Hub and switches: endocannabinoid signalling in midbrain dopamine neurons

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The last decade has provided a wealth of experimental data on the role played by lipids belonging to the endocannabinoid family in several facets of physiopathology of dopamine neurons. We currently suggest that these molecules, being intimately connected with diverse metabolic and signalling pathways, might differently affect various functions of dopamine neurons through activation not only of surface receptors, but also of nuclear receptors. It is now emerging how dopamine neurons can regulate their constituent biomolecules to compensate for changes in either internal functions or external conditions. Consequently, dopamine neurons use these lipid molecules as metabolic and homeostatic signal detectors, which can dynamically impact cell function and fitness. Because dysfunctions of the dopamine system underlie diverse neuropsychiatric disorders, including schizophrenia and drug addiction, the importance of better understanding the correlation between an unbalanced endocannabinoid signal and the dopamine system is even greater. Particularly, because dopamine neurons are critical in controlling incentive-motivated behaviours, the involvement of endocannabinoid molecules in fine-tuning dopamine cell activity opened new avenues in both understanding and treating drug addiction. Here, we review recent advances that have shed new light on the understanding of differential roles of endocannabinoids and their cognate molecules in the regulation of the reward circuit, and discuss their anti-addicting properties, particularly with a focus on their potential engagement in the prevention of relapse.

**Keywords:** addiction; dopamine neurons; endocannabinoids; peroxisome-proliferator-activated receptors; reward; rodent

1. DOPAMINE NEURONS

Dopamine (DA) neurons are a cluster of approximately 400–600 k cells in humans and 20–30 k in rats [1] within the ventral midbrain. These cells are grouped in two major divisions, those belonging to the substantia nigra pars compacta (SNpc, A9) and those in the more medial ventral tegmental area of Tsai (VTA, A10). Nigral and VTA DA neurons present numerous specificities related to their targets, inputs and molecular and electrophysiological features that led researchers to consider these cells as belonging to two functionally distinct systems: a nigrostriatal and a mesolimbic system [2]. Several authors, however, question this functional distinction [3] on the grounds that these cells are embryologically derived from a single layer, and that the boundaries between SNpc and VTA, as well as their synaptic input and output connections, are indistinct. However, this dichotomy has had long-lasting influence and still holds, and the two systems are associated with different functions: the nigrostriatal system with motor function (it degenerates in Parkinson’s disease) and the mesolimbic system with motivation and reward functions, being essential for the habit-forming effects of drugs of abuse and for motivated behaviours. For this reason, the latter DA system will be the focus of this review.

**(a) Anatomy and functions of the mesolimbic dopamine system**

Tyrosine hydroxylase (TH), the rate-limiting enzyme in DA biosynthesis, is the most reliable marker for DA neurons. TH-positive neurons constitute approximately 65 per cent of the total number of cells within the VTA [4,5]. The remaining cells contain predominantly gamma aminobutyric acid (GABA), and only a minority (approx. 5%) are glutamatergic [5,6].

VTA DA cells project densely to the ventral striatum (VS) and more sparsely to other limbic regions (i.e. the prefrontal cortex, amygdala, hippocampus and olfactory tubercle) [1]. Projections to the VS present a mediolateral and anteroposterior topography [1,7–9]. Medial and posterior sections of the VTA project to the medial portion of the VS (i.e. ‘shell’ of the nucleus accumbens, NAcc), whereas cells located in the anterior and lateral aspects of the VTA innervate the most lateral portions of the VS (i.e. the ‘core’ of the NAcc) [9]. This anatomical heterogeneity reflects a functional difference between the anterior and posterior VTA. Hence, animals more robustly self-stimulate posterior VTA and learn to self-administer drugs of abuse more vigorously in posterior than anterior VTA [9]. Self-stimulation or

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drug self-administration in the posterior VTA more readily enhances DA release in the medial VS, which appears to be uniquely involved in reward mechanisms. Noteworthy, a recent hypothesis postulates that the posterior portions of the VTA also contain GABA neurons belonging to the rostromedial tegmental nucleus (RMTg) [10,11], which sends dense inhibitory projections to DA neurons. RMTg neurons are also a target for drugs of abuse [12,13], particularly those acting on DA neurons with a disinhibitory mechanism [14], such as opiates and cannabinoids [13,15,16].

