

# Dopamine – CNS Pathways and Neurophysiology

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## Introduction

The dopamine (DA) systems of the brain have been the topic of intensive investigation since the first report of this neurochemical as an independent neurotransmitter in the brain nearly 50 years ago. The DA systems have drawn the attention of investigators due to their known role in a variety of neurological and psychiatric disorders, including Parkinson's disease, schizophrenia, and drug addiction. In this article, we review the principal electrophysiological characteristics of DA neurons, as well as the intrinsic and extrinsic regulation of their activity and firing patterns.

## Anatomy of DA Neuron Projections

As with most monoamine systems, individual DA neurons are believed to exhibit dense collateralizations, with single neurons giving rise to 500 000 to 1 000 000 synaptic terminals. However, unlike other monoamine neurons, midbrain DA neurons have discrete, topographic projections to their target regions. Three major DA neuronal systems have been identified that project to forebrain regions: (1) the nigrostriatal DA neuron projection, which arises from the substantia nigra (SN) and projects to the dorsal striatum; this system is involved in motor control and is known to degenerate in Parkinson's disease; (2) the mesolimbic DA projection, which arises from the ventral tegmental area (VTA) and projects to limbic structures such as the ventral striatum, nucleus accumbens, amygdala, and other regions involved in control of affect and likely play a role in schizophrenia and drug abuse; and (3) the mesocortical DA system, which also arises from the VTA and projects primarily to frontal cortex; this projection system is believed to be involved in higher processes related to the control of executive function.

## Electrophysiology

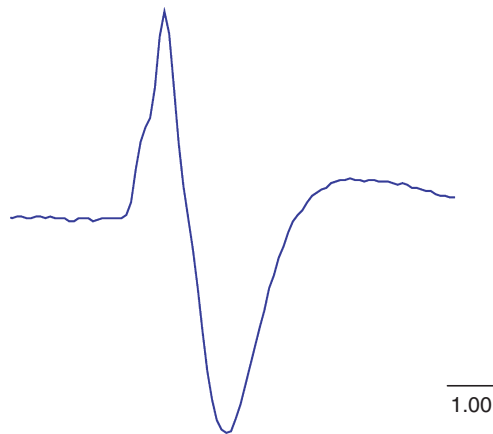
### Identification

Since the ventral mesencephalon is a heterogeneous region, the first challenge in examining the neurophysiology of DA systems is to ensure that the neurons recorded are indeed DAergic in nature. The first

extracellular recordings from putative DA neurons were performed in the 1970s. Through an examination of the neurophysiological characteristics of DA neurons and subsequent histochemical verification, it was determined that DA neurons can be identified based solely on their electrophysiological characteristics. As such, one of the most distinct features of DA neurons is the broad extracellular spike waveform they produce (Figure 1). Such waveforms are biphasic (+/-), with an inflection in the rising phase (representative of the initial segment spike). They have a pronounced negative phase to the action potential, as well as a long time course (>2 ms). More specifically, action potentials consist of a short-duration, smaller-amplitude initial segment spike, followed by a larger and longer duration somatodendritic spike. Much of this unique waveform is a consequence of the active membrane properties of the neuron, causing a train of action potentials to be variable from one waveform to the next, and readily distinguishable by the long-duration negative phase, although such differences can be obscured if improper filter settings are employed.

### Passive Membrane Properties

Intracellular recordings from identified DA neurons have provided important insights into the mechanisms underlying action potential generation in these neurons. Interestingly, DA neurons recorded from mesencephalic slices after severing of afferent processes continue to exhibit spontaneous activity that is derived from the active membrane properties of the neuron. One factor associated with spike generation in DA neurons is a large-amplitude (10–15 mV), pacemaker-like slow depolarizing potential that brings the membrane potential from rest (*c.* -55 mV) to the comparatively high action potential threshold (*c.* -40 mV). This slow depolarization is mediated by both sodium and calcium conductances, as it can be blocked by tetrodotoxin (TTX) or cobalt, both of which also inhibit spontaneous spike firing. The resultant spike is followed by a negative shift in membrane potential accompanied by an inhibition of spike firing, or an afterhyperpolarization. This afterhyperpolarization is voltage dependent and mediated by a calcium-activated potassium conductance, as it can be blocked by tetraethylammonium (TEA) and attenuated by the calcium chelator ethylene glycol tetraacetic acid (EGTA). Furthermore, it is believed that the rebound from this hyperpolarization triggers the calcium and sodium conductances comprising the slow depolarization. It is this cycle that has



**Figure 1** Electrophysiological trace of an action potential recorded extracellularly from an identified VTA DA neuron. The unique characteristics are the biphasic (+/–) waveform with an inflection in the rising phase, pronounced negative phase, as well as a long time course (>2 ms). Scale bar = 1 ms.

been proposed to underlie spontaneous pacemaker firing of midbrain DA neurons observed *in vivo* and *in vitro*.

