

The role of dopamine in reward and pleasure behaviour – review of data from preclinical research

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Objective: The purpose of this article is to review some of the basic aspects of the dopaminergic system and its role in reward and pleasure behaviour. We also discuss the association between dopamine and unpleasant symptoms that are commonly found in neuropsychiatric disorders and may also be side-effects of neuroleptic drugs.

Method: A computer-based search of the literature, augmented by extensive bibliography-guided article reviews, were used to find basic information on the dopamine and the reward systems, and symptoms such as dysphoria, anhedonia and depression.

Results: Central dopaminergic neurotransmission is complex, having multiple actions at each level of the mesocorticolimbic reward pathway. The role of dopamine in the reward process was classically associated with the ability to experience pleasure; recent data suggest a more motivational role. Dysfunction of the dopamine transmission in the reward circuit is associated with symptoms such as anhedonia, apathy and dysphoria found in several neuropsychiatric disorders, including Parkinson's disease, depression, drug addiction, and neuroleptic-induced dysphoria.

Conclusion: Viewing the dysfunctions of the reward pathways within a broader spectrum and exploring its complex relations with the dopaminergic transmission may help understand the pathophysiology of these neuropsychiatric disorders and lead to a rational development of novel treatments.

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Introduction

The neurotransmitter dopamine has initially been identified with motor function. The discovery that degeneration of the nigrostriatal dopamine pathway in patients afflicted with Parkinson's disease was central to the extrapyramidal dysfunctions has opened the studies on dopamine (1, 2). Since these early studies, a plethora of research papers have investigated the dopamine system and shown a much more complex scenario.

Studies showing that performance-sparing doses of neuroleptic drugs attenuated lever-pressing and running for food reward in hungry rats, suggested that dopamine D₂ receptor antagonists selectively blunt the rewarding impact of food and other hedonic stimuli inducing 'anhedonia' (3). In

humans, inhibition of dopamine system via D₂ receptor antagonists can be accompanied by reduced motivation, drive, spontaneity, and dysphoria (4). Dopamine has come to be identified as a central neurotransmitter in the reward system and associated with neuropsychiatric disorders that include these symptoms, such as depression, drug and alcohol dependence and Parkinson's disease.

Dopamine has also been associated with the pathogenesis of psychosis, in particular schizophrenia, based on evidence including the close relationship between clinical response and antipsychotic drug-induced dopamine D₂ receptor blockade (5), and that agents such as amphetamines, which cause excessive release of dopamine induce psychotic symptoms such as delusions and hallucinations (6, 7). The mesocorticolimbic pathway

has been implicated as the principal dopaminergic pathway involved in the aetiology of psychoses (8, 9). Recent *in vivo* neuroreceptor imaging studies have been able to demonstrate a dysregulation of dopamine transmission in schizophrenic patients using different experimental strategies (10–12). Although psychosocial interventions are fundamental, neuroleptic drug treatment is the mainstay of care for schizophrenia. All clinically effective antipsychotic drugs for schizophrenia share dopamine D₂ receptor antagonism (13). Prospective neuroreceptor imaging studies have shown an association between the ‘striatal D₂ receptor occupancy’ induced by typical neuroleptic drug treatment and both extrapyramidal side-effects and clinical response (14, 15).

The involvement of dopamine in multiple brain functions may explain the dilemma associated with dopamine-related drug therapies: the antagonism of the dopamine system desired for reducing psychosis, induces extrapyramidal dysfunctions, cognitive impairment and dysphoria (4). This article reviews some basic aspects of the dopamine system and discusses the role of dopamine in reward and pleasure behaviour. Moreover, the association between the symptoms that may be linked to the disruption of the reward system such as anhedonia, apathy and dysphoria will be discussed in this article.

Aims of the study

The present paper aims to provide some basic concepts that are critical for the comprehension of the schizophrenic patient’s subjective experience on neuroleptic drugs. Current ideas regarding the neurobiology of dysphoria, the role of dopamine, and the mechanism involved in the reward system were integrated to develop a framework.

