Endocannabinoids and the processing of value-related signals

Miriam Melis1,2, Anna Lisa Muntoni1,2,3 and Marco Pistis1,2,3*

1 B.B. Brodie Department of Neuroscience, University of Cagliari, Monserrato, Italy
2 CNR Neuroscience Institute – Cagliari, University of Cagliari, Monserrato, Italy
3 Center of Excellence for the Neurobiology of Addiction, University of Cagliari, Monserrato, Italy

Endocannabinoids serve as retrograde signalling molecules at many synapses within the CNS, particularly GABAergic and glutamatergic synapses. Synapses onto midbrain dopamine (DA) neurons in the ventral tegmental area (VTA) make no exception to this rule. In fact, the effects of cannabinoids on dopamine transmission as well as DA-related behaviors are generally exerted through the modulation of inhibitory and excitatory afferents impinging onto DA neurons. Endocannabinoids, by regulating different forms of synaptic plasticity in the VTA, provide a critical modulation of the DA neuron output and, ultimately, of the systems driving and regulating motivated behaviors. Because DA cells exhibit diverse states of activity, which crucially depend on their intrinsic properties and afferent drive, the understanding of the role played by endocannabinoids in synaptic modulations is critical for their overall functions. Particularly, endocannabinoids by selectively inhibiting afferent activity may alter the functional states of DA neurons and potentiate the responsiveness of the reward system to phasic DA.

Keywords: dopamine neurons, electrophysiology, LTD, LTP, 2-arachidonoylgllycerol, oleoylethanolamide, PPAR-α

Survival of individuals and conservation of the species strictly depend on the drive by which animals seek natural reinforcers such as food, water, sex, and maternal care. Dopamine (DA) neurons in the ventral tegmental area (VTA), lying centrally amidst the limbic circuit and the basal ganglia, have adapted to organize several aspects of motivated behaviors (Ungless, 2004;Fields et al., 2006a;Sesack and Grace, 2010;Morikawa and Paladini, 2011). Excitatory projections arise mainly from the glutamatergic prefrontal cortex and bed nucleus of the stria terminalis, and glutamatergic–cholinergic pedunculopontine and laterodorsal tegmental nuclei. These neurons project to the dopamine neuron soma and dendrites in the VTA and induce a transient increase in DA release, particularly phasic DA release, which is known to be associated with motor, cognitive, and motivational processes. In vivo, along with a regular, rhythmic discharge similar to that observed in vitro (Grace and Onn, 1989;Khaliq and Bean, 2010), spontaneously active DA neurons exhibit an irregular, single-spike firing mode, and a bursting pattern. It is the switch between these two states that is believed to differentially regulate DA output in downstream structures, with single-spike determining extracellular, “tonic” DA levels and burst firing leading to transient synaptic “phasic” DA levels (reviewed in Grace et al., 2007). Notably, “phasic” DA release is thought to represent the behaviorally relevant signal sent to postsynaptic targets to indicate reward-related cues and facilitate goal-directed action (see Grace et al., 2007 for a review and references therein).

Firing pattern of DA neurons is correlated with specific behavioral stimuli: these cells fire in bursts and release high DA levels especially when a reward is unexpected or larger than expected (Schultz, 1998, 2002, 2006;Schultz and Dickinson, 2000). After training, when reward delivery is reliably preceded by a sensory cue, DA neurons fire in bursts in response to the conditioned stimulus (Schultz, 1998). On the other hand, these cells pause their firing when no reward or punishment are delivered (Schultz, 1998).

Under this aspect, DA neurons have been postulated to encode reward prediction error (Bayer and Glimcher, 2005;Schultz, 2006) and DA to be a powerful learning signal, evolutionary adapted to energize the organism toward natural reinforcers. Phasic depression of firing rate and DA release, on the other hand, can be interpreted as a signal for reversal learning (Schultz, 1998;Robbins and Arnsten, 2009;Kehagia et al., 2010), essential for the animal to attain that degree of behavioral plasticity necessary in an ever-changing environment. Deficits in reversal learning impair the ability of the animal to devaluate reward-related cues when they no longer predict reward and to avoid idle perseveration into unproductive behaviors (Kehagia et al., 2010). This neural circuit can be hijacked by drugs of abuse, which are able to become major reinforcers and overcome the natural ones. Additionally, addicts drugs strongly impair reversal learning and maintain perseveration of drug taking despite of negative and unpleasant consequences of drug use (Dagher and Robbins, 2009).

