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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.

Contents

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].

Patients who are prescribed stimulants may abuse those stimulants as well. A study surveying ADHD patients reported that 14.3% of respondents had abused prescription psychostimulants [27]. Also, a recent study by Frauger et al. [28] reported an increment in MPH drug prescription and deviant use: individuals with drug dependence consumed MPH daily by intravenous route and reported amphetamine-like effects (cardiovascular events, weight loss, psychiatric adverse events). However, it also needs to be mentioned that a recent a recent meta-analysis based on a large number of studies suggested no increased or reduced risk of stimulant treatment in adult ADHD patients that received stimulant treatment in childhood [29]. Additionally, it has been reported that children with ADHD are at increased risk of substance abuse in adulthood and suggested that females with ADHD might be a greater risk of substance abuse compared to males with ADHD [30]. Similarly, patients with a childhood ADHD diagnose that persisted into early young adulthood showed increased chance of alcohol and marijuana use in adulthood years compared to the normal controls and to patients with ADHD treated with pharmacotherapy in childhood years [31].

On the other hand, modafinil has an interesting profile since very low abuse potential has been reported [6]. Nonetheless, it needs to be mentioned that modafinil produced dose-dependent reports of "being high" in polydrug users [32] and increased cocaine-responses in individuals subjected to training to discriminate cocaine from placebo [33]. Importantly, it is worth mentioning that with more extended testing, added benefits are being associated with modafinil use suggesting that this compound can be considered a well validated 'noo-tropic' agent [3].

Future studies are sorely needed to better understand benefit/risk ratios of psychostimulant treatment for children and adults.

3. Addictive psychostimulants: cocaine and methamphetamine

Drug addiction is considered a chronic disease of the brain that persists over time despite adverse consequences and is recognized as a serious public health problem worldwide [34]. Social environment, access to drugs, genetic factors, and psychiatric comorbidities are key factors that closely impact the development of addiction [34]. Substance use is characterized by abnormal motivational states and reward-related behaviors that depend on cortico-striatal-limbic networks. In addition, abuse of illicit drug is accompanied by different degrees of neuropsychological impairments that appear to be secondary to physiological and structural changes in cortical and subcortical regions of the brain [35]. We will discuss features of cocaine and methamphetamine, two very addictive drugs that share to some extent mechanisms of actions with legal drugs considered cognitive enhancers. Indeed, pro-cognitive as well as addictive psychostimulants alters the functionality of the dopamine transporter and would ultimately increase dopamine volume transmission in the synaptic cleft [36].

3.1. Mechanisms of action

Cocaine extends the activity of DA, noradrenaline and serotonin in synapses by blocking the presynaptic reuptake for these neurotransmitters, thus cocaine is considered a blocker for the dopamine transporter (DAT), the noradrenaline transporter (NET) and the serotonin transporter (SERT) [37,38]. Dopaminergic mechanisms are closely associated to the development of cocaine addiction but there is also evidence that indicates a role for serotonergic networks in drug addicted states. For example, it was shown that withdrawal from cocaine administration increases head-shake behavior by 5-HT2A receptor dependent mechanisms [39,40] and locomotion [41]. Moreover, 5-HT2A receptor antagonists attenuated cocaine-induced reinstatement of cocaine-seeking behavior [42]. Also, Huang et al. [43] showed that withdrawal from repeated cocaine administration decreased 5-HT2A receptor-mediated serotonergic facilitation of spontaneous EPSCs in the mPFC and this effect is likely mediated by the enhanced 5-HT2A receptor activation in response to repeated cocaine treatment [43]. Accordingly, our group has previously reported that cocaine (administered in a "binge"-like protocol in mice) increased disinhibition of ventrobasal-thalamic GABAergic neurotransmission; while MPH treated mice did not show such changes [44]. Given the fact that a significant difference between cocaine and MPH in terms of their mechanisms of actions involved SERT function (cocaine blocks SERT but MPH has little effect on SERT), we suggested that differences observed between these psychostimulants could be associated with cocaine-mediated effects on serotonergic systems. In a recent work we provided evidence that serotonin receptors (5-HT1A and 5-HT2A) at presynaptic thalamic reticular neurons are regulated by cocaine administration [45]. Therefore, our results suggest that serotonin can modulate GABA release and that this effect can be altered by cocaine. Those mechanisms might underlie abnormal thalamo-cortical interactions described in clinical and preclinical models of cocaine intake.

