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Review

The paraventricular thalamic nucleus: A key hub of neural circuits underlying drug addiction

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ABSTRACT

Drug addiction is a chronic relapsing brain disease characterized by compulsive, out-of-control drug use and the appearance of negative somatic and emotional consequences when drug access is prevented. The limited efficacy of treatment urges researchers toward a deeper understanding of the neural mechanism of drug addiction. Brain circuits that regulate reward and motivation are considered to be the neural substrate of drug addiction. An increasing body of literature indicates that the paraventricular thalamic nucleus (PVT) could serve as a key node in the neurocircuits that control goal-directed behaviors. In this review, we summarize the anatomical and functional evidence that the PVT regulates drug-related behaviors. The PVT receives extensive inputs from the brainstem and hypothalamus, and is reciprocally connected with the limbic system. Neurons in the PVT are recruited by drug exposure as well as cues and context associated with drug taking. Pathway-specific perturbation studies have begun to decipher the precise role of PVT circuits in drug-related behaviors. We also highlight recent findings about the involvement of neural plasticity of the PVT pathways in drug addiction and provide perspectives on future studies.

1. Introduction

In the early literature, the function of midline and intralaminar thalamic nuclei was obscure due to their widespread connections. Further, the paraventricular nucleus of the thalamus (PVT) was thought to have a nonspecific function in arousal [1,2]. Recently, the PVT has been increasingly appreciated as an important part of neural circuits underlying drug addiction [3–6]. Anatomically, the PVT communicates with myriad brain regions involved in reward and motivation [3]. Particularly, the prominent projections from the PVT to the nucleus accumbens (NAc) [7–9] have attracted great interest to investigate PVT pathways in addiction models. Studies demonstrated that PVT neurons are activated by a number of abused drugs, including morphine, amphetamine, and cocaine, as well as by drug-related context [10–15]. Functional perturbation studies further revealed the role of PVT circuitry in controlling several aspects of drug-related behaviors, including cocaine sensitization [16], opiate withdrawal [9], drug seeking [17,18], and reinstatement [19,20]. Recent studies have also shown that the PVT plays important roles in wakefulness control [21,22] and salience processing [23]. Those works reveal some physiological function of PVT neurons and also provide important insights into understanding how the PVT contributes to drug addiction. Thus, in this current review we discuss these results as well as evidence about alterations of intrinsic plasticity in drug addiction.

2. Anatomical properties of the PVT

The PVT is a member of the midline thalamic nuclei; it extends rostrocaudally below the third ventricle [3]. Neurons in the PVT use glutamate as a neurotransmitter and express vesicular glutamate transporter 2 (vGlut2) [24,25]. Like other thalamic nuclei, the PVT lacks local GABAergic interneurons [26,27]. PVT neurons are strongly stained for calbindin and calretinin but not parvalbumin [22,24,28].

The PVT receives extensive neuromodulatory inputs [29–34]; thus, its activity is tightly controlled by neuromodulator systems. Various neuromodulator receptors are observed in the PVT, including dopamine receptor (D2R and D3R), orexin receptor (OX1R and OX2R), corticotropin-releasing hormone receptor (CRHR1), melanin-concentrating hormone receptor, kappa opioid receptor (KOR), and thyrotropin-releasing hormone receptor [29–34]. Both alpha and beta adrenoceptors [35–37] as well as cholinergic receptors (M1-M3) are present in the PVT [38,39], and PVT neurons are densely stained for acetylcholinesterase [28]. Additionally, the human PVT is highly enriched in limbic system-associated membrane protein (LAMP) [28], a protein

