Co-transmission diversity among dopamine and glutamate neurons of the ventral tegmental area

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The ventral tegmental area (VTA) has dopamine (DA) neurons expressing tyrosine hydroxylase (TH), GABA neurons expressing vesicular GABA transporter (VGAT), and glutamatergic neurons expressing vesicular glutamate transporter (VGluT2) [1]. We have found that VTA VGluT2 neurons establish both local and long-range connections that participate in different behaviors. While most of VTA VGluT2 neurons lack both dopaminergic and GABAergic markers, some VGluT2 neurons co-express molecules for the synthesis and vesicular accumulation of either dopamine [2–4] or GABA [5]. At the local level, we had found that VTA VGluT2 neurons establish multiple asymmetric (associated with excitation) synapses on single neighboring dopamine neurons. These synapses mediate glutamate-receptor-dependent firing of some dopaminergic neurons that innervate the nucleus accumbens (NAcc), and participate in reward. Regarding long-range outputs of VTA VGluT2 neurons, we found that fibers from VTA TH-VGluT2 neurons establish asymmetric excitatory synapses on dendritic spines of medium spiny neurons (MSNs) within the NAcc. We had demonstrated that in the nAcc, individual axons from TH-VGluT2 neurons release DA and glutamate, each from mutually exclusive axonal microdomains [6]. We had also found that the subpopulation of VTA VGluT2-GAT neurons provides the major input from VTA to lateral habenula (LHb). Individual axon terminals from fibers of these mesohabenular VGluT2-GAT neurons establish both asymmetric and symmetric synapse, co-release glutamate and GABA within the LHb, and produce conditional place aversion. Regarding VTA VGluT2-only neurons, a population of nAcc parvalbumin GABAergic-interneurons is a major target of fibers from the VGluT2-only neurons. These fibers establish multiple asymmetric synapses on single parvalbumin-GABAergic interneurons, releases GABA onto MSNs, and promotes aversion [7]. These findings suggest that the midbrain glutamatergic neurons participate in different aspects of reward or aversion. In addition, some of these glutamatergic neurons have the capability to use both glutamate and dopamine or glutamate and GABA as neurotransmitters, and they target brain structures implicated in several brain disorders.

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References

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