Material and methods

The authors used a computer-based search of the literature, augmented by extensive bibliography-guided article reviews, to find basic information on dopamine and the reward system, and symptoms such as dysphoria, anhedonia and depression.

Results

Dopaminergic system

Since the work of Carlsson and Waldeck (16) on developing a method for determining dopamine, a huge amount of research has been performed to investigate all aspects of the dopamine system.

A search in the Medline database indicated that there were almost 20 000 articles on dopamine published in last 5 years. Here, we briefly summarize some basic aspects of the dopamine system, from pharmacology, through neuroanatomy to neurophysiology, that are relevant to our understanding of neuropsychiatric disorders in particular. For more detailed information about the dopaminergic system, a number of key references are recommended (17–20).

Synthesis and storage

Tyrosine is considered the starting point in the biosynthesis of dopamine and this amino acid is abundant in dietary proteins or converted from phenylalanine by phenylalanine hydroxylase – in the liver – and tyrosine hydroxylase – in the dopamine neurone (18). Tyrosine is taken to the brain by amino acid transporters and into the dopamine neurones. Once tyrosine is inside the neurone, its conversion to dihydroxyphenylalanine (L-DOPA), driven by the cytosolic enzyme tyrosine hydroxylase, is normally the rate-limiting step in dopamine biosynthesis. Aromatic amino acid decarboxylase (dopa decarboxylase) is the enzyme responsible for the cytosolic conversion of L-DOPA to dopamine. This enzyme so avidly decarboxylates L-DOPA that the levels of this amino acid in the brain are very low under normal conditions (18).

In the neurones, dopamine is transported from the cytoplasm to specialized storage vesicles, where the amine is concentrated to approximately 0.1 M (18). It worth noting that dopamine can be synthesized and released from dendrites, in addition to terminal regions. In dendrites, however, dopamine appears to be stored both in classical vesicles and in smooth endoplasmic reticulum.

Release, reuptake and metabolism

Upon the arrival of an action potential, a change in membrane protein conformation allows the influx of calcium ions, which is a key part of the stimulus responsible for the fusion of vesicles with the neuronal membrane (18). By the process of exocytosis, vesicles discharge their soluble contents in the synapse. The extent of dopamine release appears to be dependent on the rate and pattern of neuronal firing, and particularly interesting is the increased dopamine release in response to ‘burst-firing’ (21).

Dopaminergic terminals have transporters (uptake mechanisms) that are critical in terminating transmitter action and in maintaining its homeostasis. Uptake is accomplished by a high-affinity

membrane carrier that is capable of transporting dopamine in either direction, depending on existing concentration gradient (22). Under normal conditions, the transporter recycles dopamine that has been released in the synaptic cleft by actively pumping extracellular dopamine into the nerve terminal. There is some evidence that glia and non-dopaminergic neurones may, to a limited extent, take up and metabolize extracellular dopamine (18).

Several enzymes are responsible for the metabolism of dopamine, including monoamine oxidase, catechol methyltransferase, aldehyde dehydrogenase (18). As the abundance and activity of the enzymes vary according to the cell type and brain region, these factors determine the relative concentration of a particular metabolite present in a given situation.

Dopamine receptors

In 1979, Keabian and Calne (23) found that dopamine exerts its effects by binding to two receptors, known as the D_1 and D_2 receptors. These receptors could be differentiated pharmacologically, biologically, physiologically, and by their anatomical distribution (24). Pharmacologically, the hallmark of the D_1 receptor is to bind the benzazepine antagonist SCH 23390, while that of the D_2 receptor is to recognize with high affinity the butyrophenones: spiperone and haloperidol (25). These two receptors exert their biological actions by coupling to and activating different G protein complexes. The D_1 receptor interacts with the G_s complex to activate adenylyl cyclase, whereas the D_2 interacts with G_i to inhibit cyclic adenosine monophosphate production (26). The anatomical distributions of these two receptors overlap in the CNS, yet their quantitative ratios differ significantly in particular anatomical areas.