VTA DA cells can be considered as a hub between brain regions processing sensory and cognitive information and those controlling motor behaviour, such as the basal ganglia. Hence, their firing rate and pattern heavily depend on the balance between excitatory and inhibitory inputs interacting with the intrinsic properties of the membrane, which sustain the pacemaker activity observed in vitro [17,18]. The prefrontal cortex and bed nucleus of the stria terminalis provide glutamatergic projections; other glutamatergic–cholinergic inputs originate from the pedunculopontine and laterodorsal tegmental nuclei [19]. Inhibitory GABAergic afferents arise from interneurons [20–22], from the basal ganglia [18,19,23] with the exception of the NAcc [24] and from neighbouring RMTg neurons [12,13,25,26].

A precise control of DA transmission is, therefore, crucial as DA regulates essential features of motivated behaviour. As already mentioned, this is a particularly relevant issue because DA neuronal activity contributes not only to the predictive validity of information but also to learning about rewards and punishments [44,45]. Given that DA neurons are subject to major background GABA inputs [46] and that GABA afferents onto DA neurons arise from three diverse districts (i.e. ventral pallidum, RMTg nucleus, VTA), resulting in either inhibition of DA neuron spontaneous firing and/or triggering bursts and pauses in DA cells [17,47], it is crucial to dissect whether the diverse sets of synapses are equipped with discrete molecular architectures of a given endocannabinoid.

While electrophysiological evidence points to a role of 2-AG in modulating GABA inputs, no evidence supports a role for anandamide in regulating these synapses [48,49]. Indeed, either intracellular loading of DAG lipase inhibitors or G-protein inhibitor GDB-8 into DA neurons proved to block endocannabinoid-mediated actions on discrete GABA receptors [48,49] by supporting the localization of 2-AG-synthesizing enzyme DAG lipase in the DA cell [33], which would release 2-AG following group I mGluR activation [48,50]. This is of particular interest when we consider that VTA DA neurons, by releasing endocannabinoids, can regulate their ongoing spontaneous activity through activation of CB1 receptors on these three diverse presynaptic inhibitory inputs [33]. Indeed, although immunocytochemical investigation of CB1 receptors failed to precisely identify the origin of GABA afferent inputs [33], electrophysiological studies have recognized these as those arising from pallidal [49], RMTg nucleus [13] and local interneurons [51]. Given the important and discrete roles played by these inputs in controlling the number of spontaneously active DA neurons [47] and their own discharge rate [13], it is crucial to examine whether these synapses are differentially equipped/enriched with the discrete players of 2-AG signalling machinery. Because GABA removal induces disinhibition bursts [17], it is tempting to speculate that 2-AG might likely play the pivotal role in transiently silencing those inhibitory synapses, thus contributing to phasic excitation of DA cells in the framework of multiple signalling modalities. In this scenario, while NADA could bind to CB1 receptors to decrease GABA release [31], its actions appear to be far from physiological, given that its levels can only be detected

2. ENDOCANNABINOID SYSTEM

The endocannabinoid system plays a modulatory role on reward DA neurons [29,30], and this is substantiated by the expression of type 1 cannabinoid (CB1) receptors [31–33], and the abundance of their endogenous ligands, mainly anandamide and 2-arachidonoylglycerol (2-AG) within the VTA [34]. From a general point of view, endocannabinoids are released on demand by the postsynaptic neurons and travel retrogradely across the synapse to bind to and activate CB1 receptors located on the presynaptic terminals [35,36]. The result of such activation is a decreased neurotransmitter release in a short- or a long-term manner [35,37]. This general rule applies to the VTA as well [30].