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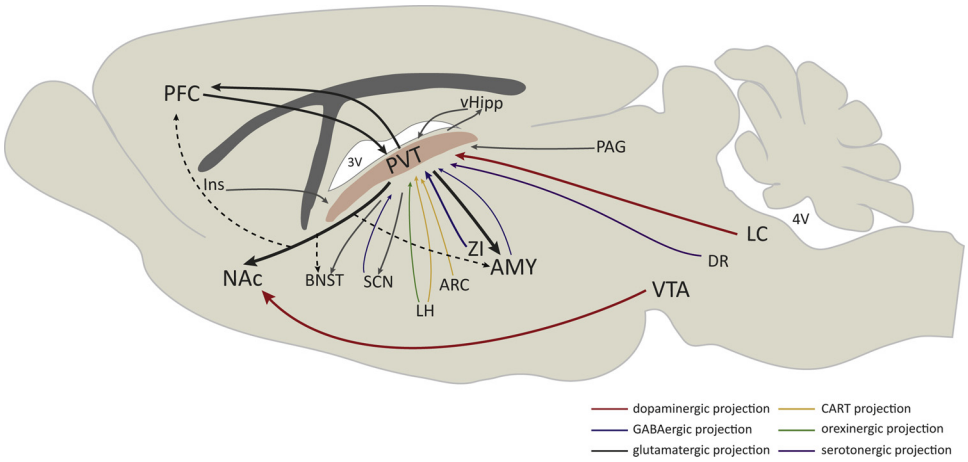

Fig. 1. Schematic representation of the input and output pattern of the PVT. Axon collaterals from the PVT are depicted by dash lines. AMY, amygdala; ARC, arcuate nucleus; BNST, bed nucleus of the stria terminalis; DR, dorsal raphe nucleus; Ins, insular cortex; LC, locus coeruleus; LH, later hypothalamus; NAc, nucleus accumbens; PAG, periaqueductal gray; PFC, prefrontal cortex; PVT, paraventricular nucleus of the thalamus; SCN, suprachiasmatic nucleus; vHipp, ventral hippocampus; VTA, ventral tegmental area; ZI, zona incerta.

specific to brain regions connected with the limbic system. Indeed, the PVT is often recognized as an interface which receives homeostatic information, including arousal, visceral, circadian, and sensory signals, and sends output to the nucleus accumbens and other limbic regions to regulate motivated behaviors [3].

2.1. Afferent inputs to the PVT

Midline thalamic nuclei integrate inputs from both the brainstem and the cerebral cortex (Fig. 1). Retrograde tracing studies reported that the PVT receives inputs from brainstem nuclei, including the locus coeruleus (LC), the deep mesencephalic reticular, pedunculopontine tegmental, dorsal raphe, and median raphe nuclei, all of which are pivotal sites implicated in the regulation of arousal and stress [40,41]. The periaqueductal gray, parabrachial nucleus, and the nucleus of the solitary tract convey nociceptive signals and visceral information related to energy homeostasis to the PVT [42–44]. Inputs from the limbic system to the PVT include efferents of the prelimbic, infralimbic, agranular insular, entorhinal cortices, amygdala, and ventral subiculum [41,45].

The PVT is especially notable among midline thalamic nuclei because it also receives massive innervation from the hypothalamus [46]. The suprachiasmatic (SCN), arcuate (ARC), dorsomedial (DMH), ventromedial hypothalamic nuclei (VMH), and lateral hypothalamic areas all project to the PVT [46–51]. Since the PVT is devoid of GABAergic interneurons, it relies on inputs from the zona incerta (ZI), lateral hypothalamus (LH), and the reticular thalamus (RE) for inhibitory regulation [52]. Additionally, the amygdala and the ARC and SCN in the hypothalamus might be potential GABAergic input sources to the PVT [50,53–55].

2.2. Projection pattern of the PVT

The PVT has been increasingly recognized as an important part of neural circuits underlying drug addiction, largely due to its prominent projections to the nucleus accumbens [7–9] – a brain region that is highly implicated in mediating addictive behavior [56,57]. The PVT innervates both the core and the shell of the NAc, which receive intense dopamine (DA) input and play a critical role in motivation and goal-directed behavior. Axons from the PVT terminate in close proximity to dopaminergic fibers in the NAc [58,59]. PVT stimulation has been reported to increases DA level in the NAc shell [60]. The PVT also projects to the central and basal amygdala and the bed nucleus of the stria terminalis (BNST), structures highly implicated in fear and anxiety. Accordingly, the PVT has been reported to control fear and anxiety-like behavior in rodent [61–63]. Thus, the PVT is also a key element in the neural circuits that regulate fear and anxiety [45,64,65]. Since drugs of abuse are considered to dysregulate hedonic homeostasis, a negative emotional state is a critical reinforcement source that contributes substantially to drug addiction behavior development [66]. The strategic position of the PVT further highlights its role in regulating drug addiction.

