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REVIEW

THE ANTERO-POSTERIOR HETEROGENEITY OF THE VENTRAL TEGMENTAL AREA

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Abstract—The ventral tegmental area (VTA) is a brain region processing salient sensory and emotional information, controlling motivated behaviors, natural or drug-related reward, reward-related learning, mood, and participating in their associated psychopathologies. Mostly studied for its dopamine neurons, the VTA also includes functionally important GABA and glutamate cell populations. Behavioral evidence supports the presence of functional differences between the anterior VTA (aVTA) and the posterior VTA (pVTA), which is the topic of this review. This antero-posterior heterogeneity concerns locomotor activity, conditioned place preference and intracranial self-administration, and can be seen in response to ethanol, acetaldehyde, salsolinol, opioids including morphine, cholinergic agonists including nicotine, cocaine, cannabinoids and after local manipulation of GABA and serotonin receptors. It has also been observed after viral-mediated manipulation of GluR1, phospholipase Cγ (PLCγ) and cAMP response element binding protein (CREB) expression, with impact on reward and aversion-related responses, on anxiety and depression-related behaviors and on pain sensitivity. In this review, the substrates potentially underlying these aVTA/pVTA differences are discussed, including the VTA sub-nuclei and the heterogeneity in connectivity, cell types and molecular characteristics. We also review the role of the tail of the VTA (tVTA), or rostromedial tegmental nucleus (RMTg), which may also participate to the observed antero-posterior heterogeneity of the VTA. This region, partly located within the pVTA, is an inhibitory control center for dopamine activity. It controls VTA and substantia nigra dopamine cells, thus exerting a major influence on basal ganglia functions. This review highlights the need for a more comprehensive analysis of VTA heterogeneity.

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Key words: dopamine, ventral tegmental area, tVTA, behavior, drugs of abuse.

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INTRODUCTION

The ventral tegmental area (VTA) is studied for its implication in a wide range of functions including the processing of salient sensory and emotional information, the control of motivated behavior, natural or drug-related reward, reward-related learning, mood, and their associated psychopathologies (Nestler and Carlezon, 2006; Fields et al., 2007; Grace et al., 2007; Bromberg-Martin et al., 2010; Hong, 2013; Creed et al., 2014; Gillies et al., 2014; Ikemoto and Bonci, 2014; Meye and

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Abbreviations: aVTA, anterior VTA; CNQX, 6-cyano-7-nitroquinoxaline-2,3-dione; CREB, cAMP response element binding protein; EM-1, endomorphin-1; NMDA, N-methyl-D-aspartate; PLCγ, phospholipase Cγ; pVTA, posterior VTA; RMTg, rostromedial tegmental nucleus; tVTA, tail of the VTA; VTA, ventral tegmental area.

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Adan, 2014; Nikulina et al., 2014; Overton et al., 2014; Walsh and Han, 2014). While most work related to the dopamine cells of the VTA, recent attention has also been given to the GABA and glutamate cell populations (Roeper, 2013; Creed et al., 2014; Morales and Root, 2014). Beyond this cellular heterogeneity, behavioral evidence has accumulated since the late nineties supporting the presence of a major antero-posterior heterogeneity within the VTA (Ikemoto, 2007). The functional difference between the anterior VTA (aVTA) and the posterior VTA (pVTA) is particularly supported by studies of the locomotor, rewarding and reinforcing properties of various drugs of abuse. However, the substrate underlying such aVTA/pVTA differences remains elusive, with hypotheses based on neuroanatomy, connectivity and cellular and molecular heterogeneity. Moreover, in the past decade, an inhibitory control center for midbrain dopamine cells was identified and named the tail of the VTA (tVTA) or rostromedial tegmental nucleus (RMTg). The tVTA is partly located within the pVTA and thus should also be considered when studying the antero-posterior heterogeneity of the VTA.

