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Beyond the reward hypothesis: alternative functions of nucleus accumbens dopamine

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According to the dopamine (DA) hypothesis of reward, DA systems in the brain, particularly in the nucleus accumbens, are thought to directly mediate the rewarding or primary motivational characteristics of natural stimuli such as food, water and sex, as well as various drugs of abuse. However, there are numerous problems associated with this hypothesis. Interference with accumbens DA transmission does not substantially blunt primary motivation for natural rewards such as food, but it does disrupt the propensity of animals to engage in effortful responding to obtain food. Electrophysiological and voltammetric studies indicate that novel stimuli, conditioned stimuli that predict reward, and instrumental behaviors that deliver natural rewards all act to stimulate DA activity. Accumbens DA acts as a modulator of several functions related to motivated behavior, and can influence normal and pathological cognitive function, activational aspects of motivation, anergia or psychomotor slowing in depression, the impact of conditioned stimuli, plasticity and a variety of sensorimotor functions.

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Current Opinion in Pharmacology 2005, **5**:34–41

This review comes from a themed issue on
Neurosciences
Edited by Graeme Henderson, Hilary Little and Jenny Morton

Available online 19th December 2004

1471-4892/$ – see front matter

DOI 10.1016/j.coph.2004.09.004

Abbreviations
CS conditioned stimuli
DA dopamine

Introduction: theories of DA function

One of the most active areas of research in psychopharmacology is the behavioral functions of brain dopamine (DA). DA has been linked to various neurological and psychiatric disorders, including Parkinson's disease, schizophrenia, depression and drug addiction. Brain DA systems participate in several functions, including motor control, learning and cognition, stress, emotion and motivation, but perhaps the most widely cited function of DA is its involvement in 'reward' processes [1•]. For more than 25 years, it has been suggested that DA systems in the brain, particularly in nucleus accumbens, directly mediate the rewarding or primary motivational characteristics of natural stimuli such as food, water and sex. In turn, it has been argued that this so-called 'natural reinforcement system' is activated by drugs of abuse, and that this activation is a critical factor involved in the development of drug addiction. Within the past few years, it has become evident that there are numerous problems with the DA reward hypothesis [2•,3•]. This review provides a brief survey of current research and opinion in this area. It emphasizes some of the aspects of primary motivational function that are preserved following interference with accumbens DA transmission, and summarizes recent research on the conditions that activate DA release. In addition, it is argued that accumbens DA does not mediate the primary motivational functions that underlie primary reinforcement for natural stimuli, and therefore mesoaccumbens DA should not be thought of as the 'natural reward system' activated by drugs of abuse. Instead, accumbens DA should be considered a modulator of several functions related to motivated behavior, which include behavioral activation, exertion of effort, response allocation and effort-related decision making, maintenance of motivated behavior over time, responsiveness to conditioned stimuli (CS), Pavlovian-instrumental interactions, learning and cognition. Pathologies related to dopaminergic function could contribute to the dysfunctions seen in numerous clinical syndromes, including psychomotor slowing in depression, schizophrenia and aspects of drug abuse.

The DA hypothesis of reward: major conceptual and empirical problems

As originally proposed, the DA hypothesis of reinforcement was a tightly integrated and testable hypothesis. The central tenet of this hypothesis was that DA systems, particularly in the nucleus accumbens, directly mediated the motivational processes underlying primary reinforcement for natural stimuli such as food, water and sex, and that this 'natural reinforcement system' was activated by drugs of abuse [4–6] (for review, see [2•]). However, as outlined in recent reviews, the DA hypothesis of reward is no longer a tightly integrated hypothesis, but instead has evolved into a loose collection of ideas about the role of DA in diverse aspects of instrumental behavior [1•,2•]. Although some of these ideas are supported by empirical evidence, some are not; furthermore, some relate directly to the central tenet of the hypothesis, whereas others do not. Several investigators emphasize the hypothesized

role of the nucleus accumbens, whereas alternative structures such as the neostriatum and prefrontal cortex are emphasized by others. In addition, core processes that are hypothesized to be mediated by DA have been defined in many ways (i.e. hedonia, primary motivation, incentive motivation, reward, response-reinforcement, 'stamping-in' of reinforced responses) and recast in recent years. For example, although Wise [5] stated in 1985 that he did not subscribe to the principle of response-reinforcement, in which responses are 'stamped-in' by reinforcers, this now appears to be the primary definition of reinforcement employed in his most recent review [1•]. For these reasons, it is important to deconstruct the various components of the DA hypothesis, examine the distinct components, and question whether these pieces fit together into a coherent hypothesis or whether a major restructuring of the field is warranted.

