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Review

Psychostimulants affect dopamine transmission through both dopamine transporter-dependent and independent mechanisms

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ABSTRACT

The precise mechanisms by which cocaine and amphetamine-like psychostimulants exert their reinforcing effects are not yet fully defined. It is widely believed, however, that these drugs produce their effects by enhancing dopamine neurotransmission in the brain, especially in limbic areas such as the nucleus accumbens, by inducing dopamine transporter-mediated reverse transport and/or blocking dopamine reuptake though the dopamine transporter. Here, we present the evidence that aside from dopamine transporter, non-dopamine transporter-mediated mechanisms also participate in psychostimulant-induced dopamine release and contribute to the behavioral effects of these drugs, such as locomotor activation and reward. Accordingly, psychostimulants could increase norepinephrine release in the prefrontal cortex, the latter then alters the firing pattern of dopamine neurons resulting in changes in action potential-dependent dopamine release. These alterations would further affect the temporal pattern of dopamine release in the nucleus accumbens, thereby modifying information processing in that area. Hence, a synaptic input to a nucleus accumbens neuron may be enhanced or inhibited by dopamine depending on its temporal relationship to dopamine release. Specific temporal patterns of dopamine release may also be required for certain forms of synaptic plasticity in the nucleus accumbens. Together, these effects induced by psychostimulants, mediated through a non-dopamine transporter-mediated mechanism involving norepinephrine and the prefrontal cortex, may also contribute importantly to the reinforcing properties of these drugs.

Contents

1. Introduction

Cocaine, and amphetamine-like psychostimulants, including methamphetamine and methylphenidate, modulate arousal and produce behavioral activation and reinforcing actions that are associated with significant abuse potential (dela Peña et al., 2010,

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2011, 2013a, 2013b; Heal et al., 2013; Kalivas, 2007; Wood et al., 2013). After the intake of a stimulant drug, temporally limited functional changes in the brain occur, which are believed to endure beyond the presence in the brain of the actual drug or metabolites in the brain (Ungless et al., 2001). Identifying the initial functional changes wrought by psychostimulants is critical in understanding further the corresponding homeostatic responses that are responsible for behavioral and subjective effects of the drug intake that outlast the presence of the drug in the brain (Koob and Le Moal, 1997; Müller et al., 2007). While previous studies have provided strong evidence that dopamine plays a key role in the reinforcing effects of psychostimulants, the precise mechanisms by which psychostimulants alter dopamine-mediated transmission remain to be fully defined. Understanding these processes will not only help explain the complex mechanism of psychostimulant addiction but also aid in the discovery of effective therapies to counteract addiction to these drugs.

2. Role of dopamine in the effects of psychostimulants

Many lines of evidence suggest that dopamine plays a central role in the above-mentioned effects of psychostimulants (for reviews see Nutt et al. (2015) and Wise (2004, 2008)). In humans, for example, blockade of dopamine receptors decreased the euphoria produced by intravenous amphetamine injection (Gunne et al., 1972; Jönsson et al., 1971). In animals, dopamine receptor blockade also attenuated the reinforcing properties of amphetamine and cocaine (Davis and Smith, 1975; Yokel and Wise, 1975). Through microdialysis studies in animals, it has been observed that psychostimulants increased dopamine release in the nucleus accumbens (Di Chiara and Imperato, 1988), a critical site for the reinforcing effects of addictive drugs (Di Chiara et al., 2004; Koob, 1992). Further support on the importance of dopamine in psychostimulant reinforcement has been provided by findings from imaging studies which revealed that administration of psychostimulants such as methylphenidate, cocaine and amphetamine increased brain dopamine levels (Volkow et al., 1999, 2007). Together, these studies implicate the role of dopamine in the behavioral and reinforcing effects of psychostimulants and that psychostimulants produce their effects by enhancing dopamine transmission in the brain, especially in limbic areas such as the nucleus accumbens (Carboni et al., 1989; Cass et al., 1992; Ikemoto, 2002, 2007; Kuczenski and Segal, 1992; Wu et al., 2001).

