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Pedunculopontine arousal system physiology—Effects of psychostimulant abuse

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ABSTRACT

This review describes the interactions between the pedunculopontine nucleus (PPN), the ventral tegmental area (VTA), and the thalamocortical system. Experiments using modulators of cholinergic receptors in the PPN clarified its role on psychostimulant-induced locomotion. PPN activation was found to be involved in the animal's voluntary search for psychostimulants. Every PPN neuron is known to generate gamma band oscillations. Voltage-gated calcium channels are key elements in the generation and maintenance of gamma band activity of PPN neurons. Calcium channels are also key elements mediating psychostimulant-induced alterations in the thalamic targets of PPN output. Thus, the PPN is a key substrate for maintaining arousal and REM sleep, but also in modulating psychostimulant self-administration.

1. Wake–sleep control by the Reticular Activating System and its influence on substance abuse

Substance abuse and the perception of withdrawal/relapse are mediated by neurobiological processes that occur when we are awake, but not when we are asleep. Furthermore, sleep disturbances (i.e., sleep deprivation) have been considered a risk for psychotimulant abuse. The Reticular Activating System (RAS) plays a central role controlling sleep homeostasis, modulating oscillatory rhythms between the thalamus and cortex that are distinguishable in the EEG during wake–sleep states [1]. The interactions between the pedunculopontine nucleus (PPN) and the thalamus are critical to its function of wake–sleep control, exerting a push–pull effect on two centers. That is, the PPN inhibits the reticular thalamic nucleus (RTN) (which decreases slow waves during sleep), and excites specific thalamic relay

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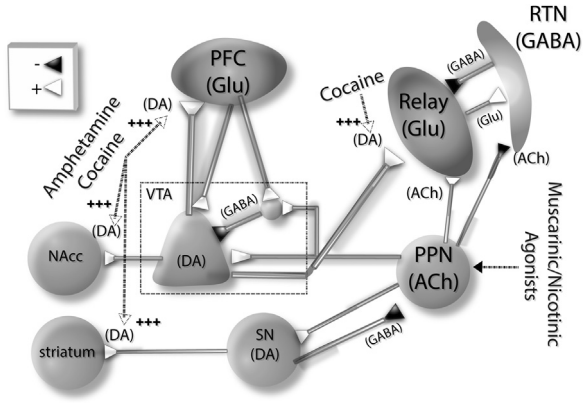

Fig. 1 – Schematic diagram showing psychostimulants/neuromodulators of PPN and thalamocortical circuits. Projections from PPN to key dopaminergic nuclei underlying psychostimulant effects. The PPN projects to the ventral tegmental area (VTA) and substantia nigra (SN). Dopaminergic VTA neurons in turn project to the medial prefrontal cortex (mPFC) and nucleus accumbens (NAcc). Amphetamines/cocaine (two stimulants that exert their effects by drastically increasing extracellular DA concentration) self-administration can be modulated by PPN efferents to VTA and SN. Cholinergic modulation by the PPN can modulate VTA and thalamic nuclei, exciting glutamatergic relay neurons while inhibiting GABAergic reticular thalamic neurons. Upper left box: (+) represents excitatory, glutamatergic or cholinergic synapses, and (−) GABAergic, or cholinergic inhibitory synapses.

nuclei (which increases tonic firing during the awake state) (Fig. 1) [2,3]. Thalamic relay neurons (which by definition send glutamatergic projections to the cortex) also receive RTN (GABAergic) afferents whose axons remain within the boundaries of the dorsal thalamic nucleus where the somata are located [4]. Thalamic relay neurons are bushy and, depending on the size of the soma, project to different layers of the cortex [5,6]. RTN neurons, on the other hand, have axons that collateralize within the nucleus and also project to dorsal thalamic nuclei, but not to the cortex; they have long dendrites, whose secondary and tertiary branches possess vesicle-containing appendages that form synapses on the dendrites of other reticular neurons [7]. The cells of the RTN are electrically coupled via gap junctions, providing a coherent recurrent inhibitory signal to thalamic relay cells, causing activation of T-type calcium channels responsible for slow waves during sleep [8]. Therefore, cholinergic afferents from the PPN to the RTN are inhibitory (pull away from slow wave sleep) [9], but excitatory to thalamic relay neurons (push towards waking). This prevents the bursting mediated by the activation of T-type calcium channels by RTN inhibition [10], and tonically depolarizes thalamic relay neurons, thus inducing a global disinhibition of thalamocortical activity. That is, when the PPN is activated, slow wave sleep is reduced and arousal is increased.