Besides extensive projections to the NAc and amygdala along the anterior-posterior axis of the PVT, the anterior PVT (aPVT) and posterior PVT (pPVT) appear to differ in their projection distributions. The efferent pattern of the aPVT is relatively widespread and includes projections to the olfactory tubercle, SCN, dorsomedial and ventromedial hypothalamic nuclei, lateral septum, infralimbic cortex, BNST, endopiriform nucleus, and ventral hippocampus [8,67–70]. In contrast, the pPVT has more restricted projections, including the anterior olfactory nucleus, olfactory tubercle, lateral BNST, and the interstitial nucleus of the posterior limb of the anterior commissure (IPAC) [8,67,68].

The PVT might exert its functional influence through multiple targets; therefore, some research has focused on identifying the distribution of axon collaterals of PVT neurons [71,72]. A single neuron in the PVT can send projections to multiple cortical and subcortical regions [72,73]. Indeed, more than 50% of PVT neurons that project to the central amygdala (CeA) or BNST also send axon collaterals to the NAc [68,74]. Thus, the PVT could broadcast information to multiple downstream brain areas to coordinate their activities.

3. The role of the PVT in drug addiction

As reviewed above, the PVT occupies a unique anatomical position in regulating goal-directed behaviors, and this allows both top-down and bottom-up control. A large and growing body of research has focused on examining the role of the PVT in drug addiction [9,71,75]. Most of the recent progress involves studies of animal models.

Incorporating the principles of classic and operant conditioning from the field of learning and memory, the development of addiction-related behaviors in animal models may be conceptualized into three stages: acquisition, withdrawal/extinction, and reinstatement [76,77]. At the acquisition stage, drug use (administrated by experimenters or through self-administration) escalates, a phenomenon that mimics when a person starts to use the substance more and more frequently [78]. Some drugs trigger hyperlocomotion, and this response increases with repeated use of the drug, a phenomenon known as locomotion sensitization [79]. Animals also develop conditioned place preference (CPP), due to the reinforcing drug effects [80]. At the withdrawal/extinction stage, access to drugs is denied, so negative effects become dominant [81]. Animals show somatic withdrawal symptoms and can acquire conditioned place aversion (CPA) [80]. Drug-seeking behaviors cease after spontaneous or forced extinction, while at the reinstatement

