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Dopamine, learning, and reward-seeking behavior

Óscar Arias-Carrión and Ernst Pöppel

Human Science Center, FESTO-Program for Applied Knowing, Ludwig Maximilian University, Goethestrasse 31, 80336 Munich, Germany

Review

Abstract. Dopaminergic neurons of the midbrain are the main source of dopamine (DA) in the brain. DA has been shown to be involved in the control of movements, the signaling of error in prediction of reward, motivation, and cognition. Cerebral DA depletion is the hallmark of Parkinson's disease (PD). Other pathological states have also been associated with DA dysfunction, such as schizophrenia, autism, and attention deficit hyperactivity disorder in children, as well as drug abuse. DA is closely associated with reward-seeking behaviors, such as approach, consumption, and addiction. Recent researches suggest that the firing of DA neurons is a motivational substance as a consequence of reward-anticipation. This hypothesis is based on the evidence that, when a reward is greater than expected, the firing of certain DA neurons increases, which consequently increases desire or motivation towards the reward.

Correspondence should be addressed to Ó. Arias-Carrión, Email: arias@exp-neuro.de

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INTRODUCTION

As early as 1959, dopamine (DA) was discovered to be a neurotransmitter in the central nervous system (Carlsson 1959). The involvement of DA in movement control has long been emphasized due to the early discovery of a direct association between the amount of striatal DA depletion and motor deficits observed in Parkinson's disease (PD) (Bernheimer et al. 1965). The discovery of the role of DA in the motor components of PD initiated a long series of experiments and clinical investigations, up to the present day. Results from these experiments have led to a number of therapeutic interventions to alleviate patients' symptoms, such as for example the L-DOPA therapy (Bernheimer et al. 1973). Today, we know that DA is involved in the neurobiology and symptoms of a myriad of neurological and psychiatric diseases, such as schizophrenia and attention deficit hyperactivity disorder and it is being considered an essential element in the brain reward system and in the action of many drugs with abuse potential (Di Chiara and Bassareo 2007).

Although DA neurons account for less than 1% of the total neuronal population of the brain, they have a profound effect on brain function (Björklund and Dunnett 2007, Björklund and Lindvall 1984). The effects of DA binding to its metabotropic receptors include modifications of synaptic plasticity believed form the substrate of learning and memory (Kandel 2001). Learning is a change in responsiveness to a particular stimulus and memory is the cellular modification that mediates that change. Signaling molecules provide the link between stimuli that have lead to synaptic actions and changes in the responsiveness of cells to stimuli that might be presented in the future (Beninger and Gerdjikov 2004). Recent evidence indicates that DA is involved in reward-related incentive learning (Berridge and Robinson 1998, Miller et al. 1990, Pessiglione et al. 2006). However, how exactly dopamine influences behavioral choice towards available rewards remains poorly understood. In this review, we examine the current view of the role of DA in cognition, with particular regard to reward-seeking behavior.

DOPAMINERGIC SYSTEM

The majority of DA-containing cells develop from a single embryological cell group that originates at the mesencephalic-diencephalic junction and projects to various forebrain targets (Hynes and Rosenthal 1999). In the adult brain, DA neurons are an anatomically and functionally heterogeneous group of cells, localized in the mesencephalon, the diencephalon, and the olfactory bulb (Björklund and Dunnett 2007, Björklund and Lindvall 1984), but nearly all residing in the ventral part of the mesencephalon (Fig. 1). Mesodiencephalic DA neurons form a specific neuronal group that includes the substantia nigra pars compacta (SNc), the ventral tegmental area (VTA), and the retrorubral field (RRF). Probably, the best known mesodiencephalic DA neurons belong to the nigrostriatal system, which originates in the SNc and extends its fibers into the caudate-putamen nucleus, and which plays an essential role in the control of voluntary movement (Barbeau 1974). More medial to this pathway are the mesolimbic and mesocortical DA systems, which arise from DA neurons present in the VTA. Both of these DA systems are involved in emotion-related behavior, including motivation and reward (Mogenson et al. 1980). The mesolimbic DA system includes the DA cells of the VTA that mainly project to the nucleus accumbens and the olfactory tubercle but also innervate the septum, amygdala, and hippocampus. In the mesocortical DA system, the VTA extends its fibers in the prefrontal, cingulated, and perirhinal cortex. Because of the overlap between these two systems, they are often collectively referred to as the mesocorticolimbic system (Wise 2004).