Altered thalamocortical dynamics are the basis for several types of neurological and neuropsychiatric conditions named *thalamocortical dysrhythmia syndrome* [11,12]. Abnormal activity of relay neurons has been related to an increase of low frequency oscillatory activity due to protracted activation of the low threshold voltage-activated (LVA) T-type calcium currents (Ca_V3 mediated), and in turn relayed to the cortical mantle resulting in a mistiming between sensory and arousal inputs. In summary, an enhancement of low frequency thalamocortical activity during awake states would underlie aberrant sensory processing [13].

The ventral tegmental area (VTA) is a key neural substrate involved in the modulation of psychostimulant abuse, and its output is essential for the rewarding effects of addictive drugs [14]. The VTA receives cholinergic RAS input from the PPN, which modulates the high frequency states of waking and rapid eye movement (REM) sleep (Fig. 1) [1]. Cholinergic efferents from the PPN to the VTA are part of a loop that includes the medial prefrontal cortex (mPFC) [15]. This loop is composed of mPFC glutamatergic efferents to dopaminergic and GABAergic neurons in the VTA and to the nucleus accumbens (NAcc) through a polysynaptic circuit that includes the PPN. In addition, the VTA sends dopaminergic and GABAergic efferents to the NAcc. Activation of the PPN thus increases VTA dopaminergic output, and increases extracellular dopamine (DA) levels in the NAcc and mPFC [16], which suggests that the PPN in part regulates the reward and motivational functions of the VTA [17].

Higher glutamatergic efferent activation from the mPFC would in turn reduce VTA dopaminergic output through its direct activation of local GABAergic interneurons within the VTA. Recent optogenetic experiments confirmed that PPN-VTA pathway stimulation can elicit psychostimulant-like behavior in the absence of any drug administration [18]. Since midbrain dopaminergic neurons originating in the VTA and substantia nigra *pars compacta* (SNc) have been previously described as the neural substrates underlying individual vulnerability to psychostimulant addiction [19–21], elucidating the functional modulation of the VTA and SNc by the PPN is a key to understanding how drug reinforcing, craving, and psychomotor-stimulant effects are modulated by a wake-promoting nuclei such as the PPN.

2. Drugs of abuse as modulators of calcium channels in the PPN and its targets

Psychostimulants—like thalamic relay neurons, about 40% of PPN cells have T-type calcium channels that mediate low threshold spikes (LTS) [1]. However, the most common calcium channels in the PPN are high threshold voltage-dependent calcium channels. Our group found that *every* PPN neuron has N- and/or P/Q-type calcium channels [22], which mediate beta/gamma band intrinsic membrane oscillations [23]. PPN calcium channels, in particular the P/Q-type, are modulated by muscarinic M2 receptors, providing a physiologically relevant fine-tuning of beta/gamma band oscillations in this nucleus [23]. P/Q-type ($Ca_v2.1$) calcium channels are widely distributed in the CNS [24,25], and play a central role in the physiology of PPN [26–28], as well as its thalamocortical targets [13,29]. High threshold voltage-dependent calcium channels, and P/Q-type channels in particular, have been described in presynaptic terminals mediating synaptic transmission in both glutamatergic pyramidal and inhibitory interneurons [24,25]. Using two-photon imaging, P/Q-type channels have been located in the dendritic compartments of thalamocortical neurons [29].

In PPN neurons, P/Q- and N-type channels have also been associated with distal dendritic compartments [27,28]. These calcium channels are critical to the induction and maintenance of high frequency oscillation states like waking and REM sleep [22,23,27,28]. The study of the effects of psychostimulants on these channels is critical to determining the role of the PPN in psychostimulant abuse.

2.1. *Amphetamines*

Amphetamine and methamphetamine induce increases in extracellular DA by acting in the terminals and cell bodies of midbrain DA neurons, where they induce the reverse transport of DA and prevent its uptake [30,31]. Amphetamine is known to enhance cyclin-dependent kinase 5 (cdk5) activity [32], contributing to neuroadaptations underlying locomotor sensitization [33]. Cdk5-mediated intracellular pathways are known to down-regulate P/Q-type calcium channels [34,35], which would mediate *thalamocortical dysrhythmic* interactions by unbalancing the normal P/Q-type vs T-type channels activation ratio [13]. Lowered PPN gamma band output is also to be expected after cdk5 activation, which would alter normal wake/REM sleep transitions [1]. Moreover, the effects of methamphetamine on the mPFC network has been recently found to alter calcium dynamics (by reducing calcium current density) in pyramidal neurons, while enhancing cationic hyperpolarization-activated I_H current density (Fig. 2) (that could also increase low-frequency firing) [36]. Additionally, methamphetamine induced lower levels of glutamatergic synaptic transmission in the mPFC, which has been suggested to underline the mPFC hypofunctionality described in human addicts [36].

