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Pharmacological inactivation of the prelimbic cortex emulates compulsive reward seeking in rats

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ABSTRACT

Drug addiction is a chronic, relapsing brain disorder characterized by compulsive drug use. Contemporary addiction theories state that loss of control over drug use is mediated by a combination of several processes, including a transition from goal-directed to habitual forms of drug seeking and taking, and a breakdown of the prefrontally-mediated cognitive control over drug intake. In recent years, substantial progress has been made in the modelling of loss of control over drug use in animal models, but the neural substrates of compulsive drug use remain largely unknown. On the basis of their involvement in goal-directed behaviour, value-based decision making, impulse control and drug seeking behaviour, we identified the prelimbic cortex (PrL) and orbitofrontal cortex (OFC) as candidate regions to be involved in compulsive drug seeking. Using a conditioned suppression model, we have previously shown that prolonged cocaine self-administration reduces the ability of a conditioned aversive stimulus to reduce drug seeking, which may reflect the unflagging pursuit of drugs in human addicts. Therefore, we tested the hypothesis that dysfunction of the PrL and OFC underlies loss of control over drug seeking behaviour, apparent as reduced conditioned suppression. Pharmacological inactivation of the PrL, using the GABA receptor agonists baclofen and muscimol, reduced conditioned suppression of cocaine and sucrose seeking in animals with limited self-administration experience. Inactivation of the OFC did not influence conditioned suppression, however. These data indicate that reduced neural activity in the PrL promotes persistent seeking behaviour, which may underlie compulsive aspects of drug use in addiction.

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1. Introduction

Drug addiction is a chronic relapsing brain disorder, characterized by persistent drug-directed behaviour even with explicit knowledge of its negative consequences (American Psychiatric Association, 2000, 2013; Leshner, 1997; O'Brien and McLellan, 1996; Volkow and Li, 2004). Addiction is an enormous public health problem with major socio-economic and legal consequences. Indeed, drug addiction has been calculated to account for more than 40% of the financial cost to society of all major neuropsychiatric disorders (Uhl and Grow, 2004). However, despite its high prevalence and costs to society, treatment options for addiction are limited in number and efficacy (Koob et al., 2009; O'Brien, 2008; Pierce et al., 2012; van den Brink, 2012) and only a minority of addicts receives any form of treatment. Since loss of control over drug use is considered to be a core feature of addiction, understanding its neural underpinnings may greatly aid the development of innovative treatments for this disorder.

Contemporary addiction theories hypothesize that loss of control over drug use is mediated by a combination of several processes, including a transition from goal-directed to habitual use, and breakdown of the cognitive control over drug intake mediated by the prefrontal cortex (PFC) (Jentsch and Taylor, 1999; Everitt and Robbins, 2005; Koob and Volkow, 2010; Pierce and Vanderschuren, 2010; Goldstein and Volkow, 2011). In order to test these hypotheses, we and others have developed animal models that explicitly capture compulsive aspects of addictive behaviour, in the form of insensitivity to adversity after prolonged drug taking experience (Deroche-Gamonet et al., 2004; Dickinson et al., 2002; Hopf et al., 2010; Lesscher et al., 2010; Pelloux et al., 2007; Vanderschuren and Everitt, 2004; Wolffgramm, 1991, for reviews see Hopf and Lesscher, 2014; Lesscher and Vanderschuren, 2012; Vanderschuren and Ahmed, 2013). Although important progress has been made in our understanding of the neural mechanisms underlying loss of control over drug seeking and taking in recent years (Chen et al., 2013; Corbit et al., 2012; Jonkman et al., 2012; Kasanetz et al., 2010, 2013; Lesscher et al., 2012; Seif et al., 2013; Zapata et al., 2010), we are only beginning to understand how compulsive aspects of addiction occur in the brain.