Methamphetamine enters synaptic terminals of DA neurons through the DAT and via passive diffusion. In the cell, it accumulates in vesicles and by disrupting the pH gradient required for vesicular DA sequestration methamphetamine can increase DA content in the cytoplasm [46]. Methamphetamine causes release of monoamines from the neuronal cytosol via plasmalemmal uptake transporters, particularly the DA transporter (DAT), the norepinephrine transporter (NET), and the serotonin (5-HT) transporter (SERT) through reverse transport [47]. Also, methamphetamine acts through the vesicular monoamine transporter 2 to cause excessive release of dopamine into the cytoplasm followed by DA release into the synaptic cleft through the DAT [47]. Methamphetamine can cause toxicity in cortical and subcortical brain areas [35]. Similarly to data discussed above regarding serotonergic contribution on cocaine-mediated effects, we need to highlight the fact that methamphetamine can induce neurotoxic damage to 5-HT neurons [48]. In fact, it was demonstrated that methamphetamine can increase of 5-HT brain levels by a presynaptic mechanism that involve 5-HT release and the inhibition of 5-HT re-uptake by SERT [49].

4. Dopamine and motivational salience

Classic theories indicated that DA is the molecule that encodes reward [50]. New theories actually propose a broader role for DA release that is to signal new and motivationally relevant environmental events [4]. Therefore, when an organism faces novelty, whether it be a positive stimulus or a negative one such as a stressor, increased activity of DA cells in the VTA and in DA release in axon terminal fields in the PFC (Fig. 1), nucleus accumbens, and limbic structures are observed [51,52]. Of course, DA is also important for the motivation and reinforcement of actions. Drugs that interfere with DA transmission affect reinforcement learning, while manipulations that enhance DA transmission, such as brain stimulation and addictive drugs, might act as "reinforcers" [53,54]. Also, DA transmission is crucial for creating a motivational tone to seek rewards [55] and it is critical for causing goals to become "wanted" in the sense of motivating actions to achieve the desired goals [56]. This idea is supported by observations that most DA neurons are strongly activated by unexpected primary rewards such as food or water producing phasic "bursts" of activity [57] and phasic excitations including multiple spikes [57]. This is consistent with the fact that DA reward responses are accompanied by synchronous phasic

