Review

Targeting cocaine versus heroin memories: divergent roles within ventromedial prefrontal cortex

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In the search for novel treatments for addiction, most research has been propelled by the hope for a 'magic bullet' that would cure all forms of addiction. More recently, the field has started to appreciate the differences between psychostimulants versus opiates. Recent data suggest that the ventromedial prefrontal cortex (vmPFC) may fundamentally serve different roles in cocaine versus heroin addiction: acting as a neural OFF switch for cocaine seeking, but an ON switch for heroin seeking. We discuss the relevance of this distinction in relationship to three main functions of the vmPFC: (i) extinction memory, (ii) the suppression of impulsive behaviors, and (iii) the transition from goal-directed behaviors to habits. We highlight the importance of dopamine in modulating corticostriatal circuits for each of these functions. Finally, we conclude by discussing the implications for treatment strategies.

Neural basis of addiction

Addiction, regardless of the substance abused, is characterized by perpetual relapse and repeated failed attempts to maintain abstinence. This common denominator in addiction has propelled attempts at a unified theory of addiction and the subsequent search for a 'magic bullet' that might cure all forms of addiction [1]. However, basic science research has provided numerous examples of major differences in the underlying neurobiology of psychostimulant versus opiate addiction, as recently reviewed by Badiani and colleagues [1]. For the purpose of this review, we will focus on cocaine and heroin as the exemplary drugs of abuse from each of these drug classes. However, it is likely that the characteristics of each drug extend to other drugs of abuse within the same class that share a similar primary mechanism of action (e.g., dopamine transporter blockade for cocaine and other stimulants versus μ opioid receptor activation for heroin and other opiates).

Animal models have provided great insight into the neural basis of addiction (Box 1). Self-administration models, which allow the animal to regulate its own intake of drug, are considered highly advantageous over models where the drug is experimenter-administered [1,2]. Conditioned place preference (CPP) models, which fall into the latter category, can also model various phases of addiction (e.g., extinction, relapse) and are useful in assessing drug-cue memories in their simplest form [1,2]. In this review, we focus on data from self-administration studies, particularly those involving extinction prior to relapse; we refer to CPP studies only when they are especially relevant. Our discussion begins with studies that have used brain site-specific inactivation techniques to assess the role of the medial prefrontal cortex in these paradigms (Box 2).

Extinction and the ventromedial prefrontal OFF switch

The medial prefrontal cortex can be subdivided into dorsal and ventral components [3] (Figure 1). The dorsomedial prefrontal cortex (dmPFC) primarily includes the prelimbic cortex, and to a lesser extent the dorsal anterior cingulate cortex, whereas the ventromedial prefrontal cortex (vmPFC) includes infralimbic cortex and portions of the dorsopeduncular cortex. Optogenetic stimulation of vmPFC pyramidal neurons in naïve, anesthetized rats inhibits dmPFC pyramidal neurons, suggesting that the vmPFC is capable of functionally inhibiting the dmPFC [4]. Behavioral data support the notion that these subregions of medial prefrontal cortex function in opposition

Glossary

Amygdala: a temporal lobe brain region known for its role in recognizing cue associations with both rewarding and aversive consequences; a part of the limbic system critical for emotional regulation of fear.
Nucleus accumbens: a brain region located in the ventral striatum that is a hub of the limbic system, critical for the perception of reward and responsible for initiating or stopping movements related to internal drives.
Renewal: a form of relapse that occurs when animals are returned to the self-administration context, after extinction has been conducted in a different context. Discrete cues (e.g., tone and light) that were paired with drug infusions during self-administration are extinguished, and return to the self-administration context 'renews' responding for these discrete cues.

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Box 1. Animal models of addiction

Self-administration model

Rats are trained to perform an operant response (e.g., a lever press or nose poke) to receive an intravenous infusion of the drug. Usually, there is one 'active' operandum for drug delivery and one 'inactive' operandum that is used as a control for nonspecific changes in responding. The self-administration phase typically lasts a period of 10 days to 3 weeks, followed by an extinction phase where rats are returned to the operant chambers and allowed to respond, but the drug is no longer available. During this phase, rats learn to stop drug seeking in light of the change in expectancy; responding on the active operandum diminishes, or extinguishes, typically over a period of 1 to 3 weeks. Thereafter, a reinstatement of drug seeking (e.g., relapse) can be induced by presenting a non-extinguished (internal or external) cue that retains its predictive association with drug availability.

Conditioned place preference (CPP) model

Rats are confined to one chamber of a multi-chambered apparatus after administration of a non-contingent injection of the drug and to another chamber (with distinct contextual cues) after a saline injection. This conditioning process typically takes place over 1 to 5 days, as the rat learns to discriminate the contexts and their association with reward or no reward. Place preference for the rewarding context can be tested by allowing the rat free access to both chambers and measuring the amount of time spent in each. Extinction can be conducted either by repeated testing (allowing free access to both chambers) or by repeatedly confining the rat to the previously drug-paired chamber. Place preference can then be reinstated by administering another non-contingent injection of the drug and testing with free access to both chambers.