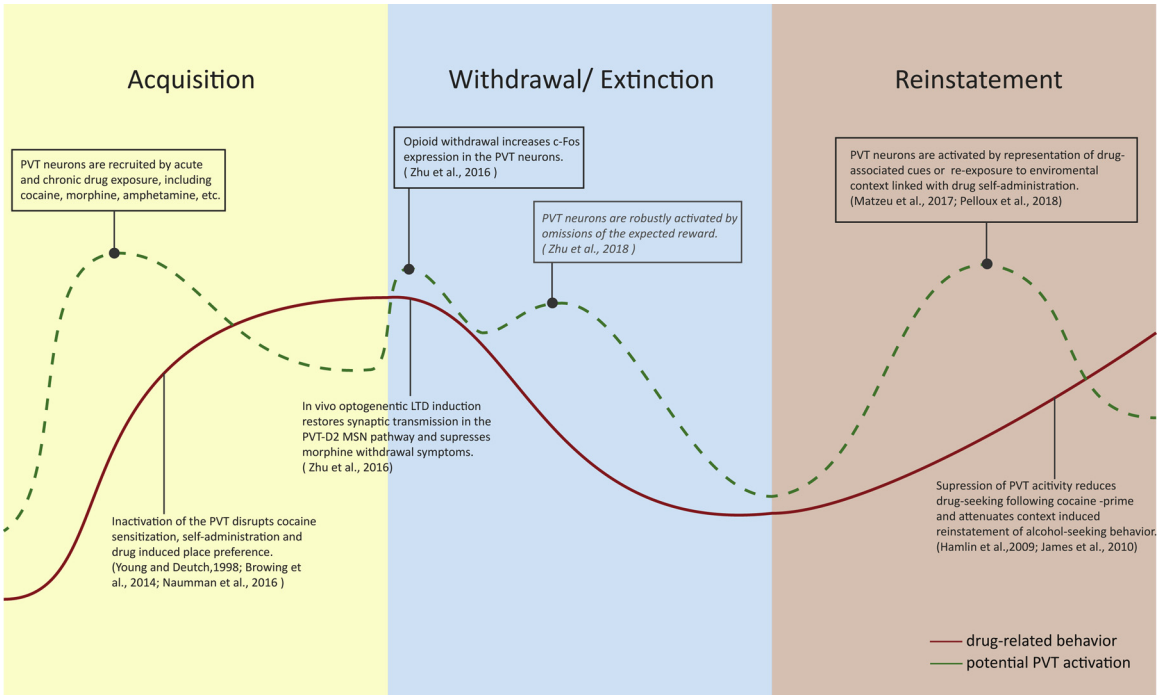

Fig. 2. Illustration of the dynamic progress of drug-related behaviors and potential activation of the PVT at different stages of addiction.

stage, drug seeking behaviors are re-established following presentation of cues or exposure to the context previously linked to drug taking [82]. Stress and drug priming are also effective triggers for drug relapse [83,84].

Since PVT neuronal activities in response to drug exposure were systematically examined, myriad experiments aim to register PVT activation at different stages of drug addiction. Moreover, circuit-specific perturbation studies have begun to explore the contribution of each PVT pathway to various aspects of addiction [71] (Fig. 2).

3.1. The PVT is activated by acute drug exposure, drug withdrawal, and drug-associated cues

Neural activation occurs in PVT neurons in response to acute exposure to a variety of addictive substance, including morphine [13,85], amphetamine [12], cocaine [10,12,86], nicotine [87], and ethanol [88]. Interestingly, increased activation of the aPVT but not the pPVT is associated with ethanol drinking and palatable food intake [11,89]. By combining a retrograde tracing technique with c-fos expression measurement, studies demonstrated that the PVT-NAc pathway is activated by acute exposure to amphetamine and morphine [9,12], and the LH-PVT pathway can be recruited by acute nicotine administration and ethanol drinking [5,90]. These results suggest that PVT subregions and pathways might be differentially affected by diverse drugs of abuse.

Notably, besides the acute effect of drugs, PVT neurons are also recruited at different periods of the drug addiction cycle. For example, presentation of discriminative stimuli previously linked with drug or re-exposure to the self-administration environment, significantly increases PVT neuronal activation [14,20,91–93]. An important recent finding is that PVT neurons that project to the NAc shell are recruited during spontaneous or naloxone-precipitated morphine withdrawal [9]. Since drug withdrawal is associated with aversive interoceptive sensations [94], this study implies that the PVT might carry information about interoceptive states during withdrawal. Thus, PVT neurons can be recruited by drug-related external cues, as well as by signals about interoceptive states during withdrawal, which might be derived from insular inputs [95]. These results are consistent with a recent study that proposed PVT neurons encode the saliency of behaviorally relevant stimuli [23], a proposition that suggests the PVT plays a fundamental role in goal-directed behaviors.

3.2. The PVT contributes to many aspects of drug addiction

Functional studies using pathway-specific perturbation further highlight the physiological significance of the PVT in regulating drug addiction. Early work revealed that a PVT lesion blocks cocaine sensitization [16]. Inactivation of the PVT with baclofen-muscimol abolishes cocaine-induced CPP [17], a result that suggests the PVT activity is important for cocaine craving. PVT activity suppression results in significant attenuation of drug-seeking behavior following cocaine priming [19] and context-induced reinstatement of alcohol seeking [20]. This effect could be mediated by the PVT-NAc pathway, because suppression of this pathway also reduces cocaine self-administration [18].