For 10 years, this two-subtype classification has accounted for most of the activities attributed to the dopaminergic system. However, this classification was dramatically changed with the application of recombinant DNA technology to the molecular characterization of the dopamine receptors. The original classification of two main groups of dopamine receptors, namely D_1 -like and D_2 -like dopamine receptors, still stands (27). The dopamine D_1 -like receptors include D_1 and D_5 . There are three types of dopamine D_2 -like receptors: D_2 , D_3 and D_4 . The dopamine D_2 receptor has two main variants, D_{2short} and D_{2long} , the latter is more commonly expressed in the brain than the short form (28). The abundance of both D_{2short} and D_{2long} is increased by denervation and by antipsychotic drug administration (29). D_{2short} and

D_{2long} differ in their ability to influence intracellular events. Dopamine is more effective on D_{2short} , compared with D_{2long} , in stimulating the binding of guanosine triphosphate to the receptor-associated G protein (30). There are also some pharmacological differences between D_{2short} and D_{2long} . Although dopamine agonists and antagonists have a similar affinity for both variants, D_{2short} has a two- to five-fold higher affinity for clozapine and several substituted benzamides (31). In addition, dopamine D_{2short} receptors are more readily internalized into the cell (32).

Dopamine neuroanatomy and physiology

Most dopamine-containing cells develop from a single embryological cell group that originates at the mesencephalic–diencephalic junction and projects to various forebrain targets (33). These long-axon dopamine cells have been subdivided into several nominal systems. The best known is the nigrostriatal system, which originates in the zona compacta of the substantia nigra (SNc) and projects primarily to the caudate–putamen, is identified most strongly with motor function. More medial are the mesolimbic and mesocortical dopamine systems, which arise from the dopamine cells located in the ventral tegmental area (VTA) and are thought to be more important for motivational function. The dopamine cells of the VTA and SNc form a continuous layer and project to adjacent and overlapping terminal fields and the boundaries between these ‘systems’ are not well defined (33). The dopamine cells of the VTA project most strongly to the ventral striatum (nucleus accumbens) and olfactory tubercle, but also innervate the septum, amygdala and hippocampus. This subset of projections is known as the mesolimbic dopamine system. The dopamine cells in the medial VTA that project to the medial prefrontal, cingulate and perirhinal cortex are known as the mesocortical dopamine system. Because of considerable overlap between the VTA cells that project to these various targets the two systems are often collectively referred to as the mesocorticolimbic dopamine system (20).

Dopamine has been found to exert actions on the neurones it innervates both directly and via G-protein-coupled receptors (17). Moreover, this transmitter can modulate afferent input within these target regions, as well as alter intercellular communication via its actions on gap junctions (17). Finally, dopamine can potently modulate its own dynamics, acting via somatodendritic autoreceptors (19). In fact, the dopamine system is under potent dynamic regulation, in the short term

by a multitude of feedback systems, and in response to prolonged alterations is subject to powerful homeostatic mechanisms that can compensate for dramatic changes in dopamine system function.

Dopamine neurone discharge is an essential component of the dopamine release process. The firing pattern is effective in modulating release, with burst firing in particular being an important regulator of dopamine transmission (21). Dopamine release appears to occur via two functionally distinct components. One is the dopamine that is released in a high-amplitude, brief pulsatile manner by means of action potentials, and then is rapidly removed from the synaptic cleft via reuptake (34). This has been termed the phasic component of dopamine release, and is believed to underlie most of the behavioural indices of this transmitter. The other is the level of dopamine present in the extrasynaptic space. This tonic dopamine exists in very low concentrations; too low to stimulate intrasynaptic dopamine receptors, but of sufficient level to activate extrasynaptic receptors, including dopamine terminal autoreceptors (thereby causing feedback inhibition of phasic dopamine release) and other extrasynaptic receptor sites (21). It is this tonic dopamine compartment that is sampled by slower measures of dopamine dynamics, such as microdialysis.