### DA Neuron Activity States

DA neurons of the brain typically display four different states of activity. The first is an inactive, hyperpolarized state suggested to result from GABAergic inhibition (see the section titled ‘Intrinsic regulation of DA neuron firing’). These spontaneously inactive neurons have a higher resting membrane potential (*c.* –65 to –75 mV) and can be activated by direct glutamate application or administration of haloperidol (IV). A separate inactive state has been demonstrated following chronic neuroleptic treatment. This state has been termed ‘depolarization block,’ caused by hyperexcitation and characterized by a depolarized membrane potential. In contrast to hyperpolarized inactive DA neurons, glutamate application will not activate DA neurons following depolarization block, and the restoration of spontaneous activity is achieved by the direct application of the ‘inhibitory’ transmitter,  $\gamma$ -aminobutyric acid (GABA).

Spontaneously active DA neurons, recorded *in vivo*, typically display two main firing patterns: a slow, irregular single-spike firing pattern and a faster bursting mode. It is the alternation between these two states that is thought to result in different levels of DA release in terminal regions, with irregular spike firing regulating extracellular, ‘tonic’ DA levels and burst firing leading to transient synaptic ‘phasic’ DA levels. Accordingly, much research has focused on the regulation of these two types of firing patterns and the mechanisms that lead to the transition from one pattern to the other.

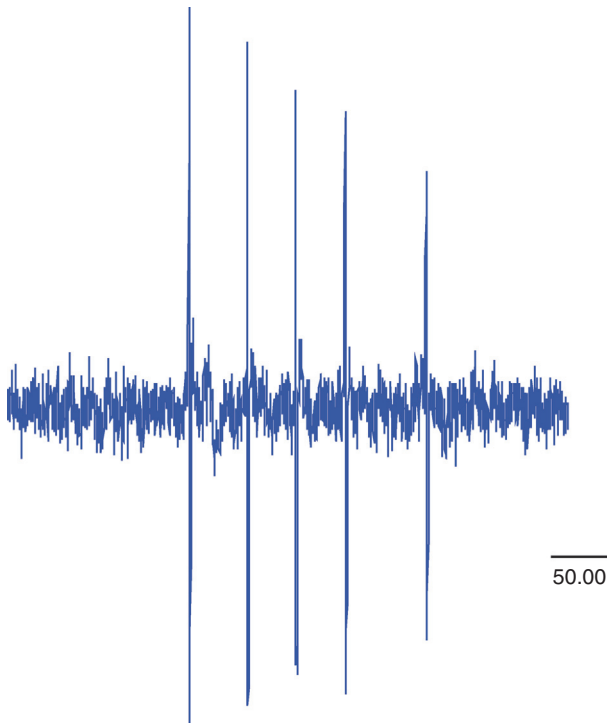
### Irregular, Single-Spike Firing

DA neurons recorded *in vivo* commonly display firing rates between 2 and 8 Hz, with an average of approximately 4 Hz, and seldom fire at rates lower than 1 Hz or exceeding 10 Hz. While in single-spike firing mode, DA neuron interspike intervals (ISIs) are fairly long (200–250 ms) and follow a normal distribution. It is thought that the slow single-spike firing pattern of DA neurons is driven by the intrinsic pacemaker depolarization, as well as the prolonged afterhyperpolarization discussed above. Interestingly, although DA neurons recorded *in vitro* display a highly regular pacemaker firing pattern, DA neurons recorded *in vivo* possess a significantly more irregular pattern of activity. This pattern of activity is likely to be associated with variations in calcium entry into the neuron during spontaneous spike firing, since the intracellular injection of EGTA into an irregularly firing neuron causes a transition to a pacemaker pattern.

