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Local control of striatal dopamine release

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The mesolimbic and nigrostriatal dopamine (DA) systems play a key role in the physiology of reward seeking, motivation and motor control. Importantly, they are also involved in the pathophysiology of Parkinson's and Huntington's disease, schizophrenia and addiction. Control of DA release in the striatum is tightly linked to firing of DA neurons in the ventral tegmental area (VTA) and the substantia nigra (SN). However, local influences in the striatum affect release by exerting their action directly on axon terminals. For example, endogenous glutamatergic and cholinergic activity is sufficient to trigger striatal DA release independently of cell body firing. Recent developments involving genetic manipulation, pharmacological selectivity or selective stimulation have allowed for better characterization of these phenomena. Such termino-terminal forms of control of DA release transform considerably our understanding of the mesolimbic and nigrostriatal systems, and have strong implications as potential mechanisms to modify impaired control of DA release in the diseased brain. Here, we review these and related mechanisms and their implications in the physiology of ascending DA systems.

Keywords: dopamine, acetylcholine, glutamate, striatum, optogenetics, axonal release, volume transmission

INTRODUCTION: ROLE OF DA IN MOTOR AND LIMBIC FUNCTION

Dopamine (DA) plays a critical role in the organization of reward-seeking behavior and motor responses (Joshua et al., 2009; Schultz, 2013). Through the mesolimbic and nigrostriatal DA systems, the forebrain receives dopaminergic input that modulates a range of functionally distinct structures, such as the basal ganglia and cerebral cortex (Björklund and Dunnett, 2007; Tritsch and Sabatini, 2012). The mesolimbic system is formed by dopaminergic neurons located in the VTA and their projections to the nucleus accumbens (NAc), cortex, amygdala and hippocampus, which participate in the configuration of reward-seeking behaviors (Björklund and Dunnett, 2007; Stuber et al., 2012; Nieh et al., 2013). The nigrostriatal system has its origin in the substantia nigra pars compacta (SNc) and projects preferentially to the dorsolateral domains of the striatum, having a more defined role in the organization of motor plans (Groenewegen, 2003; DeLong and Wichmann, 2007). Such functional distinction at the level of the striatum seems to have structural and molecular correlates on DA neurons from the SNc (Henny et al., 2012; Schiemann et al., 2012). Additional to these functional implications, dopaminergic transmission is compromised in a variety of neurological conditions such as schizophrenia, Huntington's and Parkinson's disease, drug addiction and obsessive-compulsive disorder, among others (DeLong and Wichmann, 2007; Money and Stanwood, 2013).

The striatum is the main input nucleus of the basal ganglia, and DA modulates how this input is processed (Calabresi et al., 1997; Centonze et al., 2001; Tritsch and Sabatini, 2012). However, in contrast to the traditional view of inter-neuronal chemical excitatory synaptic transmission in which structural and functional specializations are observed at the postsynaptic domains, striatal dopaminergic transmission does not always require such level of postsynaptic structural specialization (Rice and Cragg, 2008; Fuxe et al., 2012). Instead, release occurs in a diffuse manner, DA receptors are extrasynaptic and ultrastructural studies on the extension and density of DA neuron axonal arborization in the striatum point to broad, intricate projections that cover vast areas (Pickel et al., 1981; Smith et al., 1994; Moss and Bolam, 2008; Matsuda et al., 2009). This diffusely spread mode of transmission (in contrast to localized, highly spatially restricted communication), is termed "volume transmission", and is a feature of a number of transmitters such as acetylcholine, norepinephrine, DA and serotonin (Taber and Hurley, 2014). Volume transmission of DA is, however, not exclusive to the striatum and it has its own particularities through different areas (Rice and Cragg, 2008; Fuxe et al., 2012; Martin and Spühler, 2013; Taber and Hurley, 2014). DA as a volume transmitter in the striatum is thought to exert a widespread modulatory influence on excitatory—glutamatergic—transmission arriving from the cortex, basolateral amygdala (BLA), and ventral hippocampus (vHipp; Britt et al., 2012); or on inhibitory—GABAergic—transmission incoming from areas such as VTA (Van Bockstaele and Pickel, 1995) and ventral pallidum (Churchill and Kalivas, 1994).

