

Dopaminergic Transmission and Wake-Promoting Effects of Central Nervous System Stimulants

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Abstract Pharmacological agents which increase dopaminergic neurotransmission by blocking dopamine re-uptake by the dopamine transporter (DAT), such as cocaine, amphetamines and modafinil, are potent wake-promoting substances in mammals and even in invertebrates such as *Drosophila Melanogaster*. In mammals, the cell bodies of dopamine neurons controlling the sleep-wake cycle are located in the midbrain and brainstem. Midbrain dopamine neurons express high levels of DAT and play a key role in emotional arousal in response to rewarding and aversive stimuli. They are strongly excited by wake-promoting neurotransmitters such as acetylcholine and orexins/hypocretins. However, their mean firing rate does not change across the sleep-wake cycle. In contrast, wake-active brainstem dopamine neurons in the dorsal raphe/periaqueductal gray have low DAT levels and play a tonic role in controlling wakefulness. Dopamine neurons increase arousal by inhibiting the nucleus accumbens, by exciting wake-promoting basal forebrain cholinergic and brainstem serotonin neurons and by inhibiting sleep-promoting neurons in the pre-optic hypothalamus. Dopamine acts on D₁ type (D₁, D₅) and D₂-type (D₂, D₃, D₄) receptors. Both types are involved in promoting arousal but D₂ receptors in the shell of the nucleus accumbens appear to be particularly important. Dopamine D₄ receptors modulate the amplitude of cortical gamma band (30–80 Hz) oscillations important for attention and inhibit GABAergic inputs from the globus pallidus to the thalamic reticular nucleus. Dopaminergic agents are widely used in clinical practice to modulate alertness in sleep and other disorders involving disrupted cortical activation. Thus, further work on their mechanism of action is warranted.

The dopaminergic neurotransmitter system is one of the most intensely investigated in neuroscience due to its links to brain reward pathways, drug addiction, Parkinson's disease and schizophrenia. However, the mechanisms by which it

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controls sleep and wakefulness remain somewhat mysterious, despite the common use of dopaminergic agents in clinical practice to treat daytime sleepiness.

1 History of Dopaminergic Stimulants

Chewing the leaves of *Erythroxylum coca* has been practiced in South America for thousands of years as a means to boost energy, suppress sleep, inhibit appetite and combat altitude sickness (Streatfeild 2001). When combined with an alkali, the leaves of this plant release a low level of a natural stimulant, which has only been known to us in the West since the 1504 report of the Spanish explorer, Amerigo Vespucci (Streatfeild 2001). The main active ingredient, cocaine, was isolated in Goettingen, Germany by Albert Niemann in 1859 and soon became the toast of Europe and America, being incorporated into popular beverages such as Vin Mariani and Coca-cola (Streatfeild 2001). Many prominent figures espoused its wondrous properties, most notably, Sigmund Freud. Later, its addictive properties and negative cardiovascular effects became more widely known, leading to its removal from Coca-Cola and its classification as a restricted drug (Streatfeild 2001).

Amphetamine derivatives occur naturally in plants such as Khat, a plant used in the Middle East as a stimulant for hundreds of years (Rushby 1999). Amphetamine itself was first synthesized in 1887 but was not widely used until the 1930s when it was introduced into the Benzedrine inhaler to treat asthma (Boutrel and Koob 2004). Amphetamines have been and are still being used in military settings to keep soldiers awake, as well as for various medical uses (Boutrel and Koob 2004).

The most recently introduced of the psychostimulants, modafinil, was introduced as a wake-promoting compound to treat narcolepsy in France in 1988 and was approved by the FDA in the United States in 1998 (Wisor 2013). Unlike cocaine and amphetamines it does not have a strong abuse potential and a pronounced sleep rebound is not observed following its use.

The dramatic effects of drugs such as cocaine, amphetamine-like compounds and modafinil on mood and arousal have been used and abused by many different societies around the world. However, it is only in the past 50 or so years that we have gained a better understanding of their effects on the brain and their potential for treating disorders of arousal. Here I summarize our current state-of knowledge of this exciting topic.

2 Psychostimulants Promote Dopaminergic Neurotransmission

Biochemical studies in the 1960s and 1970s identified the mechanisms underlying the release and synthesis of the catecholamines (Axelrod 1971). The rate-limiting enzyme in the synthesis of all the catecholamines (Dopamine, noradrenaline and

adrenaline) is tyrosine hydroxylase (TyH), which converts L-tyrosine to L-DOPA. The carboxyl group is removed from L-DOPA by the enzyme DOPA decarboxylase to form dopamine. The action of dopamine is limited by reuptake into the presynaptic terminal by a sodium and chloride dependent transport process mediated by the dopamine transporter (DAT), as well as by other catecholamine transporters.

