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Endocannabinoids in striatal plasticity

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SUMMARY

Endocannabinoids (eCBs) are lipid metabolites found throughout the nervous system that modulate synaptic plasticity mainly via actions on the cannabinoid 1 (CB1) receptor. Within the striatum, eCBs and CB1Rs initiate both short- and long-lasting synaptic depression at intrinsic GABAergic synapses and glutamatergic synapses made by cortical afferents. Recent studies have explored the mechanisms underlying eCB-mediated synaptic depression, and the role of this plasticity in striatal function. Dopamine (DA) and its receptors promote eCB-mediated depression of glutamatergic synapses, and dopamine depletion in animal models alters corticostriatal synapses in ways that may contribute to Parkinson's disease (PD). A growing body of literature indicates that alterations in eCB signaling occur in PD patients, suggesting possible therapeutic approaches targeting this neuromodulatory system.

Keywords

Dopamine; Parkinson's disease; GABA; Glutamate

1. Introduction

Death of midbrain dopaminergic neurons, especially the neurons in substantia nigra that innervate dorsal striatum, is well known to be the underlying cause of PD. The symptoms brought about by this neurodegeneration include bradykinesia, tremors, cognitive impairment, and others. The loss of dopaminergic innervation of striatum is clearly a key part of many of these symptoms, as acute dopamine depletion produces hypokinesia, including problems with movement initiation [1]. While the disorder begins with loss of dopaminergic innervation of forebrain structures, most notably the striatum, widespread disruption of other neurotransmitter systems likely occurs secondary to this original insult. Among the neurotransmitters and neuromodulators implicated in the PD pathology are the relatively newly discovered endocannabinoids.

Endocannabinoids are endogenous lipid metabolites released by cells, including neurons, that have juxtacrine and paracrine effects on nearby cells [2,3]. Two eCB molecules, arachidonoyl ethanolamide (AEA) and 2-arachidonoyl glycerol (2-AG) have been identified,

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Conflict of interests

The authors declare that they have no competing financial interests.

and both are present in striatum and other forebrain structures. The eCBs produce their cellular actions via activation of the CB receptors. Within the brain, and especially in the basal ganglia, the CB1 receptor is the predominant eCB target. Some eCB effects in striatum have also been attributed to AEA activation of the transient receptor potential vanilloid 1 (TRPV1) receptor [4]. Studies conducted in the last 15 years have implicated eCBs in normal striatal synaptic function, interactions with dopamine in striatum, and pathological changes following DA depletion and in PD [5,6].

2. Plasticity at glutamatergic and GABAergic synapses

The most prominent form of eCB-mediated synaptic plasticity in dorsal striatum is long-term depression (LTD), a decrease in synaptic efficacy that can persist at least for hours [6]. This form of synaptic plasticity occurs at both GABAergic and glutamatergic striatal synapses onto striatal medium spiny neurons (MSNs, striatal projection neurons that constitute over 90% of total striatal neurons). Induction of LTD is produced by repetitive activation of afferents/synapses, either at low frequencies (1–5 Hz) to evoke LTD at GABAergic synapses, or at high frequencies (100 Hz) to induce LTD at glutamatergic synapses [6,7]. Experiments using pharmacological techniques and genetic manipulation have implicated retrograde eCB signaling in the LTD observed at both types of synapses. Postsynaptic intracellular application of calcium chelators and blockers of eCB synthesis or release prevent LTD induction, implicating postsynaptic processes in the induction of this plasticity [3]. Several electrophysiological measures, including paired pulse ratio, coefficient of variation of excitatory postsynaptic currents (EPSCs), and miniature EPSCs, indicate that maintained expression of eCB-LTD involves a presynaptic change, most likely a decrease in neurotransmitter release probability [3]. Antagonists of CB1 receptors also prevent LTD induction, supporting the idea of eCB involvement [3,6]. These receptors are localized almost exclusively on presynaptic terminals [3], supporting the involvement of presynaptic mechanisms in this form of plasticity. While LTD induction requires eCB signaling, the decrease in synaptic transmission becomes resistant to CB1 blockade within minutes after LTD onset [3]. This finding suggests that the long-term maintenance of LTD becomes independent of eCBs. The finding that postsynaptic release of eCBs leads to presynaptic depression, both short- and long-term, has been repeated at different synapses in numerous brain regions.