This dynamic behaviorally driven regulation of DA neuron activity must rely on efferent inputs arising from other brain regions directly involved by sensory, motor, and cognitive information. Hence, both burst firing and pauses depend on the balance between excitatory and inhibitory inputs impinging on DA neurons and interacting with the intrinsic pacemaker currents observed in vitro (Lobb et al., 2010;Morikawa and Paladini, 2011). Excitatory projections arise mainly from the glutamatergic prefrontal cortex and bed nucleus of the stria terminals, and the glutamatergic–cholinergic pedunculopontine and laterodorsal tegmental nuclei.
Endocannabinoids and synaptic plasticity in the VTA

How incoming inputs are integrated and reverberate into specific firing patterns also depends on retrograde transmitters such as endocannabinoids (Melis and Pistis, 2007).

Endocannabinoids are unconventional lipid neurotransmitters/neuromodulators – synthesized on demand from membrane phospholipids – whose functions include retrograde signaling in the brain by modulating and/or mediating several types of synaptic plasticity (Kano et al., 2009). The best characterized endocannabinoids are anandamide (Devane et al., 1992) and 2-arachidonoylglycerol (2-AG; Mechoulam et al., 1995; Sugiura et al., 1995). Once released, they activate presynaptic type 1 cannabinoid receptors (CB1) and inhibit neurotransmitter release influencing both short- and long-term forms of synaptic plasticity.

Similarly to other neurons, DA neurons use endocannabinoids as retrograde neurotransmitters (Melis and Pistis, 2007). These molecules, with particular regard to 2-AG, and endocannabinoid-like N-acylethanolamines (NAEs; see below), have been demonstrated to be efficient means to dampen the activity of external afferents and permit DA neurons to fine tune their own function (Melis et al., 2004a,b, 2010; Melis and Pistis, 2007) to optimally respond to behavioral stimuli.

Regarding endocannabinoid-mediated synaptic plasticity, the best studied synapse in the VTA is the excitatory afferent arising from rostral/cortical regions. Hence, VTA DA neurons have been shown to release endocannabinoids to decreased glutamate release (Melis et al., 2004a,b, 2006; Marinelli et al., 2006b; Haj-Dahmane and Shen, 2010; Kortlever et al., 2011). Particularly, to date, the endocannabinoids that have been identified as fine modulators of excitatory synaptic transmission within the VTA are mainly 2-AG and N-arachidonoyl-dopamine (NADA; Melis et al., 2004a; Marinelli et al., 2006b; Haj-Dahmane and Shen, 2010; Kortlever et al., 2011). Notably, anandamide – though present within the midbrain (Marinelli et al., 2003; Melis et al., 2006) – plays a role as endovanilloid on ionotropic transient receptor potential vanilloid type 1 (TRPV1; Marinelli et al., 2003) rather than as an endocannabinoid on CB1 (Melis et al., 2006). In contrast, the endocannabinoid NADA, which can act depending on the conditions on either CB1 or TRPV1 at both inhibitory and excitatory synapses, can only be detected upon K+ induced depolarization (Marinelli et al., 2006b), thus raising issues on its role under physiological conditions.
Conversely, 2-AG appears as the key signaling molecule released on demand by VTA DA neurons. Hence, 2-AG mediates depolarization-induced suppression of excitation (Melis et al., 2006), a form of short-term plasticity that might serve to limit pathological excitation of VTA DA neurons, such as under ischemic–reperfusion injury (Melis et al., 2006). Additionally, behaviorally relevant patterns of synaptic activity such as a brief burst (2 s, 5 Hz) of excitatory synaptic activity onto DA neurons activate mGlur1 and increase intracellular Ca^{2+} levels, thus leading to 2-AG release, which transiently and selectively reduces excitatory inputs and DA neuron spike and burst probability (Melis et al., 2004a; Pillolla et al., 2007). Hence, it was suggested that 2-AG operates locally within the VTA as a device for DA neurons to switch their firing pattern and activity in response to stimuli (Melis et al., 2004a). Consistently, 2-AG synthetic enzyme sn-1-diacylglycerol lipase-a has been found to be widely expressed in the VTA on DA neurons in proximity of both glutamatergic and GABAergic synapses (Mátyas et al., 2008). Accordingly, different groups have shown that 2-AG plays a role in diverse forms of long-term synaptic plasticity expressed by VTA DA neurons (Pan et al., 2008a; Haj-Dahmane and Shen, 2010; Kortleven et al., 2011). Remarkably, 2-AG mediates long-term depression (LTD; Haj-Dahmane and Shen, 2010), and inhibits long-term potentiation (LTP; Kortleven et al., 2011) at excitatory synapses, consistently with its role in short forms of plasticity at these synapses. Additionally, 2-AG mediates LTD at GABAergic synapses (LTD_{GABA}; Pan et al., 2008a,b, 2011).