Early biochemical studies suggested that cocaine and amphetamine inhibit the reuptake of dopamine, noradrenaline and serotonin into nerve terminals. In addition, amphetamines affect the transport of monoamines into synaptic vesicles. The development of radioligands for DAT led to studies which showed that the binding affinity of cocaine and amphetamine for DAT correlate well with their potencies in eliciting self-administration (Ritz et al. 1987). Similarly, a comparison of the potencies of inhibitors of dopamine and noradrenaline reuptake in inducing wakefulness in normal and narcoleptic canines revealed a correlation between the *in vitro* binding affinity for DAT but not the noradrenaline transporter (NAT), suggesting that blockade of dopamine reuptake is the most important effect (Nishino 1998). DAT inhibitors, including amphetamine and modafinil strongly increased wakefulness whereas NAT inhibitors main action was to suppress REM sleep. In a separate study in cats, the wake-promoting effect of amphetamine was maintained in animals with lesions of the main noradrenaline cell group projecting to the forebrain, the locus coeruleus (Jones et al. 1977).

The cloning of various neurotransmitter transporters, including the dopamine transporter in 1991, led to the generation of DAT knockout-mice, allowing direct testing of the hypothesis that DAT mediates the stimulant properties of these compounds. DAT KO mice had a 100-fold increase in the time constant for clearance of dopamine and did not respond to cocaine and amphetamine with an increase in locomotion (Giros et al. 1996). Cocaine and amphetamine failed to increase extracellular dopamine levels in these animals. Detailed sleep-wake analysis showed that similar to the effect of psychostimulants, DAT knockout mice had reduced non-REM sleep time and increased wakefulness independent of effects on locomotor activity (Wisor et al. 2001). Furthermore, the wake-promoting effects of metamphetamine, modafinil and a selective DAT blocker were abolished, confirming that DAT inhibition is their primary mechanism of action in increasing arousal (Wisor et al. 2001). However it should be noted that both dopamine D₁ and D₂ receptors, which are strongly implicated in the wake-promoting actions of the dopamine system (see below) are reduced by about 50 % in the ventral midbrain and striatum of DAT KO mice (Giros et al. 1996).

Modafinil is often described as a novel wake-promoting compound, in particular because its use does not lead to a pronounced sleep rebound, when compared with other psychostimulants acting on the dopaminergic system. Modafinil is a selective blocker of DAT but has a low affinity, resulting in only slow increases in extracellular dopamine, when compared to amphetamines or cocaine, likely explaining its low abuse potential (Wisor 2013). Unlike amphetamines, Modafinil increases Fos expression, a marker of neuronal activity, in orexin/hypocretin neurons (Scammell et al. 2000) and in a poorly defined anterior hypothalamic area (Lin et al.

1996). Wisor and colleagues tested the effect of amphetamine and modafinil in a strain of narcoleptic dogs which have a defective orexin/hypocretin type II receptor and in dopamine transporter knock-out mice (Wisor et al. 2001). The wake-promoting effects of these compounds were maintained in the narcoleptic dogs, consistent with their effectiveness in promoting wakefulness in narcoleptic humans with reduced levels of orexin/hypocretins. Thus, despite the increase in Fos activity in orexin/hypocretin neurons in normal animals, the wake-promoting effect does not depend on these neurons. Similarly, the effectiveness of modafinil is maintained in mice lacking neuronal histamine due to knockout of the synthesizing enzyme, histidine decarboxylase (Parmentier et al. 2007).

Thus, although, these substances affect several different neurotransmitter systems, the main wake-promoting effect of all the psychostimulants appears to be due to the enhanced release of dopamine.

3 Location of Dopaminergic Cell Groups Controlling Arousal

The potent wake-promoting action of cocaine, amphetamines and modafinil and their common site of action in increasing dopaminergic neurotransmission suggested that the endogenous dopamine systems of the brain play an important role in the control of wakefulness. Increased levels of catecholamines, including dopamine, correlate with increased wakefulness, whereas reduction of their levels promotes sleep (Monti and Jantos 2008). Depletion of catecholamines and serotonin by application of the alkaloid, reserpine, which binds to presynaptic vesicles containing these neurotransmitters and prevents their refilling, or inhibition of the synthesis of catecholamines with α -methyl para tyrosine produces an increase in sleepiness (Meyers et al. 2011) whereas drugs that enhance the extracellular concentration of catecholamines by enhancing release or blocking reuptake increase wakefulness. Similarly, wakefulness is enhanced in dopamine transporter knock-out mice (Wisor et al. 2001).