DA modulation of incoming transmission to the striatum plays a key role in the functional expression of reward-seeking behaviors and motor control. Such functions exhibit some stratification

within the striatum (Threlfell and Cragg, 2011). For example, dorso-medial and dorso-lateral areas are predominantly involved in motor control, while ventro-medial segments are mostly involved in the expression of reward processing, motivation and salience (Groenewegen, 2003; Voorn et al., 2004; Kreitzer and Berke, 2011; Stuber et al., 2012). Concurrently, cortico-striatal projections also exhibit a stratified distribution in which the motor and cingulate cortices form the primary input to the dorso-lateral striatum, while prefrontal and prelimbic cortices project mainly to ventro-medial areas of the striatum (Voorn et al., 2004). Phenomena responsible for regulation of striatal DA release can be VTA/SNc driven, or locally acting, at the striatal level. This latter possibility has long been reported, still attracts considerable attention in terms of mechanistic characterization (Cachope et al., 2012; Threlfell et al., 2012) and is considered as an opportunity for functionally-segregated intervention (Threlfell and Cragg, 2011).

MULTIPLICITY OF MECHANISMS IN THE CONTROL OF DOPAMINE RELEASE

Through what are now seminal papers, Wolfram Schultz et al. demonstrated that firing of DA neurons in the midbrain increases in response to rewarding stimuli in non-human primates (Schultz et al., 1997; Schultz, 1998), while functional imaging studies in humans point to a similar increase in cellular activity (D'Ardenne et al., 2008), suggesting correspondence with Schultz's group reports. Interestingly, it was recently described that VTA GABAergic neurons also encode reward expectation (Cohen et al., 2012). Recordings of DA neurons from the VTA or SNc areas in rodents exhibit slow, tonic firing rates that periodically switch to a high frequency events (Grace and Bunney, 1984a,b). Thus, low levels of DA release have been correlated with low frequency firing rate of DA neurons, while corresponding enhancement in striatal DA release occurs in response to high frequency firing rates (Kawagoe et al., 1992). These findings have sculpted the traditional view of striatal DA release being determined by the rate of neuronal firing of the DA neuron somatas located in either VTA or SNc. However, besides this dominant mechanism of control of DA release, local factors such as reuptake, autoreceptor-dependent modulation, and termino-terminal control exist and are recognized to play a prominent role, independently of VTA/SNc firing rate.

DA neurons projecting to the striatum establish prominent axonal trees at their destination. The volume transmission feature of striatal DA implies that a considerable amount of control is required in terms of uptake and/or negative feedback on future release events. In reaching this goal, two key mechanisms are DA transporter activity (DAT) and D2-like presynaptic autoreceptor activity. DAT activity is thought to limit the radius of DA activity (Rice and Cragg, 2008) and, by doing so, restricts activation of DA receptors (reviewed in Rice et al., 2011). In a similar manner, it is known that blockade of D2-like DA receptors in slices leads to increased DA release in response to repetitive electrical stimulation (Limberger et al., 1991; Patel et al., 1992). This effect, however, is not manifest when single pulse stimulation is used (Limberger et al., 1991; Patel et al., 1992), suggesting that there is not sufficient DA tone elicited by a single pulse to be displaced by the antagonist. Importantly, changes in D2 receptor levels and their subsequent activation are thought to play a prominent role in several neurological conditions in which DA levels are altered (Ford, 2014).

LOCAL STRIATAL CONTROL OF DOPAMINE RELEASE

GLUTAMATERGIC TRANSMISSION

Excitatory glutamatergic activity in the striatum originates mainly from frontal cortex, midline and intralaminar thalamus, basal amygdala, and hippocampus (reviewed in Sesack and Grace, 2010; Stuber et al., 2012). Additionally, DA terminals release glutamate (Sulzer et al., 1998; Joyce and Rayport, 2000; Sulzer and Rayport, 2000; Chuhma et al., 2004; Dal Bo et al., 2004; Chuhma et al., 2009; Hnasko et al., 2010), and this has recently been demonstrated by way of selective optogenetic stimulation of DA terminals (Stuber et al., 2010). However, this last report demonstrates that such possibility exists only in DA terminals that reach the NAc, not the dorsal striatum. Still, some debate prevails as to this feature not being present in the adult brain (Bérubé-Carrière et al., 2009; Moss et al., 2011), or being as widespread as initially thought (Stuber et al., 2010; for a review, see Broussard, 2012).