**NEW ENDOCANNABINOID-LIKE PLAYERS IN THE VTA: OEA AND PEA**

Along with anandamide, the enzyme N-acylphosphatidylethanolamine-hydrolyzing phospholipase D (NAPE-PLD) also generates other NAES, such as the anorectic and lipolytic oleoylethanolamide (OEA) and the anti-inflammatory palmitoylethanolamide (PEA). Although OEA and PEA are not endocannabinoids, but ligands of peroxisome proliferator-activated receptors (PPAR), they are considered endocannabinoid-related molecules (Pistis and Melis, 2010). In fact, they share with anandamide both the anabolic and degradative pathway (Lambert and Di Marzo, 1999), and they also compete with anandamide for its hydrolysis by the enzyme fatty acid amide hydrolase (FAAH), thereby causing an indirect activation of other receptors and the so-called "entourage effect" (De Petrocellis et al., 2001; Di Marzo et al., 2001; Jonsson et al., 2001; Smart et al., 2002).

Emerging evidence suggests that OEA and PEA exert their actions in the VTA (Melis et al., 2008, 2010). Particularly, they decrease spontaneous activity of VTA DA cells and the number of spontaneously active DA neurons through a rapid non-genomic mechanism downstream to activation of type alpha-PPAR (PPARα; Melis et al., 2010). In 2008, the discovery that OEA and PEA block nicotine-induced excitation of VTA DA neurons both in vivo and in vitro (Melis et al., 2008) shed light into their physiological role as negative modulators on nicotinic acetylcholine receptors containing β2 subunits (β2-nACHRs; Melis et al., 2010). These effects are blocked by the tyrosine kinase inhibitor genistein (Melis et al., 2008), thus suggesting the phosphorylation of β2-nACHRs as a plausible underlying mechanism of NAES actions (Melis et al., 2010; Pistis and Melis, 2010).

Despite the interest, the potential physiological significance, and the implications for NAES actions on VTA DA neurons, many questions remain unanswered. First, OEA and PEA levels have neither been measured in the VTA nor compared with other related lipid molecules. Second, it is not known whether these molecules are released on demand by VTA DA neurons during physiological or pathological circumstances. Third, it is not clear whether they help in controlling the state of β2-nACHRs or the number of functional surface expressed β2-nACHRs. Since NAES are found in all mammalian tissues (Hansen et al., 2001; Hansen and Diep, 2009), one could expect OEA and PEA to be constitutively present in the VTA. Additionally, it could be speculated that their synthesis and/or release occurs on demand upon cholinergic receptor activation, given their role as important negative modulators of β2-nACHRs. In a similar fashion, NAES are produced by cortical neurons in primary cultures (Stella and Piomelli, 2001). If so, under these conditions, in the VTA, 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 by cholinergic agonists (Pistis and Melis, 2010).

Given that β2-nACHRs play a crucial role in mediating the switch from "basal" to "excited" states of VTA DA neurons (Mameli-Engvall et al., 2006), we currently hypothesize that engagement of PPARα by NAES, by making DA neurons less sensitive to external information, might translate into prevention of an erroneous attribution of saliency to otherwise irrelevant stimuli. Thus, engagement of PPARα by NAES may have protective effects and confer VTA DA neurons with the exquisite resilience from excitotoxicity, which – together with individual differences in ion channel makeup – might grant them less vulnerability to metabolic dysfunction.