While the key molecular players required for 2-AG signalling have been clearly localized in the VTA [33] and provide support for its physiological role, the molecular architecture of anandamide signalling still remains elusive [38]. In the VTA, which also conserves the features of 2-AG signal throughout the brain, the 2-AG biosynthetic enzyme diacylglycerol (DAG) lipase is found in DA cells at the level of the plasma membrane, whereas both CB1 receptors and the main degrading enzyme monoacylglycerol (MAG) lipase are localized at a presynaptic level [33] (figure 1). Nonetheless, previous anatomical, biochemical and electrophysiological studies have provided compelling evidence that the N-acylphosphatidylethanolamine anandamide and the endogenous ligands to peroxisome-proliferator-activated receptor-alpha (PPARα; i.e. oleoylethanolamide, OEA; palmitoylethanolamide, PEA), as well as the endocannabinoid/vanilloid N-arachidonoyl-dopamine (NADA) are also present within the VTA [31,34,38–43], thus suggesting discrete physiological roles for each endocannabinoid and cognate molecule in the modulation of DA neuron and its related behaviour.

(a) Effect of endocannabinoids on GABA afferents

The finest regulation of DA neuronal activity results by the delicate balance between both intrinsic and extrinsic mechanisms. As already mentioned, this is a particularly relevant issue because DA neuronal activity contributes not only to the predictive validity of information but also to learning about rewards and punishments [44,45].

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upon K⁺-induced depolarization [31], unlike 2-AG and anandamide [34].

(b) Effect of endocannabinoids on glutamatergic afferents
The excitatory synapse arising from rostral/cortical regions and impinging upon VTA DA neurons and its regulation by endocannabinoids is so far the best studied [30]. Within the past decade, in fact, VTA DA neurons have been extensively shown to release on demand endocannabinoids that act to decrease glutamate release [31,32,34,50,52]. To date, three endocannabinoids have been identified as modulators of excitatory synaptic transmission onto DA neurons: 2-AG acts through activation of CB1 receptors, whereas NADA and anandamide operate mainly via ionotropic transient receptor potential vanilloid type 1 (TRPV1) [31,32,52–54]. This explains and justifies their presence within the midbrain [31,34,54] and the localization of CB1 receptors on asymmetric synapses at the opposite site of the DAG lipase [31–33]. Particularly, CB1 receptors have been identified more abundantly on VGLUT1-positive terminals in close proximity to DA neuron dendrites, predicted to be of cortical origin, rather than on VGLUT2-expressing terminals [32], expected to be of subcortical origin [55].

Thus, 2-AG appears to be the key endocannabinoid released on demand by VTA DA neurons. Indeed, it mediates both short and long forms of synaptic plasticity. It is key in the depolarization-induced suppression of excitation [34], a form of short-term plasticity that most likely serves to limit pathological excitation of DA neurons, such as that observed under ischaemic-reperfusion injury [34]. Additionally, 2-AG is released by DA neurons during behaviourally relevant patterns of synaptic activity such as a brief burst of excitatory synaptic activity [50]. Under these conditions, both mGluR1 activation and raised intracellular Ca²⁺ levels contribute to its synthesis and release, ultimately leading to transient and selective silencing of excitatory inputs onto the neuron itself, thus ensuring a fine modulation of both spike and burst probability [50].

2-AG has been also been shown to play a role in diverse forms of long-term synaptic plasticity.
expressed by VTA DA neurons [32,53]. Particularly, it mediates long-term depression (LTD) [53], and inhibits long-term potentiation (LTP) at these synapses [32]. Indeed, low frequency stimulation (LFS)-induced LTD requires 2-AG because pharmacological inhibition of either phospholipase C or DAG lipase, both critical for 2-AG biosynthesis, abolished LFS–inhibition of either phospholipase C or DAG lipase, but not its expression [32]. Thus, it appears that under circumstances of strengthened excitatory plasticity, such as those induced by cocaine [56], 2-AG released by DA cells would mediate LTD and impair LTP at the same synapses to protect DA cells from aberrant excitation, and it would simultaneously silence inhibitory afferents [48].

