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Release of endogenous cannabinoids from ventral tegmental area dopamine neurons and the modulation of synaptic processes

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Abstract

Endogenous cannabinoids play important roles in a variety of functions in the mammalian brain, including the regulation reward-related information processing. The primary mechanism through which this achieved is the presynaptic modulation of synaptic transmission. During reward- and reinforcement-related behavior dopamine levels increase in forebrain areas and this has recently been shown to be modulated by the endocannabinoid system. Therefore, understanding how endocannabinoids are mobilized to modulate synaptic inputs impinging on midbrain dopamine neurons is crucial to a complete understanding of the roles that these molecules play in reward behavior, drug abuse and addiction. Here we summarize the literature describing short-term and long-term regulation of afferent connections on dopamine neurons in the ventral tegmental area via endocannabinoid activation of cannabinoid CB1 receptors, and describe the mechanisms through which these molecules are released during reward-based behavior and exposure to abused drugs.

Keywords

ventral tegmental area; dopamine neuron; endocannabinoid; synaptic modulation; CB1 receptor

1. Introduction

Midbrain dopamine (DA) neurons are central components of the brain reward system. DA neurons fire in tonic pacemaker or phasic/burst modes, the latter of which signals reward prediction error; the discrepancy between expected and actual reward (Cohen et al., 2012; Schultz et al., 1997). This reward-related phasic activity of DA neurons is sufficient to support reinforcement learning, most likely by triggering long-term modification of synaptic connections (Glimcher, 2011; Steinberg et al., 2013). All addictive drugs affect the brain's reward circuitry by enhancing DA levels in the nucleus accumbens (NAc), which is a

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primary target of DA neurons in ventral tegmental area (VTA) (Gardner, 2011). The endogenous cannabinoid (eCB) system is increasingly seen to play an important role in modulating reward-related changes of DA levels in the NAc and other forebrain targets to thereby regulate addictive behaviors (Melis and Pistis, 2012; Oleson et al., 2012).

1.1 Endocannabinoid function in the CNS

All eCBs identified to date are lipid molecules. Although there are many eCBs that have been identified, in the context of the present review we refer to only those that act as agonists at the cannabinoid receptor type 1 (CB1R) cloned by Matsuda et al. (1990). Endocannabinoids are released by neurons during heightened activity and interact with CB1Rs expressed throughout the CNS, where they inhibit the release of neurotransmitters such as GABA or glutamate (Alger, 2002; Melis et al., 2004b; Riegel and Lupica, 2004). This form of eCB release is said to be “on demand” because it occurs when neuronal activity is high, and depends upon the influx of Ca^{2+} (Bisogno et al., 1997; Di Marzo et al., 1994). Furthermore, activity-dependent release of eCBs generally occurs in postsynaptic neurons whereas CB1Rs are most-often located on axon terminals. Therefore, eCBs are said to act in a “retrograde” manner to regulate neurotransmitter release. The transient eCB-mediated inhibition of neurotransmitter release has been labeled depolarization-induced suppression of “inhibition” (DSI) (Ohno-Shosaku et al., 2001; Wilson and Nicoll, 2001) or “excitation” (DSE) (Kreitzer and Regehr, 2001), depending on the nature of the neurotransmitter whose release is inhibited by the eCB. CB1R activation by eCBs can also initiate long-term synaptic plasticity, including long-term depression (LTD), or can modify the strength of long-term potentiation (LTP) (Carlson et al., 2002; Kortleven et al., 2011). Several excellent reviews exist to describe these long-term actions of eCBs (Alger, 2002; Chevaleyre et al., 2006; Gerdeman and Lovinger, 2003; Kano et al., 2009).

1.2 Metabolism of 2-arachidonoylglycerol

As most of the transient, activity-dependent, physiological actions of eCBs are mediated by 2-arachidonoylglycerol (2-AG), and this is the eCB involved in regulating VTA DA neuron function, we will focus on this particular molecule. Activity-dependent increases in intracellular Ca^{2+} is thought to trigger the synthesis and release of 2-AG by activation of the enzyme phospholipase C-β (PLC-β), which converts membrane bound phosphatidylinositol phosphates to diacylglycerol (DAG). The enzyme, diacylglycerol lipase-α (DGLα) then hydrolyzes DAG to 2-AG, which is a full agonist at CB1Rs. The metabolic degradation of 2-AG is thought to primarily occur via the enzyme, monoacylglycerol lipase (MAGL), which hydrolyzes 2-AG to arachidonic acid and glycerol, both of which are inactive at CB1Rs (Sugiura et al., 2002; Ueda et al., 2011).