**ROLE OF ENDOCANNABINOID-MEDIATED SYNAPTIC MODULATION ON DA NEURONS IN GOAL-DIRECTED BEHAVIOR/REWARD SEEKING**

Despite a great deal of research, how – and if – endocannabinoid-mediated modulation of DA neurons translates into behavior is still to be established. Among neurotransmitters/neuromodulators involved in the different phases of compulsive seeking of natural or drug-induced reward, the endocannabinoid system has gained particular attention. Indeed, pharmacological manipulation of endocannabinoids can influence reward-seeking behavior, but if the DA system is directly involved is less clear. For example, blockade of CB1 receptors with rimonabant inhibits nicotine-, alcohol-, and cocaine-induced phasic DA release in the ventral striatum measured with in vivo fast-scan voltammetry (Cheer et al., 2007). Earlier work by Cohen et al. (2002) showed that rimonabant inhibits nicotine-induced DA release in the nucleus accumbens, as measured by brain microdialysis, and nicotine self-administration. Despite evidence on drug-induced DA release, electrophysiological studies failed to demonstrate effects of CB1 antagonists on drug-induced excitation of DA neurons.
neurons (Melis et al., 2000, 2008), with the exception of alcohol (Perra et al., 2005). Thus, it can be inferred that endocannabinoids modulate drug-induced DA release at the synaptic level, without affecting firing rate of DA cells. This piece of evidence is at odds with the important modulatory role of endocannabinoids on synaptic afferents to DA neurons. One explanation is that endocannabinoids might be primarily involved in the effects of chronic drug administration, by modulating multiple long-term, rather than short-term, forms of synaptic plasticity, i.e., facilitating LTDGABA (Pan et al., 2008a,b, 2011) or LTD on DA neurons (Haj-Dahmane and Shen, 2010), or inhibiting LTP (Kortleven et al., 2011). How these functional opposing effects of endocannabinoids on long-term synaptic plasticity combine with each other, and, more importantly, in which phase of the addiction process they are engaged remains to be established.

One possibility is that a persistent LTP at excitatory synapses onto DA cells such as that induced by cocaine (Chen et al., 2008) would lead to 2-AG-mediated LTD at the same synapses to protect DA cells from overexcitation. However, under these conditions, 2-AG rather mediates LTDGABA (Pan et al., 2008b), thus raising questions on its own role. Hence, it seems unlikely that 2-AG would act simultaneously at both inhibitory and excitatory synapses, although most of these latter are equipped with the key molecular players required for 2-AG signaling (Mátyás et al., 2008; Kortleven et al., 2011). Alternatively, one can suggest that cocaine-induced released 2-AG, by removing the inhibitory inputs, can induce DA cells to burst (F. Georges, personal communication), consistent with the disinhibition bursts produced by removal of GABA (Lobb et al., 2010). With this in mind, one would expect that only VTA DA neurons encoding strong reward salience may use 2-AG to escape from GABAergic inhibition and enhance their burst firing (Riegel and Lupica, 2005; Mátyás et al., 2008; Figure 1B). Given that GABAergic afferents onto DA neurons arise from different districts, the precise distribution pattern of key molecular players needed for 2-AG actions can provide the correct framework to understand 2-AG contribution in the context of drug addiction.

Among behaviors related to natural or drug-induced reinforcement, reinstatement (equivalent to relapse in humans) is most sensitive to CB1 receptor activation/blockade. Indeed, following extinction of drug-seeking behaviors such as drug self-administration, CB1 receptor antagonists have been reported to reliably block cue-induced or drug-induced reinstatement of drug-seeking behavior (Fattore et al., 2003, 2005, 2007, 2011; Le Foll and Goldberg, 2005; Ward et al., 2009; Schindler et al., 2011; Yu et al., 2011). Vice versa, CB1 agonists reinitiate drug-seeking behaviors (Juniorina et al., 2008; Scherma et al., 2008; Gamaleddin et al., 2012). One hypothesis is that supramaximal stimulation of CB1 receptors, such as that attained by exogenous cannabinoid agonists, might desensitize or occlude 2-AG-mediated short- or long-term forms of synaptic plasticity primarily on glutamatergic afferents to DA neurons (such as short-lasting suppression of excitation or LTD) by which DA cells might be sensitized to priming with drugs or with drug-associated cues.