It is hardly controversial to suggest that accumbens DA is involved in several critical processes related to instrumental behavior. The more difficult and important question is which specific processes [2•,7•,8]. For example, there is little disagreement that DA in several structures, including not only nucleus accumbens but also prefrontal cortex and hippocampus, is involved in aspects of learning [1•–3•,9,10•]. However, evidence demonstrating dopaminergic involvement in learning does not provide support for the hypothesis that accumbens DA directly mediates food motivation, because primary motivational processes are distinct and dissociable from the plasticity functions that underlie learning [2•]. To demonstrate selective involvement of DA in learning processes, Kelley and colleagues [10•,11] have taken great pains to show that doses of DA antagonists known to impair learning do not impair primary food motivation. Moreover, it has become evident that DA systems and the nucleus accumbens are involved in various aspects of aversive learning, including place aversion, taste aversion and punishment [2•,3•,12,13•,14], as well as learning about aversive outcomes [15]. Thus, the involvement of DA in learning processes does not provide direct evidence for involvement in primary food motivation, nor is it strictly limited to situations involving positive reinforcement.

Similarly, it has been reported that animals will self-administer stimulants such as amphetamine directly into the nucleus accumbens, and there is little disagreement that interference with accumbens DA transmission has profound effects upon cocaine and amphetamine self-administration [16–18]. Nevertheless, there is debate over the precise interpretation of these findings. The observation that intra-accumbens injections of stimulant drugs such as amphetamine support self-administration does not necessarily establish the validity of an accumbens DA-mediated 'reward system' for natural stimuli. Instead, such a reinforcing effect could be an emergent property that results from the modulation of various channels of information passing through the nucleus accumbens. In other words, the mesolimbic DA system might not function as a natural reward system per se, but might instead be acting to promote behavioral activation, arousal, attention, conditioning and other functions related to natural reinforcement; one of the net results of pharmacological modulation of this system under some conditions could be reinforcement. Nevertheless, it should be emphasized that the observation that accumbens DA depletion affects self-administration of some drugs does not provide support for the hypothesis that accumbens DA mediates the primary motivating effects of all reinforcers, including natural stimuli such as food. The involvement of accumbens DA in reinforcement processes for natural stimuli is essentially the linchpin of the DA reward hypothesis [2•,3•], as the DA-mediated natural 'reward system' in the brain is hypothesized to be activated by drugs of abuse. Yet this central conceptual core of the general form of the DA hypothesis is the most problematic component. Studies have shown that accumbens DA depletions that impair stimulant self-administration have little effect on food-reinforced operant behavior on some schedules [16,17], and there are numerous differences between the behavioral and physiological characteristics of dopaminergic involvement in natural reinforcement and drug self-administration [19•,20].

Problems with the 'extinction' hypothesis

It is important to evaluate critically the notion that the effects of interference with DA closely resemble the effects of motivational manipulations such as extinction (i.e. withdrawal of reward), pre-feeding to reduce food motivation, and appetite-suppressant drugs. In 1978, it was proposed that blockade of DA receptors produces a decline in responding both within-session and across days that closely resembles extinction, or withdrawal of reward; this claim was reiterated in a recent review [1•]. Yet, many studies have demonstrated substantial differences between the behavioral effects of DA antagonism or depletion and extinction (for reviews, see [2•,9]). Accumbens DA depletions and intra-accumbens DA antagonism do not produce an extinction-like decline in responding [21–23], and accumbens DA depletions do not produce effects on the local rate of responding that resemble the effects of extinction [23]. It has also been suggested that the ability of stimuli to reinstate responding suppressed by DA antagonism provides evidence of drug-induced extinction [1•]. Nevertheless, as noted several years ago, this effect is characteristic of the type of sensorimotor gating performed by the basal ganglia; interference with DA, even in Parkinsonism, is not characterized by paralysis. Instead, it has been shown that environmental stimulation can reverse DA-antagonist-induced deficits in locomotion, temporarily reverse the akinesia produced by DA depletion, and stimulate 'paradoxical kinesia' in akinetic parkinsonian patients [8,24].