The localization of catecholamine neurons was facilitated by the development of the Falck-Hillarp staining technique which allowed visualization of their location based on the chemical reaction between catecholamines and formaldehyde, leading to cyclization of the catecholamines and the formation of strongly fluorescent products (Carlsson et al. 1962). Dopaminergic neurons were found in many different parts of the brain (A8–A16 cell groups). The largest groups of dopamine neurons are present in two adjacent midbrain regions, the substantia nigra (A9, projecting to the dorsal striatum) and ventral tegmental area (A10, projecting to the frontal cortex and ventral striatum = nucleus accumbens). In fact, 80 % of brain dopamine is found in the striatum. An extension of the A10 group is found intermingled with serotonin neurons in the ventral periaqueductal gray/dorsal raphe region. This region appears to have different properties from the A9/A10 cell

groups and constitutes a wake-active, wake promoting cell group (Lu et al. 2006). Several groups of dopamine neurons are located in the hypothalamus (A11–A15) but little is known about them with regards to control of the sleep-wake cycle. One study suggested increased activity of the A11 cell group during REM sleep deprivation suggesting they are wake-active (Leger et al. 2010). Dopamine-containing neurons are also located in the retina and olfactory bulb.

Many studies of the dopaminergic system are performed in rodents. However, it should be noted that while rodent dopamine systems closely resemble those in primates, there are also differences which may impact the mechanism by which dopamine affects arousal. In particular, in rodents there is only a scant dopaminergic innervation of the thalamus, but this innervation is much more pronounced in monkeys and humans, particularly amongst the mediodorsal and the midline nuclei which participate in the dorsal arm of the ascending reticular activating system (Sanchez-Gonzalez et al. 2005). In primates the dopaminergic innervation of the thalamus is comparable to dopaminergic innervation of cortex (Sanchez-Gonzalez et al. 2005). Notably, the dopamine transporter, DAT, is not expressed by all dopamine neurons equally. High levels of mRNA are seen in the substantia nigra and ventral tegmental area dopamine neurons whereas high levels of DAT protein are noted in the projection targets in the dorsal and ventral striatum but low levels are seen in dopamine neurons outside the midbrain (Cerruti et al. 1993; Ciliax et al. 1995, 1999). Thus, midbrain dopamine neurons and their striatal targets are likely to mediate the arousal promoting effects of psychostimulants which act to inhibit DAT.

4 Midbrain Dopamine Neurons Increase Arousal in Response to Behaviorally Relevant Stimuli

Large, non-specific, electrolytic lesions of midbrain dopamine neurons and surrounding areas/fiber bundles dramatically reduced arousal (Jones et al. 1973). However, single-unit recordings from the substantia nigra (SN) and ventral tegmental area (VTA) revealed that their average firing rate did not change across the sleep-wake cycle (Steinfels et al. 1983; Miller et al. 1983). In apparent conflict with these electrophysiological findings, microdialysis measurements of extracellular dopamine in the medial prefrontal cortex and nucleus accumbens revealed higher levels during wakefulness and REM sleep (Lena et al. 2005). In contrast to the other aminergic neurons, dopamine neurons have the ability to fire bursts of action potentials, which enhance neurotransmitter release in target areas and are normally triggered in the presence of external cues signaling unexpected rewards (e.g. food) (Schultz 1998). Thus, in freely behaving animals VTA dopamine neurons likely fire more bursts during waking resulting in increased release of dopamine in target areas such as the nucleus accumbens and prefrontal cortex. VTA dopamine neurons also fire more in bursts during REM sleep (Dahan et al. 2007).

Very recently, *in vivo* calcium imaging from VTA dopaminergic neurons demonstrated arousal-related changes in activity which are consistent with increased burst discharge during waking and REM sleep, and which anticipated changes in state (Eban-Rothschild et al. 2016). Furthermore, selective optogenetic or chemogenetic of VTA dopaminergic neurons or their terminals in the nucleus accumbens strongly increased wakefulness, whereas cell-body inhibition promoted sleep and sleep-associated nest building (Eban-Rothschild et al. 2016). Inhibition of VTA dopaminergic neurons prevented the increase in wakefulness produced by rewarding or aversive stimuli.

Consistent with a role in emotional arousal, VTA neurons are excited by several different neurotransmitters and neuromodulators which promote arousal (Korotkova et al. 2003, 2006). VTA dopamine neurons are strongly excited by cholinergic brainstem neurons via activation of nicotinic and muscarinic M₅ receptors (Yeomans and Baptista 1997; Yeomans et al. 2001; Pidoplichko et al. 1997). Activation of these receptors increases bursting and plays a role in reward processes/addiction. Likewise, we found *in vitro* that the wake promoting neuropeptides, the orexins/hypocretins, increase the mean firing rate and bursting of VTA dopamine neurons and neighboring GABAergic neurons (Korotkova et al. 2003). Orexin/hypocretin activation of VTA dopamine neurons has been implicated in reinstatement of drug seeking behavior (Boutrel et al. 2005). Other neurotransmitters involved in stress and emotional arousal such as corticotrophin releasing factor and substance P, also excited VTA dopamine neurons (Korotkova et al. 2006).