Despite the remarkable effect on reinstatement, consensus is emerging in the literature on the lack of effect of (endo)cannabinoids on extinction of learned appetitively motivated tasks (Hernandez and Cheer, 2011). On the other hand, endocannabinoid mechanisms are strongly engaged in extinction of negatively motivated behavior (Marsicano et al., 2002; Lutz, 2007). These pieces of evidence lead us to theorize that endocannabinoids might also participate in the modulation of neural circuits underlying behavioral responses to aversive stimuli. Although amygdala and hippocampus play a major role in aversion mechanisms, DA neurons or their afferents might be also involved. Among afferents to DA neurons, the RMTg plays a pivotal role in processing aversive and appetitive stimuli (Jhou et al., 2009). In fact, RMTg neurons are excited by noxious stimuli and inhibited by rewarding stimuli (Jhou et al., 2009; Hong et al., 2011). These cells form inhibitory synapses with DA neurons (Kauffling et al., 2010; Balcita-Pedicino et al., 2011) and activation of the RMTg inhibits DA neurons both in the rat (Lecca et al., 2011a,b) and in the monkey (Hong et al., 2011). Pauses in DA neuron firing, which encode lack of reward or punishment, might be mediated by the RMTg (Figure 1A) and be regulated by endocannabinoids. In support to this idea, cannabinoids were shown to depress firing rate of RMTg neurons by reducing the strength of excitatory postsynaptic currents (Lecca et al., 2011a; Figure 1B). Moreover, they depress inhibitory inputs on DA neurons arising from RMTg stimulation (Lecca et al., 2011b). Although the expression of CB1 receptors either in the RMTg neurons’ cell body or terminals remains to be demonstrated, electrophysiological evidence supports the notion that the endocannabinoid system might modulate these afferents and finely adjust DA neuron responses to punishment/aversion or reward omission (Figures 1A,B). Consistently, cannabinoids disrupt reversal learning by conferring behavioral inflexibility and increasing perseveration errors (Egerton et al., 2005; Hill et al., 2006; Harte and Dow-Edwards, 2011; Sokolic et al., 2011). On the other hand, RMTg terminals might be a major target for endocannabinoid-mediated short- and long-term forms of synaptic plasticity (depolarization-induced suppression of inhibition, DSI, or LTDGABA, respectively). Hence, by depressing these important inhibitory afferents, endocannabinoids might indirectly excite DA neurons and/or sensitize them toward behavioral or drug-related stimuli, this mechanism resulting into an enhanced stimulus-evoked firing activity and DA release in terminal regions (Figure 1B).

CONCLUDING REMARKS

Further studies on the knowledge of the anatomy, physiology, biochemistry, and pharmacology of these circuits might contribute to new therapeutic strategies for treatment of psychiatric disorders characterized by a dysregulation of the endocannabinoid system in the reward DA circuitry.

It appears, therefore, compelling to investigate whether diverse sets of synapses, most likely arising from extrinsic sources, are differently equipped/enriched with the discrete players of 2-AG signaling machinery. One interesting possibility could be that in the VTA, similarly to the amygdala (Yoshida et al., 2011), a unique molecular convergence of 2-AG signaling molecules would occur...
REFERENCES

Balcita-Pedicino, J. J., Omelchenko, N., Bell, R., and Sesack, S. R. (2011). The inhibitory influence of the lateral habenula on midbrain dopamine neurons: ultrastructural evidence for indirect mediation via the rostromedial mesopontine tegmental nucleus. J. Comp. Neurol. 519, 1143–1164.

Bayer, H. M., and Glimcher, P. W. (2005). Midbrain dopamine neurons encode a quantitative reward prediction error signal. Neuron 47, 129–141.

Bayer, V. E., and Pickel, V. M. (1991). GABA-labeled terminals form proportionally more synapses with dopaminergic neurons containing low densities of tyrosine hydroxylase-immunoreactivity in rat ventral tegmental area. Brain Res. 559, 44–55.

Cheer, J. F., Wasmann, K. M., Sombers, L. A., Heien, M. L., a. V., Aranzen, J. L., Aragona, B. J., Phillips, P. E. M., and Wightman, R. M. (2007). Phasic dopamine release evoked by abused substances requires cannabinoid receptor activation. J. Neurosci. 27, 791–795.

Chen, B. T., Bowers, M. S., Martin, M., Hopf, F. W., Guillory, A. M., Carelli, R. M., Chou, J. K., and Bonci, A. (2008). Cocaine but not natural reward self-administration nor passive cocaine infusion produces persistent LTP in the VTA. Neuron 59, 288–297.

Cohen, C., Perrault, G., Volz, C., Stein-Bayer, V. E., and Pickel, V. M. (2001). GABA-labeled terminals form proportionally more synapses with dopaminergic neurons containing low densities of tyrosine hydroxylase-immunoreactivity in rat ventral tegmental area. Brain Res. 559, 44–55.

