Behavioural Brain Research 231 (2012) 297–308

Contents lists available at SciVerse ScienceDirect

Behavioural Brain Research

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

Review

Amphetamine stereotypy, the basal ganglia, and the "selection problem"

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ARTICLE INFO

Article history:
Received 25 August 2011
Received in revised form 1 November 2011
Accepted 2 November 2011
Available online 11 November 2011

Keywords:
Amphetamine
Basal ganglia
Contingent tolerance
Stereotypy
Response selection/suppression
Tourette's syndrome

ABSTRACT

Amphetamine and other stimulant drugs induce stereotyped head movements in rats, which interfere with normal goal-directed behavior. However, rats given access to food while intoxicated learn to suppress these movements in order to feed. This suggests that the suppression of stereotypy is an instrumentally learned response reinforced by the ingestion of food. Consistent with this interpretation, rats learn to suppress stereotyped head movements when intraoral infusions of milk are made contingent on maintaining a stationary head position, but not when such infusions are given noncontingently. Although learning to suppress stereotypy occurs at different rates across subjects, the temporal dynamics of learning are similar in all cases. Moreover, once learned suppression is acquired, it is generally retained over long periods of time unless the contingency between suppression and reinforcement is degraded.

Conceptually, the behavioral conflict between drug-induced stereotyped movements and feeding may be viewed as a special case of the "selection problem," which arises whenever organisms are confronted with competing behavioral opportunities. Interestingly, both normal response selection and stimulant-induced stereotypy are associated with overlapping cortico-basal ganglia circuits. Preliminary findings suggest that the learned suppression of stereotypy involves the activation of particular structures within the dorsal and ventral striatal output pathways. Understanding the neural mechanisms underlying the learned suppression of stimulant-induced stereotypy may provide new insights into the process by which the nervous system solves the selection problem and lead to the development of more effective treatments for disorders characterized by insufficient response inhibition, such as Tourette's syndrome and stimulant drug addiction.

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doi:10.1016/j.bbr.2011.11.003

1. Prologue

I had the good fortune to work with Phil Teitelbaum as a postdoctoral fellow at a time when he was transitioning from studying the lateral hypothalamic syndrome to analyzing movement subsystems. This work began with an analysis of the recovery of exploratory locomotion in rats with lateral hypothalamic lesions, utilizing the Eshkol-Wachmann movement notation system [1]. The stereotyped head scanning movements along horizontal and vertical surfaces we observed in recovering lateral hypothalamic rats suggested that stereotyped movements result from the activation of independent motor subsystems, which control movement in the lateral, horizontal and vertical dimensions. Later work by Phil and his colleagues expanded this analysis to movements induced by dopaminergic (as well as other) drugs in neurologically normal rats [2]. Taken together, this line of research provided a new conceptual framework for understanding stereotyped movements as behavioral composites engendered by the selective activation and/or inhibition of particular movement subsystems.

Phil's research on movement subsystems beautifully illustrates his methodological approach to understanding behavior through the complementary processes of analysis and synthesis [3]. Simplifying the nervous system by means of lesions or drugs and simplifying the environment by utilizing behavioral "traps," which selectively elicit (and isolate) particular behavioral subsystems, serve to deconstruct exploratory locomotion into simpler behavioral units, which can then be analyzed further to discover the variables that control them. Conversely, recovery from brain damage or termination of drug action provides the opportunity for behavioral synthesis, as the behavioral components become integrated into more adaptive, flexible, goal directed responses. These sophisticated studies of movement at the behavioral level provide a rigorous framework for the analysis of behavior at the neural level.

Because stereotyped movements induced by stimulant drugs lack the flexibility, adaptiveness and goal directedness of normal "voluntary" behavior, they are often considered irrepressible. However, under appropriate conditions, they are subject to inhibitory control. In the remainder of this article, I will review evidence that rats can learn to suppress drug-induced stereotyped movements via instrumental conditioning. I will then relate these findings to the broader issue of response selection and inhibition, and present some preliminary findings regarding the neural subsystems that may mediate this phenomenon.