Evidence on the potential role of glutamate as a form of local control of DA release in the striatum has long been reported (Imperato et al., 1990; Cheramy et al., 1991; Krebs et al., 1991; Desce et al., 1992) and both ionotropic and metabotropic glutamate receptors (iGluR; mGluR, respectively) have been implicated. However, most of the initial studies were performed *in vivo* using brain microdialysis as the measuring technique to assess DA levels as well as for local administration of glutamate receptor ligands. Such findings were of course influenced by slow temporal resolution and the effects of the ligand in a complex circuit, among other factors, making a mechanistic interpretation difficult. *In vitro* experimental designs, on the other hand, allowed for more direct mechanistic description while still not directly addressing whether results were equivalent to intact-tissue conditions. These distinct experimental conditions might account for what, at the time, were apparent contradictory results. Initial *in vitro* explorations in slices and synaptosomes accounted not only for glutamate, but for a range of neurotransmitters that could affect striatal DA release locally, including acetylcholine, GABA, glycine and opiates (reviewed in Chesselet, 1984). However, further *in vivo* experiments in freely moving rats were still non conclusive; i.e., activation of AMPA receptors by exogenous ligands led to a decrease in DA release, while an increase was evident only in response to the application of NMDA receptor ligands at high concentrations (Imperato et al., 1990). Blocking uptake of endogenous release, in turn, elevated DA release in a way that was sensitive to the application of either NMDA or AMPA antagonists, suggesting the involvement of both receptor types in that response (Segovia et al., 1997). Similarly, electrical stimulation of the prefrontal cortex, a putative glutamatergic input to striatum, as well as local application of kainate or NMDA increased DA release (Cheramy et al., 1991; Krebs et al., 1991). Development of electrochemical techniques, however, greatly contributed to the clarification of these mechanisms. The use of fast-scan cyclic voltammetry (FSCV) for the detection of DA *in vitro* allowed for

better temporal resolution which was less influenced by circuit adaptive responses in the mid-term scale (minutes), which could potentially influence DA readout. Under those conditions, bath application of kainate, AMPA or NMDA elicited inhibition of DA release (Wu et al., 2000; Kulagina et al., 2001; Avshalumov et al., 2003). Moreover, electron microscopy studies were not able to demonstrate labeling of iGluRs in striatal DA terminals (Bernard et al., 1997; Bernard and Bolam, 1998). The lack of expression of iGluRs on DA terminals suggests that iGluR-mediated modulation of DA release relates to a more complex process; which may underlie interactions between multiple cellular types and/or chemical mediators. This issue, raised and investigated by Rice's group led to the identification of H_2O_2 as a key molecule in the iGluR-mediated decrease of DA release (Avshalumov et al., 2000, 2003, 2008; Avshalumov and Rice, 2003). This model describes how glutamatergic activity on ionotropic receptors in medium spiny neurons (MSNs) triggers production and release of H_2O_2, which in turn diffuses to adjacent DA terminals and promotes opening of K_{ATP} channels leading to reduction of DA release (Avshalumov et al., 2008).

In contrast to iGluRs, labeling of mGluRs has been reported in presynaptic profiles identified as DA axons (Paquet and Smith, 2003). Moreover, blocking glutamate uptake, or high-frequency stimulation of the cortico-striatal pathway modulates DA release, in a mGluR-dependent fashion followed by modulation of Ca^{++}-activated potassium channels (Zhang and Sulzer, 2003). Altogether, the existent evidence points to mGluR-mediated direct action on DA terminals, and a second MSN-mediated mechanism involving iGluR-H_2O_2 signaling.

