Please cite this article in press as: Faure P et al. Role of nicotinic acetylcholine receptors in regulating dopamine neuron activity. Neuroscience (2014), http://dx.doi.org/10.1016/j.neuroscience.2014.05.040

Neuroscience xxx (2014) xxx–xxx

REVIEW

ROLE OF NICOTINIC ACETYLCHOLINE RECEPTORS IN REGULATING DOPAMINE NEURON ACTIVITY

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Abstract—Midbrain dopamine (DA) neurons play a central role in a wide range of behaviors, from attention and motivation to motor control and reinforcement. The release of DA is modulated by a number of factors, and its deregulation has been implicated in multiple psychiatric disorders, such as addiction. In particular, nicotinic acetylcholine receptors (nAChRs) are key modulators of DA cells. Nicotine, the main addictive component in tobacco, strongly interacts with these receptors in the midbrain DA systems, resulting in reinforcing effects that are at the core of tobacco addiction. nAChRs are virtually expressed on every cell of the DA system, both at pre-, post- and extra-synaptic locations. The complex issue of interpreting the role of the large portfolio of different nAChR subtypes expressed on ventral tegmental area (VTA) and substantia nigra pars compacta (SNc) neurons, and especially their role in defining functional DAergic subpopulations, is far from being solved. In this review we will try to provide the reader with an integrative view of the nicotinic modulation of DA neurons and its influence at the cellular, systemic and behavioral levels (exploratory behavior), as well as its implication in the reinforcing effects of nicotine.

This article is part of a Special Issue entitled: [Ventral Tegmentum & Dopamine]. **© 2014 Published by Elsevier Ltd. on behalf of IBRO.**

Key words: nicotine, nAChRs, dopamine, VTA, substantia nigra.

Contents

INTRODUCTION

The midbrain dopamine (DA) systems, originating in the ventral tegmental area (VTA) and in the substantia nigra pars compacta (SNc), and mainly projecting to the ventral and dorsal striatum (mesostriatal pathway) and to the prefrontal cortex (PFC, mesocortical pathway), play a major motivational role in behavioral actions (Montague et al., 2004; Schultz, 2005; Berridge, 2012). Midbrain DA neurons exhibit a patterned spontaneous firing activity, described as a continuum between two distinguishable rhythms: a tonic mode characterized by a slow regular single-spike firing and a phasic mode characterized by a bursting activity (Grace and Bunney, 1984a,b). Regular spiking emerges from intrinsic membrane potential oscillations (Kitai et al., 1999; Roeper, 2013) while the bursting pattern, which is absent in midbrain slice preparations, critically depends on the afferent networks to DA neurons. These afferent networks include the glutamatergic inputs originating in part from the PFC, as well as cholinergic, glutamatergic and γ-aminobutyric-acid-releasing (GABAergic) projections coming from the pedunculopontine tegmental nucleus (PPTg) and the laterodorsal tegmentum nucleus (LDTg, see Grace et al., 2007), but also GABAergic inputs coming from the striatum and the rostral tegmental nucleus (RMTg, or tail

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Abbreviations: ACh, acetylcholine; AP, action potentials; DA, dopamine; ISI, interspike interval; KO, knock-out; LDTg, laterodorsal tegmentum nucleus; LFHB, low-firing, high-bursting; LFLB, low-firing, low-bursting; NAcc, nucleus accumbens; nAChRs, nicotinic acetylcholine receptors; PFC, prefrontal cortex; PPARα, peroxisome proliferator-activated receptors type-α; PPTg, pedunculopontine tegmental nucleus; SA, self-administration; SNc, substantia nigra pars compacta; VTA, ventral tegmental area; WT, wild-type.

http://dx.doi.org/10.1016/j.neuroscience.2014.05.040
0306-4522/

of the VTA see Bourdy and Barrot, 2012). Acetylcholine (ACh) plays a major role in the modulation of the activity of DAergic neurons. ACh binds to two major types of receptors; ionotropic nicotinic (nAChRs) and metabotropic muscarinic (mAChRs) acetylcholine receptors. mAChR-mediated modulation of the DA system recruits multiple ion channels, resulting mainly in an inhibition, but also in some cases in an excitation of DA neurons (Wess, 2003; Picciotto et al., 2012). In this review, we will focus on the cholinergic modulation of DA cell activity that is mediated through nAChRs.