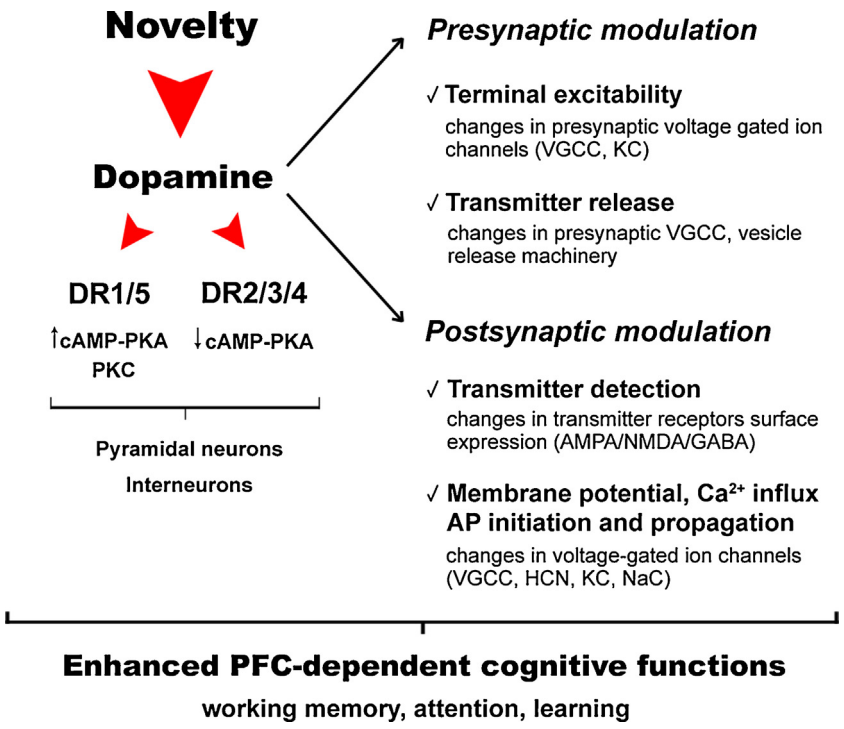

Fig. 1. Physiological roles of DA in the PFC. Upon a new stimulus, DA transmission is activated to enhance PFC-dependent cognitive functions. DA exerts its modulatory effects trough binding to DA receptors D1/5 and D2/3/4, which are expressed at presynaptic and postsynaptic sites in pyramidal neurons and interneurons. These two classes of DA receptors have opposite effects on cAMP-PKA activation, and D1/5 receptors can also activate PKC. DA presynaptic modulation can affect axon terminal excitability and transmitter release by modulating voltage gated ion channels and/or or vesicular release machinery. Postsynaptic DA receptors may influence transmitter detection by modulating the recruitment and membrane insertion of excitatory/inhibitory transmitter receptors such as glutamate AMPA/NMDA and GABA receptors. DA can also alter synaptic integration and neuronal excitability by modulating voltage gated ion channels that control resting potential, Ca^{2+} influx, and action potential (AP) initiation and propagation. VGCC—voltage gated Ca^{2+} channels; HCN—hyperpolarization-activated cyclic nucleotide-gated channels; KC—K^+ channels; NaC—Na^+ channels.

bursts, a response pattern that shapes DA release in target structures [57]. Phasic bursts, in turn, influence learning and motivation in manner distinct from tonic DA activity [57,58]. Additionally, rewarding and aversive events trigger changes in behavioral and cognitive processing aimed to engage in fitted decision-making, (see Refs. [4,51]). DA neurons are proposed to transmit their signals to distinct brain structures in order to support distinct neural systems for motivated cognition and behaviors.

4.1. DA as a synaptic neuromodulator

It is well known that DA is a neuromodulator that cannot be classified neither as an excitatory nor an inhibitory neurotransmitter. DA can mediate either potentiation or attenuate evoked transmitter release [59]. Most of postsynaptic DA receptors are located in areas far from dopaminergic presynaptic varicosities, and extrasynaptic volume dopaminergic transmission is widespread in nuclei innervated by DA [60,61]. DA can modulate ion channels (mediating Ca^{2+} influx, action potential waveforms, etc.), thus altering probability of transmitter release and synaptic integration (reviewed in Ref. [62]). Through activation of G protein-coupled receptors (GPCRs), DA exerts presynaptic and postsynaptic modulation to enhance PFC-dependent cognitive functions, by affecting the biochemical and electrical states of pyramidal cells and interneurons via a group of signaling elements including kinases, phosphatases, transcription factors, voltage-gated ion channels and membrane transmitter receptors (reviewed in Ref. [63]) (Fig. 1).

There are two classes of dopamine receptors (DRs), based on their structural, pharmacological, and biochemical properties: D1-like and D2-like (reviewed in Ref. [63]). The D1-like receptors (D1 and D5) couple to $G_{\alpha s/olf}$ family of G proteins and stimulate cAMP production by adenylyl cyclase (AC). Increased cAMP levels activate PKA, which mediates most of the effects of D1/D5Rs by phosphorylation and regulation of ionotropic glutamate and GABA receptors, voltage-gated channels (Na^+, K^+ and Ca^{2+}) and different transcription factors. The D2-like DRs (D2, D3, and D4) couple to the $G_{\alpha i/o}$, which inhibit cAMP production and inhibit AC, thereby limiting PKA activation (Fig. 1).

D1 like receptor agonists mediate the activation of $G_{\alpha q}$ proteins, triggering intracellular pathways involving phospholipase C and increasing PKC resulting on intracellular Ca^{2+} mobilization [64,65] (Fig. 1). Those intracellular pathways have been associated to both D5 activation [65,66] and to D1/D2 co-activation [67,68]. Both D2 and D3 receptors have been described to be present postsynaptically and presynaptically [69,70]. In PFC pyramidal neurons, D1/2-like are located on both pyramidal neurons and interneurons (distributed throughout layers II to VI), with a higher density in deep cortical layers [71]. The D1-like family are at least 20-fold more abundant in PFC than D2-like family receptors [72,73]. and are primarily expressed in pyramidal neurons, with a predominant subcellular localization in the spines of apical dendrites [74];D2/D4receptors are also found in a subpopulation of interneurons [75]. D5 receptors co-localize with D1 receptors in cortical pyramidal neurons, but they are found predominantly in shafts [74], which is a site where inhibitory GABAergic neurons contact [76]. This segregation of D1 and D5 subcellular localization suggests distinct excitatory and inhibitory functions mediated by these receptors. Importantly, D1-like receptors are also found in glutamatergic terminals, where DA acts as an inhibitor of presynaptic glutamate release [62,77,78]. At postsynaptic shafts and spines of

