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Invited review

Neurocircuitry of drug reward

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ABSTRACT

In recent years, neuroscientists have produced profound conceptual and mechanistic advances on the neurocircuitry of reward and substance use disorders. Here, we will provide a brief review of intracranial drug self-administration and optogenetic self-stimulation studies that identified brain regions and neurotransmitter systems involved in drug- and reward-related behaviors. Also discussed is a theoretical framework that helps to understand the functional properties of the circuitry involved in these behaviors. The circuitry appears to be homeostatically regulated and mediate anticipatory processes that regulate behavioral interaction with the environment in response to salient stimuli. That is, abused drugs or, at least, some may act on basic motivation and mood processes, regulating behavior-environment interaction. Optogenetics and related technologies have begun to uncover detailed circuit mechanisms linking key brain regions in which abused drugs act for rewarding effects.

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1. Introduction

Dopamine (DA) neurons localized in the midbrain projecting to the striatal complex, particularly the ventral tegmental area (VTA)-the ventral striatum (VStr) system, play a major role in mediating rewarding effects of drugs of abuse (Bowers et al., 2010; Fibiger and Phillips, 1986; Koob, 1992; Robbins and Everitt, 1996; Wise and Bozarth, 1987). The ascending DAergic system is thought to be a common pathway mediating response not only to psychomotor stimulant drugs but also to other drugs including ethanol and opioids (Pierce and Kumaresan, 2006; Wise and Bozarth, 1987). However, the DA system is not the sole mediator of this response because biological properties such as reward arise from the collective properties of many components (Ikemoto, 2010). To fully understand the large-scale circuitry underlying drug reward, it is necessary to identify all the key components and determine how they work together in relation to the DA systems. The aim of this paper is to review a theoretical background that helps us to understand the functional nature of "drug reward" circuitry and to outline related studies involving intracranial drug injections and optogenetics, as all together they help identify brain regions and neurotransmitter systems that are crucial components of this circuitry.

2. Theoretical framework: drug reward, motivation, and reinforcement

Before reviewing the brain regions and transmitters involved in drug self-administration, a theoretical framework is presented to help readers understand how detailed mechanisms can be put together as components of a system. After reviewing regions and transmitters that mediate reward, we will further elaborate key conceptual issues.

2.1. What is reward?

Although the VTA-VStr DA system has been identified as a key substrate for the rewarding effects of abused drugs, it has been questioned whether the DA system really mediates reward (Berridge and Robinson, 1998; Ikemoto and Panksepp, 1999; Salamone, 1994). This is in part because "reward" has not been uniformly defined. In addition, it is unclear how to integrate the

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role of DA in aversive situations (Salamone, 1994) and the lack of roles of DA in food consumption (Koob et al., 1978) and hedonic taste reaction (Berridge and Robinson, 1998). To tackle these issues, it is important to first define "reward". Rewards are things that have positive effects on behavior, attitude, relationships, etc., or in technical jargon, stimuli that reinforce behavior. In addition, reward is operationally defined, in this paper, as an *induced state that subsequently leads to conditioned approach behavior*. The latter definition is consistent with observations from manipulations of the VTA-VStr DA system (Ikemoto, 2007; Ikemoto and Panksepp, 1999). Although the roles of DA in aversive situations seem more complex than those in appetitive situations, this notion may even explain some effects of DA release or manipulations in aversive situations (Oleson et al., 2012), given that avoidance behavior is conceived as an approach behavior directed toward safety (Ikemoto and Panksepp, 1999). Moreover, this definition is not equal to or necessarily accompanied by positive conscious experience. Let us further elaborate on this.

Can activation of DA systems be accompanied by any feeling? It seems reasonable to speculate that the activation of DA systems initially alters sub-conscious processes, and then a cascade of actions, triggered by DA, eventually tap into the conscious mind and induces perceived positive changes in feelings. Based on the rewarding effects in humans of psychostimulants such as cocaine (Volkow et al., 1997), the activation of DA systems appears to be accompanied by positive emotional arousal characterized as "euphoria" rather than by hedonic sensory pleasure (Ikemoto, 2007, 2010). In any case, feelings accompanied by activation of DA systems are only the tip of the iceberg. Reward processes triggered by DA systems are mediated by an extensive set of brain structures and neurotransmitter systems (Ikemoto, 2010).

