Behavioural Brain Research 290 (2015) 17–31

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Review

Basal ganglia circuit loops, dopamine and motivation: A review and enquiry

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HIGHLIGHTS

- Substantia nigra dopamine neurons projecting to the striatum regulate mood.
- Increased activity induces reward; decreased activity induces aversion.
- Nigrostriatal dopamine neurons may also regulate approach motivation.
- Mood and approach motivation may be altered by the thalamo-cortical circuit loop.
- Mood and approach motivation may also be altered by the habenulo-mesencephalic loop.

ARTICLE INFO

Article history:
Received 6 March 2015
Received in revised form 9 April 2015
Accepted 11 April 2015
Available online 20 April 2015

Keywords:
Depression
Mania
Euphoria
Dorsal striatum
Global pallidus
Mediodorsal thalamic nucleus

ABSTRACT

Dopamine neurons located in the midbrain play a role in motivation that regulates approach behavior (approach motivation). In addition, activation and inactivation of dopamine neurons regulate mood and induce reward and aversion, respectively. Accumulating evidence suggests that such motivational role of dopamine neurons is not limited to those located in the ventral tegmental area, but also in the substantia nigra. The present paper reviews previous rodent work concerning dopamine's role in approach motivation and the connectivity of dopamine neurons, and proposes two working models: One concerns the relationship between extracellular dopamine concentration and approach motivation. High, moderate and low concentrations of extracellular dopamine induce euphoric, seeking and aversive states, respectively. The other concerns circuit loops involving the cerebral cortex, basal ganglia, thalamus, epithalamus, and midbrain through which dopaminergic activity alters approach motivation. These models should help to generate hypothesis-driven research and provide insights for understanding altered states associated with drugs of abuse and affective disorders.

Contents

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http://dx.doi.org/10.1016/j.bbr.2015.04.018

1. Introduction

Increased activity of brain dopamine (DA) induces euphoria and approach motivation, while decreased DA activity induces dysphoria and withdrawal-like conditions [1–4]. This view of DA's functions has been derived, in part, from research on drugs of abuse, and thus DA is thought to play a key role in reward action of abused drugs [5–7]. In addition, DAergic dysfunction has been implicated in affective disorders [8–14].

The roles of DA activity in motivation and reward are generally attributed to the mesolimbic DA system, consisting of DA neurons localized in the ventral tegmental area (VTA) projecting to the ventral striatum (VStr) [1,2] (But see [15]). However, recent optogenetic studies utilizing transgenic mice has produced strong evidence suggesting that reward is readily induced not only by stimulation of the mesolimbic DA system, but also the nigrostriatal DA system [16,17], consisting of DA neurons localized in the substantia nigra pars compacta (SNc) projecting to the dorsal striatum (DStr, also known as the neostriatum or caudate-putamen). These findings suggest an underappreciated role of the nigrostriatal DA system and thereby the basal ganglia (BG) in motivational functions. The view that the functional roles of VTA and SNc DA neurons are not dichotomous is consistent with a recent observation that essentially the same brain regions provide afferent inputs to DA neurons of both the VTA and SNc, although their input degrees from each region differ between them [18].

Human research has emphasized the role of the nigrostriatal DA system and the BG in movement regulation, whose dysfunction leads to disorders such as Parkinson's and Huntington's. In addition, evidence is accumulating for the involvement of the nigrostriatal DA system and BG in motivation, whose dysfunction may lead to depressed mood, apathy and anhedonia [19,20]. For example, post-stroke damage in the DStr, pallidum or BG-associated thalamo-cortical regions often result in depression and related symptoms [21–26]. Deep brain stimulation at the subthalamic nucleus of Parkinson's patients can produce side effects including improved mood, hypomanic state or apathy [27–30]. Imaging studies revealed that depression is correlated with smaller volumes of the BG and related brain regions [31,32]. Moreover, activation of the DStr is correlated with drug craving [33,34], drug euphoria [35] and happiness [36,37]. Importantly, electrical stimulation administered at the DStr can be pleasing and is self-administered in humans [38,39].

We will discuss a model describing the relationship between DA concentration of the striatum and approach motivation, and then propose a model describing circuit loops involving both VTA- and SNc-striatal DA systems and associated BG–thalamo-cortical and BG–habenulo-mesencephalic structures involved in regulating motivation. We hope to provide insights for understanding neural mechanisms underlying drug euphoria, craving and affective disorders.

2. DAergic regulation of mood and approach motivation

2.1. Approach motivation, reward and reinforcement

Before discussing motivational state in relation to these structures, it is important to clearly define the terms: approach motivation, reward and reinforcement. Particularly, DA's role in reward has been controversial. Disagreements may have arisen from differences in the focus of research (e.g., drugs vs. food), definition, or assumptions. The present paper does not make the following assumptions: One, DA only has a single effect on behavior; and two, reward is a homogeneous phenomenon. Therefore, DA can be involved in reward even if it does not alter food consumption or orofacial reaction to food.

The fundamental property that distinguishes animals from plants is that animals have the ability to approach life-sustaining things or events (i.e., rewards) and withdraw from life-threatening things or events. In the present paper, the term approach behavior is used to represent a broad set of responses, such as exploration and reward-reinforced instrumental responding. Likewise, withdrawal behavior includes responses such as freezing, escape, and their associated internal states. We assume that approach and withdrawal processes are mutually inhibitory. Furthermore, engaging in approach and withdrawal behaviors is accompanied by positive and negative mood states, respectively, and are positively and negatively reinforcing [3,40].

We define *reward*, using behavioral terms, in two ways: First, rewards are external things or events that produce and reinforce approach behavior. In addition, reward is *an induced internal state that produces and reinforces approach behavior* [3,4]. While positive reinforcement involves learning about the relationship between environment and behavior in the interest of procuring rewards [41], reward concerns not only reinforcement, but also the aroused, motivated state that drives approach behavior. Biologically important things or events trigger not only reinforcement, but also arousal that increases attention to and interaction with the environment [42–44]. Thus, reward refers to internal state reflecting both reinforcement and arousal concerning approach behavior.

2.2. Motivation and the VTA–VStr DA system: Pharmacological studies

Evidence for the role of DA in reward and approach motivation is strongly supported by research on drugs of abuse [1,2,4–7]. Psychostimulant drugs such as cocaine block the DA uptake system, and other psychostimulants like amphetamines stimulate DA release and block the DA uptake system. Thus, administration of these drugs markedly increases extracellular DA concentrations in the striatum, especially the VStr [45]. These properties are critical for their rewarding effects, as systemic injections of DA receptor antagonists readily modulate self-administration. Low doses of DA receptor antagonists increase intravenous self-administration of cocaine or amphetamine, probably due to compensatory responding for drugs' arousing effects discounted by the antagonists. On the other hand, high doses of DA receptor antagonists diminish such self-administration behavior [46,47]. Selective reduction of DA transmission with intra-VStr injections of DA receptor antagonists or 6-OH-DA lesions of VStr DA terminals also reduces or diminishes self-administration of these drugs, depending on the dose [48–52]. Interestingly, intracranial self-administration studies further indicate that of psychostimulant drugs preferentially act on the medial, rather than the lateral, part of the VTA–VStr DA system with respect to reward [2,53]. Psychostimulant drugs or DA receptor agonists are preferentially self-administered into