cortical pyramidal cells, D2-like receptors modulate both presynaptic and postsynaptic sites. At presynaptic terminals in the PFC, D2-like receptors are expressed in forebrain projecting dopaminergic as well as glutamatergic afferents. However, D4 receptors are expressed presynaptically in cortical and subcortical in GABAergic interneurons [79].

A large proportion of DRs are localized in dendritic spines (reviewed in Ref. [80]), where most of the excitatory glutamatergic synapses are formed. Dopaminergic and glutamatergic afferents are known to simultaneously innervate an important subpopulation of spines, forming the "synaptic triad" [80,81]. Such "triad-like" synaptic architecture would act as a coincidence detector, where overall DA synaptic modulation depends on the spatial and temporal summation on spines across the entire dendritic tree. Thus, neurons populated with different patterns of D1-, D2-, and D1/D2-containing triads could exhibit distinct cellular and synaptic properties. These receptors can modulate several postsynaptic mechanisms (e.g., spike dynamics, kinases and phosphatases intracellular pathways), establishing different activity states that would either strengthen or weaken synaptic activity [80,82].

4.2. DA modulation of glutamatergic neurotransmission

Glutamate NMDA, AMPA and/or metabotropic are key elements of synaptic plasticity and their functional interaction with DA receptors can play facilitating or permissive roles. D1-like receptors also regulate fast excitatory synaptic transmission. In vitro, acute administration D1/5 receptor agonists delayed onset and prolonged enhancement of NMDA- and AMPA-mediated excitatory postsynaptic currents (EPSC) in PFC pyramidal neurons [83,84]. It was also shown that D1 activation facilitates the strengthening of excitatory synapses by increasing AMPA and NMDA subunits trafficking to the membrane of PFC neurons [85,86]. Increased surface expression of AMPA receptors after D1 stimulation occurred through a PKA-dependent mechanism, by increasing their rate of externalization at extrasynaptic sites, and they translocated into synapses by subsequent NMDA receptor activation [85]. Concomitantly, D2 stimulation decreased surface and synaptic AMPA expression. Abnormal engagement of this mechanism during unregulated DA release may account for maladaptive plasticity after repeated exposure to cocaine or amphetamine [85]. In deep layer PFC synapses, D1/5 agonists facilitates, whereas antagonists impair NMDA-dependent long-term potentiation via cAMP-dependent mechanisms [87,88]. Moreover, a positive feedback loop was found between NMDA and D1 receptors, where D1 activation potentiates NMDA, and NMDA receptor activation enhances D1 receptor recruitment to the plasma membrane [89]. This positive feedback loop, if not controlled, might result in concomitant overactivation of both the D1 and the NMDA systems, perhaps triggering NMDA- and D1-dependent neurotoxicity and cell death [90,91].