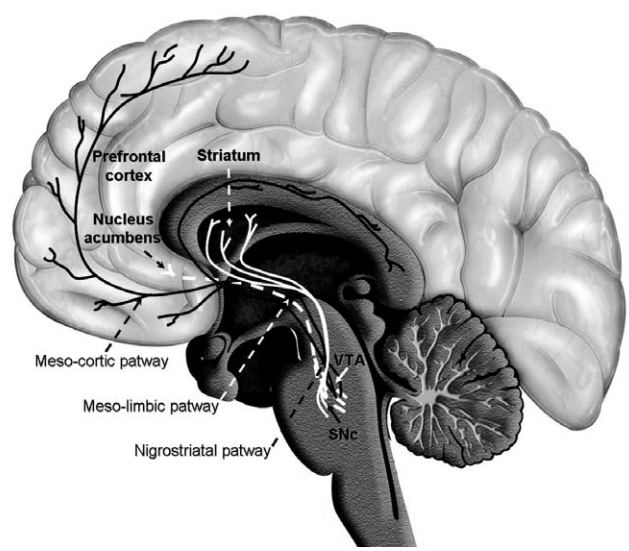

Fig. 1. Dopamine projections to the forebrain. Illustrated are projections from the ventral tegmental area (VTA) to the nucleus accumbens, and prefrontal cerebral cortex, and projections from the substantia nigra (SNc) to the dorsal striatum (caudate nucleus and putamen and related structures).

The diverse physiological actions of DA are mediated by at least five distinct G protein-coupled receptor subtypes (Missale et al. 1998). Two D1-like receptor subtypes (D1A-1D and D5) couple to the G protein Gs and activate adenylyl cyclase. The other receptor subtypes belong to the D2-like subfamily (D2, D3, and D4) and are prototypic of G protein-coupled receptors that inhibit adenylyl cyclase and activate K^+ channels.

These different dopamine receptors have several similarities, allowing them to be categorized into two groups: D1 and D2 receptors. The relative concentration of D1-like receptors compared to D2 receptors is higher in the prefrontal cortex, whereas the concentration of D2-like receptors is higher in the caudate nucleus, putamen, and nucleus accumbens of humans (Camps et al. 1989, Cortes et al. 1989, Hall et al. 1994).

DA acts *via* G-protein-coupled receptors in a typical neuromodulatory fashion (Greengard 2001): DA release sites are placed immediately outside the synaptic cleft (Sesack et al. 2003). Once released, DA diffuses in the extracellular fluid where it then slowly clears due to reuptake and metabolism (Venton et al. 2004). DA does not directly affect the conductance of receptive membranes but modifies their response to afferent input (O'Donnell 2003). These three aspects (extrasynaptic release, G-protein-coupled receptor signal transduction, and a modulatory mechanism) are characteristic of DA transmission – a long delay between stimulus-bound activity (burst firing), coupled with functional changes in the receptive elements. Following electrical stimulation of DA neurons, a change in activity has been recorded in striatal neurons after a delay of approximately 300 ms (Gonon 1997). Although burst firing of DA neurons occurs in response to motivationally relevant stimuli (Schultz 2002), it is unlikely that phasic DA signals actually influence a behavioral response (mediated by fast transmitting pathways) to a stimulus that initially triggered the DA signals. A more realistic view would involve DA as a delayed response amplifier. In this view, DA affects the behavioral impact of stimuli that follow the one that triggered its release.