5 Brainstem Dopaminergic Neurons Have Increased Activity During Wakefulness

In contrast to VTA and SN dopamine neurons, dopaminergic neurons in the ventral periaqueductal gray (vPAG)/dorsal raphe region of the brainstem appear to have tonic state-dependent variations in their activity; these dopaminergic neurons show increased activity of the immediate-early gene product, Fos, during waking when compared to sleep (Lu et al. 2006). Selective lesioning of these neurons by injections of 6-hydroxydopamine, resulted in 63 % cell loss whereas non-selective lesions with ibotenic acid were associated with 80 % cell loss. Both of these procedures caused a marked (>20 %) reduction in 24 h amounts of wakefulness, the extent of which was correlated with loss of dopamine neurons (Lu et al. 2006). In contrast, lesions of the serotonergic neurons in this area with 5,7-dihydroxytryptamine, resulting in 80 % loss of serotonin neurons did not affect 24 h amounts of sleep and waking. In fact, the effect of lesion of vPAG dopaminergic neurons on total 24 h amounts of wakefulness was larger than that seen with lesions of aminergic, cholinergic or orexin/hypocretin neurons (Blanco-Centurion et al. 2007; Gerashchenko et al. 2003).

Tracing studies showed that dopaminergic vPAG neurons project to and receive inputs from other parts of the sleep-wake circuitry such as the basal forebrain,

midline thalamus and the sleep-active VLPO neurons (Lu et al. 2006). Recent *in vitro* electrophysiological recordings from these neurons showed that they have similar intrinsic membrane properties as VTA dopamine neurons, including broad action potentials and hyperpolarization-activated cation currents (Dougalis et al. 2012). Information on the neurotransmitter regulation of these neurons, which might help explain their putative state-dependent firing is lacking at present, as are *in vivo* electrophysiological recordings from these neurons correlating their discharge with changes in behavioral state. In contrast to dopamine neurons in the SN and VTA they exhibit low levels of DAT (Ciliax et al. 1995, 1999), suggesting that they play a less prominent role in the arousing effects of psychostimulants.

6 Effector Mechanisms of Dopaminergic Control of Arousal in Mammals

Neurotransmitters and neuromodulators exert their effects on their targets by binding to specific receptor proteins and thereby leading to the opening or closing of ion channels. In the case of dopamine, the five known receptors (D_1 – D_5) are metabotropic, meaning that they are coupled to guanosine-triphosphate (GTP)-hydrolysing proteins (G-proteins) and affect ion channels indirectly. D_1/D_5 dopamine receptors are coupled to the G_s , and the related G_{olf} , G-proteins, the α subunit of which stimulates the activity of adenylyl cyclase, and affects ion channels by increasing the activity of cyclic adenosine monophosphate (AMP)-dependent protein kinases. $D_{2/3/4}$ receptors couple to G_i/o proteins, the α -subunit of which inhibits adenylyl cyclase. In addition, the $\beta\gamma$ subunits of these G-proteins can directly bind to ion channels and affect their activity. Other effects are mediated through modulation of synaptic transmission. Evidence supports a role for both D_1 -like and D_2 -like receptors in dopaminergic promotion of wakefulness, but the D_2 receptor appears particularly important in mammals. High doses of D_1 and D_2 receptor agonists increase wakefulness although low doses of D_2 agonists may cause the reverse effect, presumably due to activation of autoreceptors on dopamine cell bodies and axon terminals (Monti and Monti 2007). D_2 receptor knockout mice exhibit a significant decrease in waking amounts due to a shorter wake bout duration and a concomitant increase in sleep (Qu et al. 2010).

Where do D_1 and D_2 receptors act to promote arousal? Several lines of evidence including recent optogenetic/chemogenetic experiments (Eban-Rothschild et al. 2016) suggest that the nucleus accumbens is a sleep promoting region and that dopamine promotes arousal though inhibition of this area, although the downstream mechanisms which mediate this effect are unclear. Lesions of the nucleus accumbens increase wakefulness and reduce the duration of non-REM sleep bouts (Qiu et al. 2010). Local amphetamine injections in the vicinity of the nucleus accumbens and medial septum/preoptic area causes arousal in the rat (Berridge et al. 1999) and the wake promoting effects of modafinil are blocked by lesions of the accumbens core