4.3. DA effects on voltage-gated ion channels

Another mechanism through which DA can change neuronal excitability in PFC neurons, and elsewhere, is via direct modulation of Ca^{2+} currents. Expression of several voltage-gated calcium channels (VGCC) subtypes has been reported on basal and apical compartments of cortical pyramids: high voltage-activated L-, N-, P/Q- and R-type, and low voltage-activated T-type. High voltage-activated channels are functionally implicated in the control of neurotransmitter release throughout their capacity to modulate intracellular Ca^{2+} transients [92], which is known to trigger several intracellular pathways and biochemical events that influence neuronal excitability and gene transcription [93]. Many evidences indicate that the primary effect of D1-like receptor activation in PFC neurons is a temporary inhibition of dendritic VGCC, suppressing Ca^{2+} spikes transients amplitude [94,95]. It is well established that GPCRs regulate neurotransmitter release through voltage-dependent inhibition of presynaptic P/Q and N-type VGCC, and the mechanism involves direct binding of G-protein $\beta\gamma$ dimer to the $\alpha 1$ subunit of these channels (reviewed in Refs. [96,97]). Thus DA can interfere with Ca^{2+} influx via a direct G-protein interaction between the D1 receptor and VGCC [95,97]. GPCRs can also recruit several other distinct mechanisms including phosphorylation, lipid signaling pathways, and channel trafficking that result in voltage-independent inhibition. In this sense, it was described that D1 in medial PFC forms a signaling complex with N-type VGCC that in basal conditions enhanced its membrane expression and after D1-agonist administration potently inhibited the channel activity and removed it from the membrane [95]. Also, D1 was reported to inhibit Ca^{2+} influx via PKC [94,98]. The functional consequence of DA-induced Ca^{2+} influx inhibition would be to constrain dendritic Ca^{2+} spikes and sharpen incoming signals, increasing the signal-to-noise ratio [99,100], see Fig. 2. It was proposed that while performing a PFC-dependent task, moderate levels of D1 stimulation would enhance spatial tuning by sculpting away noise, reducing neuronal firing for non-preferred directions, while higher levels of D1 stimulation erode all task-related firing leading to working memory impairment [52,101].

Another conductance modulated by DA is the hyperpolarization-activated cation current or I_H, which is a mixed cation current activated by cAMP that is involved in the control of the resting membrane potential and neuronal rhythmic activity and neurotransmission (reviewed in Ref. [102]). I_H influx through hyperpolarization-activated cyclic nucleotide-gated channels (HCN) depolarizes the membrane potential increasing the number of inactivated VGCC at resting membrane potential, thus contributing to Ca^{2+} influx inhibition and the constrain of distal dendritic Ca^{2+} spikes. Previous research has shown that cAMP reduces PFC neuronal firing by increasing the open state of HCN channels on dendritic spines [103]. In cerebral cortex, HCN1 and HCN2 subunits form heterotetramers that are particularly responsive to cAMP [104–106] and associate with cAMP-regulating proteins in spines. HCN2 the most abundant in the mesocorticolimbic structures [107], and HCN1 is highly distributed in distal apical-dendritic compartments of medial PFC pyramids [108,109], where its activation prevents initiation of distal Ca^{2+} spikes [110]. It was shown that Ih increases with DA stimulation or D1/5 activation in the PFC [42,100,111]. Moreover, it was found that D1 colocalizes with HCN channels near excitatory-like synapses on dendritic spines in PFC, and D1-mediated increases in I_H suppress PFC network firing during a working memory task [42]. Increased I_H signaling was found in conditions characterized by increased DA tone and impaired PFC functions, like stress and schizophrenia [52,112]. As I_H elevation seems to be detrimental for cortical integrity and cognition, while I_H inhibition in PFC by HCN channel blockade or HCN1 channel knockdown improves cognitive performance [52,103,113]. I_H reduction would result in significant enhancement of local recurrent network activity in cortical networks, presumably through enhanced effectiveness of dendritic synaptic potentials to initiate action potential activity [103,113,114], see Fig. 1.

In PFC pyramidal neurons, DA can also influence action potential initiation, amplitude and propagation by modulation of persistent Na^+ and K^+ currents, influencing neuronal excitability [115]. D1 activation blocks both inward-rectifying and delayed-rectifying K^+ channels (KC), which are known to mediate transitions to up states [99,116–118]. In addition, D1 receptor activation can also prevent the activation of voltage-sensitive Na^+ currents [119,120]. Some of these effects are consistent with previously reported PKA/PKC-

