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Review article

Opioid-induced rewards, locomotion, and dopamine activation: A proposed model for control by mesopontine and rostromedial tegmental neurons

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ABSTRACT

Opioids, such as morphine or heroin, increase forebrain dopamine (DA) release and locomotion, and support the acquisition of conditioned place preference (CPP) or self-administration. The most sensitive sites for these opioid effects in rodents are in the ventral tegmental area (VTA) and rostromedial tegmental nucleus (RMTg). Opioid inhibition of GABA neurons in these sites is hypothesized to lead to arousing and rewarding effects through disinhibition of VTA DA neurons. We review findings that the laterodorsal tegmental (LDTg) and pedunculopontine tegmental (PPTg) nuclei, which each contain cholinergic, GABAergic, and glutamatergic cells, are important for these effects. LDTg and/or PPTg cholinergic inputs to VTA mediate opioid-induced locomotion and DA activation via VTA M5 muscarinic receptors. LDTg and/or PPTg cholinergic inputs to RMTg also modulate opioid-induced locomotion. Lesions or inhibition of LDTg or PPTg neurons reduce morphine-induced increases in forebrain DA release, acquisition of morphine CPP or self-administration. We propose a circuit model that links VTA and RMTg GABA with LDTg and PPTg neurons critical for DA-dependent opioid effects in drug-naïve rodents.

1. Introduction

Opioids have analgesic, anxiolytic, and euphoric effects leading to widespread use, dependence and addiction in humans (Nutt and Lingford-Hughes, 2008). Development of long-lasting, potent synthetic opioids has heightened these risks, and increased use, rates of dependence, and death (Gruber et al., 2007; Kalant, 1997; Murthy, 2017).

In rodents, the critical midbrain sites of action for opioids, and especially the circuits connecting these sites, remain controversial (see reviews by Badiani et al., 2011; Barrot et al., 2012; Ikemoto, 2010; Le Merrer et al., 2009; Madhavan et al., 2010; Smith and Berridge, 2007). Opioid-mediated disinhibition of ventral tegmental area (VTA) dopamine (DA) neurons has been an influential theory to explain DA-dependent opioid reward. Initially, it was proposed that opioids act on μ-opioid receptors (μ-ORs) to inhibit VTA gamma-aminobutyric acid (GABA) neurons that provide tonic inhibition to neighboring VTA DA neurons, in turn disinhibiting mesolimbic DA neurons (Gysling and Wang, 1983; Johnson and North, 1992; Klitenick et al., 1992; Margolis et al., 2014; Matthews and German, 1984). More recently defined rostromedial tegmental nucleus (RMTg) GABA neurons project to and inhibit VTA DA neurons (Jhou et al., 2009a,b; Lecca et al., 2012). RMTg GABA neurons are strongly inhibited by opioids and this is followed by disinhibition of VTA and substantia nigra pars compacta (SNc) DA neurons (Jalabert et al., 2011; Lecca et al., 2012, 2011; Matsui and Williams, 2011).

In our view, the most critical short-coming of previous circuit models is their inability to explain the critical role of mesopontine tegmental nuclei – the laterodorsal tegmental nucleus (LDTg) and the pedunculopontine tegmental nucleus (PPTg) – in the acquisition of opioid reward. Lesions of mesopontine tegmental nuclei or blockade of muscarinic acetylcholine receptors (mAChR) in the VTA inhibit the acquisition of opioid self-administration, conditioned place preference (CPP) or locomotion as effectively as pharmacological antagonists of DA receptors or mesolimbic DA lesions (e.g., Basile et al., 2002; Gerrits

Abbreviations: μOR, mu opioid receptor; ACh, acetylcholine; AChR, acetylcholine receptor; ChAT, choline acetyltransferase; CPP, conditioned place preference; DA, dopamine; DREADD, designer receptors exclusively activated by designer drugs; GABA, gamma-aminobutyric acid; GAD, glutamic acid decarboxylase; hM3D, muscarinic 3 designed receptor (DREADD); hM4D, muscarinic 4 designed receptor (DREADD); HSV, herpes simplex virus; KO, knockout; LDTg, laterodorsal tegmental nucleus; mAChR, muscarinic acetylcholine receptor; NAcc, nucleus accumbens; PPTg, pedunculopontine tegmental nucleus; RMTg, rostromedial tegmental nucleus; SNc, substantia nigra pars compacta; VGluT2, vesicular glutamate transporter-2; VTA, ventral tegmental area; WT, wild-type

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and Van Ree, 1996; Nader and van der Kooy, 1997; Pettit et al., 1984; Steidl and Yeomans, 2009; Vaccarino et al., 1986).