CHOLINERGIC TRANSMISSION

In contrast to striatal glutamatergic activity, which originates mainly from inputs to the striatum, sources of striatal acetylcholine release are mostly from cholinergic interneurons (CINs) that account for about 2–5% of all striatal neurons (Descarries et al., 1997; Descarries and Mechawar, 2000). Additional to CINs, a recent report shows that brainstem-based cholinergic neurons send terminals to the striatum in a topographic fashion with their origin (Dautan et al., 2014). In spite of their low numbers, CINs establish prominent and intricate axonal projections that configure an extensive planar neurotransmission system (Descarries et al., 1997; Descarries and Mechawar, 2000). Electrophysiological characterization shows that CINs are tonically active neurons that fire at a relatively low rate of about 5–10 Hz (Wilson et al., 1990; Aosaki et al., 1995). This rate, however, as in the case of DA neurons, encodes behaviorally relevant reward-related events (Apicella et al., 1991, 2011; Aosaki et al., 1994, 1995; Shimo and Hikosaka, 2001; Morris et al., 2004).

Target receptors of cholinergic activity in the striatum are both of nicotinic and muscarinic types (nAChR and mAChR, respectively). While mAChRs are seven trans-membrane domain G-protein coupled receptors, nAChRs consist of five subunits arranged as homomers or heteromers that, in mammals, are formed by subfamilies II (α7) and III (α2-6, β2-4) (Le Novère et al., 2002). Particularly, striatal DA axons express a high density of α4, α5, α6, β2 and β3 subunits in an arrangement of two αβ pairs that could be α4-β2 and/or α6-β2 and/or α4-β4, plus a fifth subunit that can be α5 or β3 (Champtiaux et al., 2003; reviewed in Threlfell and Cragg, 2011). Additionally, the β2 subunit is expressed on striatal DA axons (Jones et al., 2001) and is included in all nAChRs at these terminals. This characterization is functionally relevant because some segregation exists in which predominance of different α subunits occurs between dorsolateral striatum and the NAc. More specifically, a significant amount of work has shown that α4(non-α6)-nAChRs play a prominent role in dorsal striatum, while α4α6-nAChRs are dominant in NAc (Exley et al., 2008, 2011, 2012). Given the distinct functional role of the dorsolateral and the ventromedial striatum, it has been proposed that such differences could be taken into account as a substrate for region-specific intervention (Threlfell and Cragg, 2011).

mAChRs, in turn, are classified in two groups according to their coupling to either G_s (M_1, M_3, M_5) or G_i (M_2, M_4) subunits of G proteins, with M_2 and M_4 predominantly expressed in CINs (Yan and Surmeier, 1996). In a similar way to what has been described for nAChRs, mAChRs exhibit some dorso-ventral gradient in their ability to regulate DA release. While M_2/M_4 receptors are necessary for such regulation in the dorsal striatum, M4 is prevalent in the NAc (Threlfell et al., 2010). Additionally, expression of M_5 receptors has been reported in nigrostriatal DA neurons, although their pattern of expression on striatal DA terminals and subsequent potential role in local control of DA release remains unclear (reviewed in Threlfell and Cragg, 2011; Zhang and Sulzer, 2012).

Involvement of presynaptic cholinergic receptors on DA regulation was inferred early, mainly from experiments describing increase of DA release in response to AChR activation in slices or synaptosomes (Giorguieff et al., 1976, 1977; Wonnacott et al., 1989; Rapier et al., 1990). In a similar way to what occurred with the characterization of glutamatergic-dependent DA modulation, transition to electrochemical methods to quantify DA allowed for a better temporal resolution. Importantly, FSCV has been critical in determining a high dependence of DA release on stimulation frequency under the effect of nicotine. More specifically, in a striatal slice, the maximum peak of DA release does not change significantly through different frequencies (5, 10, 25, 50 Hz) of electrical stimulation. However, in the presence of nicotine or the nAChR antagonist mecamylamine, DA release at low frequencies is decreased, while at high frequencies release is enhanced (Rice and Cragg, 2004).

While electrical stimulation combined with pharmacological and genetic manipulations have produced a wealth of information on cholinergic control of DA release (Giorguieff et al., 1977; Cheramy et al., 1991; Krebs et al., 1991; Desce et al., 1992; Tremblay et al., 1992; Chéramy et al., 1996; Schmitz et al., 2003; Zhang and Sulzer, 2003, 2012; Exley and Cragg, 2008; Exley et al., 2011; reviewed by Cragg, 2006; Rice et al., 2011; Threlfell and Cragg, 2011; Zhang and Sulzer, 2012), the advent of optogenetics offered the previously unseen possibility of selective control of CINs. This would allow inducing AChR activation by means of endogenous release of ACh, obtained by