In vivo, however, positive modulation of CB1 receptors has been shown to enhance the firing rate of DA neurons [57,58], most likely through a marked reduction of the inhibitory inputs arising from the RMTg nucleus [12,13]. Nonetheless, one should not rule out differences existing between the effects of on demand production of endocannabinoids and the administration of CB1 agonists. Alternatively, to resolve this paradox, one should take into account the net yield produced by activated CB1 receptors on both GABA and glutamatergic terminals on VTA DA neuronal firing. While drawing the ultimate conclusion from the most diverse experimental conditions under which the above-mentioned studies were carried out is not possible, one could simply suggest two scenarios: (i) 2-AG may not efficiently silence GABA neuronal activity within the VTA at those times when VTA DA cells receive excitatory afferent activation that drives their bursting activity, such as following cocaine administration; and (ii) VTA DA neurons may use 2-AG to escape from GABA inhibition and enhance their burst firing, consistently with the disinhibition bursts produced by removal of GABA [17], thus contributing to increased DA cell firing and bursting activity that can be observed following cocaine administration (F. George 2012, personal communication).

(c) Effect of endocannabinoids on cholinergic afferents
The DA cell firing pattern is also controlled by extrinsic cholinergic inputs arising from the laterodorsal tegmental nucleus [59] through activation of nicotinic receptors (nAChRs) [60,61]. Two major forms of nAChRs are found on DA cells, high-affinity β2*-nAChRs and low-affinity α7*-nAChRs [62], where β2*-nAChRs enable the transition from tonic to phasic activity [61].

In 2008, the discovery that pharmacological inhibition of fatty acid amide hydrolase (FAAH), main degrading enzyme of anandamide, prevented nicotine-induced excitation of DA neurons via nuclear receptor PPARα [41] has highlighted the role of N-acylethanolamines (NAEs) other than anandamide in the modulation of the brain reward pathway [63]. Particularly, because of the role played by VTA DA neurons projecting to the NAcc, these findings opened new avenues in both understanding and treating nicotine addiction [63]. Remarkably, both the enzyme FAAH and N-acylphosphatidylethanolamine-hydrolyzing phospholipase D (NAPE-PLD), key in degradation and synthesis of anandamide, tightly regulate levels of other NAEs along with anandamide [64,65]. Indeed, substrates such as the anorectic OEA [66] and the anti-inflammatory PEA [67] by sharing with anandamide both the anabolic and degradative pathway [68] can produce an indirect activation of other receptors and the so-called ‘entourage effect’ [69–72]. Thus, although OEA and PEA are not regarded as endocannabinoids, but rather endogenous ligands of PPARs, they are considered as belonging to the endocannabinoid family [63].

As lipid mediators, OEA and PEA suppress nicotine actions on the DA system by acting on PPARα [41,43,73] through negative regulation of β2*-nAChRs [42]. Particularly, because they decrease spontaneous activity of VTA DA cells and the number of spontaneously active DA neurons through a rapid non-genomic mechanism of downstream activation of PPARα, it appears that their physiological role is to negatively modulate β2*-nAChRs and DA cell activity [42]. These effects, rapid in onset and blocked by the tyrosine kinase inhibitor genistein [41], suggest the phosphorylation/dephosphorylation of β2*-nAChRs as a plausible underlying mechanism of NAE actions [42,63]. Because NAEs are found in all mammalian tissues [74] and the PPARα blockade exerts powerful actions on DA cell firing activity [42], one could expect OEA and PEA to be constitutively present in the VTA to enable DA cells to switch between tonic/phasic modes of activity that are tightly regulated by β2*-nAChRs [61]. Additionally, similar to cortical neurons [75], one could speculate that their synthesis and/or release occurs on demand upon cholinergic receptor activation. If so, in VTA DA neurons, acetylcholine and NAEs might control each other in a negative feedback mechanism, where OEA and PEA negatively modulate β2*-nAChRs downstream to PPARα activation, and their biosynthesis is increased under hyper-cholinergic conditions [30].

