Behavioural Processes 127 (2016) 3–17

Contents lists available at ScienceDirect

Behavioural Processes

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

The pharmacology of effort-related choice behavior: Dopamine, depression, and individual differences

John D. Salamone[a,*], Merce Correa[a,b], Samantha Yohn[a], Laura Lopez Cruz[a,b], Noemi San Miguel[a,b], Luisa Alatorre[c]

[a] Dept. of Psychology Sciences, University of Connecticut, Storrs, CT 06269-1020, USA
[b] Area de Psicobiol., Dept. Psic., Universitat de Jaume I, Castelló 12071, Spain
[c] University of El Paso, El Paso, TX, USA

ARTICLE INFO

Article history:
Received 9 December 2015
Received in revised form 8 February 2016
Accepted 12 February 2016
Available online 19 February 2016

Keywords:
Dopamine
Adenosine
Effort
Work
Reinforcement
Behavioral economics
Depression

ABSTRACT

This review paper is focused upon the involvement of mesolimbic dopamine (DA) and related brain systems in effort-based processes. Interference with DA transmission affects instrumental behavior in a manner that interacts with the response requirements of the task, such that rats with impaired DA transmission show a heightened sensitivity to ratio requirements. Impaired DA transmission also affects effort-related choice behavior, which is assessed by tasks that offer a choice between a preferred reinforcer that has a high work requirement vs. less preferred reinforcer that can be obtained with minimal effort. Rats and mice with impaired DA transmission reallocate instrumental behavior away from food-reinforced tasks with high response costs, and show increased selection of low reinforcement/low cost options. Tests of effort-related choice have been developed into models of pathological symptoms of motivation that are seen in disorders such as depression and schizophrenia. These models are being employed to explore the effects of conditions associated with various psychopathologies, and to assess drugs for their potential utility as treatments for effort-related symptoms. Studies of the pharmacology of effort-based choice may contribute to the development of treatments for symptoms such as psychomotor slowing, fatigue or anergia, which are seen in depression and other disorders.

Contents

* Corresponding author at: Board of Trustees Distinguished Professor, Head, Behavioral Neuroscience, Dept. of Psychological Sciences, University of Connecticut, Storrs, CT 06269-1020, USA.
E-mail address: john.salamone@uconn.edu (J.D. Salamone).

http://dx.doi.org/10.1016/j.beproc.2016.02.008
0376-6357/

1. Introduction

The ability to interact with the environment in order to obtain access to significant stimuli such as food and water is critical for survival. In a complex environment, organisms usually have the option to pursue multiple reinforcers, which can vary in quality (e.g. palatability of food) and magnitude. Furthermore, the instrumental actions that allow access to these reinforcers can be quite varied in terms of the kinetic requirements of the individual responses, as well as the overall work requirements across large units of time (e.g. ratio requirements, area of space to be covered). Thus, organisms must develop patterns of behavior that allocate behavioral resources across multiple response and reinforcer domains, which means that the animal must make choices between the various options available. There are several research areas in behavioral science (e.g. response-reinforcement matching, optimal foraging theory, behavioral economics) that have emerged in order to characterize the choice behavior observed in these complex environments (Baum, 1974; Allison, 1981, 1993; Salamone, 1987; Heyman et al., 1987; Williams, 1988; Hursh et al., 1988; Hursh and Winger, 1995; Madden et al., 2000; Aparicio, 2001, 2007; Vuchinich and Heather, 2003; Hengeveld et al., 2009; Madden and Kalman, 2010). This research has provided approaches for understanding how reinforcement value, as well as response requirements, influence the relative allocation of instrumental behavior across multiple options.

Work-related response costs are an important factor influencing choice behavior (Staddon, 1979; Kaufman, 1980; Kaufman et al., 1980; Salamone, 1986, 1987, 1992; Hursh et al., 1988; Foltin, 1991; Tustin, 1995; Madden et al., 2000; Salamone et al., 2012), and considerable research has focused on the brain mechanisms that are involved in the exertion of effort and effort-related choice. This paper will review the literature on how various drugs and neurochemical manipulations affect effort-based choice, with a particular emphasis on drugs that alter dopamine (DA) transmission. Moreover, because some human psychopathologies are characterized by reduced exertion of effort or blunted behavioral activation, the present discussion will emphasize how tests of effort-related choice behavior can be developed into formal models that are useful for testing a variety of drugs for their potential clinical utility.