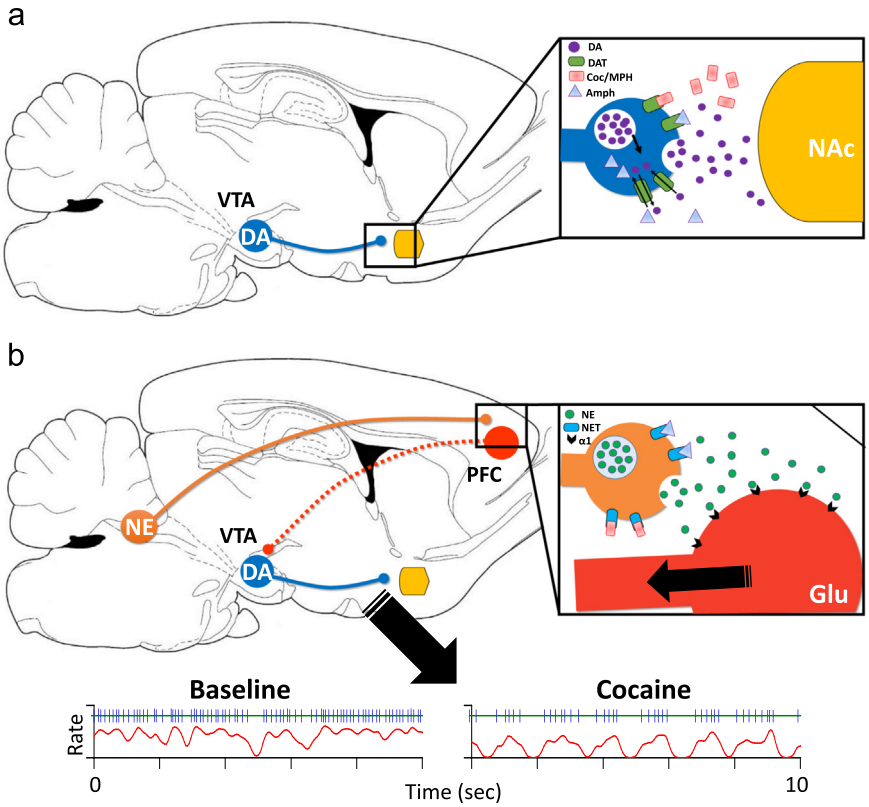

Fig. 1. Psychostimulants affect dopamine transmission through both dopamine transporter (DAT)-dependent and independent mechanisms. The reinforcing effects of psychostimulants have long been associated with the ability of these drugs to increase dopamine (DA) levels in the brain, especially in limbic areas such as the nucleus accumbens (NAc). (a) The widely-accepted theory of psychostimulant-induced dopamine increase involves binding of stimulant drugs to the dopamine transporter to inhibit dopamine reuptake (e.g. cocaine [Coc] and methylphenidate [MPH]), and/or to induce reverse transport of dopamine via the dopamine transporter (e.g. amphetamine [Amph]). (b) Some evidence, however, suggests non-dopamine transporter-mediated mechanisms of dopamine release induced by psychostimulants, one of which, as proposed in this review, involves norepinephrine transporters (NET) in the prefrontal cortex (PFC). Accordingly, psychostimulants bind to norepinephrine transporters in the prefrontal cortex, causing enhancement of norepinephrine levels in the prefrontal cortex and subsequent activation of alpha-1 adrenergic receptors. This effect may lead to activation of input derived directly or indirectly from the prefrontal cortex to dopamine neurons, resulting in changes in firing pattern of dopamine neurons in the ventral tegmental area (VTA), which then alters action potential-dependent dopamine release. Shown below b is an example of recordings from a dopamine neuron before and after cocaine injection. The blue and red traces are spike trains and smoothed rate histograms, respectively. As illustrated, cocaine significantly increased the slow oscillatory firing resembling repetitive bursting (for details see Zhou et al. (2006)). As described in the text, this change in firing pattern induced psychostimulants would lead to alterations in not only the amount, but also the temporal pattern of dopamine release. Specific temporal pattern of dopamine release may be required for certain forms of synaptic plasticity in the nucleus accumbens and may facilitate or inhibit a synaptic input to nucleus accumbens neurons depending on the timing of the input relative to dopamine release. Furthermore, evidence discussed in this paper suggests that the non-dopamine transporter-mediated mechanism involving norepinephrine and the prefrontal cortex is critical in mediating some of the behavioral effects of psychostimulants such as locomotor activation and reward. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)