PVT neurons are recruited by stress [64,65], and activation of hypothalamic input in the PVT induces fear- and anxiety-like behaviors [96,97]. Those findings suggest that PVT plays a role in regulating negative emotional state. A negative emotional state is a key element of drug withdrawal; it serves as a negative reinforcer that promotes drug taking [66,98]. Consistently, Zhu et al. demonstrated that PVT-NAc pathway suppression with optogenetic or chemogenetic approaches significantly reduces somatic signs of morphine withdrawal, as well as the withdrawal-induced CPA [9].

Taken together, these results imply that specific PVT pathways or output patterns might be differentially associated with diverse aspects of drug-related behaviors. Indeed, the aPVT-NAc and aPVT-CEA pathways might exert opposing effects on sucrose taking [89]. Further investigations of PVT connections with addiction-related brain areas, including the BNST, CEA, and LC, are warranted. Moreover, although the PVT-NAc D2 pathway has been suggested to contribute to opiate withdrawal, the function of the PVT-NAc D1 signaling is yet to be elucidated. It is of great importance to dissect the molecular mechanism of different signaling pathways.

4. Neuromodulation of PVT neurons in drug addiction

Addcitive drugs exert distinct actions in the brain, but their effects converge in dopamine system modulation. PVT neurons receive massive dopaminergic input. Unexpectedly, projections from midbrain dopaminergic neurons to the PVT are rare, and the source of dopamine input to the PVT has been debated for decades [99,100]. Recently, it was demonstrated that the LC is the major source of dopaminergic input to the PVT [30]. A study by Clark et al. showed that D2R activation hyperpolarizes the membrane potential and reduces spiking rate in tonic firing PVT neurons in slice recording [31]. Additionally, they found that D2R overexpression in the PVT attenuates locomotion sensitization induced by cocaine administration, a finding that is consistent with previous results that PVT lesion blocks cocaine sensitization [16]. Contrarily, Beas et al. recently showed that D2R activation enhances neuronal excitability in the PVT through a disinhibition mechanism, evidenced by a reduction in miniature inhibitory postsynaptic currents (mIPSCs) and reduced density of gephyrin puncta in the dendrites of pPVT neurons after application of a D2 agonist [30]. Although a previous study demonstrated that D2R activation inhibits dopamine neurons by enhancing potassium conductance in the ventral tegmental area [101], the mechanism of D2R activation in the PVT remains to be elucidated. Therefore, further investigations are warranted to understand the role of dopaminergic input to the PVT and to disentangle the effect of potential co-release of DA and noradrenalin from the LC.

The PVT receives intense neuromodulator innervations from the brainstem and the hypothalamus, including orexin/hypocretin, cocaine- and amphetamine-regulated transcript, agouti-related peptide (ARGP), neuropeptide Y (NPY), enkephalin, and neurotensin [3,102,103]. Orexins/hypocretins are neuropeptides that regulate arousal, feeding, motivation, and the stress response [104,105]. Notably, the orexin system is preferentially recruited by drugs compared to natural rewards, such as palatable food [106]. The PVT is one of the brain regions with the densest distribution of orexin-containing innervations [48]. Orexin signaling from the LH to the PVT is important for wakefulness regulation [21]. Orexins enhance the excitability of PVT neurons, probably through regulation of potassium channels [107–109]. Orexin infusion into the PVT promotes ethanol drinking [11,110], while application of orexin receptor antagonists prevents the expression of morphine-withdrawal-associated CPA [111]. Dynorphins are opioid peptides often co-released with orexins, but they mediate aversion [112–114]. Dynorphins preferentially bind to KORs, and *KOR* mRNA is highly expressed in the PVT [115,116]. Infusion of a KOR agonist into the PVT prevents reinstatement of alcohol seeking [117]. Therefore, the balance between orexin and dynorphin signaling in the PVT may be affected by drug experience and apparently significantly contributes to compulsive drug seeking [118].

The PVT is also densely innervated by cocaine- and amphetamine-regulated transcript (CART) [49]. CART attenuates PVT neuron firing in cocaine-exposed animals [119]. CART microinfusion into the PVT reduces cocaine seeking in drug-primed rats [19]. Most CART inputs to the PVT originate from the ARC, and only a small fraction come from the LH [49]. Interestingly, some LH neurons provide divergent axon collaterals to the PVT and the NAc shell [51], and thus they might simultaneously coordinate the activities of these two brain regions to affect drug-seeking behaviors.

