Biochemical Pharmacology 86 (2013) 1173–1180

Contents lists available at ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Review

Cortical control of VTA function and influence on nicotine reward

Jie Wu [a,b,*], Ming Gao [a], Jian-Xin Shen [b], Wei-Xing Shi [c], Andrew M. Oster [d], Boris S. Gutkin [e]

[a] Divisions of Neurology, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, AZ 85013-4496, USA
[b] Departments of Physiology, Shantou University Medical College, Shantou, Guangdong, China
[c] Department of Pharmaceutical and Basic Sciences, Loma Linda University Schools of Pharmacy and Medicine, Loma Linda, CA 92350, USA
[d] Department of Mathematics, Eastern Washington University, Cheney, WA 99004, USA
[e] Group for Neural Theory, LNC INSERM U960, Department d'Etudes Cognitive, Ecole Normale Superieure, 29, rue d'Ulm, 75005 Paris, France

ARTICLE INFO

Article history:
Received 1 May 2013
Accepted 16 July 2013
Available online 7 August 2013

Keywords:
Prefrontal cortex
Nicotinic acetylcholine receptor
Nicotine reward
Ventral tegmental area
Dopamine neurons

ABSTRACT

Tobacco use is a major public health problem. Nicotine acts on widely distributed nicotinic acetylcholine receptors (nAChRs) in the brain and excites dopamine (DA) neurons in the ventral tegmental area (VTA). The elicited increase of DA neuronal activity is thought to be an important mechanism for nicotine reward and subsequently the transition to addiction. However, the current understanding of nicotine reward is based predominantly on the data accumulated from *in vitro* studies, often from VTA slices. Isolated VTA slices artificially terminate communications between neurons in the VTA and other brain regions that may significantly alter nicotinic effects. Consequently, the mechanisms of nicotinic excitation of VTA DA neurons under *in vivo* conditions have received only limited attention. Building upon the existing knowledge acquired *in vitro*, it is now time to elucidate the integrated mechanisms of nicotinic reward on intact systems that are more relevant to understanding the action of nicotine or other addictive drugs. In this review, we summarize recent studies that demonstrate the impact of prefrontal cortex (PFC) on the modulation of VTA DA neuronal function and nicotine reward. Based on existing evidence, we propose a new hypothesis that PFC–VTA functional coupling serves as an integration mechanism for nicotine reward. Moreover, addiction may develop due to nicotine perturbing the PFC–VTA coupling and thereby eliminating the PFC-dependent cognitive control over behavior.

Contents

1. Introduction

Tobacco use is a major public health problem. Nicotine acts on widely distributed nicotinic acetylcholine receptors (nAChRs) in the brain and excites dopamine (DA) neurons in the ventral tegmental area (VTA), which elevates DA release from VTA to the nucleus accumbens (NA) and the prefrontal cortex (PFC) with both nicotine reward and reinforcement generated as a result [1–3]. The mammalian VTA (A10) is a midbrain region that acts as an integrative center mediating incentive and motivational effects for

Abbreviations: nAChR(s), nicotinic acetylcholine receptor(s); PFC, prefrontal cortex; VTA, ventral tegmental area; DA, dopamine; ACh, acetylcholine.

* Corresponding author at: Division of Neurology, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, 350 West Thomas Road, Phoenix, AZ 85013-4496, USA. Tel.: +1 602 406 6376; fax: +1 602 406 7172.
E-mail address: Jie.Wu@DignityHealth.org (J. Wu).

0006-2952/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.bcp.2013.07.013

almost all addictive drugs, including nicotine. The VTA DA neurons and their associated ascending projections to their targets (NA and PFC) comprise the well-characterized mesolimbic and mesocortical pathways. The VTA receives both direct and indirect excitatory glutamatergic as well as indirect inhibitory GABAergic inputs from the mPFC [4,5]. During cigarette smoking, nicotine rapidly acts on widely distributed nicotinic acetylcholine receptors (nAChRs) in the brain, which in turn, alters a number of neuronal circuits and leads to an increase in VTA DA neural firing and elevates the extracellular dopamine levels in DA targets, such as the NA and the medial prefrontal cortex (mPFC). This process is likely a key pathway responsible for nicotine reward and reinforcement [6]. Although it is well known that the PFC efficiently controls VTA function [7–11], the impact of this cortical control in nicotine reward is not fully understood [12]. In this review, we summarize recent advances that validate the role of the PFC in modulation of VTA neuronal function and nicotine reward.

2. Cortical control of VTA neurons: anatomical and functional evidence

Anatomically, mPFC pyramidal neurons send descending glutamatergic projections to the VTA both directly and indirectly. It is known that VTA DA neurons receive glutamatergic innervations from the mPFC and that the enhancement of this glutamatergic pathway underlies drug addiction [13,14]. However, emerging data indicate that most mPFC projections do not directly terminate on VTA DA neurons [15,16], but rather form direct contacts onto GABAergic cells [7], and then, indirectly innervate VTA DA neurons. Therefore, the mPFC modulates VTA DA neuronal function through complex mechanisms including direct (and/or indirect) excitatory and indirect inhibitory innervations on VTA DA neurons.