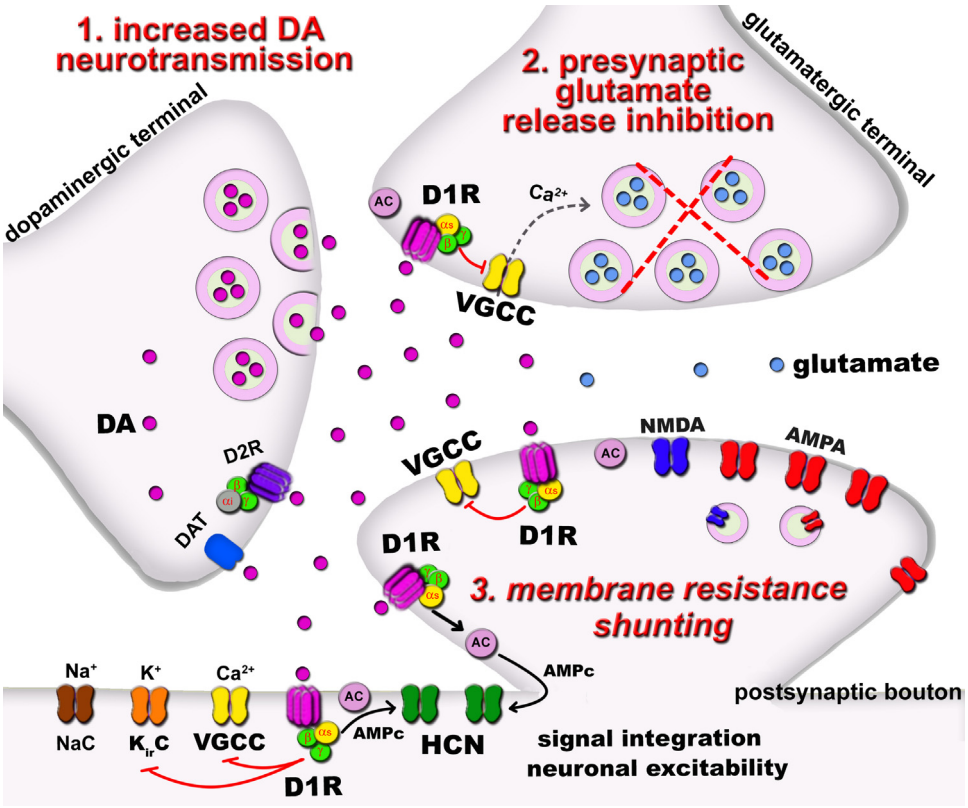

Fig. 2. Schematic representation of a PFC "synaptic triad" under supra-optimal levels of DA stimulation. (1) Increased DA neurotransmission: addictive psychostimulants cause supra-physiological increases in DA volume transmission from dopaminergic terminals. (2) Presynaptic glutamate release inhibition: DA binds to presynaptic D1-like receptors (D1R) located in neighboring glutamatergic terminals, inhibiting Ca^{2+} entry through voltage-gated calcium channels (VGCC) (dashed line) involved in vesicle fusion and neurotransmitter release, thereby diminishing glutamate release probability and AMPA/NMDA postsynaptic activation. (3) Membrane resistance shunting: DA will also bind to post-synaptic D1R, leading to increased G-protein βγ dimer inhibition of VGCC (red lines). D1 supra-activation will also increase adenylyl cyclase (AC) cAMP production and hyperpolarization-activated cyclic nucleotide-gated channels (HCN) activation, causing hyperpolarization-activated cation current (I_H) influx and lowering the resting membrane potential, further inhibiting VGCC activation. DA also affects neuronal excitability by inhibiting K^+ inward-rectifying ($K_{ir}C$) and Na^+ (NaC) channels, influencing action potential initiation, amplitude, and active propagation along dendrites. The membrane resistance shunting will affect neuronal excitability and dampen dendritic integration.

dependent modulation of Na^+ currents [121]. D1-like receptors can also mediate those effects in PFC neurons [121].

4.4. Inverted U shaped effects of dopamine receptor 1 in PFC physiology

D1/5 receptors enhance signal-to-noise gain following an inverted-U dose-response curve to DA [101,122]. Changes in extracellular DA levels ought to reach optimal concentrations to mediate efficient physiological signaling and performance. Indeed, preclinical and clinical studies showed a direct relationship between prefrontal DA activity and working memory, suggesting that low or excessive D1 activation in PFC might result in cognitive deficits (reviewed in Refs. [122,123]). It has been previously suggested that stimulants at low doses modifies arousal, attention and improves cognition while moderate to high doses can lead to euphoria, cognitive impairment and psychotic episodes [17]. Optimal cognitive performance can be achieved with a moderate amount of monoamines, while high levels might induced decreases in performance [124].

