Drago F, Iuvone T, Di Marzo V (2006) Endocannabinoids and beta-amyloid-induced neurotoxicity in vivo: effect of pharmacological elevation of endocannabinoid levels. Cell Mol Life Sci 63:1410–1424
35. Baker D, Pryce G, Croxford JL, Brown P, Pertwee RG, Makriyannis A, Khanolkar A, Layward L, Fezza F, Bisogno T, Di Marzo V (2001) Endocannabinoids control spasticity in a multiple sclerosis model. FASEB J 15:300–302
36. Centonze D, Bari M, Rossi S, Prosperetti C, Furlan R, Fezza F, De Chiara V, Battistini L, Bernardi G, Bernardini S, Martino G, Maccarrone M (2007) The endocannabinoid system is dysregulated in multiple sclerosis and in experimental autoimmune encephalomyelitis. Brain 130:2543–2553
37. Cupini LM, Costa C, Sarchielli P, Bari M, Battista N, Eusebi P, Calabresi P, Maccarrone M (2008) Degradation of endocannabinoids in chronic migraine and medication overuse headache. Neurobiol Dis 30:186–189
38. Giuffrida A, Leweke FM, Gerth CW, Schreiber D, Koethe D, Faulhaber J, Klosterkötter J, Piomelli D (2004) Cerebrospinal anandamide levels are elevated in acute schizophrenia and are inversely correlated with psychotic symptoms. Neuropsychopharmacology 29:2108–2114
39. González S, Cascio MG, Fernández-Ruiz J, Fezza F, Di Marzo V, Ramos JA (2002) Changes in endocannabinoid contents in the brain of rats chronically exposed to nicotine, ethanol or cocaine. Brain Res 954:73–81
40. Centonze D, Rossi S, De Chiara V, Prosperetti C, Battista N, Bernardi G, Mercuri NB, Usiello A, Maccarrone M (2007) Chronic cocaine sensitizes striatal GABAergic synapses to the stimulation of cannabinoid CB1 receptors. Eur J Neurosci 25:1631–1640
41. Hill MN, Miller GE, Ho WS, Gorzalka BB, Hillard CJ (2008) Serum endocannabinoid content is altered in females with depressive disorders: a preliminary report. Pharmacopsychiatry 41:48–53
42. Hohmann AG, Suplita RL, Bolton NM, Neely MH, Fegley D, Mangieri R, Krey JF, Walker JM, Holmes PV, Crystal JD, Duranti A, Tontini A, Mor M, Tarzia G, Piomelli D (2005) An endocannabinoid mechanism for stress-induced analgesia. Nature 435:1108–1112
43. Patel S, Roelke CT, Rademacher DJ, Hillard CJ (2005) Inhibition of restraint stress-induced neural and behavioural activation by endogenous cannabinoid signalling. Eur J Neurosci 21:1057–1069
44. Coddington E, Lewis C, Rose JD, Moore FL (2007) Endocannabinoids mediate the effects of acute stress and corticosterone on sex behavior. Endocrinology 148:493–500
45. Rademacher DJ, Hillard CJ (2007) Interactions between endocannabinoids and stress-induced decreased sensitivity to natural reward. Prog Neuropsychopharmacol Biol Psychiatry 31:633–641
46. Marsicano G, Wotjak CT, Azad SC, Bisogno T, Rammes G, Cascio MG, Hermann H, Tang J, Hofmann C, Zieglgänsberger W, Di Marzo V, Lutz B (2002) The endogenous cannabinoid system controls extinction of aversive memories. Nature 418:530–534
47. White NM, Salinas JA (2003) Mnemonic functions of dorsal striatum and hippocampus in aversive conditioning. Behav Brain Res 142:99–107
48. Balleine BW, Delgado MR, Hikosaka O (2007) The role of the dorsal striatum in reward and decision-making. J Neurosci 27:8161–8165
49. Szabo B, Dorner L, Pfreundtner C, Norenberg W, Starke K (1998) Inhibition of GABAergic inhibitory postsynaptic currents by cannabinoids in rat corpus striatum. Neuroscience 85:395–403