Several neurotransmitters, receptors and ion channels have been implicated in the induction of striatal eCB-LTD. At glutamatergic synapses, plasticity begins with barrage of glutamatergic input that activates both AMPA-type ionotropic glutamate receptors (AMPARs) and group I metabotropic glutamate receptors (mGluRs) [7]. The AMPAR activation depolarizes neurons such that voltage-gated calcium channels are activated. When MSNs are maintained at membrane potentials of −80 to −70 mV, eCB-LTD cannot be induced at glutamatergic synapses. Calcium influx through the low threshold-activated CaV1.3 L-channel appears to be crucial for induction of this form of LTD [8]. Activation of mGluRs can stimulate 2-AG production through activation of phospholipase C, and might also contribute to increases in postsynaptic calcium through inositol phosphate-induced intracellular calcium release. These intracellular signals appear to stimulate eCB production and/or release from the postsynaptic neuron. The eCB is then thought to traverse the synapse

in a retrograde direction, perhaps assisted by a carrier molecule [3], to activate presynaptic CB1 receptors. Activation of CB1 alone produces synaptic depression, but does not appear to be sufficient to induce LTD in and of itself [3,9], and it appears that activity in the presynaptic terminal is required for LTD induction [9]. Examination of CB1 mRNA expression indicates that CB1 is expressed in deep layer cortical neurons that project to striatal MSNs, but there is little, if any, CB1 expression in thalamic neurons [Allen Brain Atlas, http://mouse.brain-map.org/brain/Cnr1/283/thumbnails.html?ispopup=1]. This finding suggests that glutamatergic eCB-dependent LTD at MSNs occurs predominantly, if not exclusively, at corticostriatal synapses.

At GABAergic synapses eCB-LTD also appears to involve mGluR activation, but does not require activation of ionotropic glutamate receptors [6]. L-type calcium channel activation is also implicated in GABAergic eCB-LTD in striatum [6]. However, preliminary findings suggest that GABAergic eCB-LTD can be activated at synapses onto MSNs when recordings are made at holding potentials too hyperpolarized to allow L-channel activation [10]. It is not yet clear what mechanisms contribute to eCB-LTD induction at these hyperpolarized potentials. As with LTD at glutamatergic striatal synapses, the bulk of evidence supports retrograde eCB signaling, CB1 activation, and synergism between CB1 and presynaptic activity in eCB-LTD at GABAergic synapses in striatum [6].

3. Dopamine roles in LTD

Conspicuously absent from the preceding discussion was any mention of the role of DA in striatal synaptic plasticity, despite the abundant innervation from the substantia nigra into dorsal striatum. Indeed, DA has been strongly implicated in striatal eCB-LTD at glutamatergic synapses onto MSNs. Calabresi and coworkers found that antagonists of both D1- and D2-like DA receptors prevented striatal LTD induction, in their initial description of this form of plasticity [2]. These investigators also demonstrated that LTD was lost following dopamine depletion in dorsal striatum, and could be restored by DA application to slices. Subsequent studies have confirmed the role of D2 receptors, using both pharmacological and knockout mouse approaches [3,7,11]. The blockade of striatal LTD by D1-like antagonists appears to involve blockade of D5 receptors on interneurons [7].

Two subclasses of striatal MSNs have been identified based on their projection targets and predominant dopamine receptor subclass. Direct pathway MSNs project to the substantia nigra pars reticulata and express predominantly D1 receptors in preference to D2Rs, while indirect pathway neurons project to the globus pallidus with preferential D2 expression [12]. Given the role of D2Rs in glutamatergic striatal LTD, it is tempting to speculate that indirect pathway neurons should be the only type expressing this form of plasticity. However, this has been a controversial hypothesis. While some investigators have found pathway-specific eCB-LTD [13,14], a considerable body of evidence indicates that striatal LTD can be induced in direct pathway MSNs [6,8,15,16]. The reasons for these discrepancies are not completely clear. It appears that weak afferent stimulation or a spike-timing-dependent pairing of low frequency afferent stimulation and postsynaptic activation lead to indirect pathway-specific LTD. Stronger afferent activation at higher frequencies appears to induce LTD at glutamatergic synapses onto all MSNs. Cholinergic synaptic transmission from local