Cheer, J. F., Wasmann, K. M., Sombers, L. A., Heien, M. L., a. V., Aranzen, J. L., Aragona, B. J., Phillips, P. E. M., and Wightman, R. M. (2007). Phasic dopamine release evoked by abused substances requires cannabinoid receptor activation. J. Neurosci. 27, 791–795.

Chen, B. T., Bowers, M. S., Martin, M., Hopf, F. W., Guillory, A. M., Carelli, R. M., Chou, J. K., and Bonci, A. (2008). Cocaine but not natural reward self-administration nor passive cocaine infusion produces persistent LTP in the VTA. Neuron 59, 288–297.

Cohen, C., Perrault, G., Volz, C., Stein-Bayer, V. E., and Pickel, V. M. (2001). GABA-labeled terminals form proportionally more synapses with dopaminergic neurons containing low densities of tyrosine hydroxylase-immunoreactivity in rat ventral tegmental area. Brain Res. 559, 44–55.

Cheer, J. F., Wasmann, K. M., Sombers, L. A., Heien, M. L., a. V., Aranzen, J. L., Aragona, B. J., Phillips, P. E. M., and Wightman, R. M. (2007). Phasic dopamine release evoked by abused substances requires cannabinoid receptor activation. J. Neurosci. 27, 791–795.

Chen, B. T., Bowers, M. S., Martin, M., Hopf, F. W., Guillory, A. M., Carelli, R. M., Chou, J. K., and Bonci, A. (2008). Cocaine but not natural reward self-administration nor passive cocaine infusion produces persistent LTP in the VTA. Neuron 59, 288–297.

Cohen, C., Perrault, G., Volz, C., Stein-Bayer, V. E., and Pickel, V. M. (2001). GABA-labeled terminals form proportionally more synapses with dopaminergic neurons containing low densities of tyrosine hydroxylase-immunoreactivity in rat ventral tegmental area. Brain Res. 559, 44–55.

Cheer, J. F., Wasmann, K. M., Sombers, L. A., Heien, M. L., a. V., Aranzen, J. L., Aragona, B. J., Phillips, P. E. M., and Wightman, R. M. (2007). Phasic dopamine release evoked by abused substances requires cannabinoid receptor activation. J. Neurosci. 27, 791–795.
Lecca, S., Melis, M., Luchicchi, A., Ennas, M. G., Castelli, M. P., Muntoni, A. L., and Pistis, M. (2011a). Effects of drugs of abuse on putative rostromedial tegmental neuronal targets in midbrain dopamine cells. *Neuropharmacology* 56, 589–602.

Lecca, S., Melis, M., Luchicchi, A., Muntoni, A. L., and Pistis, M. (2011b). Inhibitory inputs from rostromedial tegmental neurons regulate spontaneous activity of midbrain dopamine cells and their responses to drugs of abuse. *Neuropsychopharmacology*. doi: 10.1038/npp.2011.302. [Epub ahead of print].

Lobb, C. J., Wilson, C. J., and Paladini, C. A. (2010). A dynamic role for GABA receptors on the firing pattern of midbrain dopaminergic neurons. *J. Neurophysiol.* 104, 403–413.

Lutz, B. (2007). The endocannabinoid system and extinction learning. *Mol. Neurobiol.* 36, 92–101.

Mameli-Engwall, M., Errard, A., Pons, S., Maskos, U., Svensson, T. H., Changeux, J. P., and Fauré, P. (2006). Hierarchical control of dopamine neuron-firing patterns by nicotinic receptors. *Neuron* 50, 911–921.

Marinelli, M., Rudick, C. N., Hu, X. T., and White, F. J. (2006a). Excitability of dopamine neurons: modulation and physiological consequences. *CNS Neurosci. Disord. Drug Targets* 5, 79–97.

Marinelli, S., Di Marzo, V., Ferrenzano, F., Pezza, F., Viscomi, M. T., Van Der Stelt, M., Bernardi, G., Molinari, M., Maccarrone, M., and Mercuri, N. B. (2006b). N-arachidonoyl-dopamine tunes synaptic transmission onto dopaminergic neurons by activating both cannabinoid and vanil-loid receptors. *Neuropsychopharmacology* 32, 298–308.

Marinelli, S., Di Marzo, V., Berretta, N., Mattias, L., Maccarrone, M., Bernardi, G., and Mercuri, N. B. (2005). Presynaptic facilitation of glutamatergic dopaminergic neurons to the rat substantia nigra by endogenous stimulation of vanilloid receptors. *J. Neurosci.* 23, 3136–3144.

