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Local and afferent synaptic pathways in the striatal microcircuitry

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The striatum is the largest structure of the basal ganglia, receiving synaptic input from multiple regions including the neocortex, thalamus, external globus pallidus, and midbrain. Earlier schemes of striatal connectivity presented a relatively simple architecture which included primarily excitatory input from the neocortex, dopaminergic input from the midbrain, and intrastriatal connectivity between projection neurons and a small number of interneuron types. In recent years this picture has changed, largely due to the introduction of new experimental methods to reveal cell types and their connectivity. The striatal microcircuit is now considered to consist of several newly defined neuron types which are intricately and selectively interconnected. New afferent pathways have been discovered, as well as novel properties of previously known afferents such as the midbrain dopaminergic inputs. In this review we aim to provide a summary of these recent discoveries.

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Striatal neuron types

The striatum consists of a majority of projection neurons, the medium spiny neurons (MSNs) and a small, yet diverse population of interneurons. Interneurons were initially divided into four subtypes, including three types of GABAergic interneurons, and the tonically active cholinergic interneurons [1,2]. These electrophysiologically defined subtypes also fitted a molecular profile based on immunostaining for markers such as parvalbumin (PV), calretinin (CR), somatostatin (SOM), and choline-acetyltransferase (ChAT). Some of the markers used in the characterization of the neurons were co-localised such as nitric oxide synthase (NOS), neuropeptide-Y (NPY) and SOM, whereas others appeared to be mutually exclusive, as in the case of SOM and PV. The use of transgenic mice selectively expressing fluorescent markers under the control of promoters of specific markers has led to the identification of several classes of interneuron and enabled a systematic characterization of the various types, resulting in more refined classification schemes.

Tyrosine hydroxylase-expressing interneurons

Using a BAC transgenic mouse expressing EGFP in tyrosine-hydroxylase (TH) expressing neurons (EGFP-TH$^+$), Ibanez-Sandoval and colleagues [3] defined four interneuron subtypes based on their electrophysiological properties. The interneurons are all GABAergic, most of which have novel intrinsic electrophysiological properties. TH was not co-expressed with NOS, PV, or calretinin, suggesting that this population of interneurons is indeed novel and not part of previously characterized groups. Interestingly, TH expression increased following midbrain 6-hydroxydopamine (6-OHDA) lesions, which could suggest a compensatory mechanism following dopamine depletion [4], however, the TH-expressing interneurons have been shown to release GABA but not dopamine [5] and thus represent populations of GABAergic neurons.

NPY-expressing interneurons

Using a similar approach to that used in the discovery of TH-positive interneurons, the use of a transgenic GFP-NPY reporter mouse line has revealed the existence of at least two distinct types of interneurons that express NPY [6]. One type was the previously described 'low-threshold spiking' (LTS) interneuron and the other was defined as 'NPY-neurogliaform' (NPY-NGF), based on its similarity to the cortical neurogliaform interneurons. The two NPY-GFP interneurons exhibit different electrophysiological, morphological, molecular, and synaptic profiles, thus justifying the division into two distinct subtypes. One important feature of the NPY-LTS interneurons recorded in mouse striatum is their tonic activity [7], making them the second tonically active interneuron type in the striatal microcircuit in addition to cholinergic interneurons [8]. Interestingly, in rats, no NPY-NGF have been reported, and NPY interneurons expressing NOS do not display tonic discharge *in vivo* [9].

5HT3a-expressing interneurons

Using BAC transgenic eGFP mouse lines, Fishell, Rudy, and colleagues have identified a population of neocortical

GABAergic interneurons that express the 5HT3a serotonin receptor [10,11]. In the neocortex, the 5HT3a-expressing neurons are prevalent in superficial cortical layers and together with the PV- and SOM-expressing interneurons, could account for almost all GABAergic interneurons. In the same mouse line 5HT3a-expressing interneurons were also characterized in the striatum, revealing a large and diverse population [12]. Similar to TH-expressing interneurons, striatal 5HT3a-EGFP interneurons exhibit distinct electrophysiological subtypes, as well as different co-expression patterns with PV, NOS, TH, and calretinin. The greatest degree of overlap was between 5HT3a and PV, which was also reflected in the fast-spiking electrophysiological phenotype of more than 30% of recorded 5HT3a-GFP interneurons. One subtype of 5HT3a interneuron was shown to be activated by nicotinic input from cholinergic interneurons and provides GABAergic input to MSNs [13].