region (Qiu et al. 2012). The nucleus accumbens contains high levels of both D_2 and adenosine A_{2a} receptors, located on the somata and excitatory afferents to enkephalin containing neurons projecting to the ventral pallidum and lateral hypothalamus (Zhang et al. 2013). These two receptors have opposite effects on intracellular signaling and sleep-wake behavior. A_{2a} receptors stimulate adenylyl cyclase, whereas activation of D_2 receptors inhibits this signaling pathway. A_{2a} receptors promote sleep since antagonism of these receptors by caffeine promotes wakefulness, an effect dependent on the nucleus accumbens (Lazarus et al. 2011). In contrast, D_2 receptors inhibit adenylyl cyclase and promote arousal. Injection of a D_2/D_3 receptor agonist into the nucleus accumbens increased wakefulness, whereas an antagonist increased sleep (Barik and de Beaurepaire 2005). These two receptors have important functional interactions such that blockade or inhibition of one subtype affects the expression of the other subtype (Salmi et al. 2005), likely explaining the enhanced response to caffeine in DAT knockouts which have reduced D_2 receptors. One interesting feature of the nucleus accumbens is that it expresses particularly high levels of dopamine D_3 receptors, although to date the role of these receptors in the control of sleep-wake has not been investigated in any detail.

In addition to the nucleus accumbens, other brain areas may contribute to the wake-promoting effects of dopamine. In the dorsal raphe, activation of normally inhibitory postsynaptic D_2 receptors causes neuronal excitation via opening of non-selective cation channels (Haj-Dahmane 2001). In addition, at high concentrations, as will be produced by psychostimulants, dopamine can act at adrenergic receptors. In vitro, dopamine inhibits the activity of sleep-active melanin-concentrating hormone neurons in the hypothalamus (Alberto et al. 2011) and REM-active dorsal subcoeruleus nucleus (Yang et al. 2014) via α_2 adrenoceptors. Surprisingly, in vitro studies also report that dopamine inhibits orexin/hypocretin neurons in the hypothalamus, either via activation of α_2 receptors (Yamanaka et al. 2006) or via activation of D_2 dopamine receptors (Li and van den Pol 2005), an effect which should promote sleep.

Less is known about the location of D_1 receptors which mediate the arousal effects of dopamine in mammals. A preliminary in vitro study identified excitatory effects of dopamine on basal forebrain cholinergic neurons (Arrigoni and Saper 2003). Dopamine increased firing rate, caused depolarization and decreased after-hyperpolarizations. These effects were mimicked by a D_1 receptor agonist. Dopamine D_1 receptors are also highly expressed in the dorsal and ventral striatum 'direct pathway' neurons which project to the internal segment of the globus pallidus and substantia nigra pars reticulata and release substance P.

Both D_1 and D_2 receptors are required for the arousing effects of modafinil (Qu et al. 2008). Systemic administration of a D_1 receptor antagonist (SCH23390, 30 μ g/kg) or a D_2 receptor antagonist (raclopride, 2 mg/kg) prior to low doses (22.5 or 45 mg/kg) of modafinil, completely blocked the arousing effect in wild-type mice. At high doses (90 or 180 mg/kg) of modafinil, the effect was not blocked by the D_1 receptor antagonist and was only partly blocked by raclopride, suggesting additional mechanisms mediate the effect at these doses. Modafinil-induced arousal was blunted in D_2 receptor knockout mice and the effect was completely blocked by pretreatment with SCH23390.

7 Dopaminergic Control of Arousal in *Drosophila*

Dopaminergic neurotransmission not only regulates arousal in vertebrates but even in simpler animals such as the fruit fly, *Drosophila melanogaster* (Shaw et al. 2000; Hendricks et al. 2000). Flies have active and inactive (rest) periods which resemble mammalian wake and sleep periods. As in mammals, waking is increased by stimulants in *Drosophila*. Administration of methamphetamine (Andretic et al. 2005) or cocaine (Lebestky et al. 2009) increases wakefulness by increasing the duration of waking bouts and counteracts the effect of sleep deprivation. Mutant flies (*fumin*, *fmn*) with autosomal recessive mutations resulting in deletions in the *Drosophila* homologue of DAT, leading to loss of function, have high levels of activity, reduced sleep and lack a homeostatic sleep response (Kume et al. 2005). Conversely, flies lacking the synthesizing enzyme for dopamine, tyrosine hydroxylase, in the central nervous system have reduced arousal and increased sleep (Riemensperger et al. 2011), as do flies exposed to an inhibitor of TH (Andretic et al. 2005). Dopamine receptors in flies fall into similar categories as in mammals i.e. D₁-like and D₂-like. There are two D₁-like receptors (DA1/DopR and DopR2) and a D₂-like receptor (D2R). Flies lacking the dopamine D₁ receptor have reduced arousal (Lebestky et al. 2009) and are implicated in the response to sleep deprivation. Flies treated with the D₂R agonist, bromocriptine, showed increased nocturnal locomotor activity which was inhibited in D₂R knockouts (Lee et al. 2013). Thus, both D₁-like and D₂-like receptors have been implicated in the control of arousal in flies.