2. Introduction

Stereotypy-inducing drugs like amphetamine and cocaine clearly disrupt the normal integrative activity of the brain. At the behavioral level, this is evident in the disruption of goal-directed behaviors like feeding and drinking. For example, when a hungry rat is injected with 2 mg/kg amphetamine and given access to sweetened milk, it stands directly in front of the bottle and engages in continuous sniffing and head scanning stereotypies, apparently unable to suppress the movements in order to drink [4]. If the rat is then given chronic injections of amphetamine without having access to food, stereotypy becomes sensitized. Head scanning movements become more rapid and spatially focused, and eventually may be replaced by repetitive licking and biting movements directed at the wire mesh walls and floor of the cage [5–8]. If, at this point, sweetened milk is again presented, the rat appears to be totally oblivious to it.

One might conclude from this description that following chronic administration, stimulant drugs "highjack" the neural circuits that control normal motivated behavior, rendering them relatively unresponsive to biologically meaningful stimuli [9]. Indeed, chronic administration of amphetamine and cocaine induces long-lasting neuroadaptations in cortico-basal ganglia circuits that control both movement and appetitive motivation and these neural changes (interacting with environmental and experiential factors) are believed to be responsible for behavioral sensitization [10]. It should be noted, however, that for purposes of experimental control, most studies of behavioral sensitization involve testing rats in environments devoid of biologically meaningful goal objects. When the environment contains such objects (e.g., food), rats gradually acquire the ability to suppress stereotyped movements and to engage in goal-directed behavior, despite the development of neural sensitization [11].

3. Contingent tolerance to amphetamine

The discovery that stereotyped movements can be voluntarily inhibited grew out of attempts to understand the development of tolerance to what was assumed to be the anorexic effects of amphetamine. As described above, rats given injections of 2 mg/kg amphetamine prior to a feeding test initially eat very little. However, if tested chronically, tolerance develops to this effect; i.e., feeding gradually recovers, often to baseline levels of intake. One might assume that such tolerance is due to pharmacokinetic or pharmacodynamic changes brought about by chronic exposure to the drug *per se*. However, if a control group is given the same number of injections of amphetamine but *after* each feeding test, the rats do not exhibit tolerance when later tested with the drug prior to feeding [12]. Because tolerance to amphetamine is contingent on the relationship between the time of drug injection and feeding, Carlton and Wolgin [12] called this phenomenon "contingent tolerance." Similar results have been found with other stimulant drugs, including cocaine [13], methylphenidate [14] and cathinone [15].

Why is the timing of the injections critical? One possibility is that rats injected prior to feeding lose reinforcement (from failing to eat the food) and therefore learn to compensate for the anorexic effect of the drug [16]. The importance of reinforcement loss was demonstrated in a study by Schuster, Dockens and Woods [17]. Rats were given injections of amphetamine (1 mg/kg) and tested on a multiple schedule of reinforcement consisting of fixed interval (FI) and differential reinforcement of low rate (DRL) components. In two rats, amphetamine initially induced increased rates of responding on both components of the schedule, which resulted in a loss of reinforcement on the DRL component, but not on the FI component. With chronic administration of the drug, tolerance developed in the DRL component, but not in the FI component. However, in a third rat, amphetamine initially caused a decrease in FI responding, resulting in a loss of reinforcement. In this rat, tolerance developed in the FI component. Thus, loss of reinforcement seems to generate tolerance to the drug. Similarly, in contingent tolerance, rats injected with amphetamine before feeding lost reinforcement and became tolerant whereas rats injected after the tests did not. The fact that tolerance was expressed differentially in both of these paradigms suggests that a behavioral mechanism, rather than a pharmacological one, is involved.

There are, however, two problems with the "reinforcement loss" hypothesis. First, it does not specify what, precisely, the mechanism is [16,18]. Second, it seems incompatible with the notion that amphetamine induces anorexia (loss of appetite). If amphetamine suppresses appetite, then food should no longer be reinforcing. In that case, what is the motivation to recover feeding? These questions prompted us to reevaluate the mechanism by which amphetamine and other stimulant drugs suppress feeding.