DOPAMINERGIC MODULATION OF BRAIN FUNCTION

The large distribution of DA innervation in anatomically segregated neuronal systems that involve the integration of motor, limbic and cognitive aspects of behavior and the tonic mode of functioning confer on the DA subsystems a key role in the coordination and integration of the different aspects of behavior (Nieoullon 2002). Selective lesioning of DA innervation often reproduces the effects of the lesion itself and disorganizes behavior (Ungerstedt 1971). Suppression of the main components of brain DA innervation does not suppress the ability to perform behavior, which, however, generally becomes less well adapted to environmental changes, as exemplified by a lack of flexibility and shifting capacity (Nieoullon 2002). The integrative properties of the DA system are probably associated more with direct contributions to cognitive functions at the cortical level, namely in working memory, executive functions and possibly time estimation processes. Since DA brain activity apparently decreases with normal aging, correlated impairment in behavior – such as lack of flexibility and adaptive capacities, deficits in selective attention processes or working memory, and executive function deficiencies – may be related to impairment of central DA transmission (Cools 2006). Consequently, stimulating DA transmission in the elderly could represent a reliable strategy for improving behavioral deficits, as shown in pathological situations such as PD, where the impairment of DA transmission is massive (Cools 2006). Stimulating DA transmission could represent "more discrimination, more representative behavioral inhibition and more attention" (Le Moal and Simon 1991), leading to greater flexibility and adaptation to environmental and internal changes.

DOPAMINE AND ASSOCIATED PATHOLOGIES

One of the major neurodegenerative disorders associated with DA is cell loss in PD. The main pathological hallmark of PD is a progressive loss of neuromelanin-containing DA neurons in the SNc of the ventral midbrain. This results in severe dopamine depletion in the striatum, and is responsible for the motor symptoms associated with PD, especially bradykinesia, tremor, rigidity and loss of postural control (Cools 2006). Other less severe lesions are also observed, such as degeneration of DA cells in the VTA, the noradrenergic locus coeruleus, and the ascending cholinergic pathway from the Meynert basalis nucleus, (Candy et al. 1983). In this context, it is interesting to note that

the main signs of the pre-frontal syndrome in humans, including, for example, decreases in interest in the environment, sensory neglect, distractibility, visuomotor impairment, time estimation deficit, working memory deficit or even the planning of action, are all supposed to be affected by DA regulation (Nieoullon 2002). Furthermore, negative symptoms of schizophrenia or even Alzheimer's disease, where an alteration of the integrity of the DA neurons has been reported (Gibb et al. 1989), could be associated with deficits in motivation, which may be due to a lack of DA regulation onto the cortico-subcortico-cortical circuits involving the limbic part of the basal ganglia (Brown and Pluck 2000). Stimulating DA transmission could, therefore, result in enhanced cortical control and motivation. A decrease in D1 receptor density in the frontal cortex of schizophrenic patients has been shown to be correlated with the severity of negative signs, whereas no change in the striatum was seen in these patients (Okudo et al. 1997).

DOPAMINE AND LEARNING

Previc (1999) proposed correlating the origins of human intelligence to the contribution of DA systems in human cognition, because of a key role of DA in cognitive skills, which, hypothetically, characterize hominid evolution. Previc also emphasizes a putative essential contribution of cortical DA to executive function and also to language production, which critically involves working memory processes. The term "intelligence" possibly does not reflect exactly the contribution of DA, although the involvement of the neurotransmitter in the regulation of cognitive functions has been convincingly demonstrated. A lateralization of the DA systems with a permanent dominance in the left hemisphere has been shown in humans and, besides its well-documented contribution to language production, it has been suggested that motor programming is solely due to this hemisphere (Greenfield 1991). Thus, predominance in the DA innervation of the left hemisphere supports the theory of a specialization of this hemisphere in regulating cognitive functions and adaptive brain capacities, although other neuronal systems, such as cholinergic, serotoninergic or noradrenergic systems, also show some evidence of asymmetrical organization. In rodents, the asymmetrical organization of the DA systems has been shown for a long time and involves about 10% of the striatal DA content (Glick and Shapiro 1985). However, no clear correlation has been demonstrated yet at behavioral level with side preference, although some side differences in the sensitivity to psychostimulants of the DA system have been shown. More recent work has shown that the cognitive effects of DA drugs also depend on baseline levels of performance in the control state (Granon et al. 2000, Mehta et al. 2000, Pessiglione et al. 2006).