Exogenous transmitters also potently regulate dopamine neurones. Thus, gamma aminobutyric acid (GABA) afferents both from striatonigral neurones as well as from local circuit neurones in the midbrain cause inhibition of dopamine neurone activity by both, a GABA-A and GABA-B, mediated action (35). Glutamate has also been shown to exert multiple actions on dopamine neurone activity, when applied *in vivo* increases burst firing. *N*-methyl-D-aspartate receptor activation mediates a slow excitatory postsynaptic potential in these neurones, whereas metabotropic glutamate agonists are reported to depress both excitatory and inhibitory afferent input to these neurones (34, 17). This latter effect is apparently shared by muscarinic receptors, which also depress both excitatory and inhibitory afferents, presumably via a presynaptic action (36).

Reward system and pleasure behaviour

Reward pathways in the brain were first described by Olds and Milner (37). They observed that when electrodes were placed in certain areas of the brain, rats would actively self-stimulate these areas, often to the exclusion of all other activities, including eating. The circuits involved in this process have been referred to as reward system. Since then,

several studies using animal models of reward and measuring the *in vivo* release of dopamine with microdialysis reveal that natural rewarding stimuli such as food, drink, sex and other pleasurable stimuli increase dopamine release in the nucleus accumbens (38).

The dopaminergic reward pathways progress from the VTA to the nucleus accumbens, olfactory tubercle, ventral striatum and frontal cortex (39). Nucleus accumbens is a vaguely defined anatomical area of the basal forebrain, situated between the subcortical striatal system and the limbic system. Two parts of the accumbens are now identified – a central striatal ‘core’, and a limbic ‘shell’. The shell is a part of the extended amygdala, rich in dopaminergic neurones that are implicated in mediating substance abuse and possibly psychotic states (40). The functional significance of this neuro-anatomical differentiation is supported by recent observations suggesting that typical neuroleptics exert their actions on both the core and the shell, while atypical antipsychotic drugs act predominantly on the core of the nucleus accumbens and medial prefrontal cortex, as demonstrated by the neurotensin and Fos immunoreactivity studies (41, 42). This circuit is the critical substrate for the expression of drug reward (43). While each substance of abuse appears to act on this circuit at a different step, the end result is the same: the release of dopamine, the primary chemical messenger of reward, at such reward sites such as the nucleus accumbens (44, 45). Although the neurones involved preferentially utilize dopamine and opioids, a wide range of other neurotransmitters modulate them. Di Chiara and North (46) proposed that the reward pathways can be divided into two parts with the opioid system being associated with consummatory, satiated aspects of reward including sedation, rest and ‘bliss’, while the dopaminergic system is associated with incentive, preparatory of acquisition aspect of reward typically experienced as a sense of thrill, urgency, or craving.

This notion is supported by humans and animals common experiences which show that waiting for the expected reward may be, at least, as pleasurable as the reward itself. The important significance of anticipation can be noted by sexual behaviour in most animals that engage in prolonged nuptial rituals before copulation. Consistent with this pattern is the observation that pleasure connected with flirting is highly appreciated in all human societies. Moreover, the strong link between reward and anticipation of pleasure can explain several aspects of addiction, particularly craving induced by cues related with the use of the drug, such as watching films showing heroin injection (47).

Di Chiara (48) has also attributed an important role in the reward-associated learning processes to mesolimbic dopaminergic transmission. The author postulates that natural rewards induce a very rapid adaptive change after a few experiences, named habituation, and the novelty and unexpectedness of the reward seems to play a major part in the initial response. Thus, the reward stimulus causes strong dopaminergic activation, which reduces upon repetition and learning, until reward presentation does not evoke dopaminergic stimulation. However, drug-induced rewards is not influenced by the habituation and each dose of the drug stimulates the release of dopamine. This might lead to a non-adaptative and even progressively enhanced release of dopamine after repeated administration of addictive drugs, which could increase the association between a salient stimulus and reward.