Here we review where opioids act in the brain to induce DA activation, locomotion, and reward in drug-naïve animals. We emphasize the involvement of PPTg and LDTg neurons and their reciprocal projections to the VTA and RMTg in the behavioral responses of drug-naïve animals to initial opioid exposure (Lavezzi et al., 2012; Lavezzi and Zahm, 2011; Omelchenko and Sesack, 2006, 2005; Wasserman et al., 2016, 2013; Watabe-Uchida et al., 2012). In this review, we primarily focus on acute opioid exposure and do not address the potential brain changes resulting from long-term exposure to opioids or neurobiological mechanisms of dependence and relapse.

2. Rewarding effects of opioids and dopamine

Intracranial morphine self-administration was first achieved with cannulae placed in the VTA near mesolimbic DA neurons (Bozarth and Wise, 1981a; David and Cazala, 1994; David et al., 2002; Devine and Wise, 1994; Welzl et al., 1989) where μ-ORs are found (Erbs et al., 2015; Kitchen et al., 1997; Mansour et al., 1987). VTA infusions of morphine, or DAMGO, a μ-OR agonist, or endomorphin-1, an endogenous μ-OR ligand, also lead to the acquisition of CPP (Bals-Kubik et al., 1993; Phillips and LePiane, 1980) or support self-administration (Zangen et al., 2002). μ-OR blockers, such as naloxone, infused near the VTA block morphine CPP of systemic opioids (Olmstead and Franklin, 1997). Early studies also showed that DA receptor blockers or 6-OHDA lesions attenuated heroin CPP or self-administration (Bozarth and Wise, 1981b; Spyraki et al., 1983). However, further studies showed that mesolimbic DA terminals or DA receptors in nucleus accumbens (NAcc) are not necessary for either heroin self-administration (Ettenberg et al., 1982; Pettit et al., 1984) or locomotion induced by intra-NAcc infusions of an enkephalin analog (Kalivas et al., 1983; Vaccarino et al., 1986).

In addition, morphine infusions into the NAcc, where high densities of opioid receptor subtypes are expressed (Erbs et al., 2015; Kitchen et al., 1997; Mansour et al., 1987) − downstream from dopaminergic synapses − support self-administration in rats and mice (Olds, 1982; David and Cazala 2000). Injections of the opioid antagonist methylnaloxonium into the NAcc, for example, have been shown to block locomotion induced by systemic heroin in rats (Amalric and Koob, 1985). However, while DA is not necessary for opioid-induced locomotion in rats, chronic blockade of dopaminergic transmission by either mesolimbic 6-OHDA lesions (Stinus et al., 1985) or prolonged systemic neuroleptic drugs (Stinus et al., 1986) results in supersensitivity to locomotion induced by NAcc injections of morphine, suggesting that a functional DA system in fact reduces sensitivity to NAcc opioid-induced locomotion.