In addition to the Ca^{2+}-dependent mobilization of 2-AG, the activation of several $G_{q/11}$ protein-coupled neurotransmitter receptors (GPCRs), such as group I metabotropic glutamate receptors (mGluRI), muscarinic acetylcholine receptors (mAChR), type 1 neurotensin receptors (NT1R), and orexin receptors, can stimulate 2-AG synthesis independently of Ca^{2+} (Maejima et al., 2001; Kim et al., 2002; Haj-Dahmane and Shen, 2005; Kortleven et al., 2012). These GPCRs, through coupling to $G_{q/11}$ proteins, directly stimulate PLC-β, which then hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP_2) to

DAG and inositol triphosphate (IP_3). DAG is then hydrolyzed by DGLα to form 2-AG. Calcium-dependent, and GPCR-dependent 2-AG synthesis can also occur together, and the elevation of intracellular Ca^{2+} during $G_{q/11}$ activation can synergistically increase 2-AG production (Hashimotodani et al., 2005; Maejima et al., 2005; Kano et al., 2009).

2. eCBs released from DA neurons modulate synaptic transmission in the VTA

2.1 The eCB system in the VTA

Similar to other brain areas (Wilson and Nicoll, 2002), synthetic CB1R agonists inhibit both excitatory postsynaptic currents (EPSCs) mediated by glutamate, and inhibitory postsynaptic current (IPSCs) mediated by GABA through the inhibition of synaptic transmission in VTA (Szabo et al., 2002; Melis et al., 2004b; Riegel and Lupica, 2004; Pan et al., 2008b). The 2-AG biosynthetic enzyme, DGLα, has been found on the plasma membranes of both dopaminergic and non-dopaminergic neurons in the VTA, where it can be located adjacent to postsynaptic membrane specializations, and opposite CB1R-expressing glutamate and GABA axon terminals (Matyas et al., 2008). This suggests that both DA and non-DA neurons in the VTA may synthesize and release 2-AG, and that this eCB is likely involved in regulating VTA function by modulating neurotransmitter release (Melis et al., 2004b; Pan et al., 2008b; Riegel and Lupica, 2004). During whole-cell recordings in brain slices, the depolarization of VTA DA neurons from −70 to +40 mV for 5–10 s elicits brief depression of EPSCs (Melis et al., 2004b; Melis et al., 2004a). This transient inhibition of glutamate synaptic transmission was shown to be dependent upon the retrograde action of an eCB because it was blocked by antagonism of CB1Rs, by intracellular chelation of Ca^{2+} with 1,2-bis(2-aminophenoxy)ethane-N,N,N′,N′-tetraacetic acid (BAPTA) (which presumably prevents activation of PLC-β), or by mGluRI antagonism (Melis et al., 2004a).

2.2 eCBs are released from DA neurons during burst activity

A defining property of midbrain DA neurons is their ability to fire action potentials in a tonic pacemaker pattern, as well as in bursts (Hyland et al., 2002). In addition, DA neuron burst firing is associated with the availability of salient appetitive stimuli (reward expectancy), with the presentation of unexpected rewards, or the removal of expected rewards (reward prediction error; Schultz et al., 1997; Cohen et al., 2012). Burst firing also releases greater amounts of DA in the target areas of these neurons (Gonon, 1988), which is essential to the reinforcing properties of most abused drugs. Since heightened neuronal activity facilitates eCB release in many brain regions, we sought to determine whether bursting in VTA DA neurons augments endocannabinoid modulation of synaptic inputs to these cells (Riegel and Lupica, 2004). Blockade of small conductance calcium-sensitive potassium channels (S_k) with the bee venom constituent, apamin, is known to facilitate bursting *in vitro*, as is an increase in glutamate neurotransmission (Johnson et al., 1992; Seutin et al., 1993; Kitai et al., 1999). We found that either S_k channel blockade, or facilitation of glutamate release through blockade of autoreceptors on glutamatergic afferents (with mGluRIII antagonists) could initiate bursting in VTA DA neurons *in vitro*, and this was associated with a large increase in eCB release from these neurons (Riegel and Lupica, 2004). Based on these data, it is likely that behaviorally-relevant DA neuron