2.2. How do we study the neurocircuitry of drug reward?

It is reasonable to assume that the mammalian brain has never been selected for its capacity to take or seek drugs through its phylogeny (Nesse and Berridge, 1997). Drug reward seems to arise from brain's capacities that have already evolved to perform functions unrelated to drug taking or seeking. In addition, although the DA systems are key components of the circuitry, the entire circuitry is most likely much more complex and vast (Ikemoto, 2010). Thus, a key question is how we should begin to study the neurocircuitry responsible for drug reward. First, we briefly turn to rich scientific literature on laboratory animal behavior in appetitive and aversive conditions. These studies can provide insights and theoretical grounds on the functional system that abused drugs alter to elicit rewarding effects. Although it is not the focus of this review, it should be noted that while a common functional system appears to be involved in the rewarding effects of many drugs, each drug exerts additional unique actions not related to reward, which makes it difficult to identify the common substrates.

2.3. Coordinating processes of approach behavior

The distinction between hedonic sensation and emotional euphoria is rooted from the distinction in behavioral research between consummatory and approach behaviors. This distinction arose from the recognition that consummatory behavior (e.g., feeding) is regulated by different factors from approach behavior (e.g., instrumental behavior, which is guided by anticipatory processes) (Bindra, 1968; Konorski, 1967). While consummatory behavior is partly controlled by *proximal stimuli* (e.g., taste), approach behavior is largely guided by *distal stimuli* (e.g., visual cues), which allow organisms to anticipate what may happen and give time and space for behavioral action. Indeed, approach behavior can be dissociated from consummatory behavior by behavioral and neural manipulations. For example, rats that have been previously trained to approach and feed under a hungry state will seek out food regardless of being hungry or sated, if they have not experienced eating food under a sated state in the same context (Dickinson and Balleine, 1994). Approach and consummatory responses can also be dissociated by brain manipulations, for example, by the suppression of VTA-VStr DA system. Microinjections of GABA into the VTA or the DA receptor antagonist flupentixol into the VStr can selectively disrupt approach behavior without altering reward consumption (Ikemoto and Panksepp, 1996). These findings help us understand why systemic injections of amphetamine, which suppress food appetite, can increase responding previously reinforced by food if animals are tested without food (i.e., during an extinction phase) (Clark, 1966; Cohen, 1991; Herling et al., 1979; Olds, 1970).

Such anticipatory approach behaviors are conceived to arise from coordinating processes integrating sensory, perceptual, cognitive, motor, and visceral signals into a coherent whole (Ikemoto, 2010). In other words, the anticipatory coordinator integrates information from specialized processors to regulate *behavioral interaction with the environment in response to salient stimuli*, including novel stimuli and classical rewards.

Behavioral research over the past few decades has suggested that increase in approach behavior is associated with positive affect, while their suppression with negative affect (Dickinson and Pearce, 1977; Konorski, 1967; Mackintosh, 1983; Rescorla and Solomon, 1967). For example, approach responses rewarded by food are readily disrupted by the presentation of a distal cue associated with aversive footshock (Estes and Skinner, 1941). Conversely, the presentation of a cue signaling food disrupts avoidance behavior guided by another cue signaling footshock (Grossen et al., 1969). Strikingly, the presentation of cues signaling food appears to elicit the same affective quality as the omission of footshock, because simultaneous presentations of food-signaling cue and shock omission cue have additive effects on approach behavior (Grossen et al., 1969). Conversely, cues signaling the absence of food have the same affective quality as those signaling footshock, because simultaneous presentations of these cues have additive effects on avoidance (Grossen et al., 1969). These findings and many others led to the proposal that two affectively dichotomous processes are associated with the activation and suppression of approach behavior, respectively (Dickinson and Pearce, 1977; Konorski, 1967; Mackintosh, 1983; Rescorla and Solomon, 1967; Schneirla, 1959).

Our working hypothesis is that neural mechanisms that regulate approach behavior (i.e., anticipatory processes) are major substrates of rewarding effects of many drugs including psychomotor stimulant drugs. In other words, many abused drugs appear to alter the mechanisms in such a way to stimulate approach-behavioral processes, which are accompanied by positively affective states.

2.4. Reward, reinforcement and learning

Another issue that needs to be mentioned is that reward and anticipatory processes, either related to natural rewards or abused drugs such as cocaine, are intricately tied with synaptic and cellular mechanisms that are also shared by learning and memory processes (for reviews on this topic, see Bowers et al., 2010; Lüscher and Malenka, 2011). Drug use can alter many aspects of the nervous system, which will then influence how animals and humans act in future. Animals and humans will learn about the environmental stimuli associated with drug taking, which will help them predict the opportunity or occurrence of drug administration (so