50. Gerdeman G, Lovinger DM (2001) CB1 cannabinoid receptor inhibits synaptic release of glutamate in rat dorsolateral striatum. J Neurophysiol 85:468–471
51. Di S, Malcher-Lopes R, Marcheselli VL, Bazan NG, Tasker JG (2005) Rapid glucocorticoid-mediated endocannabinoid release and opposing regulation of glutamate and gamma-aminobutyric acid inputs to hypothalamic magnocellular neurons. Endocrinology 146:4292–4301
52. Rademacher DJ, Meier SE, Shi L, Vanessa Ho WS, Jarrahian A, Hillard CJ (2008) Effects of acute and repeated restraint stress on endocannabinoid content in the amygdala, ventral striatum, and medial prefrontal cortex in mice. Neuropharmacology 54:108–116
53. Patel S, Roelke CT, Rademacher DJ, Cullinan WE, Hillard CJ (2004) Endocannabinoid signaling negatively modulates stress-induced activation of the hypothalamic-pituitary-adrenal axis. Endocrinology 145:5431–5438
54. Freund TF, Katona I, Piomelli D (2003) Role of endogenous cannabinoids in synaptic signaling. Physiol Rev 83:1017–1066
55. Musella A, De Chiara V, Rossi S, Prosperetti C, Bernardi G, Maccarrone M, Centonze D (2009) TRPV1 channels facilitate glutamate transmission in the striatum. Mol Cell Neurosci 40:89–97
56. Maccarrone M, Rossi S, Bari M, De Chiara V, Fezza F, Musella A, Gasperi V, Prosperetti C, Bernardi G, Finazzi-Agrò A, Cravatt BF, Centonze D (2008) Anandamide inhibits metabolism and physiological actions of 2-arachidonoylglycerol in the striatum. Nat Neurosci 11:152–159
57. Herman JP, Adams D, Prewitt C (1995) Regulatory changes in neuroendocrine stress-integrative circuitry produced by a variable stress paradigm. Neuroendocrinology 61:180–190
58. Hill MN, Carrier EJ, McLaughlin RJ, Morrish AC, Meier SE, Hillard CJ, Gorzalka BB (2008) Regional alterations in the endocannabinoid system in an animal model of depression: effects of concurrent antidepressant treatment. J Neurochem 106:2322–2336
59. Bortolato M, Mangieri RA, Fu J, Kim JH, Arguello O, Duranti A, Tontini A, Mor M, Tarzia G, Piomelli D (2007) Antidepressant-like activity of the fatty acid amide hydrolase inhibitor URB597 in a rat model of chronic mild stress. Biol Psychiatry 62:1103–1110
60. Willner P (2005) Chronic mild stress (CMS) revisited: consistency and behavioural-neurobiological concordance in the effect of CMS. Neuropsychobiology 52:90–110
61. Hillard CJ, Hill MN, Carrier EJ, Shi L, Cullinan WE, Gorzalka BB (2006) Regulation of cannabinoid receptor expression by

chronic, unpredictable stress in rats and mice. Soc Neurosci Abstr 746:19
62. Kamprath K, Marsicano G, Tang J, Monory K, Bisogno T, Di Marzo V, Lutz B, Wotjak CT (2006) Cannabinoid CB1 receptor mediates fear extinction via habituation-like processes. J Neurosci 26:6677–6686
63. Rossi S, De Chiara V, Musella A, Kusayanagi H, Mataluni G, Bernardi G, Usiello A, Centonze D (2008) Chronic psychoemotional stress impairs cannabinoid-receptor-mediated control of GABA transmission in the striatum. J Neurosci 28:7284–7292
64. Rossi S, De Chiara V, Musella A, Mataluni G, Sacchetti L, Siracusano A, Bernardi G, Usiello A, Centonze D (2008) Caffeine drinking potentiates cannabinoid transmission in the striatum: interaction with stress effects. Neuropharmacology 56:590–597
