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Review

Cognitive enhancers versus addictive psychostimulants: The good and bad side of dopamine on prefrontal cortical circuits

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ABSTRACT

In this review we describe how highly addictive psychostimulants such as cocaine and methamphetamine actions might underlie hypoexcitabilty in frontal cortical areas observed in clinical and preclinical models of psychostimulant abuse. We discuss new mechanisms that describe how increments on synaptic dopamine release are linked to reduce calcium influx in both pre and postsynaptic compartments on medial PFC networks, therefore modulating synaptic integration and information. Sustained DA neuromodulation by addictive psychostimulants can "lock" frontal cortical networks in deficient states. On the other hand, other psychostimulants such as modafinil and methylphenidate are considered pharmacological neuroenhancement agents that are popular among healthy people seeking neuroenhancement. More clinical and preclinical research is needed to further clarify mechanisms of actions and physiological effects of cognitive enhancers which show an opposite pattern compared to chronic effect of addictive psychostimulants: they appear to increase cortical excitability. In conclusion, studies summarized here suggest that there is frontal cortex hypoactivity and deficient inhibitory control in drug-addicted individuals. Thus, additional research on physiological effects of cognitive enhancers like modafinil and methylphenidate seems necessary in order to expand current knowledge on mechanisms behind their therapeutic role in the treatment of addiction and other neuropsychiatric disorders.

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Abbreviations: 5-HT, 5-hydroxytryptamine; AC, adenylyl cyclase; ADHD, attention deficit hyperactivity disorder; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; cAMP, 3′,5′-cyclic adenosine monophosphate; DA, dopamine; DAT, dopamine transporter; dlPFC, dorsolateral prefrontal cortex; EPSCs, excitatory postsynaptic currents; ERK, extracellular signal-regulated kinases; GABA, gamma-aminobutyric acid; GPCRs, G protein-coupled receptors; HCN (I_H), hyperpolarization-activated cyclic nucleotide-gated channels; mEPSC, miniature excitatory postsynaptic currents; mPFC, medial prefrontal cortex; MPH, methylphenidate; NAc, nucleus accumbens; NET, noradrenaline transporter; NMDA, *N*-methyl-D-aspartate; PFC, prefrontal cortex; PKA, protein kinase A; PKC, protein kinase C; SERT, serotonin transporter; TH, tyrosine hydroxylase; VGCC, voltage-gated calcium channels.

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1. Introduction

Psychostimulant use is associated with diverse behavioral and cognitive effects, both beneficial and harmful. Indeed, some of these drugs, i.e., modafinil and methylphenidate, are considered pharmacological neuroenhancement agents that are popular among healthy people seeking neuroenhancement [1]. Main reasons for psychostimulant consumption without a specific medical purpose include improving concentration, focusing for a specific task or counteracting sleep deficit [2]. It has been suggested that these compounds share the ability to improve behavior and cognition by targeting online cognitive processes, such as attention and executive function, offline processes, such as memory consolidation, or a combination of functions [3]. The prefrontal cortex (PFC) plays critical roles in executive functions and has the ability to exert control on other cortical and subcortical brain areas. For example, motivationally-driven behavior, including value attribution depends on the PFC integrity [4]. Thus, cognitive enhancers-mediated changes in frontal cortical excitability might underlie improvements in cognitive tasks.

Still, psychostimulants are a class of drugs that are also well known for their highly addictive profile. Patients suffering from substance use disorders show evidence of PFC activation after drug intake or presentation of drug-related cues that is substituted by profound PFC hypo-activity during exposure to emotional challenges or withdrawal states [5]. PFC roles closely related to drug dependence include self-control and self-awareness, arousal driven by motivation and salience attribution.