The finding of baseline-dependent effects has implications for studies of individual differences and clinical application. The effects of the D2 receptor agonist bromocriptine on cognition were shown in humans to depend on the individual baseline level of working memory performance (Kimberg et al. 1997). This principle might also apply to effects of other monoaminergic agents, including D1 agonists, which are difficult to study selectively in humans at present (Schultz 2007). The possibility that baseline differences in performance on different types of task, interacting with factors such as arousal, stress (Zahrt et al. 1997), and motivational factors, might affect the way in which cognition is modulated by DA receptor agents, may be an important principle in determining possible therapeutic effects of such agents in many clinical disorders. Behavioral studies show that DA projections to the striatum and frontal cortex play a central role in mediating the effects of rewards on approach behavior and learning (Schultz 2007). These results are derived from selective lesions of different components of DA systems, systemic and intracerebral administration of direct and indirect DA receptor agonist and antagonist drugs, electrical self-stimulation, and self-administration of major drugs of abuse, such as cocaine, amphetamine, opiates, alcohol, and nicotine (Schultz 2007). Therefore, more information is required from animal models, where functional studies are possible.

Most goal-directed motivation – even the seeking of food or water when hungry or thirsty – is learned (Changizi et al. 2002). It is largely through selective reinforcement of initially random movements, that the behavior of the neonate comes to be both directed at and motivated by appropriate stimuli in the environment (Hall et al. 1975, Johanson and Hall 1979). For the most part, one's motivation is to return to the rewards experienced in the past, and to the cues that mark the way to such rewards. It is primarily through its role in the selective reinforcement of associations between rewards and otherwise neutral stimuli that DA is important for such motivation. Once stimulus-

reward associations have been formed, they can remain potent for some time even after the reward has been devalued by the absence of appropriate drive states such as hunger or thirst (Balleine 1992, Mendelson 1996, Morgan 1974), or because the DA system of the animal is blocked (Dickinson et al. 2000, McFarland and Ettenberg 1995). Once a habit has been established, it remains largely autonomous until the conditioned significance of incentive motivational stimuli has been extinguished or devalued through experience. Extinction of the conditioned significance of such stimuli can result from repeated unrewarded trials (Wise et al. 1978), repeated trials in the absence of an appropriate drive state (Mendelson 1996, Morgan 1974), or repeated trials under the influence of neuroleptics.

The ability of phased DA release to augment the motivation that is induced by drives and conditioned stimuli is thought to involve DA's actions in the nucleus accumbens (Cornish and Kallivas 2000). However, DA appears to be important for learning and memory in most terminal fields of the nigrostriatal, mesolimbic and mesocortical DA systems.

DOPAMINE AND REWARD-SEEKING BEHAVIOR

Rewards are experienced as "making things better" and are thus liked, desired (wanted), and pursued (Berridge and Robinson 1998, Di Chiara and Bassareo 2007). Thus, consumption of rewards (e.g., palatable food, mating, cocaine) produces hedonic consequences (pleasure) which initiate learning processes that consolidate liking the rewarding goal, learning cues that predict its availability and actions that permit its consumption, and assigning value and motivational status to the reward so that the organism can select among numerous behavioral options and determine what level of resources to put toward obtaining a specific goal. Motivational states such as hunger, sexual arousal, and perhaps early symptoms of drug withdrawal increase the incentive salience of reward-related cues and the reward itself (Kelley and Berridge 2002). The greater the hunger, the greater the likelihood that behavioral sequences aimed at obtaining food will be initiated and carried to conclusion despite distractions and obstacles that may arise. Positive reinforcement involves an increase over time in the frequency of behaviors that lead to a reward.