In this review, we will first describe the behavioral and physiological evidence supporting the antero-posterior heterogeneity of the VTA. Indeed, historically, the first data highlighting the importance of the VTA antero-posterior functional heterogeneity came from experiments of behavioral pharmacology. Most of these studies did a direct side-by-side comparison of intra aVTA and pVTA drug injections. We will then provide information on the possible bases for such heterogeneity, including the presence of subnuclei within the VTA and the presence of potential differences in connectivity, in cell types and in molecular cell characteristics. It is indeed important to also consider the available information on VTA anatomical heterogeneity, even though no direct link has been established yet between the antero-posterior functional heterogeneity and the precise VTA subnuclei. Last, we will summarize the present knowledge on the tVTA, a structure with its most rostral portion within the pVTA and extending caudally beyond the VTA, that exerts a major control over the activity of mesencephalic dopamine cells. The tVTA may have a critical role in basal ganglia functions. While published work has not directly compared the aVTA, pVTA and tVTA, some evidence suggests that the latter structure might be mediating some of the functions that were previously attributed to the pVTA.

VTA ANTERO-POSTERIOR FUNCTIONAL HETEROGENEITY

GABA transmission

A third of a century ago, it was observed that injections of GABA modulators in the VTA had different effects on locomotor activity depending on the injection site (Arnt and Scheel-Kruger, 1979) (Table 1). Agonists of $GABA_A$ receptors increased locomotor activity when delivered in the pVTA but not in the aVTA, while $GABA_A$ antagonists increased activity when delivered in the aVTA but not the pVTA. In the late nineties, Ikemoto et al. observed that Wistar rats self-administered antagonists of the $GABA_A$ receptor, such as picrotoxin and bicuculline, into the aVTA but not into the pVTA (Ikemoto et al., 1997b; Ikemoto, 2005), whereas they self-administered the $GABA_A$ agonist muscimol into the pVTA but not into the aVTA (Ikemoto et al., 1998). These data (Table 1) highlighted the presence of a prominent functional heterogeneity at the level of the GABAergic transmission along the antero-posterior axis of the VTA. However, it may be challenging to control for the anatomical selectivity of local injections, due to the diffusion of injected compounds. Thus, the rewarding effects of $GABA_A$ antagonist in the aVTA were later proposed to be associated with the supramammillary nucleus, a hypothalamic area anterior to the VTA and that plays also a role in reward (Ikemoto, 2005, 2010). Nevertheless, differences in the consequences of pVTA and aVTA manipulations remained valid, and these first functional data on the antero-posterior heterogeneity of the VTA opened the path to other studies, in particular in the field of ethanol action and alcoholism (Table 1). It should be noted that, for a long time, the ''aVTA'' and the ''pVTA'' were functionally compared without the frontier between them being anatomically defined. A study on the response to cocaine showed that the aVTA/pVTA limit in rats was around −5.5 mm from the bregma, which neuroanatomically corresponds to the position of the interpeduncular nucleus below the VTA ((Olson et al., 2005), see cocaine section below).

Ethanol, acetaldehyde and salsolinol

Ethanol behavioral studies. Manipulations of the VTA can modify the ethanol intake in rats (Hodge et al., 1993; Katner et al., 1997). While rats directly self-administer ethanol into the VTA, this reinforcing property displays a neuroanatomical selectivity (Fig. 1, Table 1). Indeed, rats self-administer ethanol into the pVTA but not into the aVTA (Rodd-Henricks et al., 2000, 2003; Rodd et al., 2004b, 2005d; Ding et al., 2014), and the infusion of ethanol into the pVTA also increases the rat locomotor activity (Sanchez-Catalan et al., 2009). Considering data obtained in a strain of alcohol-preferring rats, the preferential sensitivity of the pVTA may be relevant to the vulnerability to alcohol. Alcohol-preferring rats self-infuse lower doses of ethanol into the pVTA than Wistar rats (Rodd et al., 2004a), and the dose of ethanol eliciting self-infusion in the pVTA is even lower after chronic ethanol drinking (Rodd et al., 2005b,c).

Ethanol can act through several ion channels and neurotransmitter systems (Morikawa and Morrisett, 2010), a major mediator of its action being the GABAergic system. In this context, the alcohol intake (Melon and Boehm, 2011) and the conditioned place preference to ethanol (Bechtholt and Cunningham, 2005) may be decreased by a manipulation of $GABA_A$ or $GABA_B$ receptors in the pVTA respectively. However another study was also supportive of an influence of aVTA $GABA_A$ receptors on ethanol intake (Nowak et al., 1998). Despite the pVTA selectivity for ethanol self-administration, it should be noted that the oral ethanol intake and the locomotor effects