interneurons is likely to be a crucial factor in pathway-independent LTD [8]. In the presence of muscarinic antagonists, LTD can be induced by HFS even when D2Rs are blocked. It appears that activation of cholinergic interneurons leads to activation of M1-type mAChRs on MSNs. These receptors normally inhibit CaV1.3-type channels and tend to suppress LTD. Activation of D2 receptors suppresses cholinergic neuron activity and/or ACh release, thus relieving calcium channel suppression and allowing LTD. It is possible that D2Rs on indirect pathway MSNs participate in LTD induction when low–moderate DA levels are present in striatum. When dopamine levels are higher, D2Rs on cholinergic interneurons may come into play, extending LTD to direct pathway MSNs. All studies that have examined the question consistently show the actions of CB1Rs on glutamatergic synapses innervating both direct and indirect pathway MSNs. Thus, it is likely that these receptors participate in synaptic plasticity, with the most likely scenario that LTD can occur at all cortical glutamatergic synapses in vivo.

Pharmacological studies indicate that DA has a modulatory role in the induction of striatal eCB-LTD at glutamatergic synapses. Kreitzer and Malenka [11] showed that LTD can be induced by application of group I mGluR agonists to brain slices. Induction of LTD in this manner is not blocked by D2 antagonist treatment. The findings of Wang et al. [8], mentioned above, also fit with the idea that DA is modulatory, rather than strictly necessary, for LTD induction. At present, there is not much information on DA roles in eCB-LTD at GABAergic striatal synapses.

4. Endocannabinoids and Parkinson’s disease

To examine possible roles of striatal LTD in PD, investigators have examined effects of DA depletion in rodent models. Calabresi and coworkers have contributed the most to this work, demonstrating that DA depletion eliminates striatal LTD, as well as striatal LTP [7]. These investigators also showed that DA application to previously depleted slices restored LTD, an effect that was blocked by antagonists of either D1- or D2-like receptors and mimicked by simultaneous activation of both DA receptor subtypes [7]. Notably, DA depletion also enhances striatal eCB levels, perhaps activating abnormal synaptic plasticity [17]. The Calabresi group has also used PD model mice to show temporal correlations between the loss of plasticity and the onset of motor symptoms of the disorder [7,18]. Kreitzer and Malenka [13] also examined effects of DA depletion on eCB-LTD in mouse. In this study, eCB-LTD was found to be restricted to glutamatergic synapses onto D2 receptor-expressing, indirect pathway neurons in striatum, as mentioned above. Dopamine depletion led to a loss of eCB-LTD, measured in striatal slices from these mice. In the intact mouse, treatment with drugs that increase eCB levels ameliorated the effects of DA depletion on movement. Investigators also examined effects of prolonged L-DOPA treatment on eCB-mediated synaptic plasticity in rat, to determine possible roles in dyskinesia [16]. This study revealed that DA-depletion-induced loss of striatal LTD was prevented by in vivo L-DOPA treatment in animals that did not develop dyskinetic movements. However, LTD could not be induced in brain slices from DA-depleted rats showing L-DOPA-induced dyskinesia. Thus, abnormal eCB-mediated synaptic plasticity may also contribute to dyskinesia.

5. Discussion

Studies in PD patients are beginning to reveal changes in the eCB/CB1 system associated with the disorder. Levels of AEA in cerebrospinal fluid are elevated in idiopathic PD patients, compared to age-matched controls, and the levels are normalized following chronic L-DOPA or DA receptor agonist treatment [5,19]. Postmortem CB1 binding and activation studies have indicated increased receptor expression and activation of G-proteins in PD patients [5,19]. Newly published data using positron emission tomographic CB1 localization in live brain shows decreased CB1 levels in substantia nigra, with increased levels in striatum in both early- and late-stage PD patients [20]. Thus, the receptor changes may develop early in the disorder. Disruptions in the endocannabinoid system may contribute to action-learning disruption in PD. To date, no eCB- or CB1-based therapies for PD or L-DOPA-induced dyskinesia have been successfully developed [5]. However, given the many molecular targets that can be manipulated to alter eCB levels and/or CB1 actions, it is possible that therapeutic development in this area may advance in the near future.

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