The basic behavioral effect of amphetamines is to induce hyperlocomotion, which can be used as a predictor of future propensity to amphetamine self-administration [37]. Acute total sleep deprivation has been described to potentiate amphetamine-induced locomotion [38]. Direct interactions between the PPN and VTA were demonstrated using excitotoxic lesions of the PPN [39]. GABAergic neuronal firing rates decrease during slow wave sleep and increase during REM sleep [40], suggesting a novel PPN control over VTA. More experiments are needed to further clarify this possibility as well as its possible modulation by psychostimulants.

PPN-lesioned animals showed a clear reduction in the response to a progressive ratio self-administration schedule of amphetamine [39]. Lesions of the PPN blocked the motivational (measured using a conditioned place preference paradigm) effects of amphetamine [41]. Muscarinic agonists have been shown to reduce amphetamine-induced hyperlocomotion [42], while muscarinic antagonists mediated facilitation of amphetamine-induced rotation through M2 receptors [43]. Unfortunately, all of these experiments were performed using systemic administration of muscarinic receptor modulators, making it difficult to determine the exact neural substrate of these actions in the brain (i.e., it is possible that muscarinic receptor modulation might affect the activity of other cholinergic nuclei such as the nucleus basalis that projects to cortex and to the RTN) [44].

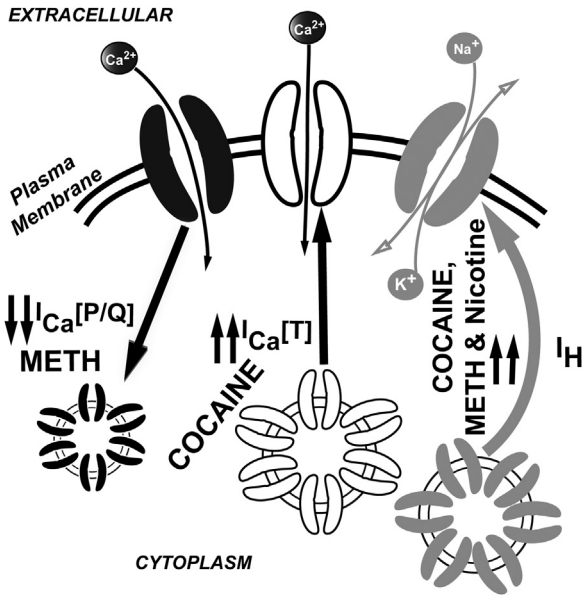

Fig. 2 – Illustration of psychostimulant/neuromodulator dependent turnover of calcium and cationic hyperpolarization-activated I_H currents on PPN and thalamocortical neurons. Systemic administration of cocaine is known to up-regulate membrane expression of T-type calcium and I_H cationic currents [49–51]. Systemic administration of METH reduced P/Q type calcium channel currents in medial prefrontal cortex (mPFC) [36]. In addition, nicotine upregulated I_H cationic current density in PPN neurons (Garcia-Rill et al. [80]).

2.2. *Cocaine*

The rewarding properties and abuse potential of cocaine is derived in part from elevated levels of DA neurotransmission in limbic circuits [45,46]. Cocaine can also increase serotonin (5-HT) neurotransmission via inhibition of its re-uptake [47]. Individual vulnerability to cocaine self-administration has been associated with changes in neuronal intrinsic properties, in particular, with higher action potential frequency and bursting of VTA neurons, and to a lesser extent SNc neurons. In addition, animals that manifested higher self-administration rates also exhibited higher locomotor responses to a novel environment prior to psychostimulant-administration [48], strongly suggesting that the basal modulation of VTA neurons by the PPN can be considered critical to psychostimulant abuse liability.

While Schmidt et al. [49] showed that enhanced glutamatergic transmission in the PPN promoted cocaine priming-induced reinstatement of cocaine seeking, others [50] used the infusion of a diphtheria toxin conjugated to urotensin-II into the PPN (which resulted in the loss of >95% of PPN cholinergic neurons) to describe no significant alterations in cocaine self-administration. A possible explanation for the discrepancies described in recent years may be related to the strong serotonergic effects of cocaine [47]. Indeed, cocaine-mediated blocking effects of both DA and serotonin reuptake could alter the activity of PPN efferents to VTA, as well as the degree of activation of serotonergic afferents from the raphe nuclei to the PPN. Such a possibility has been recently

proposed to explain the differential actions of cocaine and methylphenidate on GABAergic transmission in mouse ventrobasal thalamic nucleus [51]. A cocaine-mediated enhancement in GABA release has been described to induce *thalamocortical dysrhythmic* interactions in mice due to the over activation of T-type calcium channels expressed in thalamocortical neurons (Fig. 2) [52]. Indeed, pre-treatment with T-type channel blockers was shown to prevent the effects of cocaine on the thalamocortical system, suggesting a new role mediating GABA release of the T-type channels located in the presynaptic terminals of parvalbumin-rich reticular thalamic neurons [53]. After three-day systemic treatment with cocaine, both T-type and P/Q-type calcium channels were over expressed [51], suggesting a compensatory mechanism by which thalamocortical neurons attempt to cope with the deleterious effects of cocaine.