65. Yang CH, Huang CC, Hsu KS (2006) Novelty exploration elicits a reversal of acute stress-induced modulation of hippocampal synaptic plasticity in the rat. J Physiol 577:601–615
66. Yang J, Hou C, Ma N, Liu J, Zhang Y, Zhou J, Xu L, Li L (2007) Enriched environment treatment restores impaired hippocampal synaptic plasticity and cognitive deficits induced by prenatal chronic stress. Neurobiol Learn Mem 87:257–263
67. Gardner EL (2005) Endocannabinoid signaling system and brain reward: emphasis on dopamine. Pharmacol Biochem Behav 81:263–284
68. Hill MN, Patel S, Carrier EJ, Rademacher DJ, Ormerod BK, Hillard CJ, Gorzalka BB (2005) Downregulation of endocannabinoid signalling in the hippocampus following chronic unpredictable stress. Neuropsychopharmacology 30:508–515
69. Di Marzo V, Gobbi G, Szallasi A (2008) Brain TRPV1: a depressing TR(i)P down memory lane? TiPS 29:594–600
70. Kasckow JW, Mulchahey JJ, Geracioti TD (2004) Effects of the vanilloid agonist olvanil and antagonist capsazepine on rat behaviors. Prog Neuropsychopharmacol Biol Psychiatry 28:291–295
71. Marsch R, Foeller E, Rammes G, Bunck M, Kössl M, Holsboer F, Zieglgänsberger W, Landgraf R, Lutz B, Wotjak CT (2007) Reduced anxiety, conditioned fear, and hippocampal long-term potentiation in transient receptor potential vanilloid type 1 receptor-deficient mice. J Neurosci 27:832–839
72. Li HB, Mao RR, Zhang JC, Yang Y, Cao J, Xu L (2008) Antistress effect of TRPV1 channel on synaptic plasticity and spatial memory. Biol Psychiatry 64:286–292
73. Kathuria S, Gaetani S, Fegley D, Valiño F, Duranti A, Tontini A, Mor M, Tarzia G, La Rana G, Calignano A, Giustino A, Tattoli M, Palmery M, Cuomo V, Piomelli D (2003) Modulation of anxiety through blockade of anandamide hydrolysis. Nat Med 9:76–81
74. Gobbi G, Bambico FR, Mangieri R, Bortolato M, Campolongo P, Solinas M, Cassano T, Morgese MG, Debonnel G, Duranti A, Tontini A, Tarzia G, Mor M, Trezza V, Goldberg SR, Cuomo V, Piomelli D (2005) Antidepressant-like activity and modulation of brain monoaminergic transmission by blockade of anandamide hydrolysis. Proc Natl Acad Sci U S A 102:18620–18625
75. Hill MN, Ho WS, Sinopoli KJ, Viau V, Hillard CJ, Gorzalka BB (2006) Involvement of the endocannabinoid system in the ability of long-term tricyclic antidepressant treatment to suppress stress-induced activation of the hypothalamic-pituitary-adrenal axis. Neuropsychopharmacology 31:2591–2599
76. Hill MN, Barr AM, Ho WS, Carrier EJ, Gorzalka BB, Hillard CJ (2007) Electroconvulsive shock treatment differentially modulates cortical and subcortical endocannabinoid activity. J Neurochem 10:47–56
77. Steiner MA, Marsicano G, Nestler EJ, Holsboer F, Lutz B, Wotjak CT (2008) Antidepressant-like behavioral effects of impaired cannabinoid receptor type 1 signaling coincide with exaggerated corticosterone secretion in mice. Psychoneuroendocrinology 33:54–67
78. Van Gaal LF, Rissanen AM, Scheen AJ, Ziegler O, Rössner S, RIO-Europe Study Group (2005) Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. Lancet 365:1389–1397
79. Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J, RIO-North America Study Group (2006) Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. JAMA 295:761–775