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Depletion of nucleus accumbens dopamine leads to impaired reward and aversion processing in mice: Relevance to motivation pathologies

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ABSTRACT

Dopamine (DA) neurotransmission, particularly the ventral tegmental area-nucleus accumbens (VTA-NAcc) projection, underlies reward and aversion processing, and deficient DA function could underlie motivational impairments in psychiatric disorders. 6-hydroxydopamine (6-OHDA) injection is an established method for chronic DA depletion, principally applied in rat to study NAcc DA regulation of reward motivation. Given the increasing focus on studying environmental and genetic regulation of DA function in mouse models, it is important to establish the effects of 6-OHDA DA depletion in mice, in terms of reward and aversion processing. This mouse study investigated effects of 6-OHDA-induced NAcc DA depletion using the operant behavioural test battery of progressive ratio schedule (PRS), learned non-reward (LNR), learned helplessness (LH), treadmill, and in addition Pavlovian fear conditioning. 6-OHDA NAcc DA depletion, confirmed by ex vivo HPLC-ED, reduced operant responding: for gustatory reward under effortful conditions in the PRS test; to a stimulus recently associated with gustatory non-reward in the LNR test; to escape footshock recently experienced as uncontrollable in the LH test; and to avoid footshock by physical effort in the treadmill test. Evidence for specificity of effects to NAcc DA was provided by lack of effect of medial prefrontal cortex DA depletion in the LNR and LH tests. These findings add significantly to the evidence that NAcc DA is a major regulator of behavioural responding, particularly at the motivational level, to both reward and aversion. They demonstrate the suitability of mouse models for translational study of causation and reversal of pathophysiological DA function underlying motivation psychopathologies.

1. Introduction

Dopamine (DA) neurons with cell bodies in the ventral tegmental area (VTA) innervate several brain regions, and primary among these are the nucleus accumbens (NAcc), prefrontal cortex (PFC), amygdala and hippocampus (Lammel et al., 2008; Sesack and Grace, 2010). The NAcc is part of the ventral striatum and has extensive connectivity with other brain regions: in addition to the VTA input, it receives excitatory afferents from PFC and amygdala and inhibitory afferents from ventral pallidum (VP). Major projection regions of the NAcc include, reciprocally, VP and VTA (Sesack and Grace, 2010). Nucleus accumbens DA signalling modulates behavioural responsiveness to stimuli in terms of stimulus-stimulus learning, response-stimulus (operant) learning, and the motivation underlying behaviour directed at positive and negative stimuli (Salamone and Correa, 2012; Wise, 2004). Altered processing of positive- and negative-valence stimuli is characteristic of various psychiatric disorders, including depression and schizophrenia (Eshel and Roiser, 2010; Wang et al., 2015). For example, low motivation for reward underlies the core loss-of-interest symptom in depression and the core negative symptoms in

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schizophrenia; low motivation to cope with aversive stimuli likely contributes to both the perceived loss of control underlying helplessness (Nunes et al., 2013; Pryce et al., 2011; Treadway and Zald, 2011) and to fatigue (Demyttenaere et al., 2005). In the research domain criteria (RDoC) framework for mental health research (Cuthbert and Insel, 2013), motivation for reward is a dimension in the domain Positive valence systems, and emotions to and motivations induced by aversive stimuli are dimensions in the domain Negative valence systems (Cuthbert and Insel, 2013). Integrating the evidence for the importance of DA in regulating motivation with that for motivation pathologies, reduced DA function has been hypothesized as a major pathophysiological factor in depression (Dunlop and Nemeroff, 2007) and negative symptomatology in schizophrenia (Whitton et al., 2015). For example, using functional magnetic resonance imaging, reduced activity in the ventral striatum when anticipating reward was observed in both depression and schizophrenia patients compared to healthy controls (Arrondo et al., 2015; Hagele et al., 2015).

Animal studies are essential to increase understanding of contributions of DA to adaptive and disrupted processing of rewarding and aversive stimuli. Much of the evidence for the importance of NAcc DA function in the modulation of goal-directed behaviour has been obtained in loss-of-function experiments conducted in rats. Infusion of the monoamine neurotoxin 6-hydroxydopamine (6-OHDA) into the NAcc, leading to specific degeneration of DA fibre terminals (Stott and Barker, 2014), is the most established method (Aberman and Salamone, 1999). It has been primarily applied to study NAcc DA in the processing of gustatory reward stimuli. In rat, in a free-choice paradigm, NAcc DA depletion delays development of preference for sucrose solution relative to water (Martinez-Hernandez et al., 2012). NAcc DA depletion impairs both the operant acquisition of response-outcome learning and the motivation to respond, with the latter effect being most pronounced when high effort is required (Aberman and Salamone, 1999). Such findings demonstrate that NAcc DA regulates the motivation for ("wanting") sweet-tasting stimuli (Nunes et al., 2013). In contrast, NAcc DA does not regulate appetite for homeostatic dietary need (Cousins and Salamone, 1994) or hedonic responding to ("liking") sweet stimuli (Smith et al., 2011). There is also interest in DA regulation of the motivation required under cognitively effortful conditions. For example, VTA DA projection to prefrontal cortex (PFC) has been proposed to maintain goal-directed behaviour when challenged by distracter stimuli (Cools et al., 2011; van Schouwenburg et al., 2010). Reversal learning involves changes in response-outcome contingency and requires inhibition of responding to a stimulus previously associated with reward i.e. inhibition of perseveration, and disinhibition of responding to a stimulus previously associated with non-reward i.e. suppression of learned irrelevance/non-reward. Serotonin in PFC inhibits perseveration in common marmoset (Clarke et al., 2004), and glutamate within orbital PFC suppresses learned irrelevance in a reversal test that separates perseveration and learned non-reward, in rat (Tait and Brown, 2007). Recently, a learned non-reward (LNR) test was described for mouse, allowing for the specific study of operant responding to a stimulus that previously had a negative valence (non-reward) and now has a positive valence (reward) in the absence of perseveration (Nilsson et al., 2012).