bursting is associated with eCB release from these cells, and we hypothesize that the activation of CB1Rs by eCBs modulates afferents impinging upon these cells to further sculpt neuronal activity in the VTA (Lupica and Riegel, 2005). In support of this hypothesis, more recent work has shown that the ability of abused drugs to increase the release of DA in the NAc is partly dependent upon eCB activity *in vivo* (Cheer et al., 2007; Oleson et al., 2012). This suggests that eCBs released in the VTA can shape DA signals in the NAc during exposure to several abused drugs, and that these molecules likely play roles in reward and addiction.

2.3 eCBs and Long-term synaptic plasticity in VTA

In addition to short-term forms of plasticity such as DSI and DSE, eCBs are also involved in several forms of long-term synaptic plasticity (Heifets and Castillo, 2009; Kano et al., 2009). LTD is characterized by a long-lasting suppression of synaptic transmission. In VTA DA neurons in rat brain slices, cocaine application, paired with electrical stimulation that is normally sub-threshold for synaptic plasticity, results in LTD of $GABA_A$ receptor-mediated IPSCs (Pan et al., 2008b). The reliance upon eCB function for this inhibitory LTD (I-LTD) was shown by blocking 2-AG synthesis with the DGLα inhibitor, tetrahydrolipostatin (THL), or by CB1R antagonism (Pan et al., 2008b). Additional studies suggested that activation of mGluRI mobilized 2-AG in postsynaptic DA neurons, and that DA-D2 receptor activation facilitated I-LTD induction via inhibition of cAMP-dependent protein kinase A (PKA) at presynaptic terminals (Pan et al., 2008a; Yu et al., 2013). The cyclic AMP/PKA and extracellular signal-regulated kinase (ERK) signaling pathways also served as the downstream effectors for CB1Rs and were required for eCB-mediated I-LTD induction (Pan et al., 2008a; Pan et al., 2011). Finally, the treatments that were effective in blocking cocaine-induced 2-AG-dependent I-LTD *in vitro* also impaired the acquisition of cocaine conditioned place preference (Pan et al., 2011; Zhong et al., 2012; Yu et al., 2013). Together, these data suggest that repetitive activation of afferents to DA neurons during cocaine exposure induces a 2-AG-dependent form of synaptic plasticity of inhibitory afferents that may be involved in mediating the behavioral effects of the drug.

Endocannabinoid-mediated LTD of glutamatergic transmission has also been observed in VTA DA neurons. Thus, pairing DA neuron depolarization with low-frequency (2 Hz) stimulation of afferents for 5–6 min caused a long-term reduction in glutamate EPSCs (Haj-Dahmane and Shen, 2010). This form of LTD was blocked by CB1R antagonism and by inhibition of 2-AG synthesis, and was independent of NMDA receptor activation. Furthermore, unlike the studies described above for I-LTD, eCB-dependent LTD of glutamatergic neurotransmission was independent of mGluRI activation (Haj-Dahmane and Shen, 2010). However, like I-LTD, the cAMP/PKA pathway was involved in this form of LTD, since activation of CB1 receptors by 2-AG inhibited cAMP/PKA and decreased the probability of glutamate release from axon terminals (Haj-Dahmane and Shen, 2010).