selective stimulation of striatal CINs. Taking advantage of *in vitro* slices, electrochemistry, and optogenetics, both the laboratory of Stephanie Cragg (Threlfell et al., 2012) and ours (Cachope et al., 2012) were interested in characterizing changes in striatal DA levels in response to endogenous AChR activation. Interestingly, both research groups were advancing on characterizing similar phenomena in functionally different striatal areas, showing how endogenous release of ACh directly triggers DA release in the dorsal striatum and the NAc, respectively. Additionally to demonstrating how selective activation of CINs is enough to trigger DA release in striatum and NAc, respectively, both reports confirmed the role of nAChRs and mAChRs in modulating such output. Moreover, Cragg's report very nicely unveiled circuital mechanisms by which thalamic input synchronizes CIN firing, subsequently promoting DA release (Threlfell et al., 2012). Our experiments focused instead on the possibility of CINs-triggered DA release *in vivo* (Cachope et al., 2012). Consistently with the *in vitro* data, optogenetic stimulation of CINs in the anesthetized mouse was sufficient to trigger elevation of DA concentrations in the NAc. Also, following Sabatini's group's report regarding the ability of CINs to evoke glutamatergic responses (Higley et al., 2011), we showed that ACh-evoked DA release is sensitive to AMPA blockers (Cachope et al., 2012).

In the case of mAChRs, they can also locally modulate DA release in the striatum. *In vitro* experiments with FSCV show how a wide range mAChR antagonist (oxotremorine) decreases DA release evoked by single pulse electrical stimulation, but enhances DA levels in response to train stimulation (Threlfell et al., 2010). A similar effect was observed using selective optogenetic stimulation, in which single pulse optical stimulation did not affect DA release, but instead 5 and 10 Hz stimulation enhanced DA release under application of the mAChR antagonist scopolamine (Cachope et al., 2012; Threlfell et al., 2012).

A complex interaction between diverse neurotransmission and neuromodulatory systems takes place in the control of striatal DA release. Although we have focused on the effect of glutamatergic and cholinergic systems, a handful other receptors have been identified as able to alter striatal DA levels; including GABA, cannabinoid, purinergic and opioid. Interestingly (and, up to some point expected), the possibilities for diversity on this local control are dependent on the type of receptor, not just the type of transmitter/modulator being released. Both in the case of glutamate and acetylcholine, different receptors lead to distinct and even opposite effects. As illustrated in **Figure 1**, mGluR activation on DA terminals and iGluR activation on MSNs result both in modulation of K conductances decreasing DA release. In contrast, activation of nAChRs on DA terminals leads to increased DA release, while activation of mAChR autoreceptors expectedly result in decreased DA release. More importantly, all these results demonstrate that firing rate at the VTA and SNc does not entirely determine striatal DA output, leaving enough room for control mechanisms driven by input from other areas (glutamatergic), as well as by interneurons (cholinergic), which might exert considerable impact on it.