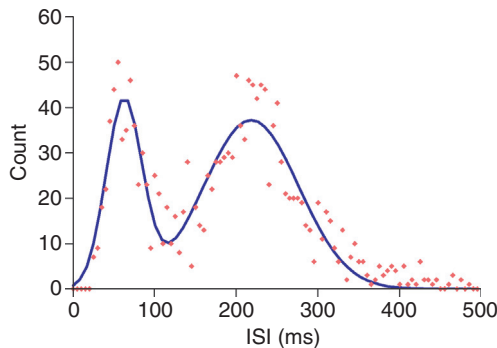
### Burst Firing

The firing rates of DA neurons fall into a fairly limited range, usually 2–8 Hz, which consequently might limit the flexibility of DA neurons to release differential amounts of DA in terminal regions. However, this is overcome by a change in firing pattern from single-spike firing to burst firing. Burst firing in DA neurons induces increases in DA release that are 2–3 times that of increases in tonic firing rates of the same magnitude. Moreover, DA released during burst firing has been demonstrated to be localized to the synaptic cleft and is considered the functionally relevant signal sent to postsynaptic sites. These bursts are comprised of a series of spikes that display accommodation, with decreasing amplitude and increasing action potential duration (Figure 2). DA neuron bursts are typically comprised of two to eight spikes which ride on top of a membrane depolarization. While the first two of these spikes are separated by an ISI of 80 ms or less, following spikes tend to have increasing ISIs of up to 160 ms. As such, DA neurons firing in burst tend to display a bimodal ISI distribution (Figure 3). Bursts of DA neurons tend to be different from bursting described for neurons in other regions in three primary ways: (1) they cannot be elicited by short, depolarizing current pulses; (2) they have a much larger ISI than is typical for bursting neurons; and (3) they can be blocked by intracellular calcium chelators such as EGTA.

The transition from irregular single-spike firing to burst firing is dependent on an excitatory amino acid, since activation of glutamatergic afferents or direct microiontophoretic application of glutamate induces burst firing in DA neurons *in vivo*. Furthermore, direct application of competitive *N*-methyl-D-aspartate



**Figure 2** Extracellular recording of a single burst of action potentials recorded from a burst firing DA neuron. These bursts are comprised of a series of spikes that display accommodation, with decreasing amplitude and increasing action potential duration. Scale bar = 50 ms.



**Figure 3** An ISI histogram from a burst-firing DA neuron depicting the characteristic bimodal distribution. Diamonds represent individual bin values, and the line is the fitted average curve. The early peak is the ISI within the burst, and the later peak is the time between bursts.

(NMDA) receptor antagonists potently blocks spontaneous burst firing. Taken as a whole, there is a significant literature demonstrating a primary role for NMDA receptor-mediated glutamatergic transmission in the regulation of DA neuron burst firing. On the other hand, glutamate alone is not sufficient to mediate burst firing. Thus, DA neurons recorded

from mesencephalic slices obtained from adult rats, in which afferent input has been severed, display a regular pacemaker firing pattern and cannot be made to fire in bursts in response to glutamate agonist administration or alterations in membrane potential alone.

Based on the role of  $\text{Ca}^{2+}$  and  $\text{K}^{+}$  conductances in the generation of burst firing *in vivo*, the first reported instance in which burst firing was observed *in vitro* was in the presence of apamin, a toxin derived from bee venom and a potent and irreversible inhibitor of small conductance (SK)  $\text{Ca}^{2+}$ -activated  $\text{K}^{+}$  channels (gKCa). Interestingly, in studies that include apamin in the perfusate, DA neuron activity more closely resembles that seen *in vivo* with a decreased regularity of firing and the potential to display burst firing in response to depolarizing current injections and NMDA application. Taken as a whole, these data suggest that DA neuron burst firing is regulated by at least two mechanisms, the first being a permissive inactivation of the SK  $\text{Ca}^{2+}$ -activated  $\text{K}^{+}$  channels that by itself does not necessarily induce burst firing but is required for burst firing to occur, and the second being an afferent-derived glutamatergic drive. Interestingly, these mechanisms are not necessarily mutually exclusive, since recent reports have demonstrated a  $\text{Ca}^{2+}$ -mediated feedback loop whereby SK channels can regulate NMDA-dependant  $\text{Ca}^{2+}$  influx within individual dendritic spines. Afferent inputs that may be responsible for altering membrane conductances and allowing for the shift from single-spike, irregular firing mode to bursting mode are reviewed below.