Too little D1 receptor activation (i.e., mediated by D1 antagonists) would not facilitate functional glutamatergic afferents to PFC. However, if DA levels rise beyond optimal range, like concentration achieved using iontophoresis application of D1 agonists, stress or acute amphetamine administration, then over activation of presynaptic D1 receptors would impair working memory [122,123]. Also, an inverted U-shaped relationship between D1 receptors and dendritic retraction has been described for mPFC networks [125].

Fig. 2 illustrates potential mechanisms underlying psychostimulant-induced PFC impairment characterized by: (1) increased levels of DA transmission that would over-activate D1-like receptors, (2) increased cAMP-PKA signaling pathways might thus inhibit pre- and post-synaptic VGCC. Pre-synaptic glutamatergic VGCC blockade by D1 receptor activation would then lead to less Ca^{2+} entry and glutamate release [77,78,83,126]. Also, post-synaptic cAMP-mediated enhancements can dampen Ca^{2+} transients throughout massive opening of HCN, reducing membrane input resistance. In addition to their effects on G protein-regulated pathways, DRs can alter membrane trafficking of VGCC as well as AMPA and NMDA receptors through direct protein-protein interactions or downstream signaling pathways activation [77,85,95], changing signal integration and neuronal excitability.

5. Psychostimulant-mediated modulation of PFC network excitability: evidence of dopamine actions

Methylphenidate administered at low-doses can enhance cognitive function [127]. At the single cell level, it was reported that low-doses of MPH significantly increased excitability on cortical pyramidal neurons in animals and suggested that increases in cortical excitability is the result of MPH enhancing the concentration of dopamine in the synaptic cleft [128]. In contrast, high-dose

MPH produced a profound suppression of evoked responses, essentially rendering the PFC non-responsive and functionally taking it "off-line". These actions would contribute to cognitive impairment and behavioral activation induced by high dose psychostimulant administration [129]. It was described age-dependent effects of MPH since in juvenile rat PFC pyramidal neurons MPH can enhance I_H conductance with a concomitant decrease in excitability [130]. Further research is needed in order to clarify mechanisms behind MPH-induced changed in cortical excitability.

Modafinil at a dose of 400 mg/kg increased perfusion in fronto-cortical areas in healthy volunteers during human neuroimaging studies [131]. Other studies have also indicated that in normal volunteers as well as in narcoleptic and schizophrenic patients, modafinil improved information processing within PFC [132–134]. Human neuroimaging results have shown that modafinil strongly contributes to fronto-cortical systems activation. When amphetamine was tested in neuroimaging setting a robust activation was observed across various cortical regions [135], and lacked much of the subcortical and fronto-cortical focal activation observed with modafinil. These findings are consistent with the different pharmacological profile of the two drugs [136]. Indeed, modafinil mechanism of action appears to be capable of preferentially activating dopaminergic neurotransmission in the PFC, without inducing changes in 5-HT efflux [137]. To the best of our knowledge, detailed preclinical studies addressing the effect of modafinil on cortical excitability are not available; therefore further studies are sorely needed. Our laboratory has previously suggested that modafinil could be considered a promising protective agent aimed to counteract cognitive deficits that relay on PFC functioning in mice. Indeed, modafnil rescued methamphetamine-induced object recognition memory deficits in mice [138]. Methamphetamine-treated mice showed impaired ERK phosphorylation in mPFC, which, in rodents, is detected shortly after novelty [139,140]. Modafinil administration also restored novelty-induced ERK phosphorylation in the mPFC. It is known that ERK, a member of the MAPK family, is critically linked to dopaminergic neurotransmission and long-term memory [140,141]. ERK pathway was also linked to D1 receptor activation and cAMP-PKA signaling [140,141]. Our results in mPFC demonstrated dose-dependent effects of modafinil on ERK phosphorylation that might be related to modafinil ability to stimulate DA transmission and D1 receptors activation in fronto-cortical areas [142]. Future research is needed to better understand the synaptic effects of modafinil at a cortical cellular and network level effects that might underlie its pro-cognitive functional effects.