2.4 Peptide-eCB interaction during long-term plasticity in the VTA

More recently, eCB-mediated long-term regulation of glutamatergic transmission in DA neurons involving the activation of $G_{q/11}$-coupled neuropeptide receptors has been reported (Kortleven et al., 2012). In this study, neurotensin application to VTA slices caused a

decrease in glutamatergic EPSCs in DA neurons, via activation of neurotensin 1 (NT1) receptors. This inhibition persisted long after neurotensin washout from the VTA brain slices, and antagonism of CB1Rs, but not NT1Rs, reversed this long-term effect. This suggests that neurotensin triggered the long-term release of an eCB that acted at CB1Rs to inhibit glutamate release (Kortleven et al., 2012). The neurotensin-induced depression was independent of postsynaptic calcium, as it was not blocked by loading DA neurons with the calcium chelator BAPTA, but it was blocked by inhibitors of G proteins, PLC-β, or DGLα. Therefore, the neurotensin-induced LTD was mediated by 2-AG that was released via activation of a $G_{q/11}$-linked NT1Rs and the PLC/DGLα pathway (Kortleven et al., 2012). Since NT1 receptors and neurotensin are found at relatively high concentrations in the VTA (Dana et al., 1989; Hokfelt et al., 1984), these data suggest that this neuropeptide system may be involved in regulating the activity of this nucleus, at least partly through the mobilization of 2-AG.

Peptide-related eCB release has also been observed for insulin, a circulating catabolic peptide (Labouebe et al., 2013). In this study, insulin caused LTD of glutamatergic transmission in the DA neurons of the VTA when it was applied directly *in vitro*. The insulin-induced LTD was blocked by DGLα inhibitor, indicating a role for 2-AG. The activation of CB1Rs was only required for the induction of this form of LTD, but once established LTD was not reversed by CB1R antagonism. The insulin receptor belongs to the family of tyrosine kinase receptors (Ward and Lawrence, 2009), and this study demonstrated that the PI3K/Akt/mTOR pathway was the downstream signaling pathway involved in the insulin-induced LTD (Labouebe et al., 2013). However, the mechanism through which receptor tyrosine kinase activation lead to mobilization of 2-AG was not established (Labouebe et al., 2013).

3. Conclusion

Evidence obtained in the preceding decade strongly implicates the eCB system in the modulation of the behavioral effects of abused drugs (Linsenbardt and Boehm, 2009; Oleson et al., 2012; Melis and Pistis, 2012). Furthermore, the key observations that midbrain neurons possess the machinery for the synthesis and degradation of the eCB, 2-AG (Matyas et al., 2008), and the localization of CB1Rs on axon terminals impinging upon these neurons (Szabo et al., 2002; Melis et al., 2004b; Riegel and Lupica, 2004; Matyas et al., 2008), provide the likely substrates upon which these molecules act to modify reward behavior through actions in the VTA. We hypothesize that the modulation of ongoing synaptic activity by eCBs will impact the firing activity of VTA dopamine neurons to thereby alter behavioral output. Future work will seek to determine the mechanisms through which abused drugs may alter eCB function in brain reward pathways, and the ways in which the eCB system is involved in reward-based learning.

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Abbreviations

2-AG	2-Arachidonoylglycerol
BAPTA	1,2-bis(2-aminophenoxy)ethane-N,N,N′,N′-tetraacetic acid
cAMP	cyclic adenosine monophosphate
CB1	cannabinoid receptor type 1
CNS	central nervous system
DA	dopamine
DAG	diacylglycerol
DGLα	diacylglycerol lipase-α
DSE	depolarization-induced suppression of excitation
DSI	depolarization-induced suppression of inhibition
eCB	endogenous cannabinoid/endocannabinoid
EPSCs	excitatory postsynaptic currents
ERK	extracellular signal regulated kinase
GABA	gamma-aminobutyric acid
GPCRs	G protein-coupled receptors
I-LTD	inhibitory LTD
IP3	inositol triphosphate
IPSCs	inhibitory postsynaptic current
LTD	long-term depression
LTP	long-term potentiation
mAChR	muscarinic acetylcholine receptors
MAGL	monoacylglycerol lipase
mGluRI	group I metabotropic glutamate receptors
NAc	nucleus accumbens
NT1R	type 1 neurotensin receptors
PIP2	phosphatidylinositol 4,5-bisphosphate
PKA	protein kinase A
PLC-β	phospholipase C-β
S_k	small conductance calcium-sensitive potassium channels
THL	tetrahydroli postatin
VTA	ventral tegmental area

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