3. OVERVIEW
(a) Endocannabinoid role in dopamine-dependent behaviour
A precise regulation of DA neuronal activity by the endocannabinoid system and the resulting changes in extra-synaptic DA levels in the target regions [76] is central for the control of DA-dependent behaviour [30,77,78]. Sub-second changes in DA levels within target regions such as the NAcc are important in reward processing [78,79], and VTA DA stimulation is sufficient to drive intracranial self-stimulation (ICSS) [80,81]. ICSS is also accompanied by increased endocannabinoids that act via CB1 receptors whose blockade reduces the behaviour itself [82,83]. In fact, the electrical stimulation of the medial forebrain bundle, which is used to elicit ICSS, is able to evoke
back-propagating action potentials to VTA DA cells [84] and enables the enhancement of endogenous endocannabinoid levels whose transport towards CB1 receptors takes part in the regulation of VTA DA cell activity [83]. Thus, by modulating DA cell firing, endocannabinoids also contribute to the rewarding properties of ICSS. This is particularly remarkable given that ICSS is not only associated with positive reinforcement [80,81,85], but also with cue-induced craving [86,87]. Notably, these two features strongly resemble human facets of drug addiction, where quitting and long-term abstinence are the most difficult tasks to be achieved. According to DSM-IV-TR [88], in fact, addiction is characterized by a persistent state of compulsion to drug-seeking and -taking, which is accompanied by a loss of control in limiting drug intake even with the awareness of ensuing negative consequences and of a negative emotional state, once drug access is banned.

The endocannabinoid system, therefore, being part of homeostatic mechanisms subverted by ICSS, might be exploited to understand the mechanisms underlying dysregulated motivation. In fact, because the majority of VTA DA neurons are activated by reward or a cue predicting the reward when a salient stimulus occurs without anticipation [89], whereas they are inhibited by reward omission, the most common accepted theory regarding DA neuron function is that they encode for the prediction error of reward [80]. Thus, the possibility of developing drugs aimed at treating drug addiction by modulating the endocannabinoid system appears intriguing, especially under conditions such as stress exposure, which triggers activation of the endocannabinoid system whose involvement is required for the stress-induced relapse to drug-seeking [91,92].

(b) Reward versus aversion, addiction and therapeutic potential

Although the endocannabinoid system is a target for novel treatments for addiction, concerns have been raised by the clinical use of rimonabant, the first and only cannabinoid antagonist licensed for the market as an anti-obesity drug. Rimonabant was withdrawn owing to increased risk of depression and suicide [93]. Accordingly, human studies indicate that this drug reduces functional magnetic resonance response of homeostatic mechanisms subverted by ICSS, might be exploited to understand the mechanisms underlying dysregulated motivation. In fact, because the majority of VTA DA neurons are activated by reward or a cue predicting the reward when a salient stimulus occurs without anticipation [89], whereas they are inhibited by reward omission, the most common accepted theory regarding DA neuron function is that they encode for the prediction error of reward [80]. Thus, the possibility of developing drugs aimed at treating drug addiction by modulating the endocannabinoid system appears intriguing, especially under conditions such as stress exposure, which triggers activation of the endocannabinoid system whose involvement is required for the stress-induced relapse to drug-seeking [91,92]. Conversely, CB1 agonists reinstate extinguished drug-seeking behaviour (which is equivalent of relapse in humans) for cannabinoids [100,101], opioids [102,103], ethanol [104,105] and nicotine [106]. In humans, relapse is a major problem in the treatment of addiction, and relapse prevention is the main goal to achieve in addicts. Paradoxically, indirect cannabinoid agonists, i.e. those compounds that increase endogenous levels of endocannabinoids by inhibiting either their catabolic enzymes (e.g. FAAH) or uptake mechanisms (e.g. anandamide membrane transport inhibitors, such as AM404 or VDM11) are more promising than CB1 antagonists. Indeed, indirect cannabinoid agonists have been demonstrated to be effective particularly in suppressing reinstatement of drug-seeking behaviour in laboratory animals, including non-human primates (see Marinelli et al. [91] and references therein). To date, it is not clear whether endocannabinoid–DA system interactions are involved in reinstatement mechanisms. However, because DA neurons might be sensitized to priming with drugs or with drug-associated cues, and might trigger reinstatement, one possibility is that potentiation of endocannabinoid signalling (rather than an indiscriminate activation of CB1 receptors by exogenous agonists) might blunt their stimulus-driven responses by selectively suppressing glutamate release from impinging excitatory axons. Accordingly, cue-induced reinstatement to nicotine self-administration is particularly sensitive to blockade by both FAAH inhibition, AM404 and VDM11 [40,107,108]. In regards to this, it must be pointed out that inhibition of FAAH enhances NAE levels that could depress responses to nicotine via modulation of nAChRs (see above). A role for CB1, however, cannot be excluded, because the endocannabinoid uptake inhibitors, which suppress reinstatement of nicotine self-administration, modify brain anandamide levels without affecting those of OEA and PEA [107,108]. Remarkably, one advantage of an indirect agonist at CB1 receptors such as inhibitors of FAAH and endocannabinoid uptake, and that might pave the way for their clinical use, is that they do not show frank abuse liability in laboratory animals ([108,109], but see Bortolato et al. [110] for AM404).

