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Mini-review

Neurotransmitter roles in synaptic modulation, plasticity and learning in the dorsal striatum

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ABSTRACT

The dorsal striatum is a large forebrain region involved in action initiation, timing, control, learning and memory. Learning and remembering skilled movement sequences requires the dorsal striatum, and striatal subregions participate in both goal-directed (action-outcome) and habitual (stimulus–response) learning. Modulation of synaptic transmission plays a large part in controlling input to as well as the output from striatal medium spiny projection neurons (MSNs). Synapses in this brain region are subject to short-term modulation, including allosteric alterations in ion channel function and prominent presynaptic inhibition. Two forms of long-term synaptic plasticity have also been observed in striatum, long-term potentiation (LTP) and long-term depression (LTD). LTP at glutamatergic synapses onto MSNs involves activation of NMDA-type glutamate receptors and D1 dopamine or A2A adenosine receptors. Expression of LTP appears to involve postsynaptic mechanisms. LTD at glutamatergic synapses involves retrograde endocannabinoid signaling stimulated by activation of metabotropic glutamate receptors (mGluRs) and D2 dopamine receptors. While postsynaptic mechanisms participate in LTD induction, maintained expression involves presynaptic mechanisms. A similar form of LTD has also been observed at GABAergic synapses onto MSNs. Studies have just begun to examine the roles of synaptic plasticity in striatal-based learning. Findings to date indicate that molecules implicated in induction of plasticity participate in these forms of learning. Neurotransmitter receptors involved in LTP induction are necessary for proper skill and goal-directed instrumental learning. Interestingly, receptors involved in LTP and LTD at glutamatergic synapses onto MSNs of the "indirect pathway" appear to have important roles in habit learning. More work is needed to reveal if and when synaptic plasticity occurs during learning and if so what molecules and cellular processes, both short- and long-term, contribute to this plasticity.

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1. Neurotransmitters in striatum: it's a jungle in there

The striatum is the major input nucleus of the basal ganglia, and as such it plays a crucial role in action control and action learning (Saint-Cyr et al., 1995; Graybiel, 1998; Lalonde and Botez-Marquard, 1997; Yin and Knowlton, 2006). These roles are accomplished via striatal generation of neuronal activity that initiates and terminates action sequences, processing of afferent inputs that influence this activity, and controlling the activity of downstream efferent target nuclei through inhibitory GABAergic projections. A rich interplay of the actions of numerous neurotransmitters is involved in the input, processing and output functions of the striatum (see Lovinger et al., 2003; Schmidt, 1995; Tepper et al., 2007 for review). As is the case for most large forebrain regions, the striatum contains a variety of small molecule and neuropeptide transmitters. The small molecules act both on ligand-gated ion channels (LGICs) to produce fast synaptic transmission, and on G-protein coupled receptors (GPCRs) to produce neuromodulation. Endocannabinoids, lipid metabolites that activate the CB1 GPCR, are an intriguing subclass of small molecules that modulate synaptic transmission in striatum (Lovinger et al., 2010), and more will be said about their emerging role in striatal function later in this review. Neuropeptides act predominantly, if not exclusive, through modulatory GPCRs. In this review, discussion of synaptic modulation and plasticity will be focused on the dorsal striatum (caudate and putamen nuclei in primates).

The striatum contains a single class of projection neurons known as medium spiny neurons (MSNs). These GABAergic neurons make up the vast majority of the total striatal neuronal complement (Tepper et al., 2007). Each MSN receives tens of thousands of glutamatergic inputs from cortex and intralaminar thalamus, most of which synapse on the heads of the dendritic spines that stud the outer two-thirds of the MSN dendritic arbor (Tepper et al., 2007). MSNs also receive extensive GABAergic synaptic input from other

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MSNs as well as striatal interneurons (Tepper et al., 2004). Striatal interneurons are much less numerous than MSNs, but form extensive connections within the striatum. Neurons with a large, elongated soma (20–25 μm on the long axis) display tonic activity even in the brain slice preparation (the large aspiny neurons), and are known to be cholinergic (Bennett and Wilson, 1999; Zhou et al., 2002). The remainder of the interneurons in striatum are GABAergic, and most prominently include fast-spiking interneurons (FSNs) that express the calcium-binding protein parvalbumin, and low-threshold-spiking (LTSNs) that express neuropeptide Y (Tepper et al., 2004). These interneurons also receive glutamatergic synaptic input, with the balance between cortical and thalamic input varying with neuronal subtype. GABAergic connections among interneurons are likely to occur, but characterization of these connections is just beginning (Partridge et al., 2009).

Glutamatergic synapses act mainly through AMPA-type receptors to produce fast synaptic excitation, and NMDA-type receptors can also contribute to transmission and plasticity (Calabresi et al., 1992c, 2000a). GABAergic synapses produce fast inhibition exclusively through the $GABA_A$-type receptors. There is also evidence for GABA-mediated excitation through this receptor type, but as yet there is not strong consensus as to when and where this occurs within the striatum (Bracci and Panzeri, 2006). Acetylcholine coming from the large aspiny neurons could potentially act via nicotinic ACh receptors, and these LGICs are abundant in striatum (Zhou et al., 2002). However, as yet there is little evidence for direct fast-acting ACh-nAChR-mediated synaptic responses in striatal neurons, with the exception of excitatory actions on fast-spiking interneurons (Koos and Tepper, 2002).