### Electrical Coupling

Electrical coupling between DA neurons was suggested following the observation that intracellular injection of Lucifer yellow dye into a single DA neuron can result in the labeling of adjacent DA neurons. Further evidence for electrical coupling stems from the fact that some DA neurons located in close proximity have been shown to fire in nearly synchronous firing patterns (with ISIs on the order of 2–3 ms). Administration of D2 receptor blockers such as haloperidol is reported to increase the incidence of simultaneous spike discharge among DA neurons. Furthermore, near-synchronous firing seems to occur more frequently during burst firing patterns. More recently, direct evidence for DA neuron coupling has been observed by simultaneous patch-clamp recordings from DA neuron pairs. This study demonstrated that depolarization of a DA neuron can result in an increased firing frequency of a neighboring electrically coupled DA neuron. In summary, there is significant evidence for electrical coupling between adjacent DA neurons that may result in synchronous firing under appropriate conditions.

## Afferent Input to Midbrain DA Neurons

Given the importance of the VTA in encoding reward prediction or indicating incentive salience, it is perhaps not surprising that this region is a site of extensive integration of afferent information. As such, early anatomical studies demonstrated a widespread convergent input to the VTA. This afferent input has since been confirmed and extended using more selective and sensitive techniques. Thus, afferent inputs to the VTA from a large number of regions have been described, which include the prefrontal cortex, nucleus accumbens, ventral pallidum (VP), lateral preoptic area, lateral hypothalamus, and brain stem regions including the pedunculopontine tegmentum (PPTg) and laterodorsal tegmentum (LDTg), among other areas. In addition, the VTA is a heterogeneous structure containing GABAergic interneurons and dendritodendritic synaptic appositions. As such, the output of the VTA is a function of its intrinsic organization as well as regulation by extrinsic factors.

## Intrinsic Regulation of DA Neuron Firing

### Autoreceptor-Mediated Inhibition

DA neurons display an autoregulatory mechanism important in the determination of their activity levels. DA neuron dendrites in the VTA contain tyrosine hydroxylase (the rate-limiting enzyme in DA synthesis), contain D2 autoreceptors located near the cell body, and DA has been shown to be released in a calcium-dependent manner from the somatodendritic region of DA neurons. Furthermore, investigations using a number of different methods have shown that somatodendritic DA release in the VTA is altered under different behavioral and pharmacological conditions. This local DA release provides a potent autoinhibitory role in the VTA by decreasing DA cell firing rate via activation of D2 receptors. Iontophoresis of DA onto DA neurons causes inhibition of neural activity. Moreover, low doses of DA agonists administered systemically will preferentially activate these highly sensitive somatodendritic D2 autoreceptors. Moreover, application of D2 antagonists enhances DA neuronal firing even following transection of feedback pathways from postsynaptic targets, suggesting a tonic level of autoreceptor activation of DA neurons. D2 antagonists also block DA-induced suppression of DA neuron firing. These data therefore demonstrate a potent autoinhibitory role for DA within the nigrostriatal and mesolimbic DA system.

### GABA

The midbrain DA neuron regions are heterogeneous structures containing not only DAergic and

non-DAergic projection neurons, but also a number of GABAergic interneurons. Investigations into the effects of these intrinsic GABAergic neurons on DA neuron firing patterns demonstrated the somewhat surprising observation that systemic administration of a GABA agonist (muscimol) actually increases DA neuron firing rate *in vivo*. Further study determined that this ‘paradoxical excitation’ was correlated with a decrease in firing rates of non-DA neurons. Moreover, DA neurons recorded intracellularly *in vivo* have been shown to be under a constant bombardment with large-amplitude GABAergic inhibitory postsynaptic potentials (IPSPs). These data demonstrate that the increase in DA neuron firing induced by systemic muscimol is secondary to the inhibition of tonically active GABAergic interneurons, and thus demonstrates a tonic role for local inhibitory regulation of DA neuron firing.

## Afferent Connectivity

### GABAergic Inputs

As stated above, intracellular recordings from identified DA neurons of the rat midbrain *in vivo* have demonstrated that these neurons are constantly bombarded by GABAergic IPSPs. Indeed, it has been suggested that up to 50% of the midbrain DA neurons are quiescent due to GABAergic-mediated hyperpolarization. Moreover, these IPSPs are not observed *in vitro*, suggesting a prominent and tonically active GABAergic tone to this region in addition to that supplied by intrinsic interneurons. One region providing such input is the pallidal complex; a GABAergic structure that receives GABAergic inputs from the striatum and nucleus accumbens (among other regions) displays relatively high rates of spontaneous activity and exerts a powerful tonic inhibitory influence over efferent structures. Since anatomical studies have demonstrated a substantial projection from the globus pallidus to the SN DA neurons and from the VP to the VTA, the pallidum is well positioned to influence DA neural activity. Investigations have demonstrated that inactivation of the VP results in a dramatic increase in the number of spontaneously active DA neurons observed per electrode track (a standard measure of DA neuron population activity) that is correlated with a significant increase in extracellular ‘tonic’ DA release in the nucleus accumbens. Taken as a whole, these data demonstrate a prominent tonic inhibition of DA neuron firing by the VP.