Sleep has been hypothesized to reflect a compensatory response to synaptic potentiation occurring during waking (synaptic homeostasis hypothesis) (Tononi and Cirelli 2003) and experiments in *Drosophila* have provided structural evidence which supports this hypothesis (Bushey et al. 2011). In *Drosophila*, the intensity of social experience during waking modified sleep need and architecture. This response was dependent on dopaminergic and cyclic AMP signaling pathways, consistent with evidence linking these pathways to long-term potentiation and memory formation in other species (Ganguly-Fitzgerald et al. 2006). More fine-grained analysis of the effect of activation of the dopaminergic system revealed that activation of dopamine D₁ receptors in the mushroom bodies, a region implicated in learning, rescued sleep-loss induced learning impairments in an aversive phototaxis suppression task (Seugnet et al. 2008). Separate from the dopamine effect on the mushroom bodies, two recent studies identified a dopaminergic projection to the dorsal fan-shaped body, and acting on DopR/DA1, as being key mediators of dopamine control of arousal (Ueno et al. 2012; Liu et al. 2012). In contrast to mammals, activation of the DA1 receptor causes neural inhibition, consistent with other experiments which suggest that the dorsal fan-shaped body is a sleep-promoting region (Donlea et al. 2011).

8 Effect of Sleep Deprivation on Dopaminergic Neurotransmission

Sleep homeostasis refers to the process which increases the amount and intensity of sleep following a period of extended wakefulness. Fly, rodent and human studies all suggest that sleep deprivation affects dopaminergic neurotransmission. In *Drosophila*, mutations in DAT, resulting in reduced dopamine clearance, showed a greater sleep rebound following sleep deprivation (Greenspan et al. 2001). Effects of dopamine on sleep homeostasis in this species appear to require downregulation of A-type potassium channels of the Shaker family and upregulation of two-pore leak potassium channels (Pimentel et al. 2016). In the basal forebrain of rats, levels of dopamine metabolites are increased during SD (Zant et al. 2011). Sleep deprivation in humans was associated with a decrease in dopamine D₂/D₃ receptors in the nucleus accumbens, which would be consistent with an increase in sleepiness, if dopamine inhibits this sleep-promoting area via these receptors. In humans, there are polymorphisms in DAT, associated with variable numbers of a 40 base pair sequence, with 9 or 10 repeats being most common. 10 repeat allele homozygotes have 15–20 % reduced DAT availability in the striatum when compared with heterozygous and homozygous 9-repeat allele carriers and show an increased homeostatic response to sleep deprivation (increased NREM duration and intensity) (Holst et al. 2014). Furthermore, 10 repeat carriers responded to the stimulating effect of caffeine, whereas 9-repeat carriers did not. The altered homeostatic response to sleep deprivation may involve D₁-like receptors since homeostatic regulation of sleep was unaltered in D₂R KO mice (Qu et al. 2010).

Sleep loss impairs cognition in humans and animals (McCoy and Strecker 2011). Dopaminergic stimulants counteract the negative effects of sleep deprivation on cognitive performance in humans (Pigeau et al. 1995). Similarly in *Drosophila*, activation of the dopaminergic system can counteract the effects of sleep loss (Seugnet et al. 2008). This important action provides a rationale for the use of these substances to treat sleep disorders causing excessive daytime sleepiness.

9 Dopaminergic Control of Theta, Beta and Gamma Oscillations

Wakefulness in mammals is characterized by increased amplitude of EEG oscillations in the theta (4–8 Hz), beta (14–30 Hz) and gamma (30–80 Hz) ranges (Brown et al. 2012). Administration of methylphenidate or amphetamine to rodents increases hippocampal theta activity (Dzirasa et al. 2006). DAT KO mice show a pronounced increase in hippocampal theta oscillations in response to exposure to novelty which does not require an increase in locomotor activity (Dzirasa et al. 2006).

Methylphenidate increases beta activity in anesthetized rats (Chemali et al. 2012) and cocaine increases beta activity in awake humans, as originally shown by the