2. Short-term modulation of striatal synaptic transmission

Neuromodulation strongly impacts striatal function, and deficits in this more subtle type of synaptic communication play key roles in neurological disorders involving this brain region. A strong dopaminergic afferent input from the substantia nigra pars compacta innervates MSNs and striatal interneurons. The midbrain neurons that give rise to this input degenerate in Parkinson's disease, and it is clear that loss of dopaminergic input causes hypokinesia and other facets of this disorder. Dopamine can only act via GPCRs, and thus only modulates striatal neuronal function and synaptic transmission (Richfield et al., 1989; Surmeier et al., 2007). Glutamate, GABA and ACh can also act through GPCRs to influence the function of striatal neurons (Lovinger, 1991; Calabresi et al., 1991; Seabrook et al., 1991; Sugita et al., 1991). In addition, small molecule neurotransmitters such as adenosine, serotonin and endocannabinoids act predominantly, if not exclusively, via GPCRs to affect striatal neurons and synapses (Lovinger et al., 2010). Among the neuropeptides known to be expressed in striatum are opioid peptides, neurotensin, NPY, somatostatin and substance P. Many of the responses to these peptides are poorly characterized, but it is clear that GPCRs underlie the known actions. The gaseous small molecule neurotransmitter nitric oxide (NO) is also made by at least one subclass of striatal neuron, and appears to have important modulatory functions in striatum.

The full spectrum of striatal neuromodulation will not be discussed in the present review. The focus will be on synaptic modulation and plasticity, and thus GPCR effects on voltage-gated ion channels will not be discussed in any detail. While this topic would be a fitting and timely subject for another review, pertinent information can be found in a recent article (Surmeier et al., 2007). In addition, the intent of this paper is not to provide an exhaustive list of types of synaptic modulation produced by GPCR-acting receptors, but rather to highlight the dominant motifs in these modulatory actions within the striatum.

Before considering synaptic modulation known to occur in striatum, it is worth mentioning that certain modulatory responses that are common in other brain regions are not observed in striatal neurons, at least in MSNs. For example, GPCR activation of G-protein-activated inwardly rectifying potassium (GIRK) channels does not occur in MSNs. This is most likely due to the fact that GIRK channels are not expressed in these neurons. Thus, one prominent mechanism for slow inhibition of neurons does not operate in these cells. Modulation of neuronal excitability by altered function of the KCNQ-type potassium channel (also known as the m-channel), is another common response to GPCR activation in many forebrain neurons. The KCNQ2 and 3 subtypes are expressed MSNs (Shen et al., 2005), where they may reside on dendrites (Cooper et al., 2001). Shen et al. (2005) have shown that activation of muscarinic ACh receptors inhibits the current mediated by these channels, enhancing the excitability of MSNs.

Neuromodulatory GPCR-mediated effects on ligand-gated ion channels have been observed in striatum. For example, dopamine acting via the D1 class of receptors and the downstream DARPP-32 protein acts to maintain normal levels of function of AMPA-type glutamate receptors (Yan et al., 1999). This action appears to involve inhibition of phosphatases that, if unchecked, dephosphorylate AMPARs and cause a gradual decrease, or "rundown" of channel function. It should be noted, however, that this mechanism has not been shown to be activated by endogenous, synaptically-released dopamine. Dopamine also alters the function of GABAA receptors (Yan and Surmeier, 1997). Once again, there is no evidence as yet that this action is mimicked by endogenous dopamine.

Perhaps the most consistently observed form of synaptic modulation in striatum is presynaptic inhibition of neurotransmitter release. GPCRs that activate the Gi/o class of G-proteins are known to inhibit neurotransmitter release at synapses throughout the nervous system (Miller, 1998; Wu and Saggau, 1997). A variety of subtypes of these receptors have been identified at both glutamatergic and GABAergic synapses in striatum. For example, activation of adenosine A1, CB1 cannabinoid, $GABA_B$, muscarinic ACh and group II and III metabotropic glutamate receptors has been shown to inhibit glutamatergic synaptic transmission in striatum (Lovinger, 1991; Lovinger and McCool, 1995; Calabresi et al., 1991, 1993; Gerdeman and Lovinger, 2001; Malenka and Kocsis, 1998; Pisani et al., 1997; Sugita et al., 1991). All of these effects appear to involve a presynaptic decrease in glutamate release. This form of synaptic inhibition can provide an effective brake on excitation of MSNs that prevents information flow into and through the basal ganglia. Less is known about which presynaptic receptors regulate GABA release in striatum. However, it is clear that CB1 cannabinoid receptors have such an action (Narushima et al., 2006, 2007; Szabo et al., 1998; Adermark et al., 2009; Adermark and Lovinger, 2009). In addition, activation of delta opiate, adenosine A1, $GABA_B$ and muscarinic ACh receptors reduces GABAergic transmission via an apparent presynaptic action (Centonze et al., 2001; Jiang and North, 1991; Seabrook et al., 1991; Sugita et al., 1991; Waldmeier et al., 1988). Clearly, this disinhibitory modulation provides an important mechanism to produce a subtle increase in excitation of MSNs.

Dopamine produces modulation of neurotransmitter release at both GABAergic and glutamatergic striatal synapses (Bamford et al., 2004a; Centonze et al., 2004; Cepeda et al., 1993; Flores-Hernandez et al., 1997; Yin and Lovinger, 2006). However, it is not clear if these effects are due to dopamine receptors that reside directly on presynaptic terminals. Activation of D2 receptors inhibits glutamate release, but this effect is not readily observed when afferent inputs are activated at low stimulus frequencies (Bamford et al., 2004b; Centonze et al., 2004; Cepeda et al., 1993; Flores-Hernandez et al., 1997; Nicola and Malenka, 1998; Yin and Lovinger, 2006). This action contrasts with that of the other presynaptic Gi/o-coupled