Functionally, the mPFC and VTA are closely coupled. Stimulation of the mPFC increases burst firing in VTA DA neurons, while inhibition of the PFC induces the opposite effect [7–11]. Under non-stimulation conditions, the activity of VTA DA neurons co-varies with mPFC neuronal activity [17]. A slow oscillation (of approximately 4 Hz) has been identified that is thought to adaptively synchronize the PFC, VTA and hippocampal activities [18]. Further experimental studies, using simultaneous dual field potential recordings from the mPFC and the VTA, showed that slow oscillations (0.5–1.5 Hz) in the mPFC lead those in the VTA by approximately 30 ms, suggesting that these slow oscillations from the mPFC propagate to the VTA [17]. This idea is further supported by experiments, in which, a dysfunction of the mPFC abolished the neuronal slow oscillations within the VTA. These lines of evidence suggest that the mPFC control of VTA neuronal firing may be through a slow oscillatory pattern [17]. In addition, accumulating studies demonstrate that the mPFC–VTA circuit plays a key role in the attribution of incentive value to addictive drug-associated cues. The mPFC is an associative brain region that contributes to cognitive processes such as attention, spatial learning, behavioral planning and working memory [19]. Nicotine, acting on mPFC nAChRs, enhances working memory and attention [20–22]. There is strong evidence suggesting that mPFC is instrumental to many dimensions of drug abuse, including the expression of behavioral sensitization to psychostimulants [23–25] and drug-primed reinstatement of drug-seeking behavior [26]. Therefore, the mPFC provides functionally important input to the VTA neurons, which may directly control their function. Moreover, systemic exposure to nicotine alters mPFC–VTA coupling, which may also underlie an executive mechanism for both nicotine reward and reinforcement.

3. Neuronal slow oscillation (SO) as an important indicator of PFC–VTA functional coupling

1) *What is the slow-oscillation?* VTA DA neurons exhibit robust oscillatory activity in anesthetized animals over a range frequencies (0–10 Hz). After spectral analysis, oscillations between 0.5 and 1.5 Hz were found to be most dominant in VTA DA neurons, with this range defined as the slow oscillation (SO) [27]. Neurons demonstrating considerable spontaneous SO constituted 50–70% of all VTA DA neurons under resting conditions; we refer to these neurons as high SO neurons. The remaining neurons are collectively referred to as non-SO or low-SO neurons.
2) *How is the SO produced?* Experimental results from rat brain slices and rats with forebrain hemisections show a lack of SO, suggesting that forebrain input plays an important role in generating the SO (Fig. 1). Consistent with this possibility, SO has been observed in mPFC pyramidal neurons [28,29] and in NA neurons [30–33]. Both structures are located in the forebrain and both regions project to VTA DA neurons. Peters et al. show that local field potential recordings in the VTA display a SO that was highly synchronized with oscillations observed in the mPFC [34]. The findings of Peters et al. and Gao et al. suggest that the SO in VTA neurons is related to the activity in the mPFC [17,34].
3) *What is the significance of neuronal SO?* The frequency of the SO is in the low delta band. At the electroencephalographic (EEG) level, delta rhythms are most apparent in slow wave sleep and in general anesthesia but are also detected in wakeful states. For example, human cortical delta oscillations are significantly increased while performing the Wisconsin Card Sorting Test [35]. In the NA of freely moving rats, delta rhythms are highest in amplitude and regularity during wakeful immobility and face washing [35]. Oscillatory firing (1 Hz) of VTA DA neurons may lead to increased DA release [36]. Oscillations may also play a role in somatic and dendritic information processing in DA neurons. Neuronal oscillations functionally regulate input selection, facilitation of synaptic plasticity, and the promotion

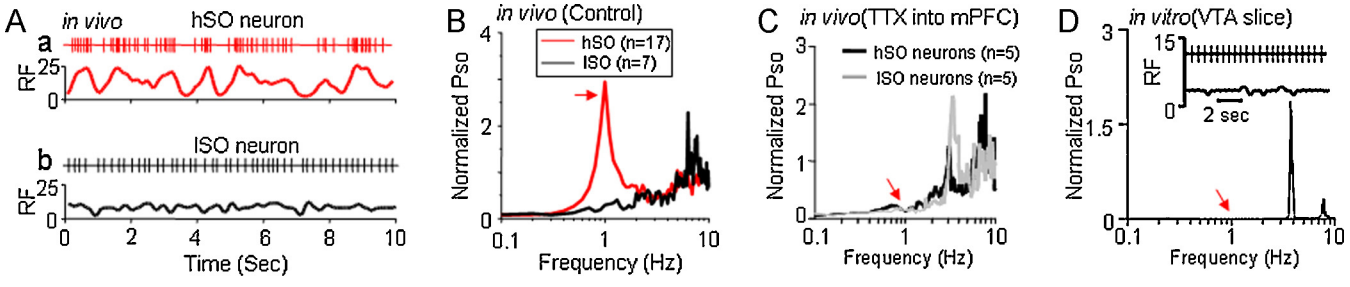

Fig. 1. Two functional states of VTA DA neurons *in vivo*. (A) Representative typical traces of high slow oscillation (h-SO) and low slow oscillation (l-SO) DA neurons recorded from the VTA, shown in (Aa) and (Ab), respectively. Identification of DA neurons was performed using a well-documented protocol. The upper trace illustrates segments of spontaneous spiking, and the bottom trace shows the corresponding smoothed 50 ms bin-width firing-rate histograms. (B) Spectral analysis showed an averaged slow-oscillation power of high slow oscillation (red) and low slow oscillation (black) neurons. (C) Local infusion of TTX (10 ng/μl in PBS, 2 μl) into the mPFC abolished high slow oscillations. (D) In VTA slices, all recorded DA neurons are low slow oscillation neurons ($n = 16$).