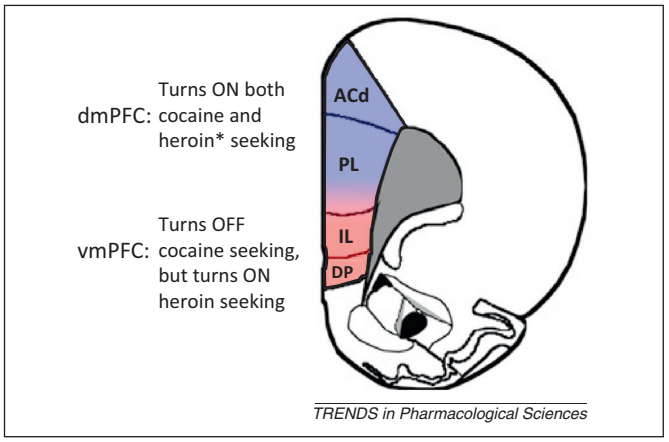

Figure 1. The OFF switch in the ventromedial prefrontal cortex (vmPFC) is converted to an ON switch for heroin seeking. Previous studies have indicated that a functional distinction can be drawn between the dorsomedial prefrontal cortex (dmPFC, blue) and the vmPFC (red). The dmPFC includes the prelimbic cortex (PL) and portions of the dorsal anterior cingulate cortex (ACd), whereas the vmPFC includes the infralimbic cortex (IL) and portions of the dorsopeduncular cortex (DP). Manipulations of these regions using pharmacological and optogenetic methods indicate that activity in the dmPFC promotes both cocaine and heroin seeking, whereas activity in the vmPFC produces opposing effects on these behaviors – namely, inhibiting cocaine seeking and promoting heroin seeking. Therefore, the OFF switch function normally served by the vmPFC is converted to an ON switch for heroin seeking. *For certain forms of heroin seeking (e.g., renewal), activity in the dmPFC is not necessary; activity in the vmPFC is critical to turn heroin seeking ON.

to one another; for example, in studies on conditioned fear, the dmPFC promotes fear expression, whereas the vmPFC suppresses fear expression [3,5]. In these models, the vmPFC is recruited to the neural circuitry controlling fear expression as a result of extinction learning and memory [3,5]. Thus, a neural ON/OFF switch for fear exists within the dorsal/ventral subregions of the medial prefrontal cortex.

Cocaine seeking seems to rely on a similar ON/OFF switch in the medial prefrontal cortex (Figure 1; see Peters *et al.* [3] for a review). Whereas effects on fear expression are elicited by prefrontal projections to discrete amygdala (see Glossary) subregions, effects on cocaine seeking are controlled via divergent projection patterns to the nucleus accumbens (see Glossary), with the dmPFC preferentially targeting the core, and the vmPFC the shell, of the accumbens [3]. Indeed, the dorsal pathway from the dmPFC to the core has been dubbed a 'final common pathway' for relapse, because glutamate release from this pathway is important for initiating many forms of relapse for many different drugs of abuse, including both cocaine and heroin [6–8]. However, certain forms of heroin relapse additionally (or exclusively) rely on the vmPFC projection to the shell [9–11]. This stands in stark opposition to the role of this ventral projection in cocaine seeking, which promotes extinction, not relapse [12–14]. Thus, the neural OFF switch in the vmPFC appears to be converted to an ON switch for heroin seeking (Figure 1).

What could account for this switch in vmPFC function in heroin-seeking animals? Dopaminergic tone in the accumbens shell is capable of masking the inhibitory function of the vmPFC in cocaine-seeking animals [14]. Indeed, dopamine directly administered to the shell can induce cocaine seeking, and this effect overrides the upstream inhibitory signal from the vmPFC [14]. For the renewal of heroin seeking in particular, dopamine release in the shell, but not the core, of the accumbens seems to be critical [15]. This may account, at least in part, for the apparent lack of inhibitory function in the ventral pathway for this form

Box 2. Brain site-specific inactivation techniques

Pharmacological inactivation

The most commonly used method in this category involves microinjecting a cocktail of GABA-A receptor and GABA-B receptor agonists (e.g., muscimol + baclofen, respectively) in small volumes sufficient to inactivate neurons within the surrounding brain tissue for a period of 1 to 2 h. Lidocaine is sometimes used instead, but has a shorter effective duration. The microinjection is typically performed just prior to a relapse test, and if relapse is prevented, the targeted brain region is concluded to be an essential component of the neural circuitry controlling relapse. Alternatively, the microinjection can be performed prior to an additional extinction session. If the targeted brain region is an essential part of the neural circuitry controlling extinction, inactivation of the region will release this inhibition and effectively reinstate responding.

Optogenetic silencing and stimulation

More recently, optogenetic strategies have provided a more temporally precise form of neuronal silencing and stimulation. Neurons can be infected using a viral vector carrying a gene for a light-activated rhodopsin of choice, driven by a strong pan-neuronal promoter (e.g., synapsin), or a cell-type specific promoter for restricted expression in neuronal subtypes. Halorhodopsin (NpHR) and archeorhodopsion (ArchT) are used to achieve inhibition, whereas channel rhodopsin (ChR2) is used for activation of neurons. An optic fiber can be inserted through a chronically implanted guide cannula targeted to a specific brain region, and rhodopsins can be stimulated using a specific wavelength of light. In this manner, neurons can be turned on or off within milliseconds, allowing precise control over the timing of inhibition or stimulation.