Diversity of DA activity and functions

The dynamic modes of DA cell activity (tonic versus phasic) and their associated DA release underlie the proposed functional and cognitive roles of DA signaling. Their dysregulation is associated with various pathological conditions and notably with addiction (Grace, 1995; Berridge and Robinson, 1998; Schultz, 2007). The burst-firing mode is of particular interest since it causes a DA release of substantially higher amplitude than regular spiking (Gonon, 1988; Tsai et al., 2009). Such a high DA release in the nucleus accumbens (NAcc) promotes appetitive and goal-directed behaviors (Montague et al., 2004; Schultz, 2005). It may also encode unpredicted rewards and prediction of a reward, which are at the basis of various forms of motivation (Berridge and Robinson, 1998; Berridge, 2004; Bromberg-Martin et al., 2010) or reinforcement learning (Schultz, 2007; Dayan and Niv, 2008). Besides encoding appetitive events, it is now proposed that some DA neurons also encode non-rewarding, aversive and alerting events (Brischoux et al., 2009; Matsumoto and Hikosaka, 2009; Bromberg-Martin et al., 2010; Lammel et al., 2011). Noxious stimuli were generally believed to cause an inhibition of DA neurons (Ungless et al., 2004), which would convey a negative motivational signal to target structures. However, recent studies suggest that DA neurons activated and inhibited by aversive events do coexist, and that they are anatomically segregated (Brischoux et al., 2009). These stimuli- and network-dependent processes by which different VTA DA subpopulations are simultaneously excited and inhibited emphasize a critical functional role in the balance of DA release in projection areas. Consistent with this picture, optogenetic bilateral control of the ventral mesostriatal versus the mesocortical pathway was shown to differentially influence behaviors related to stress and depression, respectively (Chaudhury et al., 2013). Therefore, rather than being one DA system, there are many, and rather than being uniform, DA neurons are heterogeneous in their encoding properties, their afferences and their projections, suggesting that DA subpopulations have distinct roles in motivational control. In this review, we analyze the modulation of DA activity by nAChRs, asking whether they can participate in the observed diversity of DA cells in terms of both firing dynamics and network relationship.

Diversity of nicotinic modulation of DA activity

Nicotinic modulation of DA signaling has been of great interest and much research has been focused on studying its mechanisms and its behavioral and cognitive outcomes (Changeux et al., 1998; Di Chiara, 2000; Dani and Bertrand, 2007; Changeux, 2010). Endogenous ACh binds to nAChRs, which are well-characterized, transmembrane allosteric oligomers composed of five identical or different subunits (homo- or hetero-pentamers, respectively) (Changeux et al., 1998; Gotti et al., 2006; Dani and Bertrand, 2007; Taly et al., 2009). Nine α (α2–α10) and three β (β2–β4) subunits are expressed in the vertebrate brain. They can assemble in different combinations to produce receptors with distinct functional and pharmacological properties. Depending on their subunit composition, the receptors show very different affinity for acetylcholine or nicotine (see table in Fig. 1A) (Changeux and Edelstein, 2005). Notable nAChRs include the α7 homopentamer, which has a low affinity for ACh, high calcium permeability and rapid activation and desensitization kinetics, and the α4β2* heteropentamers (asterisk indicates the possible presence of other subunits) which are highly sensitive to agonists and strongly upregulated during chronic nicotine exposure. nAChRs are widely expressed throughout the central nervous system (CNS), at pre-, post- and extra-synaptic locations. They influence neurotransmitter release, neuronal excitability and activity-dependent plasticity in most, if not all, mammalian brain structures. In the midbrain they modulate DA cell activity and DA release according to their location on DA cell bodies, dendrites and terminals in the striatum, but also on glutamatergic, cholinergic and GABAergic afferents of the VTA DA neurons (Fig. 1 B-C). GABA neurons of the VTA and SNc express several nAChRs, including α7 and α4β2 occasionally associated with α3 (Klink et al., 2001; Dani and Bertrand, 2007), whereas the vast majority of DA neurons express α4, α5, α6, α7, β2, β3 and possibly α3 and β4 subtypes (Klink et al., 2001; Grady et al., 2007). The diversity in biophysical properties and location of nAChR subtypes offers a wide range of fine regulation of the DA system. There is also evidence that nAchR-dependent mechanisms in the VTA can be dysregulated, as in the case with nicotine, the main psychoactive molecule found in tobacco. Activation of these receptors has been shown to be necessary and sufficient for reinforcement, tolerance and sensitization to nicotine (Picciotto et al., 1998; Tapper et al., 2004; Maskos et al., 2005). nAChRs are thus pivotal, at the crossroads between physiological modulations of DA cell activity by ACh and pathological conditions such as after nicotine exposure. Recent reviews have extensively described the role of nAChRs at the terminal level in the modulation of DA release (Cragg, 2006; Exley and Cragg, 2008). Here, we will focus on the somatic roles of nAChRs, i.e. on the control of burst firing, their subsequent effects on behavior (with emphasis on exploration), and their implications in nicotine reinforcement. We also concentrate on studies that have used genetic tools to selectively interrogate the roles of nAChRs in the DA systems. To date however, there are no electrophysiological recordings of the VTA DA cells in awake nicotinic mutant mice. Thus the interpretation of behavioral deficits in terms of electrophysiological differences observed in anesthetized animals should be taken with care (see discussion).

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