3. Mesopontine cholinergic and glutamate neurons activate DA neurons and rewards

3.1. LDTg or PPTg activation excites mesolimbic or nigrostriatal dopamine pathways

The LDTg and PPTg provide sources of input to the VTA and SNc (Geisler and Zahm, 2005; Oakman et al., 1999, 1995; Watabe-Uchida et al., 2012; Woolf, 1991). Within each of the LDTg and PPTg, three largely separate populations of neurons are found: cholinergic neurons expressing choline acetyltransferase (ChAT), glutamatergic neurons expressing the vesicular glutamate transporter-2 (VGluT2), and GABAergic neurons expressing glutamic acid decarboxylase (GAD) (Wang and Morales, 2009). Electrical stimulation of the LDTg or PPTg in urethane-anesthetized rats increases DA efflux in the NAcc or striatum, respectively. These DA outputs depend on both cholinergic and glutamatergic receptors in the VTA and the neighboring SNc (Forster and Blaha, 2000, 2003). Increases in NAcc DA, immediately following LDTg electrical stimulation (Fig. 1A), and increases in dorsal striatal DA, immediately following PPTg electrical stimulation, depend on nicotinic and ionotropic glutamate receptors in the VTA or SNc, respectively. After a decrease in basal DA levels (due to inhibitory M2 and M4 muscarinic autoreceptors in LDTg or PPTg), DA levels increase again and remain elevated for approximately 60 min. The late and prolonged phase in increased accumbal or striatal DA efflux is completely blocked in rats by the mAChR antagonist, scopolamine, in the VTA or SNc, respectively (Forster and Blaha, 2003, 2000), or by systemic knockout of M5 mAChRs in mice (Fig. 1B; Forster et al., 2002b; Steidl et al., 2011). Therefore, M5 mAChR − the only subtype of mAChR expressed by midbrain DA neurons (Vilaro et al., 1990) − are responsible for most of the excitatory effects of LDTg or PPTg electrical stimulation on forebrain DA efflux (Yeomans et al., 2001).

Electrophysiological recordings from VTA DA neurons support the critical role of the LDTg in regulating mesolimbic DA activity. DA neurons burst firing induces large transient increases in forebrain DA that are thought to be functionally relevant for encoding reward prediction and incentive salience (Berridge and Robinson, 1998; Cooper, 2002; Grace, 1991; Schultz, 1998). Following LDTg chemical inactivation, VTA DA neurons fail to burst fire, either in response to activation of PPTg inputs, which usually reliably elicit burst firing, or in response to direct VTA application of glutamate (Floresco et al., 2003; Lodge and Grace, 2006).

3.2. Rewarding effects of acetylcholine and glutamate in the ventral tegmental area

A role for cholinergic input to the VTA in reward function has been clearly established over the last 3 decades. Feeding, drinking, rewarding electrical brain stimulation of the lateral hypothalamus, or intravenous cocaine self-administration each increase ACh levels in VTA (Rada et al., 2000; You et al., 2008). In rats, brain-stimulation reward thresholds are dose-dependently increased by up to 100% by the muscarinic blockers atropine or scopolamine infused into the VTA, or by 20% by nicotinic blockers infused into the VTA (Kofman and Yeomans, 1988; Yeomans and Baptista, 1997; Yeomans et al., 1985). Inhibition of M5 gene expression in the VTA by M5 antisense oligonucleotides similarly increases reward thresholds by 30–100% (Yeomans et al., 2000). Muscarinic blockers in the VTA also block the acquisition of food self-administration in rats (Sharf et al., 2006; Sharf and Ranaldi, 2006) and increase intravenous cocaine self-administration in rats (You et al., 2008). VTA infusions of the cholinergic receptor agonist carbachol induce CPP and support operant self-administration (Ikemoto and Wise, 2002; Yeomans et al., 1985). VTA infusions of the cholinesterase inhibitor neostigmine also support operant self-administration in rats (Ikemoto and Wise, 2002). VTA self-administration of carbachol is reduced by VTA co-administration of either a muscarinic or a nicotinic receptor antagonist.

VTA cholinergic signaling is also associated with conditioned rewarding effects. Muscarinic AChR antagonists in the VTA reduce conditioned responding for food-associated cues (Addy et al., 2015; Wickham et al., 2015) and cue-driven cocaine seeking (Solecki et al., 2013). Conversely, VTA microinjections of physostigmine, an inhibitor of acetylcholinesterase, increase cue-induced reinstatement responding of extinguished heroin seeking (Zhou et al., 2007). In addition, VTA ACh levels, measured by microdialysis in rats trained to self-administer intravenous cocaine, increase following cocaine or following conditioned cues associated with cocaine (You et al., 2008).

Unlike the cholinergic agonist carbachol, rats do not self-administer the glutamate receptor agonist AMPA into the VTA (Ikemoto et al., 2004), and VTA infusions of the glutamate receptor agonist NMDA are also only weakly reinforcing (Ikemoto, 2004). VTA glutamatergic signaling is also associated with conditioned rewarding effects. VTA glutamate levels, measured by microdialysis in rats self-administering intravenous cocaine (You et al., 2007) or heroin (Wang et al., 2012), increase following conditioned cues for the drug, but not following