Dopamine release and increase in cell firing are not restricted to the presentation of pleasant stimuli, but also to aversive, novel and motivationally relevant environmental stimuli (38). This has contributed to the notion that enhanced dopamine release in the nucleus accumbens signals the appearance of an important event that requires the creation and engagement of an adaptive behavioural strategy. This signal is supplied to numerous forebrain structures constituting the limbic cortex and basal ganglia and presumably initiates the recruitment of cortically derived memories and cognitive strategies, as well as motor output. In doing so, dopamine plays a role in initiating and establishing neuroplastic changes associated with developing behavioural strategies necessary to adapt to novel stimuli. As stated before, release of dopamine decreases with repeated exposure to the same stimulus as the organism establishes an adaptive behavioural response. Hence, dopamine contributes to the establishment of neuroplastic changes that mediate behavioural adaptation to relevant environmental stimuli, but may be not necessary for the expression of those behaviours (38). Rather, once a behavioural response to a stimulus has been established, the familiar stimulus elicits the behaviour via interactions among the limbic cortex, thalamus, and basal ganglia, with less involvement by mesocorticolimbic dopamine transmission (49).

Although several studies have shown that the dopamine system is activated by natural rewarding, it is becoming evident that dopamine is not the reward signal per se, but instead is necessary for the acquisition of reinforcing stimuli. Thus, when a task is well learned, dopamine neurone firing no longer is a necessary correlate of the reward signal.

Overall, studies support the suggestion that dopamine actions in the prefrontal cortex may have a greater involvement in the regulation of novel circumstances, with the striatum involved more in expression of learned behaviours (50). This model is consistent with the physiologic studies that show that dopamine can selectively activate circuits within frontal cortex and striatal complex, potentially facilitating information flow along new pathways when a change occurs, but playing less of a role once a new stable steady state is achieved at which the internal representation is at equilibrium with the predicted external events (17). Nevertheless, stimulus-reward associations are, in turn, crucial for the subsequent motivation in a previous-reward situation.

The dopaminergic receptors are also clearly associated with abnormal reward-seeking behaviours such as hyper-sexuality, gambling, binge eating, risky behaviour and taking addiction drugs. These behaviours were postulated to be a compensation for an abnormal development of reward system, which has to be more stimulated to afford the normal level of well-being (47). This idea is consistent with the results of a recent positron emission tomography neuroimaging study, in which the authors have shown that brain D₂ dopamine receptor levels predict reinforcing responses to methylphenidate (a psychostimulant drug that like cocaine, blocks the dopamine transporters) in non-drug abusers. The subjects in whom methylphenidate induced feeling of pleasure had low D₂ brain dopamine receptors, while the subjects who had unpleasant methylphenidate effects had high D₂ brain dopamine receptors (51). Nevertheless, it should be pointed that dopamine is not the only neurotransmitter engaged in reward and pleasure behaviour. The serotonergic system can also initiate and sustain cocaine self-administration in dopamine-transporter knockout mice (52).

Anhedonia, apathy and dysphoria

Several symptoms are associated with disruption of the reward system, including anhedonia (the inability to experience pleasure), apathy (lack of motivation), and dysphoria (mixture of unpleasant emotions, such as feeling miserable, irritable, and edgy) (4, 53). These symptoms are commonly found in neuropsychiatric disorders such as depression, drug and alcohol dependence, Parkinson's disease, late luteal phase dysphoric disorder and schizophrenia (4). These symptoms can also be induced by chronic use and/or abstinence of addictive drugs such as cocaine, amphetamines, or cannabis. Moreover, it can be an unpleasant neuroleptic

side-effect that can have an important role for medication adherence as detailed by Awad and Voruganti (54), Naber et al. (55) and Marder (56).