Acute total sleep deprivation potentiated cocaine-induced hyperlocomotion in mice [54]. Therefore, PPN activation is important in the modulation of cocaine self-administration, although the mechanisms underlying such an effect need further characterization.

2.3. *Modafinil, a non-addictive psychostimulant, deserves separate discussion*

We found that the prescription drug modafinil, which is used for the treatment of narcolepsy and daytime sleepiness, prevented the neurotoxic effects of methamphetamine on striatal circuits [55,56]. Modafinil acts by increasing electrical coupling especially in GABAergic neurons [58,59], which decreases input resistance in GABAergic cells throughout the brain, but particularly in the PPN. Such an effect would disinhibit glutamatergic and dopaminergic interactions between PPN and VTA nuclei. In addition, modafinil can counteract methamphetamine-mediated impairments in mPFC function [57,60], which is a key area regulating cognition and normal sleep physiology [58,61]. More studies are still needed in order to address the possible role of calcium channels in the apparent cognitive-enhancing profile of modafinil for the treatment of deficits mediated by methamphetamine.

Modafinil is known to mediate its effect on thalamocortical neurons through a CaMKII-dependent intracellular pathway [59] that has been described to enhance P/Q-type channel function [62]. These mechanisms might explain why modafinil-mediated over activation of the CaMKII intracellular pathways can lead to enhance walking time.

2.4. *Nicotine*

Nicotinic receptor agonists induced a depolarization early in development (~day 12) that switched across days 15–17 until they elicited hyperpolarization by day 21 in the rat PPN [63]. Nicotine has also been found to have an inhibitory effect on the PPN, initially reducing arousal. This may explain the initial anxiolytic effects of cigarette smoke [64,65]. Nicotine in the fetus may have long-term consequences on RAS activity. Nicotine from cigarette smoke can cross the placenta, exposing the fetuses from smoking mothers to higher nicotine concentrations in both amniotic fluid and umbilical vein than the ones in maternal vein serum [66]. Toxicological effects of perinatal cigarette smoke exposure include lower birth weight [67], higher rate of spontaneous abortion [68], and increased incidence of sudden infant death syndrome [69]. Maternal smoking during pregnancy can lead to increased aggression [70], and problems with sustained attention and impulsivity in adolescent offspring [71]. Children of smoking mothers are at increased risk behavior problems [72,73], behavioral disorders [74,75], drug abuse [70], and for high rates of violent and persistent criminal offenses [70,76].

Behavioral deficits related to arousal and attentional problems in humans have been identified in rats exposed to nicotine prenatally. These animal models show deficits in attention and memory in maze performance [77,78], learning [77], and operant behaviors [79]. We studied the effects of prenatal exposure to cigarette smoke on the physiology of PPN cells postnatally [80]. We found that PPN neurons exhibited lower resting membrane potential and lower action potential threshold (tending to increase PPN firing), both of which could be related to an increase in hyperpolarization-activated I_H current (that could also increase low-frequency firing). I_H current enhancement has been also described for cocaine-mediated effects on thalamocortical neurons (Fig. 2) [52]. I_H and T-type currents have been described to mediate low frequency oscillatory activity in the thalamaocortical system [52]. We speculate that hyperpolarization-activated cyclic nucleotide-gated proteins may be over activated by prenatal cigarette smoke exposure, and that a possible down regulation of I_H proteins may be responsible for the enhancement in arousal as well as for the attentional deficits [72], as well as impulse control problems (exaggerated fight-or-flight responses) reported in the children of mothers who smoked during pregnancy [71,73].

3. Conclusion

Drug abuse is a major global health problem. Although some people that have suffered from psychostimulant abuse are able to recover, relapse occur in almost half of the cases. Also, addicts to drugs of abuse have shown persistent neuropathological changes that may be related to the profound dysfunction present in addict populations [81]. Thus, psychostimulant addiction is treated like a chronic illness, requiring repeated episodes of therapy. The symptoms of relapse are similar to those in depression and anxiety, which may require pharmacological therapy in addition to cognitive therapy and support groups. These functions all involve arousal and, therefore, the RAS. For example, impaired sleep is present during withdrawal, and insomnia-like symptoms are present in heroin, cocaine, methamphetamine, and addicted users of other drugs [82]. Basically, disturbed sleep predicts relapse to alcohol and psychoactive drug abuse [83]. Just as with psychiatric and neurological disorders, rebalancing the wake–sleep homeostatic system is key to treatment response and, in fact, signals successful alleviation of symptoms. In addition, future work characterizing the role of psychostimulants on voltage-gated calcium channels in the RAS and target areas may shed some light on their mechanisms and their possible treatment.

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