EEG pioneer, Hans Berger (Herning et al. 1985). Early EEG analysis was restricted to frequencies below 30 Hz i.e., excluded the gamma range. More recent studies have shown that gamma oscillations are important for a variety of high-level cognitive functions and are abnormal in diseases involving impaired cortical activity such as schizophrenia (Woo et al. 2010). In vitro and in vivo data suggest a possible role for dopamine D₄ receptors in the control of gamma (30–80 Hz) oscillations, consistent with their preferential location in fast-spiking parvalbumin-positive cortical interneurons (Mrzljak et al. 1996) involved in generating gamma oscillations (Sohal et al. 2009). In hippocampal slices a selective D₄ agonist, PD168077, increased gamma oscillation power, due to increased synchronization of fast-spiking interneurons (Andersson et al. 2012). Similarly, systemic administration of a D₄ agonist, A-412996, in vivo enhanced beta and gamma power in the hippocampus and in several different neocortical areas (Kocsis et al. 2014). In humans, polymorphisms in both DAT and the D₄ receptor have been linked to variation in gamma power (Demiralp et al. 2007). In particular the 10/10 genotype of DAT, which reduces DAT expression and thereby increases extracellular dopamine, enhances gamma band responses to target auditory stimuli. Together, these studies demonstrate that in addition to promoting wakefulness, activation of the dopaminergic system promotes higher-frequency oscillations required for cognition.

10 Use of Dopaminergic Stimulants to Increase Alertness/Arousal in Sleep Disorders, Disorders of Cortical Activation and Anesthesia

Although they have significant cardiovascular side effects, dopaminergic stimulants may be useful clinically to treat sleep disorders and other conditions involving impaired arousal.

Narcolepsy. Almost all cases of human narcolepsy result from degeneration of orexin/hypocretin neurons in the hypothalamus (Taheri et al. 2002). Orexin neurons densely innervate the VTA dopamine neurons (Peyron et al. 1998) and orexins have a potent excitatory effect on both dopamine and GABAergic VTA neurons in vitro (Korotkova et al. 2003, 2006). Thus, loss of these excitatory effects may contribute to excessive daytime sleepiness in this disorder. In contrast, orexins do not affect substantia nigra dopamine neurons (Korotkova et al. 2002). Dopamine reuptake inhibitors promote wakefulness in narcoleptic canines (Nishino et al. 1998) and in orexin knockout mice (Burgess et al. 2010). Modafinil and other psychostimulants are prescribed to treat excessive daytime sleepiness in human narcolepsy. Modafinil does not improve cataplexy, unlike inhibitors of the noradrenaline reuptake transporter, an additional line of evidence suggesting that its arousal promoting properties result from effects on the dopamine system (Nishino and Mignot 1997).

Emergence from Anesthesia. In rodents, administration of methylphenidate decreases the time to emerge from isoflurane (Solt et al. 2011) or propofol

anesthesia (Chemali et al. 2012). Similar effects are produced by application of the D₁ receptor agonist, chloro-APB (Taylor et al. 2013) or by electrical stimulation of the VTA (Solt et al. 2014) but not by the D₂ receptor agonist, quinpirole (Taylor et al. 2013) or by electrical stimulation of the SN (Solt et al. 2014). Methylphenidate, chloro-APB and electrical stimulation of the VTA all decrease EEG delta activity but there are differences observed in other frequency bands with methylphenidate causing a marked increase in theta and beta activity, which was less marked or absent with the other two manipulations. Overall, it appears that dopaminergic stimulants may be useful in hastening the recovery from anesthesia, at least in animal models.

Vegetative state/minimally conscious state (VS/MCS). Alterations in arousal and consciousness produced by general anesthesia resemble those observed in patients in comatose or vegetative states (Brown et al. 2010). Similar to their effects on anesthesia in animals models, dopaminergic stimulants have shown beneficial effects in a small number of brain-damaged patients, although appropriate diagnostic criteria for VS/MCS were not always applied. Matsuda and colleagues tested the effect of L-DOPA in a small group of VS/MCS patients (4 in VS and one in MCS) who had been in these states for 3–22 months (Matsuda et al. 2005). All 5 patients had suffered a closed head injury in a traffic accident. Remarkably, following the beginning of L-DOPA treatment, this small group of patients showed evidence of emergence from VS/MCS within 4 days–1.5 months, improved motor symptoms, an ability to communicate or to use objects functionally and the ability to obey simple verbal commands. However, in a study such as this without a control group it is not possible to determine if recovery might have occurred without drug treatment. Similar to the effect of L-DOPA, the dopaminergic receptor agonist, Bromocriptine, a potent agonist at D₂/D₃ receptors, as well as several other monoaminergic receptors, improved functional recovery in a group of 5 VS patients (Passler and Riggs 2001).

Another drug which acts on the dopamine system is amantadine. Amantadine blocks dopamine re-uptake and facilitates dopamine synthesis. In addition, it acts as an NMDA receptor antagonist. In an initial study in one patient who had been in a MCS for 5 months, amantadine had a dose-dependent effect on arousal as assessed by coma-near coma scores (Zafonte et al. 1998). More recently, in a placebo-controlled trial, amantadine accelerated the pace of functional recovery in patients with post-traumatic disorders of consciousness (Giacino et al. 2012). This is currently the only pharmacological agent which has been shown to be effective in improving clinical and motor function in VS/MCS in a well controlled clinical trial.