Anhedonia, dysphoria, and avolition are common symptoms of schizophrenic, depressive and substance misuse patients during withdrawal. These symptoms may be caused by a functional deficit of dopaminergic transmission in the dopaminergic reward system, ascending from the mesencephalon to the ventral striatum (nucleus accumbens). The high incidence of dysphoria and depression among Parkinson's disease patients have suggested that damage of the mesocorticolimbic dopamine projections (reward-related systems) may be directly implicated in these symptoms (57). A dysfunction of both ascending dopaminergic pathways is therefore expected to cause psychomotor slowing, dysphoria and anhedonia.

Studies with neuroleptic drugs have shown that dopamine transmission blockers impede the motivational properties of rewarding as well as aversive stimuli. Atypical, unlike typical neuroleptics have been shown to have significantly less inhibition of the reward systems (58). It is suggested that neuroleptic drugs rather than simply blocking the rewarding impact of positive reinforcers (anhedonia) exert a more general influence on conditioned behaviour by blocking the affective impact of negative as well as positive reinforcers (apathy, lack of motivation) (58). Perhaps a useful way of describing dopamine's role in the reward process is the incentive/motivational salience hypothesis (59). According to which, dopamine mediates the conversion of the neuronal representation of an external stimulus from a neutral fragment of information into an attractive or aversive entity. In particular, the mesolimbic dopamine system is seen as a critical component in the 'attribution of salience', a process whereby events and thoughts come to grasp attention, drive action, and influence goal-directed behaviour because of their association with reward or punishment.

It was often hypothesized that anhedonia is associated with a dysfunction of the mesolimbic dopaminergic reward system. However, studies in humans and animal models indicate that dysfunction of central dopaminergic neurotransmission interferes with the process of motivation rather than with the ability to experience pleasure (60). The latter may be more mediated by other neurotransmitters, such as opioids and serotonin (61). In addition, animal studies have shown that a reduction of central dopaminergic neurotransmission is associated with a decrease in incentive salience of reward-indicating stimuli and not with anhedonia per se (62).

Discussion

Advances in the neurobiology of the dopaminergic system reviewed here have provided evidence for its central role in the reward circuit. Dopamine is a complex system with specific actions in different brain regions (mesocorticolimbic pathway), through several dopamine receptors (postsynaptic and autoreceptors), with specific neurophysiologic mechanisms (e.g. phasic and tonic release) and integrated with various neurotransmitter systems (glutamate, opioids and serotonin).

Although dopamine release in the ventral striatum (nucleus accumbens) has fundamental role in the natural and 'unnatural' reward process, the actions of dopamine are not restricted to the hedonic experiences. Dopamine exerts multiple actions at each level of integration within the cortico-striato-pallido-thalamo-cortical of the reward pathway. The actions of dopamine in the prefrontal cortex may have a greater involvement in the regulation of novel circumstances, with the striatum involved more in expression of learned behaviours. Dopamine is directly involved in attributing attractive or aversive valence to the stimuli, suggesting that dysfunction of central dopaminergic neurotransmission interferes with the process of motivation rather than with the ability to experience pleasure.

The involvement of dopamine is central to pleasure and motivational behaviour, addictive process and neuroleptic side-effects, in specific anhedonia and dysphoria. Dysfunction of dopamine in the reward circuit is associated with a variety of clinical syndromes characterized by subtle alterations in mood, hedonic deregulation and apathy found in several neuropsychiatric disorders, such as Parkinson's disease, depression, drug addiction, and neuroleptic-induced dysphoria. Viewing the dysfunctions of the reward pathways within a broader spectrum and exploring the complexity of the dopaminergic transmission could help understand the pathophysiology of these neuropsychiatric disorders and aid the rational development of treatment for such conditions.

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