In the present study, we tested the involvement of two PFC subregions, i.e. the prelimbic cortex (PrL) and the orbitofrontal cortex (OFC) in compulsive cocaine and sucrose seeking in rats. We chose to investigate these regions, because of their possible involvement in cognitive control processes that may serve to limit drug use. Thus, the PrL has been implicated in response inhibition (Chudasama and Muir, 2001; Bari et al., 2011), and lesions of the PrL have been shown to facilitate the development of rigid stimulus-response habits (Killcross and Coutureau, 2003), that have been hypothesised to contribute to the development of compulsive drug seeking (Everitt and Robbins, 2005; Pierce and Vanderschuren, 2010). In the context of addictive behaviour, an important role for PrL function has been demonstrated in the reinstatement of drug seeking (Martín-García et al., 2014; McLaughlin and See, 2003; Pelloux et al., 2013; Peters et al., 2008, for review see Bossert et al., 2013). Interestingly, using setups to study compulsive aspects of drug seeking, recent studies have revealed a role for the PrL in control over cocaine seeking (Chen et al., 2013; Kasanetz et al., 2013; Mihindou et al., 2013, but see Pelloux et al., 2013). The OFC has been ascribed an important role in value-based decision making (Schoenbaum et al., 2009), and in various aspects of impulse control (Chudasama et al., 2003; Eagle et al., 2008; Mar et al., 2011), processes which, if impaired, may contribute to compulsive aspects of drug use. Disrupting OFC function has been shown to reduce the influence of drug-associated cues on behaviour (Fuchs et al., 2004; Hutcheson and Everitt, 2003; Lasseter et al., 2009), and to disinhibit cocaine seeking and taking (Fuchs et al., 2004; Grakalic et al., 2010; Lasseter et al., 2009).

In order to investigate the involvement of the PrL and the OFC in compulsive seeking behaviour, we used a conditioned suppression setup, in which cocaine or sucrose seeking is reduced by presentation of a footshock-associated conditioned stimulus (CS) (Kearns et al., 2002; Vanderschuren and Everitt, 2004; Limpens et al., 2014). We have previously shown that the ability of conditioned aversive stimuli to suppress cocaine seeking is diminished after an extended cocaine self-administration history (Vanderschuren and Everitt, 2004; Limpens et al., 2014), which is thought to reflect the unflagging pursuit of drugs observed in human addicts (American Psychiatric Association, 2000, 2013; Volkow and Li, 2004). Thus, assuming that hypofunction of the PFC contributes to loss of control over drug use in addiction, we hypothesised that temporary, pharmacological inactivation of the PrL and the OFC would inhibit conditioned suppression in animals with limited self-administration experience.

2. Results

2.1. Histology

Infusion sites are presented in Fig. 1. Infusion sites in the OFC were within the lateral and ventrolateral subregions of the OFC.

2.2. Pharmacological inactivation of the PrL reduces conditioned suppression of sucrose and cocaine seeking

The effect of PrL inactivation on conditioned suppression of sucrose seeking is presented in Fig. 2A and B. There was a main effect on suppression ratio [$H(3)=12.6$, $p<0.05$]. Post-hoc analysis showed that the suppression ratio in the CS-shock-saline group was significantly higher than in the control-saline group [$U=4.5$, $p<0.05$]. Infusion of B&M into the PrL had no effect on suppression ratio in the control group (control-saline vs. control-B&M: [$U=6.5$, n.s.]). In the CS-shock group, however, B&M infusion reduced suppression ratio (CS-shock-B&M vs. CS-shock-saline [$U=2.0$, $p<0.05$]). Suppression ratio did not differ between the CS-shock-B&M group and the control-B&M [$U=12.5$, n.s.] (Fig. 2A). Although a visual impression of the seeking latency data yields a comparable pattern of effects as the suppression ratio data, there was no main effect on latency to first response [$H(3)=5.3$, n.s.]) (Fig. 2B). Fig. 2C and D shows the effect of inactivation of the PrL on conditioned suppression of cocaine seeking. There was a main effect on suppression ratio [$H(3)=10.4$, $p<0.05$]) (Fig. 2C). Post-hoc analysis revealed that, compared