Nucleus accumbens DA also modulates goal-directed behaviour relative to unconditioned aversive stimuli. Dopamine is released acutely in the NAcc in response to electric footshock (Young et al., 1993) and social stress (Cabib and Puglisi-Allegra, 2012), for example. In the case of inescapable/uncontrollable stimuli, the initial increase in NAcc DA is followed by a decrease below pre-stress tonic levels (Cabib and Puglisi-Allegra, 2012). As with positive stimuli, NAcc DA appears to modulate both the response-outcome learning and motivational aspects of behaviour relative to aversive stimuli. In rat, depletion of NAcc DA leads to a deficit in operant lever pressing or two-way shuttling to avoid-escape footshock (McCullough et al., 1993; Wenzel et al., 2015). In DA-deficient mice in which DA expression could be reactivated region-specifically, restoration of DA signalling to both entire striatum and amygdala was necessary and sufficient to enable mice to learn two-way active avoidance (Darvas et al., 2011). Also in mice, DA depletion in VTA and substantia nigra pars compacta led to increased sensitivity to inescapable footshock, expressed as a response deficit in a lever-press escape test i.e. learned helplessness (Winter et al., 2007). With respect to aversive stimulus-stimulus learning, studied primarily using Pavlovian fear conditioning, conditioned stimuli (CS e.g. tone) that predict footshock stimulate DA release in the NAcc (Pezze and Feldon, 2004; Wenzel et al., 2015). Whether NAcc DA depletion affects CS fear conditioning or expression remains to be investigated (Pezze and Feldon, 2004).

The present study investigated the effects of NAcc DA depletion in a battery of behavioural tests for assessment of responding to positive- and negative-valence stimuli in mice. The tests used are given in Table 1, together with the outcome stimulus and type of effort required to attain it, as well as the mediating behavioural dimensions according to the terminology of the RDoC framework (Cuthbert and Insel, 2013). The first test was operant responding for gustatory reward on a progressive ratio schedule (PRS) of reinforcement (Ineichen et al., 2012). Mice learned the operant response-outcome association prior to 6-OHDA administration, so that effects of NAcc DA depletion on approach motivation under physical effort could be investigated per se (Table 1). The second test was responding to operant stimuli with changing association with gustatory reward in a learned non-reward (LNR) test (Nilsson et al., 2012): mice were trained through a series of simple + LNR discrimination stages prior to 6-OHDA administration. Then the effects of NAcc DA depletion were investigated on a final simple + LNR discrimination stage, the latter providing a test of cognitive effort and the maintaining of approach motivation when the association between an operant stimulus and reward shifts from negative to positive (Table 1). The third test was a learned helplessness (LH) test (Pryce et al., 2012), conducted after NAcc DA depletion. Mice were pre-exposed to inescapable footshock, followed by a two-way footshock escape test. The latter provided a test of motivation to escape aversion (safety motivation) requiring physical effort and cognitive perception of response-outcome contingency (Table 1). The fourth test was a treadmill running test (Azzinnari et al., 2014), conducted after NAcc DA depletion. Mice learned that forward movement on the treadmill resulted in operant avoiding or escaping of footshock, using a slow speed. In the subsequent test conducted at a higher speed, running time provided a measure of motivation to avoid-escape aversion (safety motivation) under physical effort (Table 1). Whilst behaviour in each of these four tests was motivated by different stimulus outcomes and required different forms and degrees of effort to attain that outcome, each was based on operant learning. In contrast, the fifth test was auditory CS-footshock fear conditioning, based on stimulus-outcome (Pavlovian) learning (Table 1). The behavioural effects of 6-OHDA depletion of NAcc DA were investigated in each of these tests. In addition, because 6-OHDA infusion onto NAcc also resulted in DA depletion in PFC, and given the importance of PFC in regulating cognitive aspects of goal-directed behaviour, effects of 6-OHDA infusion onto PFC were also studied directly for specific tests. This was the case for the LNR test where re-learning operant stimulus valence was required, and for the LH test because the PFC is critical to processing stimulus control and loss thereof (Amat et al., 2008). To our knowledge, this is the first study of the effects of NAcc DA depletion in the PRS and CS fear conditioning tests