Marsicano, G., Wotjak, C. T., Azad, S. C., Bisogno, T., Rammes, G., Cascio, M. G., Hermann, H., Tang, I., Hofmann, C., Ziegglansberger, W., Di Marzo, V., and Lutz, B. (2002). The endogenous cannabinoid system controls extinction of aversive memories. *Nature* 416, 530–533.

Mátyás, F., Urban, G. M., Watanabe, M., Mackie, K., Zimmer, A., Freund, T. F., and Katona, I. (2008). Identification of the sites of 2-arachidonoylglycerol synthesis and action imply retrograde endocannabinoid signaling at both GABAergic and glutamatergic synapses in the ventral tegmental area. *Neuropsychopharmacology* 34, 95–107.

Mehoulam, R., Ben-Shahat, S., Hansus, L., Ligumsky, M., Kaminski, N. E., Schatz, A. R., Gopher, A., Almagor, S., Martin, B. R., Compton, D. R., Per-twee, R. G., Griffin, G., Bayevitch, M., Barg, I., and Vogel, Z. (1995). Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. *Biochem. Pharmacol.* 50, 83–90.

Mils, M., Carta, S., Fantore, L., Tolu, S., Yasar, S., Goldberg, S. R., Fratta, W., Maskos, U., and Pistis, M. (2010). Peroxoax proliner -activated receptors-alpha modulate dopaminergic neuron activity via nicotoxin receptors. *Biopolymers* 86, 256–264.

Mils, M., Gessa, G. L., and Diana, M. (2000). Different mechanisms for dopaminergic excitation induced by opiates and cannabinoids in the rat midbrain. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 24, 993–1006.

Melis, M., Perra, L., Muntoni, A. L., Pillolla, G., Lutz, B., Marsicano, G., Di Marzo, V., Gessa, G. L., and Pistis, M. (2004a). Preferential cortical stimulation induces 2-arachidonoyl-glycerol-mediated suppression of excitation in dopamine neurons. *J. Neurosci.* 24, 10707–10715.

Melis, M., Pistis, M., Perra, S., Muntoni, A. L., Pillolla, G., and Gessa, G. L. (2004b). Endocannabinoids mediate presynaptic inhibition of glutamatergic transmission in rat ventral tegmental area dopamine neurons through activation of CB1 receptors. *J. Neurosci.* 24, 15–27.

Melis, M., Pillolla, G., Bisogno, T., Minassi, A., Petrosino, S., Perra, S., Muntoni, A. L., Lutz, B., Gessa, G. L., Marsicano, G., Di Marzo, V., and Pistis, M. (2006). Protective activation of the endocannabinoid system during ischemia in dopamine neurons. *Neurobiol. Dis.* 24, 15–27.

Melis, M., Pillolla, G., Luchicchi, A., Muntoni, A. L., Yasar, S., Goldberg, S. R., and Pistis, M. (2008). Endogen-ous Fatty Acid Ethanolamides Suppress Nicotine-Induced Activation of Mesolimbic Dopamine Neurons through Nuclear Receptors. *J. Neurosci.* 28, 13985–13994.

Melis, M., and Pistis, M. (2007). Endocannabinoid signaling in mesolimbic dopamine neurons: more than physiology? *Curr. Neuropharmacol.* 5, 268–277.

Morikawa, H., and Paladini, C. A. (2011). Dynamic regulation of midbrain dopamine neuron activity: intrinsic, synaptic, and plasticity mechanisms. *Neuroscience* 198, 95–111.

Omelchenko, N., and Sesack, S. R. (2009). Ultrastructural analysis of local collaterals of rat ventral tegmental area neurons: GABA pheno-type and synapses onto dopamine and GABA cells. *Synapse* 63, 895–906.

Pan, B., Hillard, C. J., and Liu, Q. S. (2008a). D2 dopamine receptor activation facilitates endocannabinoid-mediated long-term synaptic depression of GABAergic synaptic transmission in midbrain dopamine neurons via cAMP-protein kinase A signaling. *J. Neurosci.* 28, 14018–14030.

Pan, B., Hillard, C. J., and Liu, Q. S. (2008b). Endocannabinoid signaling mediates cocaine-induced inhibitory synaptic plasticity in midbrain dopamine neurons. *J. Neurosci.* 28, 1385–1397.