5. Adaptations of neural plasticity in the PVT circuitry in drug addiction

Drug experiences reshape behavior by inducing synaptic plasticity and remodeling neural circuits. Substantial research has focused on investigating synaptic adaptation in excitatory synapses from the prefrontal cortex, basolateral amygdala, and ventral hippocampus to the NAc [120–122]. Prominent excitatory input from the PVT to the NAc was long neglected until recently. Neumann et al. revealed that selectively silencing the PVT-NAc pathway decreases cocaine self-administration in rats [18]. They also observed that silent synapses increase following cocaine self-administration, and their level can return to baseline after prolonged withdrawal [18]. In the NAc, medium spiny neurons (MSNs) that express D1R or D2R have different projection targets and are thought to regulate reward and aversion responses, respectively [123,124]. Studies identified monosynaptic projections from the PVT onto D1 and D2 MSNs [9,18,122]. Zhu et al. found that PVT-NAc D2 synaptic transmission is selectively enhanced after chronic morphine exposure [9]. Most importantly, by using an optically induced long-term depression protocol to restore PVT-NAc D2 synaptic function, they significantly alleviated morphine withdrawal symptoms in animals [9]. These results reflect the complexity of synaptic adaptations in drug addiction; different types of drugs may have distinct impacts on this circuit. It is necessary to elucidate the molecular mechanism that mediates the diverse actions of drugs [125].

Drug exposure also changes the electrophysiological properties [126] of the PVT neurons. The PVT neurons exhibited two modes of action potential discharge in response to depolarizing current stimulation, tonic firing and non-tonic firing. Cocaine administration increases the percentage of tonic firing PVT neurons [119]. This effect may be mediated by enhanced function of the orexin system after cocaine exposure [96,127]. Orexins are also known to activate PVT neurons and increase input resistance of PVT neurons through potassium channel closure [109]. Other possibilities are that cocaine alters neuronal excitability by increasing the release of noradrenaline and/or serotonin in the PVT [128–130]. In contrast, opioids might exert an inhibitory effect on PVT neuronal excitability. Indeed, μ-opioid receptor activation inhibits thalamic neurons by activating an inwardly rectifying potassium conductance [131]. Dynorphin hyperpolarizes PVT neurons through activation of KORs [132]. Apart from receptor function modulation, substance abuse might also disturb neural plasticity by altering gene expression [29,96,133]. For instance, ethanol intake increases *OX2R* mRNA in the aPVT [11]. Additionally, cocaine-associated context increases special AT-rich sequence binding protein 2 (SATB2) expression in the PVT [134].

In brief, drugs of abuse could induce changes in the synaptic plasticity as well as intrinsic excitability, which together affect the signal-to-noise ratio of PVT pathways and contribute to the addiction phenotypes.

Additionally, several human neuroimaging studies demonstrated that both structural and functional abnormality of the thalamus can occur in drug-dependent individuals [75,135], although the PVT could not be pinpointed due to relatively low spatial resolution.

6. Conclusions and future perspectives

As reviewed above, the PVT is well placed in the neurocircuit that controls drug addiction. PVT neurons are recruited by drug exposure and contribute to various aspects of drug-related behaviors. However, it is not clear from which pathways the PVT acquires information associated with drugs and how the PVT integrates such inputs. For instance, the LC controls the stress-responsivity of pPVT neurons and enhances aversive learning. Thus, it would be very interesting to investigate how the LC-pPVT pathway might contribute to drug withdrawal and relapse [30]. Electrophysiological recordings of PVT activities in behaving animals while silencing individual inputs are critical experiments for answering these questions. So far, researchers have achieved advancements in understanding the role of the PVT-NAc pathway in drug addiction, but attention should also be given to other targets, including the BNST and CEA. These areas are important candidates, through which PVT might control drug abuse and relapse [136,137]. On the other hand, specific PVT cell types are yet to be identified. Future studies that examine the expression and transcriptional profile of PVT neurons would assist in resolving the molecular mechanism that mediates drug addiction.

Conflicts of interest

None.

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