Other views of DA action have been developed from reinforcement-learning models. Such models begin from the assumption that an animal will act to maximize future rewards (Montague et al. 2004, Sutton and Barto 1998). According to this theory, the brain estimates and holds in memory the value of possible actions based on the amount of reward each action has yielded in the past (Hyman et al. 2006). The animal uses these stored values to predict, for any possible action, the likely resulting rewards or punishments. The actual reward gained from an action is then compared with the prediction; the difference constitutes a "reward prediction error." DA has been hypothesized to encode such a reward prediction error and would thus act to shape future behavior to maximize reward. A reinforcement learning model of DA action is consistent with a role for DA in assigning incentive salience (Montague et al. 2004) but is also consistent with broader roles for DA in reward-related learning. Schultz and colleagues have examined the applicability of reinforcement-learning models to the primate brain and behavior (Hollerman and Schultz 1998, Schultz 1998, 2006, Schultz et al. 1993, 1997). They recorded from VTA DA neurons in alert monkeys as they underwent classical conditioning. Monkeys were trained to expect a set amount of sweet juice at a fixed time after a sensory cue. In awake monkeys, DA neurons exhibit a relatively consistent basal (tonic) pattern of firing; superimposed on this basal pattern are brief phasic bursts of spike activity, the timing of which is determined by the prior experience of the monkey with rewards. Specifically, an unexpected reward in these experiments, delivery of juice produces a transient (phasic) increase in firing. As the monkey learns that a signal reliably predicts a reward of a certain magnitude after a certain time interval, there is no increase in the firing of DA neurons when the juice is made available. The reward is "just as expected"; thus there is no prediction error. As the monkeys learn the cues that predict reward, DA neurons fire at the earliest reliable predictor. The earliest predictor is, by definition, unexpected. If a cue normally predicts reward, but the reward is withheld, there is a suppression of the tonic firing of DA neurons at the time the reward would have been expected. In the language of reinforcement-learning models, tonic activity signals that things are "as expected," phasic bursts signal a positive reward-prediction error "better than expected", and pauses in firing signal a negative prediction error "worse than expected" (Montague et al. 1996, 2004).

Partial support for this model comes from recent recordings from single midbrain DA neurons. Bayer and Glimcher (2005) found that the average firing rate of DA neurons could encode a reward prediction error of the kind required by reinforcement learning models if the outcome was better than expected (positive reward-prediction errors). When the outcome was worse than expected (negative reward-prediction errors), the firing rate was always 0 Hz and therefore had limited informational content. The authors concluded that another system had to be involved for encoding quantitative information about negative reward-prediction errors.

A recent study on the other hand, showed faster learning as well as an increase in winning at gambling in response to DA consumption (Pessiglione et al. 2006). A simple betting game study by Pessiglione and colleagues (2006) showed that participants spotted winning strategies at a faster rate if they were given DA in the form of L-DOPA (repetitive). When people win a bet, they seem to experience a DA "high" in the form of a reward, which in turn helps them to remember to make the same choice the next time. When the reward for winning was increased through a monetary reward, DA recipients only noticed winning symbols but not the "losing" symbols. These results might explain why L-DOPA treated PD patients become sometimes addicted to gambling (Cools 2006). DA surges might also explain some of the delusions experienced by people with schizophrenia (Nieoullon 2002). Different works have shown that DA is involved in addiction. When people take drugs such as cocaine or amphetamines, they experience artificially induced DA surges which give them the rewarding "high" they crave (Wise 2004). The same DA "highs" also occur in people with other addictive behaviors such as gambling, sex and exercise (Hyman et al. 2006). DA is the brain's mean for reinforcing behavior. Possibly, this work is a system for minimizing prediction errors. Unexpected rewards result in a particularly high amount of DA release and greater learning.

CONCLUSIONS

Much progress has been made in understanding the neural substrates of reward-seeking behavior, but much remains to be learned, and much integration needs to go on among information at the molecular, cellular, systemic, and behavioral levels. The pursuit of mechanisms underlying reward has been hampered by the limitations of current animal models and thus requires that basic investigators exchange ideas with those involved in human experimental biology and clinical research. It is clear that neurotransmitters other than DA must play important roles in regulating hedonic states and even in reward-related learning. The new research on the importance of DA in motivated learning agrees with the hypothesis that learning has to be embedded in a hedonic system (Pöppel 1982).

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