### Glutamatergic Inputs

As mentioned above, the transition from irregular single-spike firing to a burst firing pattern has been

largely attributed to increased glutamatergic input. As such, direct microiontophoretic application of glutamate has been demonstrated to increase burst firing in DAergic neurons. This effect has largely been attributed to actions at the ionotropic NMDA receptor, since it is blocked by MK-801, a highly potent and selective noncompetitive NMDA receptor antagonist. Furthermore, it has been suggested that glutamatergic transmission is required for burst firing *in vivo* since both glutamate-induced and natural burst events can be blocked by inactivation of glutamatergic afferents or the administration of glutamatergic or NMDA receptor antagonists. There is significant literature suggesting a primary role for NMDA receptor-mediated glutamatergic transmission in the regulation of DA neuron burst firing. Given that DA neuron burst firing is considered to be the functionally relevant signal sent to postsynaptic sites to encode reward prediction or indicate incentive salience, glutamatergic inputs to the VTA have garnished significant attention. Such inputs have been demonstrated to arise from the prefrontal cortex, PPTg, and lateral preoptic-rostral hypothalamic area.

The prefrontal cortex is a region associated with planning complex cognitive behaviors such as executive function and expression of appropriate social behavior. A significant literature has been accumulated implicating the medial prefrontal cortex (mPFC) in the regulation of DA neuron burst firing. Thus, chemical stimulation of the mPFC increases burst firing in a proportion of DA neurons, whereas inactivation of this area has been found to reduce spontaneous burst activity. Furthermore, electrical stimulation of the mPFC induces events that resemble natural burst firing in a subset of DA neurons. It is important to note that recent anatomical studies have demonstrated that terminals from the mPFC synapse exclusively onto mesocortical DA neurons, suggesting that glutamatergic inputs from the mPFC provide direct regulatory control over an important subset of VTA DA neurons.

Another major excitatory input to the VTA arises from the PPTg, a glutamatergic/cholinergic region driven by limbic afferents, including the prefrontal cortex and extended amygdala. The PPTg is activated by auditory, visual, and somatosensory stimuli, and has been demonstrated to directly regulate burst firing of DAergic neurons. Thus, electrical stimulation of the PPTg produces time-locked bursts of action potentials in DA neurons that resemble natural bursts. Furthermore, chemical activation of the PPTg induces a significant increase in DA neuron burst firing. Taken as a whole, the PPTg serves as a site of convergence whereby a variety of sensory inputs can modulate DA neuron burst firing.

### Association between GABA and Glutamatergic Inputs

Given that the midbrain DA system is a site of extensive integration of afferent inputs, it is perhaps not surprising that in addition to providing independent control over distinct DA neuron activity states, afferent pathways also interact to modulate DA neuron responsiveness. For example, it has been suggested that activation of excitatory inputs to the VTA results in burst firing only in DA neurons that are already spontaneously active. Thus, DA neurons that are inactive, presumably due to GABA-mediated hyperpolarization, are unresponsive to activation of glutamatergic afferents, likely attributable to  $Mg^{2+}$  blockade of the NMDA receptor-channel complex. This suggests the presence of a unique interdependence of the GABAergic and glutamatergic VTA inputs, that is, only neurons that are not under GABA-mediated hyperpolarization are capable of entering a burst firing mode in response to a glutamatergic input. Indeed, we have previously reported that the hippocampus can gate phasic DA transmission by regulating the number of spontaneously active DA neurons that can be further modulated by excitatory inputs to induce a graded phasic response. Hence, although independent inputs to the VTA can regulate distinct DA neuron activity states, these afferents also interact to regulate DA neuron responsiveness.

### Regulatory Inputs

Although there is significant literature demonstrating a primary role for NMDA receptor-mediated glutamatergic transmission in the regulation of DA neuron burst firing, glutamate alone is not sufficient to induce burst firing in DA neurons recorded from mesencephalic slices *in vitro* (in which afferent processes have been severed). As reviewed above, in contrast to what is seen *in vivo*, DA neurons recorded *in vitro* from mesencephalic slices do not exhibit burst firing under baseline, depolarization, or glutamate-stimulated conditions. Thus, although glutamatergic transmission is critical, it is not the sole determinant of the generation of burst firing *in vivo*.