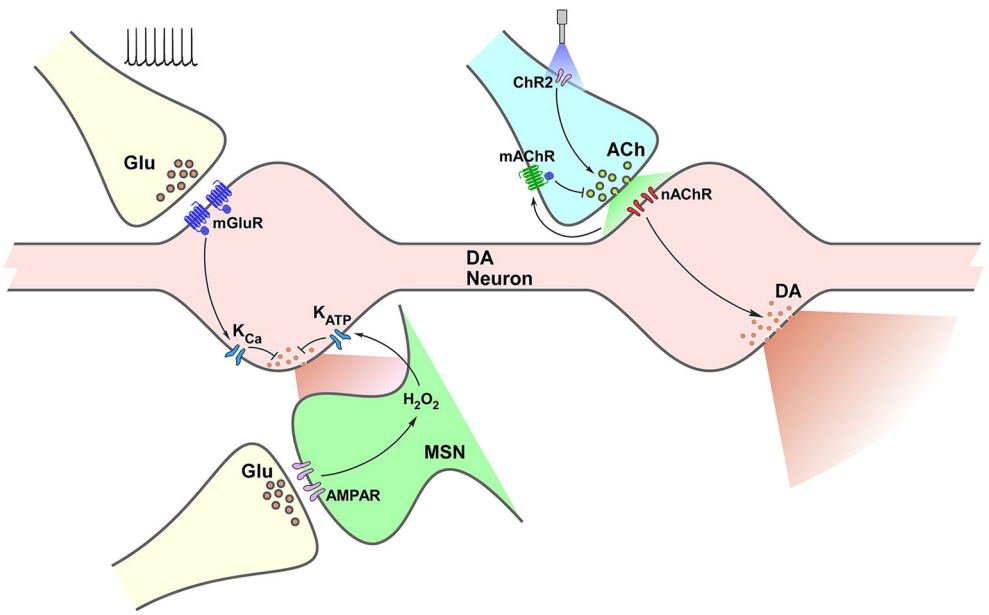

FIGURE 1 | Termino-terminal control of dopamine (DA) release in the striatum. Model diagram of glutamatergic (left side of graph) and cholinergic (right side of graph) local influences on striatal DA release. Electrically-evoked glutamate release activates mGluRs located on dopaminergic varicosities increasing Ca^{++}-sensitive K channels (K_{Ca}) conductance, which leads to reduction of DA release. Activation of iGluRs on MSNs elevates production of H_2O_2, which diffuses to DA varicosities enhancing ATP-sensitive K channels (K_{ATP}) conductance reducing DA release. Optogenetic selective activation of cholinergic interneurons (CINs) through channelrhodopsin (ChR2) triggers ACh release, increasing nAChR activation on DA varicosities, triggering DA release. Activation of mAChRs on cholinergic terminals decreases ACh release and further nAChR activation, which would result in decreased DA release.

CONCLUDING REMARKS

The role of DA in essential behaviors such as reward-seeking, motivation and motor control has been extensively studied. Regulation of DA release at both the dorso-lateral striatum and the NAc is considered to be mainly the consequence of changes in firing rate at the level of DA somata in the SNc and the VTA, correspondingly. Local control at the level of the striatum has been traditionally linked to DA reuptake and to feedback control on DA release through activation of D2 autoreceptors. However, reports on termino-terminal control of DA release, although scarce decades ago provided key findings in understanding a more complex control system than the one defined just by firing rate at DA neuronal somata. To date, the influence of non-DA striatal terminals on striatal DA release has been explored in a variety of experimental conditions, including synaptosomes, *in vitro* slices and *in vivo* preparations. Not only pharmacological, but genetic, optogenetic, electrophysiological and electrochemical strategies have been used to unveil the localization, role, extent and functional impact of such local influences. Glutamatergic and cholinergic systems have attracted the most attention so far. Still, although highly characterized in terms of types of receptors and neurotransmitters involved, there is not enough evidence on the functional impact of these forms of regulation in the behavioral setting. CINs modify their firing rate in animals subject to behavioral tasks encoding reward delivery as a decrease in firing rate, following a mild increase in frequency of firing (Apicella et al., 1991, 2011; Aosaki et al., 1994; Shimo and Hikosaka, 2001; Morris et al., 2004). Also, a recent report shows a differential role of DA neurons modulating CINs firing in dorsal striatum and NAc (Chuhma et al., 2014). However, there is no clarity as to how prominent all those interactions are in terms of their ability to affect DA release, and even less is known about the role of such variations, if they might impact behavior, or if DA transmission is otherwise still VTA- and SNc-driven.

One of the main strategies to fully develop yet is the potential of targeting these modulation systems to affect striatal DA release in conditions such as Parkinson's disease, schizophrenia, addiction, Huntington's disease, in which DA levels have been reported to be altered. As already outlined by Threlfell and Cragg (2011), modulating the striatal cholinergic system through subunit-specific modulation of nAChR and mAChR promises to be a useful approach. Temporal dynamics are a critical feature of inter-neuronal transmission. Behavioral events have, for example, phasic changes in striatal DA levels as correlates in the limbic and motor areas (O'Neill and Fillenz, 1985; Schultz, 2007a,b; Joshua et al., 2009). A significant proportion of therapeutic strategies are based on ligands that exert a sustained effect on neurotransmitter receptors, cancelling such changes over time. While DA neuron somata drive phasic changes in DA release, termino-terminal control might be seen as a mechanism that allows for fine regulation over that main drive, still preserving most of the temporal dynamics.

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