Additionally, preclinical studies strongly suggest that PPARα could be an effective target for anti-smoking medication [39,41–43,73,111,112]. Noteworthy, being PPARα-mediated actions directed at controlling either function and/or number of β2-nAChRs, their effects are restricted to nicotine. Accordingly, pharmacological inhibition of FAAH by URB597 neither modified self-administration for THC or cocaine [109], nor prevented the effects of either morphine or cocaine on VTA DA neuronal activity [39]. This discriminative property can be ascribed to larger levels of NAEs acting as PPARα ligands following FAAH inhibition, and ultimately acting on VTA DA cells where phosphorylation of β2-nAChRs is the ultimate mechanism. Whether the phosphorylation leads to a reduced ion influx into the DA cell or to fewer nAChRs expressed on the surface of DA cell membranes, the outcome appears as a diminished/abolished response of VTA.
DA neurons to nicotine, as well as to endogenous acetylcholine [42]. This scenario would provide a plausible cellular mechanism for the lack of effect of nicotine in increasing extracellular DA levels in the shell of the NAcc following URB597 treatment [40]. Accordingly, synthetic PPARα ligands, such as lipid lowering fibrates, prevent nicotine-induced excitation of DA cells and increases of extracellular DA levels in the NAcc shell [73]. Given that prolonged nicotine exposure upregulates nAChRs within the VTA [113–115], PPARα negative modulation of β2*-nAChRs by fibrates, medications currently available to improve lipid profiles and prevent cardiovascular disease [116], might represent a promising therapeutical avenue to treat nicotine addiction. Particularly, Panililo et al. [73] demonstrated that clofibrate not only decreased nicotine taking in experienced animals, but it also prevented the relapse-inducing effects of re-exposure to nicotine as well as nicotine-associated cues after a period of abstinence. Thus, fibrates could effectively be the best choice to quit smoking, a habit that is hard to break and is still the largest public health threat the world has ever faced. Fibrate medications, thus, could be used to successfully help people stop abusing nicotine and to prevent relapses. Lastly, fibrate medications appear particularly interesting also because they could help in reducing smoking-related cardiovascular morbidity by improving lipid profiles.

4. CONCLUDING REMARKS

Given the emerging and prominent role of the endocannabinoid system in modulating DA neuronal activity and synaptic transmission within the mesocorticolimbic pathway, pharmacotherapies aimed at tightly regulating the endogenous levels represent a promising treatment for diverse psychiatric and neurological disorders. Because different endocannabinoids and endocannabinoid-related molecules appear to regulate a given synapse, whose precise identity remains elusive, it is imperative to understand the specificity of synaptic tuning by each of these lipid mediators within the VTA. Thus, activity-dependent changes in either endocannabinoid and NAE levels allow, through activation of discrete receptors, a selective and narrow tuning of synapses impinging upon the DA cell—like a switch being turned on and off.

A deeper understanding of endocannabinoid signaling within the mesocorticolimbic DA pathway as well as of the complex interactions between these two systems is paramount. Given the high comorbidity of addiction with depressive, anxious and anger states, the importance of further insights into these interactions cannot be overstated. Because endocannabinoids are involved in mood and anxiety disorders as well as drug addiction, and because boosting endocannabinoid and/or NAE tone has proved useful as an alternative therapeutic approach in animal models of these disorders, investigating whether or not an altered functionality of this system contributes as a predisposing factor is the logical path forward. Thus, endocannabinoid system dysfunctions related to either physiological and/or behavioural features of individuals vulnerable to drug addiction—if they in fact do exist—could open up new possibilities to treat drug addiction.

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