Therefore, we have recently demonstrated that a critical factor required to allow spontaneous and glutamate-driven burst firing *in vivo* depends on tonic drive from the LDTg. After baclofen/muscimol inactivation of this region, DA neuron discharge patterns more closely resemble those observed *in vitro*; as pacemakers that lack spontaneous burst firing. Interestingly, neither activation of the PPTg nor direct glutamate iontophoresis *in vivo* are capable of inducing burst firing following LDTg inactivation. Taken

as a whole, these data demonstrate that a functional input from the LDTg is essential for DA neuron burst firing *in vivo*.

### Neuromodulatory Inputs

As discussed above, the predominant excitatory and inhibitory neurotransmitters, glutamate and GABA, respectively, potently and dramatically regulate DA neuron activity states. It is important to recognize, however, that there are also significant inputs to the VTA that contain biogenic amines, neuropeptides, or nonclassical transmitters (i.e., nitric oxide or arachidonic acid derivatives). Moreover, a number of these have been shown to modulate DA neuron firing patterns. These include cholinergic, adrenergic, serotonergic, and peptidergic inputs arising from a number of regions. Given the large number of neuromodulators present in the VTA, it would not be possible to discuss them all in this review; as such, we focus on the two that have been at the center of recent significant advances, namely, the cannabinoids and the orexins.

### Cannabinoids

Research into the neurobiological actions of cannabis has demonstrated that the active ingredient of marijuana,  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC), increases extracellular DA efflux in the accumbens. In addition, further research demonstrated that systemic administration of  $\Delta^9$ -THC (and other cannabinoid agonists) increases the firing rate and burst firing of identified VTA DA neurons. Interestingly, in contrast to the mechanism of action of classical neurotransmitters, endocannabinoids appear to act in a retrograde manner. As such, it is believed that endocannabinoids are released from postsynaptic neurons due to membrane depolarization, and that they migrate to adjacent presynaptic targets where they can modulate neurotransmitter release by activating presynaptic CB1 receptors. This retrograde neurotransmitter function of endocannabinoids has been identified recently in the VTA. Therefore, the activity-dependent release of endocannabinoids in the VTA has been suggested to act as a regulatory feedback mechanism to modulate presynaptic glutamatergic and GABAergic release. As a result, it is likely that endogenous cannabinoids act to provide an additional level of autoregulatory feedback in the VTA.

### Orexin

Orexins are neuropeptides that are found in neurons of the lateral hypothalamus associated with arousal, feeding, and appetitive behaviors. Due to the significant orexigenic input from the LH to DA neurons of

the VTA, it has been suggested that orexin modulates DAergic neurotransmission. Indeed, the direct application of orexin increases the firing rate of DA neurons recorded *in vitro*, suggesting a role for the orexin system in the modulation of DA neuron activity. More recent data have expanded previous observations and demonstrated a unique role for these neuropeptides in the regulation of DA neuronal activity. Specifically, the application of orexin *in vitro* has been shown to augment NMDA neurotransmission by inducing the insertion of NMDA receptors into the membrane of DA neurons. Such findings provide evidence for a role of the endogenous orexin system in the regulation of DA neuronal activity and plasticity.

### Conclusion

The functional output of a brain region is dependent on both the intrinsic properties of the neurons and its regulation by extrinsic inputs. Here we illustrate that VTA DA neurons display distinct patterns of activity and furthermore that these activity states can be dynamically regulated by intrinsic and extrinsic inputs. This ability to integrate a variety of incoming signals and dynamically regulate DA neural firing patterns therefore provides the flexibility essential for the role of the VTA in the regulation of cognitive and motivational behaviors.

*See also:* Addiction: Neurobiological Mechanism; Animal Models of Parkinson's Disease; Dopamine; Dopamine in Perspective; Dopamine Receptors and Antipsychotic Drugs in Health and Disease; Dopamine Neurons: Reward and Uncertainty; Dopamine: Cellular Actions; Dopaminergic Differentiation; Dopaminergic Agonists and L-DOPA; Drug Addiction: Behavioral Neurophysiology; Parkinsonian Syndromes; Schizophrenia: Epidemiology, Clinical Features, Course and Outcome; Substance Abuse and Dependence.

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