In one patient, a fast recovery from MCS was observed following administration of the dopamine receptor agonist apomorphine (Fridman et al. 2009), somewhat reminiscent of the effect of dopaminergic agents in promoting emergence from anesthesia. Apomorphine acts on both D₁-like and D₂-like receptors at nanomolar concentrations. This patient showed improvements in consciousness and responsiveness within a few hours on the first day of administration of apomorphine, 104 days post-injury, although the patient had previously been unsuccessfully treated with two other dopaminergic stimulants, methylphenidate and bromocriptine.

Parkinson's disease is characterized by loss of dopamine neurons in the substantia nigra and parts of the VTA. These patients suffer from daytime sleepiness which is normalized by treatment with L-DOPA, and movement disorders during sleep (Rye 2004a, b). However, dopamine neurons are not the only neurons to be affected by this disease and in fact early degeneration of brainstem REM muscle atonia neurons is thought to lead to REM sleep behavior disorder (RBD), which can anticipate the later development of Parkinson's (Boeve et al. 2001).

Schizophrenia. The dopaminergic system has long been implicated in schizophrenia since classic neuroleptics are potent inhibitors of dopamine D₂ receptors. In addition, the atypical antipsychotic, clozapine, has strong affinity for dopamine D₄ receptors (Van Tol et al. 1991). Schizophrenia is increasingly recognized as a disorder involving aberrant cortical activation in the gamma frequency (30–80 Hz) range in response to sensory stimuli and during cognitive tasks (Uhlhaas and Singer 2010; Woo et al. 2010). Thus, it is of interest that activation of the dopamine system promotes gamma oscillations. Dopamine D₄ receptors also inhibit the inhibitory inputs from the external segment of the globus pallidus to the thalamic reticular nucleus (Govindaiah et al. 2010; Gasca-Martinez et al. 2010), which in turn controls the level and pattern of activity of thalamic relay neurons, including the midline and intralaminar neurons involved in control of arousal. Thus, modulation of the dopaminergic system and in particular D₄ receptors may be beneficial in correcting gamma band abnormalities associated with cognitive dysfunction in this disorder.

11 Conclusions

Psychostimulants such as cocaine, amphetamine, methylphenidate and modafinil increase arousal primarily by blocking the dopamine transporter located on midbrain dopamine neurons projecting to the nucleus accumbens, thereby potentiating the inhibitory effect of D₂ receptor activation on striatopallidal neurons. The downstream effects of this inhibition of nucleus accumbens neurons to increase arousal are still unclear but do not require orexin/hypocretin or histamine neurons. Additional effects of psychostimulants to promote arousal, particularly at high concentrations, result from activation of D₁ receptors on striatal/accumbens neurons, D₂ receptors on dorsal raphe neurons and adrenergic effects on sleep-promoting neurons, either through inhibition of noradrenaline uptake or through dopamine binding directly to these receptors.

Physiological roles for the dopamine system to promote arousal appear to result from a tonic action of vPAG dopamine neurons on several nodes of the sleep-wake circuitry and emotional arousal mediated by VTA neuron projections to the nucleus accumbens. In *Drosophila*, dopamine promotes arousal by inhibition via D₁-like receptors in the sleep-promoting dorsal fan-shaped body as well as D₁-receptor effects on the mushroom body regions involved in learning and memory.

Genetic variations in dopamine clearance affect sleepiness associated with prolonged wakefulness. Alterations in the availability of dopamine D₂ receptors in the nucleus accumbens following prolonged wakefulness may be involved in this homeostatic regulation of sleepiness.

Dopaminergic stimulants effectively counteract this sleepiness and ameliorate cognitive impairments associated with sleep deprivation in mammals and in *Drosophila*, supporting the use of wake-promoting dopaminergic agents to treat excessive daytime sleepiness in narcolepsy and Parkinson's disease. Dopaminergic agents can also increase arousal in anesthetized patients or brain damaged patients with disorders of consciousness.

In addition to increasing wakefulness per se, activation of the dopaminergic system increases the higher frequency EEG oscillations typical of this state. Activation of dopamine D₄ receptors, in particular increases gamma frequency oscillations, likely via effects on fast-spiking cortical interneurons containing parvalbumin and modulation of the activity of the thalamic reticular nucleus. Modulation of this effect may be useful in treating gamma oscillation deficits in schizophrenia and other disorders such as autism.

Study of the role of the dopaminergic system in arousal has the potential to better inform our understanding of the brain control of wakefulness and lead to novel stimulants to treat excessive daytime sleepiness, emergence from anesthesia and disorders of cortical activation.

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Conflicts of Interest

The author declares no competing financial interests.

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