Finally, it is not clear whether a within-session decline in responding, or decrements in responding over days, necessarily mean that extinction of reinforcement is being produced [2•]. Haase and Janssen in 1985 (cited in [2•]) reported that the micrographia and finger tapping intensity shown by patients with neuroleptic-induced Parkinsonism are characterized by progressive worsening within a session. DA antagonists cause within-session alterations in parameters such as lick force and response duration in rats [25]. In addition, sensitization of some of the effects of DA antagonists with repeated administration does not necessarily or specifically support the extinction hypothesis. Although haloperidol-induced suppression of lever pressing showed sensitization with repeated daily injections, it also enhanced the shift from lever pressing to food consumption in rats performing on concurrent choice procedures [26]. Many responses, including Parkinsonian effects such as microcatalepsy and oral tremors, can sensitize with repeated injection of DA antagonists [27,28]. Indeed, repeated administration of haloperidol leads to the development of an environmentally specific sensitization of the catalepsy response [29].

In addition to these problems with the 'extinction hypothesis', several studies have shown that the effects of interference with DA systems do not closely resemble those of pre-feeding to reduce food motivation [30–32]. Moreover, the detailed patterns of effects produced by DA antagonists on food consumption do not closely resemble effects produced by appetite suppressant drugs on a range of feeding paradigms [33]. Finally, it is important to emphasize that depletions of accumbens DA do not substantially impair appetite or produce a general disruption of all aspects of primary food motivation [2•,3•]. On the basis of observations that injection of D1 or D2 receptor antagonists into either the core or the shell of the nucleus accumbens impaired locomotion and rearing, but did not suppress food intake, Baldo *et al.* [34•] concluded that these drug manipulations 'did not abolish the primary motivation to eat'. In various choice procedures, rats with accumbens DA depletions, despite the behavioral impairments that arise, remain directed towards the acquisition and consumption of food [3•,35]. Together with data reviewed above, these findings indicate that there are substantial problems with one of the core tenets of the DA hypothesis of reward. It has become evident that dopaminergic involvement in learning or drug self-administration cannot be used to support the broader hypothesis that accumbens DA specifically mediates primary reinforcement processes for all natural stimuli.

Behavioral characteristics of interference with accumbens DA transmission

The results of interference with accumbens DA transmission are selective and dissociative; accumbens DA antagonism and depletion impair some features of instrumental behavior, while leaving others intact [2•,7]. Intra-accumbens infusions of DA antagonists at doses that impair sucrose-reinforced runway performance did not impair sucrose intake [36]. DA depletions that impaired performance on ratio schedules did not impair performance of the FR1 schedule, in which a rat only has to press once to receive reinforcement [32,37]. The relative preservation of FR1 performance after accumbens DA depletions is important in view of the fact that this task is a simple schedule of reinforcement, in which every bar press is followed by primary reinforcement, and which is sensitive to reinforcer devaluations such as pre-feeding as well as extinction and appetite-suppressant drugs [2•,3•]. If the major effect of accumbens DA depletions was to blunt primary food reinforcement, then the FR1 schedule should be one of the most sensitive tasks for assessing the effects of DA depletions; instead, it is among the least sensitive. Recent research has indicated that higher ratio requirements on an operant task (i.e. the requirement for more lever presses per reinforcer) make rats more sensitive to the effects of accumbens DA depletions [32,37–39,40•]. Other tasks sensitive to the effects of accumbens DA depletions include choice procedures that allow animals to select between distinct reinforcers that can be obtained by instrumental responses having different effort requirements [3•]. Using the concurrent choice procedure described above, it has been shown that accumbens DA depletions, or injections of selective DA antagonists into either core or shell subregions of the accumbens, suppress lever pressing but increase chow consumption in rats [2•,3•]. Rats with accumbens DA depletions also shifted their choice behavior on a T-maze task, which reduced their selection of the arm that required more effort [3•]. These studies demonstrate that rats with accumbens DA depletions remain directed towards the acquisition and consumption of food; nevertheless, they appear to show alterations in response allocation based upon a cost/benefit analysis, and they become biased towards the selection of low-cost alternatives for food procurement. These effects might result from an impairment of the tendency to exert effort, a lack of behavioral activation in response to CS, or an inability to sustain effort over time in the absence of primary reinforcement [38,40•,41].