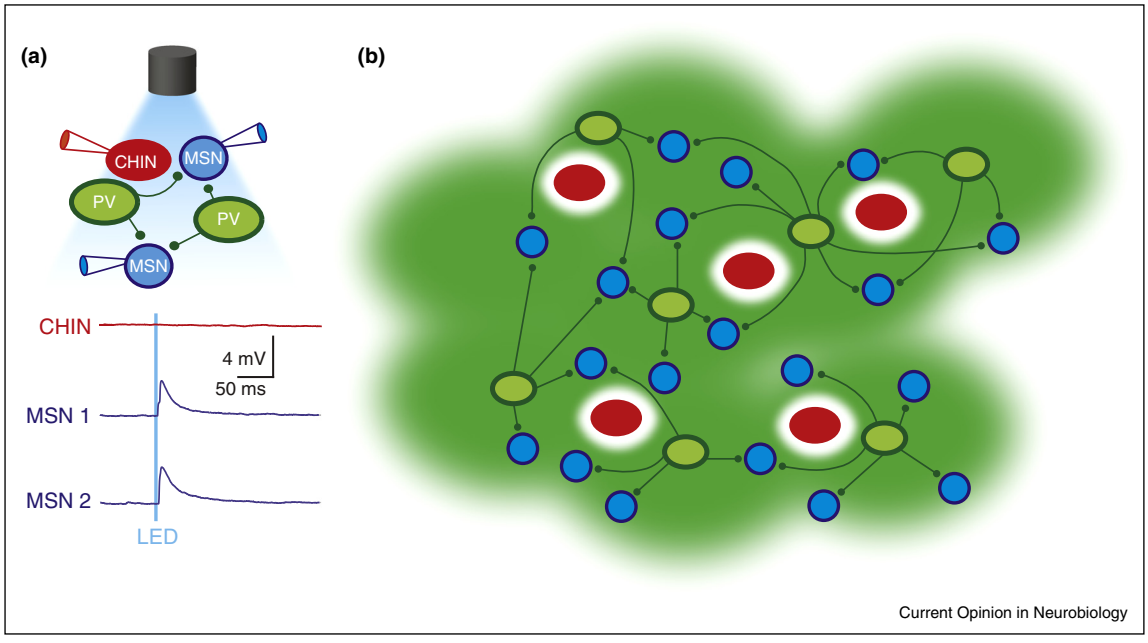
Summary

The number of striatal neuron subtypes is larger than previously assumed and is likely to change in the coming years and vary according to different classification schemes used in the field. The classification is not always straightforward due to the overlap of the different molecular, electrophysiological, and morphological properties, as well as differences between species. New directions towards the resolution of cell type classification may now be provided by single cell RNA sequencing [14] and fate mapping [15] studies, where the electrophysiological, morphological, and network properties of neurons are correlated to their developmental origin and molecular fingerprint.

Striatal interneuron connectivity

Striatal interneurons of the different types are instrumental in sculpting striatal output *via* intrastriatal synaptic connections. Perhaps the most prominent of the intrastriatal synapses are the GABAergic synapses formed between FS interneurons and MSNs [16] (Figure 1). These synapses are characterized by a very high connection probability, with each FS interneuron contacting a majority of its neighboring (within ~100 μm radius) MSNs [17]. A single FS-MSN IPSP is sufficient to alter the discharge pattern of the postsynaptic MSN [16,18]. The same presynaptic FS interneurons contact both direct and indirect pathway MSNs, with preference towards direct pathway (D1 expressing MSNs) [17,19], which is reversed following 6-OHDA induced dopamine depletion by selective increase in the connections onto D2 MSNs [20•]. Striatal FS interneurons share many of the morphological, electrophysiological, and synaptic properties with cortical FS interneurons, however, one striking difference is the lack of reciprocity between them and their targeted projection neurons. In the neocortex there is a high degree of reciprocity between FS

Figure 1



A selective 'blanket' of inhibition by striatal PV interneurons. **(a)** Schematic representation of an experiment showing robust inhibition of MSNs by optogenetic activation of fast-spiking PV-expressing interneurons and avoidance of a simultaneously recorded neighboring cholinergic interneuron (CHIN). **(b)** Blanket of feed-forward inhibition by PV interneurons onto MSNs, with 'holes' representing the avoided cholinergic interneurons.Adapted from [27,28•].