Pan, B., Zheng, P., Sun, D., and Liu, Q. S. (2011). Extracellular signal-regulated kinase signaling in the ventral tegmental area mediates cocaine-induced synaptic plasticity and rewarding effects. *J. Neurosci.* 31, 11244–11255.

Perra, S., Pillolla, G., Melis, M., Muntoni, A. L., Gessa, G. L., and Pistis, M. (2005). Involvement of the endogenous cannabinoid system in the effects of alcohol in the mesolimbic reward circuit: electrophysiological evidence in vivo. *Psychopharmacology (Berl.)* 183, 368–377.

Pillolla, G., Melis, M., Perra, S., Muntoni, A. L., Gessa, G. L., and Pistis, M. (2007). Medial forebrain bundle stimulation evokes endocannabinoid-mediated modulation of ventral tegmental area dopamine neuron firing in vivo. *Psychopharmacology (Berl.)* 191, 843–853.

Pistis, M., and Melis, M. (2010). From surface to nuclear receptors: the endocannabinoid family expands its assets. *Curr. Med. Chem.* 17, 1450–1467.

Riegel, A. C., and Lupica, C. R. (2005). Independent presynaptic and postsynaptic mechanisms regulate endocannabinoid signaling at multiple synapses in the ventral tegmental area. *J. Neurosci.* 24, 11070–11077.

Reynolds, T. W., and Arnsten, A. F. T. (2006). The neuropharmacology of fronto-executive function: monoaminergic modulation. *Annu. Rev. Neurosci.* 29, 136, 452–458.

Sokolic, L., Long, L. E., Hunt, G. E., Arnold, J. C., and McGregor, I. S. (2011). Disruptive effects of the prototypical cannabinoid Delta-9-tetrahydrocannabinol and the fatty acid amide inhibitor URB-597 on go/no-go auditory discrimination performance and olfactory reversal learning in rats. *Behav. Pharmacol.* 22, 191–202.

Stella, N., and Piemelli, D. (2001). Receptor-dependent formation of endocannabinoids in cortical neurons. *Eur. J. Pharmacol.* 425, 189–196.

Sugiura, T., Kondo, S., Sukagawa, A., Nakane, S., Shimoda, A., Doh, K., Yamada, A., and Waku, K. (1995). 2-Arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain. *Biochem. Biophys. Res. Commun.* 215, 89–97.
Ungless, M. A. (2004). Dopamine: the salient issue. Trends Neurosci. 27, 702–706.
Ward, S. J., Rosenberg, M., Dykstra, L. A., and Walker, E. A. (2009). The CB1 antagonist rimonabant (SR141716) blocks cue-induced reinstatement of cocaine seeking and other context and extinction phenomena predictive of relapse. Drug Alcohol Depend. 105, 248–255.
Xia, Y., Driscoll, J. R., Wilbrecht, L., Margolis, E. B., Fields, H. L., and Hjelmstad, G. O. (2011). Nucleus accum-bens medium spiny neurons target non-dopaminergic neurons in the ventral tegmental area. J. Neurosci. 31, 7811–7816.
Yoshida, T., Uchigashima, M., Yamazaki, M., Katona, I., Yamazaki, M., Sakimura, K., Kano, M., Yoshioka, M., and Watanabe, M. (2011). Unique inhibitory synapse with particularly rich endocannabinoid signaling machinery on pyramidal neurons in basal amygdaloid nucleus. Proc. Natl. Acad. Sci. U.S.A. 108, 3059–3064.
Yu, L. L., Zhou, S. J., Wang, X. Y., Liu, J. F., Xue, Y. X., Jiang, W., and Lu, L. (2011). Effects of cannabinoid CB receptor antagonist rimonabant on acquisition and reinstatement of psychostimulant reward memory in mice. Behav. Brain Res. 217, 111–116.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 01 December 2011; paper pending published: 12 December 2011; accepted: 12 January 2012; published online: 02 February 2012.

Citation: Melis M, Muntoni AL and Pistis M (2012) Endocannabinoids and the processing of value-related signals. Front. Pharmacol. 3:7. doi: 10.3389/fphar.2012.00007
This article was submitted to Frontiers in Neuropharmacology, a specialty of Frontiers in Pharmacology.
Copyright © 2012 Melis, Muntoni and Pistis. This is an open-access article distributed under the terms of the Creative Commons Attribution Non Commercial License, which permits non-commercial use, distribution, and reproduction in other forums, provided the original authors and source are credited.