Several lines of evidence indicate that the nucleus accumbens participates in the process of responding to CS [2•,3•,9,19•,42,43]. CS, including contextual and temporal cues, help to sustain responding during periods of delayed reinforcement or intermittent reinforcement. Approach responses to Pavlovian CS were disrupted by accumbens DA depletion [44•]. In addition, nucleus accumbens cell body lesions abolished amphetamine-induced increases in lever pressing for a conditioned reinforcer [45,46]. Intra-accumbens amphetamine injections were shown to facilitate Pavlovian-to-instrumental transfer [47]; nucleus accumbens lesions impaired this effect [46]. The specific contributions of discrete core and shell

subregions of nucleus accumbens to these functions appear to differ depending upon the task. For example, conditioned locomotor approach and Pavlovian-instrumental transfer are dependent upon the integrity of nucleus accumbens core [43]. Evidence also indicates that interference with accumbens DA can impair acquisition on various learning procedures, including place conditioning, taste aversion and lever pressing [2•,3•,10•, 13•,14]. The specific processes that underlie these effects remain uncertain; however, it is clear that dopaminergic manipulations that impair the acquisition of lever pressing behavior do not impair consumption of the reinforcer, indicating that the impairments in acquisition are not dependent upon deficits in primary motivation [10•].

In summary, despite the preponderance of evidence indicating that nucleus accumbens DA does not directly mediate primary motivation or appetite for natural reinforcers such as food, it is clear that this nucleus, and its DA innervation, participate in several important aspects of instrumental behavior. Accumbens DA enables organisms to overcome obstacles (i.e. work-related response costs) that separate them from significant stimuli such as food [2•,3•]. Nucleus accumbens DA is also critically involved in activational aspects of motivation, and is a key modulator of response speed, vigor and persistence in instrumental behavior; these functions enable organisms to exert effort in reward-seeking behavior. DA in accumbens amplifies responsiveness to CS, which is important for phenomena such as responding in the absence of primary reinforcement, Pavlovian-instrumental transfer and conditioned reinforcement. Cellular mechanisms in this nucleus are involved in various information processing and plasticity processes, and these functions appear to be important for the acquisition of some learning procedures.

Conditions that activate DA neurons: electrophysiology, voltammetry and microdialysis studies with natural reinforcers

Although administration of several drugs of abuse can elevate extracellular levels of DA in accumbens, aversive or stressful conditions (including those produced by anxiogenic drugs) can also increase accumbens DA release [14]. Several studies have used microdialysis methods to characterize the effects of motivationally relevant procedures, including food intake and lever pressing, on accumbens DA release. Some have shown small increases in extracellular DA in accumbens during food intake or sucrose consumption; some revealed a rapidly habituating neurochemical response; whereas others showed no effect or a much smaller effect than instrumental behaviors such as lever pressing [48–51]. Exposure to a procedure that involved both anticipatory and consummatory components of feeding was shown to increase accumbens DA release [52]. Microdialysis studies have also shown that accumbens DA release is elevated in response to appetitive and aversive Pavlovian conditioning [14,51,53], as well as operant responding [48,54]. In a study using several operant schedules to generate different levels of food delivery as well as different response rates, increases in nucleus accumbens core and shell DA release were not correlated with the total amount of food presented, but were significantly correlated with response rate [54]. However, lever pressing behavior is not always reported to be accompanied by increases in accumbens DA efflux. For example, presentation of CS paired with amphetamine led to an increase in lever pressing that was not accompanied by increases in DA-related voltammetric signals in nucleus accumbens [55].