Several cognitive alterations have been associated to chronic use of cocaine [143]. Cocaine dependent patients show altered patterns of brain activity during cognitive tasks [34,144–147]. Functional alterations of PFC network have been suggested to mediate cocaine-mediated dysfunctions [148], since patients who suffer damage in these brain region manifest similar cognitive problems [149]. This suggestion is fully supported by neuroimaging studies in cocaine abusers, reporting functional "hypofrontality" during the execution of attentional tasks [144,148]. Although these cocaine-associated deficits have been known for a while, their biochemical and structural bases remain to be elucidated. In preclinical studies, it was shown that long-term cocaine self- administration reduced prelimbic cortex excitability [150]. Recently, it was shown that under cocaine self-administration withdrawal, cocaine cues actually increased increase in firing evoked by depolarizing currents as compared with those from control rats [151]. This study shows that cocaine self-administration followed by protracted withdrawal can elicit drug-seeking associated with abnormally increased responses of mPFC pyramidal neurons to excitatory stimuli.

Methamphetamine users show several alterations in brain activation patterns observed during neuroimaging studies [152–160]. These studies reported decreased frontal cortical activation associated with impaired decision making [152] and cognitive control [160]. Methamphetamine users who showed impaired attention [154] and impaired cognitive control [158] also exhibited abnormalities in fronto-cortical brain regions [143]. The development of drug addiction is believed to derive in large part from maladaptive neurobiological responses to drugs of abuse within the corticostriatal glutamate and mesostriatal DA systems of the brain. In animal models of self-administration methamphetamine reduced basal glutamate in the Nucleus Accumbens an in the mPFC [159].

Our group and others have shown that chronic non contingent METH administration in mice leads to visual cognitive impairments, evidenced by reduced novel object recognition memory that was associated with deficits on mPFC ERK1/2 phosphorylation [138]. We have also found that METH detrimental effects on medial PFC is associated with a reduction in voltage-dependent Ca^{2+} current- density, reduced probability of glutamate release (both spontaneous and locally evoked) together with increased I_H current-density at resting membrane potential [161]. Also, higher levels of HCN2 mRNA expression might correlate with higher I_H current-density. METH-induced effects on Ca^{2+} currents and glutamate release described by our study have shown to be dependent on D1-like receptor activation [162], since pre-treatment with the D1- antagonist SCH23390 was able to fully prevent these effects [161]. The METH-induced reduction of glutamate release was also reported in the PFC of rats subjected to methamphetamine self-administration [159].

Similar results were described in vitro using bath-application of 10 μM amphetamine, which acting through D1-like receptors, significantly depressed glutamate release probability and excitatory field potentials (EPSPs) in medial PFC [126]. Sustained activation of D1-like receptors in medial PFC could be a potential mechanism behind METH-induced I_H increments and mEPSC frequency reduction. These alterations associated with reduced Ca^{2+} influx indicate functional alterations of medial PFC pyramidal neurons induced by methamphetamine.

6. Concluding remarks

In this review we have highlighted that highly addictive psychostimulants such as cocaine and METH can induce hypoexcitabilty in frontal cortical areas that are key to cognition. Results from preclinical and clinical studies suggest that by sustained activation of physiological features of DA neuromodulation, addictive psychostimulants can "lock" frontal cortical networks in deficient states. Our group and others have suggested that a feature of synaptic DA release is to reduce calcium influx in the postsynaptic compartment [161], therefore modulating synaptic integration and information. However, sustained DA alterations induced by chronic increased dopaminergic tone in PFC pyramidal neurons might in turn impair PFC adaptability and function, for example: increased adaptations of PFC circuits to continued DA might cost PFC a decreased capacity to flexibly alter behavior.

Moreover, studies summarized here suggest that there is frontal cortex hypoactivity and deficient inhibitory control in drug-addicted individuals. Clearly, 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 the one produced after chronic intake of addictive psychostimulants. Neuroenhancement drugs reviewed here appear to increase cortical excitability. Interestingly, pro-cognitive legal psychostimulants (modafinil and methylphenidate) have been used *off label* to treat substance use

disorders [6,136,163]. Normalizing functions affected by chronic drug use, using empirically based and targeted pharmacological interventions (i.e., prescribed/controlled administration of legal psychostimulants) associated with cognitive-behavioral therapy might improve therapeutic outcomes in the treatment of addiction. In that regard, it has suggested that psychostimulant medications, prescribed as "replacement therapy" might not be useful for treating amphetamine dependence [164] whereas promising results have been shown for psychostimulant treatment on cocaine abuse [165].

Conflict of interest

The authors declare that there are no conflicts of interest.

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