The available evidence strongly indicates that the cognition enhancing and/or therapeutic actions of psychostimulants implicate dopaminergic neurotransmission in the PFC. Therefore, in this review we will discuss normal physiological roles of DA in the PFC and possible altered synaptic mechanisms behind profound PFC alterations induced by addictive psychostimulants. Moreover, we will discuss evidence that suggest that differential modulation of cellular components of frontal circuits may contribute to define pro-cognitive or harmful effects of psychostimulants.

2. Cognitive enhancers: modafinil and methylphenidate

2.1. Mechanisms of action

Modafinil is approved for the medical management of narcolepsy. Currently, is commonly used as a wake-promoting drug to counteract excessive daytime sleepiness. In the USA modafinil is a Schedule 4 Controlled Drug (C-IV), but in other countries is not classified as a controlled substance [7]. Modafinil has a multifaceted pharmacological profile that is very different from those of the catecholaminergic stimulants like amphetamine or methylphenidate. Modafinil acts as a weak DA transporter (DAT) inhibitor [8] but has no affinity for the noradrenaline transporter (NET) or 5-hydroxytryptamine transporter (SERT) [9]. Modafinil influences GABAergic, glutamatergic, noradrenergic, histaminergic, and orexinergic systems [8,10]. Interestingly, Urbano et al. [11] described that modafinil has the ability to increase electrotonic coupling among cortical neurons via of gap junctions [11]. Our laboratory also has reported neuroprotective properties of modafinil against methamphetamine-induced brain toxicity [12,13]. Modafinil prevented methamphetamine-induced striatal toxic effects including DA depletion and reductions in tyrosine hydroxylase (TH) and DAT levels [12]. In addition, modafinil also decreased methamphetamine-induced hyperthermia, activation of astroglia and microglia, and pro-apoptotic proteins expression in the mice striatum [13]. Additionally, modafinil is been used *off label* to treat several diseases such as depression, fatigue, cocaine and nicotine addiction, schizophrenia, attention deficit disorder, bipolar depression and seasonal affective disorder [6].

Positive symptoms of schizophrenia are often adequately treated using antipsychotic medication but a significant subpopulation of patients show persistent negative symptoms that can be impairing and long lasting [14]. Negative symptoms have been found to be associated with deficits in prefrontal cortex functions [15]. Interestingly, modafinil treatment was associated with a significant reduction in negative symptom ratings without improving or worsening positive symptoms or psychopathology ratings in acute ill schizophrenic patients [16]. Thus, used as adjuvants, DA agonists like modafinil, may improve negative symptoms in patients that are stable and under antipsychotic treatment [14].

Methylphenidate (MPH) is a psychostimulant approved for the pharmacological treatment of medical conditions such as narcolepsy and attention deficit hyperactivity disorder (ADHD). Psychostimulants (MPH and dexamphetamine) are first choice medications for ADHD in children and adults [17]. Current research indicated that some cases of ADHD continues into adulthood [18] where it is linked with various psychosocial impairments [19]. The expression of ADHD in adults is to some extent different from that in children and the diagnostic descriptions of some of the features need to be adapted to adults [20]. This feature of adult ADHD might be one factor behind existing controversy on MPH prescription for adults across Europe [20].

MPH is a controlled substance since is also well recognized to have some potential for abuse and dependence [17]. Methylphenidate mechanism of action involves inhibition of DA and norepinephrine reuptake, with little effect on the SERT [21]. Also, it has been reported that MPH has the ability to bind to muscarinic and serotonin receptors [22]. Similarly to neuroprotective effects observed with modafinil, MPH also showed neuroprotective properties against methamphetamine-induced neurotoxicity in rats [23,24].

2.2. Abuse potential of cognitive enhancers

Several studies have suggested that differences between psychostimulant-mediated performance enhancement and dependence are highly contingent on doses and method of administration [25,26]. High doses and rapid routes of administration seem crucial to the progress of abuse, probably due to associative learning between drug pharmacokinetic and pharmacodynamics profiles and drug-induced sensations. In healthy subjects a common abuse feature of modafinil is academic doping, similar to what is reported for MPH [17].