It does appear, from electrophysiology and voltammetry studies, that the simple prediction that DA release or neuronal activity is a direct marker of the delivery of primary reinforcement has not been supported. Pennartz [56] reviewed the literature in this area, and concluded that a reinforcement signaling function of DA fails to draw support from anatomical and electrophysiological evidence. DA neurons are activated by exposure to novelty [57•,58•] and also respond to aversive Pavlovian CS [59]. From instrumental conditioning procedures conducted in trained animals, it is generally observed that DA neurons respond to the presentation of CS or during the period of instrumental responding [60•]. Schultz [61] has reported that DA neurons respond both to CS that predict reinforcement and to reward prediction errors, which might provide important signals related to learning. Nevertheless, in trained animals, DA neurons lose responsiveness to the primary reinforcer [61]. Nishino *et al.* [62] took recordings from electrophysiologically identified DA neurons in the ventral tegmental area during fixed ratio lever pressing, and reported that firing rate in these cells increased while animals were pressing the lever, yet decreased when food was delivered. Richardson and Gratton [63] observed similar results for DA-related voltammetric signals. Recently, Roitman *et al.* [64•] employed sensitive and sophisticated voltammetric analyses of DA-related signals, and reported that increases in DA release occurred during the presentation of CS that set the occasion for instrumental responding. These increases in DA signals temporally overlapped with the lever pressing response; however, DA release tended to decrease towards baseline with the presentation of sucrose reinforcement.

Conclusions

Despite on-going revisions of the DA hypothesis of reward [1•], there continue to be persistent problems with using the many and varied forms of this hypothesis as a conceptual framework for understanding the behavioral functions of nucleus accumbens DA. Observations suggest that activation of a so-called 'natural reward system', supposedly mediated by accumbens DA, cannot

reasonably be used as a general explanation for drug abuse or drug addiction. Of course, this does not mean that accumbens DA is without involvement in critical aspects of motivation or reinforcement-seeking behavior. Although it is not a simple marker of reward or hedonia, DA in nucleus accumbens does appear to regulate multiple channels of information passing through this nucleus, and thus participates in a variety of behavioral processes. Substantial evidence from behavioral as well as electrophysiology studies supports the notion that nucleus accumbens acts as a gate, a filter, or an amplifier of information passing through from various cortical or limbic areas on its way to motor areas of the brain. Everitt *et al*. [65] suggested that the impact of information about conditioned reinforcers is 'gain amplified by increases in dopamine transmission' in nucleus accumbens. The idea that DA acts as a gain amplifier of information passing though the accumbens is also consistent with studies showing involvement of this structure in sensorimotor gating [66], behavioral activation and effort-related decision making [2•,3•], incentive salience [7], stress [14] and learning [10•]. Electrophysiological studies suggest that the nucleus accumbens is organized into ensembles of task-specific neurons that are modulated by DA [67–69]. The activity of accumbens neurons is thought to encode information related to the predictive value of environmental stimuli and the specific behaviors required to respond to them [70]. A recent report indicates that accumbens DA is necessary for modulating both the electrophysiological and behavioral responses to these environmental cues [71•].

In summary, recent electrophysiological studies, coupled with behavioral research, suggest that accumbens DA modulates various channels of information that have a high degree of behavioral relevance. Thus, although it might no longer be tenable to suggest that drugs of abuse are simply activating the brain's 'natural reward system' [2•,3•], it clearly is the case that accumbens DA participates in the brain circuitry that regulates vital components of instrumental behavior and motivation [2•,3•,13•,45•,72]. Moreover, accumbens DA has been implicated in modulating work output in drug-seeking behavior as well as effort expenditure related to natural stimuli [3•,73,74]. It has been suggested that some of the motivational functions of accumbens DA are relevant for understanding aspects of schizophrenia [75]. Moreover, the behavioral activation functions of accumbens DA are thought to be related to anergia or psychomotor slowing in depression [3•]. Such observations have important implications for our understanding of the neural mechanisms of motivation, and also emphasize the potential clinical significance of accumbens DA.

Update

Recent articles have focused on the involvement of limbic, striatal and cortical circuitry in aspects of responding for delayed or intermittent reinforcement [76•,77•]. It is critical for future research to characterize the involvement of forebrain systems in aspects of impulsive choice, and identify the relative contribution that effort and time requirements play in making some tasks sensitive to the effects of nucleus accumbens DA depletions.

Acknowledgements

Much of the work cited in this paper was supported by a grant to JS from the US National Science Foundation.

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