2. Problems with the “REWARD” hypothesis of DA function

Before considering the involvement of DA in work-related aspects of instrumental response allocation and effort-based choice, it is useful to provide some historical background on the hypothesized functions of DA. There have been substantial theoretical developments in the last few years related to the hypothesized behavioral functions of DA, particularly the mesolimbic DA system, with its major input into nucleus accumbens. For several decades, it was typical to label DA as the “reward” transmitter in the neuroscience literature. DA was thought to mediate feelings of subjective pleasure or motivational appetites that regulate or drive positive reinforcement phenomena. Nevertheless, considerable research has demonstrated that there are empirical problems and conceptual limitations with the traditional DA hypothesis of “reward” (Salamone et al., 1997, 2005, 2007, 2009a,b, 2012; Salamone, 2010a,b; Barbano and Cador, 2007; Baldo and Kelley, 2007). Although it was suggested years ago that administration of DA antagonists produces an effect that closely resembles extinction (Wise et al., 1978), several subsequent studies have shown that the pattern of effects produced by DA antagonism and accumbens DA depletion on positively reinforced instrumental behavior differ substantially from extinction (Evenden and Robbins, 1983; Asin and Fibiger, 1984; Salamone, 1986; Salamone et al., 1995; Rick et al., 2006). Also, the processes most directly evoked by the use of the term reward (i.e., subjective pleasure, primary motivation) have been shown to be problematic in terms of demonstrating the involvement of DA systems (Salamone et al., 2007). The idea that accumbens DA mediates the subjectively reported pleasure associated with primary positive reinforcers has been hotly debated and strongly challenged (Salamone et al., 2007; Berridge, 2007; Berridge and Kringlebach, 2008). DA antagonism or depletion does not generally impair appetitive taste reactivity for sucrose (Berridge, 2007; Berridge and Kringlebach, 2008), which is a commonly used behavioral marker of hedonic reactivity in rodents. Administration of DA antagonists or nutritional depletion of DA generally has typically failed to blunt the subjectively rated euphoria produced by drugs of abuse in humans (Gawin, 1986; Brauer and De Wit, 1997; Haney et al., 2001; Nann-Vernotica et al., 2001; Wachtel et al., 2002; Venugopalan et al., 2011).

Neurochemical and physiological studies in animals clearly indicate that DA neuron activity is not simply tied to the delivery of primary positive reinforcers across a broad range of conditions (Marinelli and McCutcheon, 2014; Salamone et al., 2015b; Stauffer et al., 2015). Several studies have indicated that fast phasic DA neuron responses represent a reward prediction error, and it has been suggested that this could be related to the expected utility of rewards (Stauffer et al., 2015). In addition, there also is evidence that prolonged DA signaling in response to cues that are distant from the reinforcer can provide a sustained motivational drive during maze learning that maintains instrumental behavior (Howe et al., 2013). Consistent with this observation, Hamid et al. (2016) studied DA signaling as measured by fast cyclic voltammetry responses in rats that were responding on distinct phases of a flexible decision making task. They observed that phasic DA responses increased as animals progressed towards the increasing likelihood of reinforcement, and reported that these DA signals were correlated with important features of behavioral output, such as response latencies. These responses increased as the animals progressed through the phases of the task even when reward was predicted, and thus did not represent a reward prediction error response. This led to the suggestion that mesolimbic DA helps to translate estimates of reinforcer availability into decisions to work for reward, and that mesolimbic DA release could being used as a motivational signal regulating behavioral activation and the decision of whether or not to engage in effortful activity (Hamid et al., 2016).

Some studies involving food reinforcement in trained animals have shown that increases in DA release were more strongly associated with the instrumental response, or conditioned stimuli signaling reinforcer availability, rather than reinforcement delivery per se (Sokolowski et al., 1998; Roitman et al., 2004; Segovia et al., 2011). Furthermore, the role of DA systems in instrumental learning (e.g. Beninger and Gerdjikov, 2004) is not limited to situations involving positive reinforcement. Striatal mechanisms in general, and accumbens DA in particular, also participate in aspects of aversive learning, punishment, and responsiveness to aversive stimuli (Salamone, 1994; Munro and Kokkinidis, 1997; Blazquez et al., 2002; Pezze and Feldon, 2004; Delgado et al., 2008; Faure et al., 2008; Martinez et al., 2008). Research employing various imaging methods has demonstrated that the human nucleus accumbens responds to stress, aversion and hyperarousal/irritability (Liberzon et al., 1999; Pavic, 2003; Jensen et al., 2003; Phan et al., 2004; Pruessner et al., 2004; Levita et al., 2009; Delgado et al., 2008, 2011). Animal studies have shown that DA neuron activity and DA release can be activated by a number of different aversive (e.g. footshock, tailshock, tail pinch, restraint stress, aversive conditioned stimuli, aversive drugs, social defeat stress; McCullough and Salamone 1992; McCullough et al., 1993; Guarraci and Kapp, 1999; Young, 2004; Marinelli et al., 2005; Broom and Yamamoto, 2005 Anstrom