Kullmann, D.M., and Lamsa, K.P. (2007). Nat. Rev. Neurosci. *8*, 687–699.

Levine, J.D., and Alessandri-Haber, N. (2007). Biochim. Biophys. Acta *1772*, 989–1003.

Marsch, R., Foeller, E., Rammes, G., Bunck, M., Kossl, M., Holsboer, F., Zieglgansberger, W., Landgraf, R., Lutz, B., and Wotjak, C.T. (2007). J. Neurosci. *27*, 832–839.

McMahon, L.L., and Kauer, J.A. (1997). Neuron *18*, 295–305.

Mezey, E., Toth, Z.E., Cortright, D.N., Arzubi, M.K., Krause, J.E., Elde, R., Guo, A., Blumberg, P.M., and Szallasi, A. (2000). Proc. Natl. Acad. Sci. USA *97*, 3655–3660.

Steenland, H.W., Ko, S.W., Wu, L.J., and Zhuo, M. (2006). Mol. Pain *2*, 34.

Szallasi, A., Cortright, D.N., Blum, C.A., and Eid, S.R. (2007). Nat. Rev. Drug Discov. *6*, 357–372.

Toth, A., Boczan, J., Kedei, N., Lizanecz, E., Bagi, Z., Papp, Z., Edes, I., Csiba, L., and Blumberg, P.M. (2005). Brain Res. Mol. Brain Res. *135*, 162–168.

Mesoprefrontal Dopamine Neurons Distinguish Themselves

Christopher P. Ford[1] and John T. Williams[1,*]
[1]Vollum Institute, Oregon Health Sciences University, 3181 SW Sam Jackson Park Road, Portland, OR 97239, USA
*Correspondence: williamj@ohsu.edu
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By distinguishing groups of dopamine neurons that differ in their projection patterns and intrinsic properties, Lammel and colleagues report in this issue of *Neuron* that mesocorticolimbic dopamine neurons of the ventral tegmental area (VTA) form a distinct subclass of dopamine cells.

Dysregulation of dopamine systems underlies a variety of disorders, ranging from Parkinson's disease to drug addiction. Understanding the physiology of these dopamine neural networks is a key first step in determining the etiology of these diseases. In the midbrain, dopaminergic neurons are broadly classified anatomically into the Substantia Nigra pars compacta (SNc) (A9) and the ventral tegmental area (VTA) (A10). Projections from different dopamine cells innervate the striatum, cortical regions such as the prefrontal cortex, and limbic structures such as the nucleus accumbens (NAc) and amygdala. In very broad terms, cells of the VTA innervate mesocorticolimbic structures and cells of the SNc innervate the dorsal striatum. This is an oversimplification since substantial anatomical overlap of these networks is known to exist (Bjorklund and Dunnett, 2007; Ikemoto, 2007).

To identify dopamine cells that form specific networks, it is important (1) to be able to relate the targets of individual dopamine cells to specific behaviors (Ikemoto, 2007), and (2) to catalog the properties of the individual groups of dopamine cells that project to those targets. Recent work has begun to assign intrinsic and pharmacological properties to dopamine cells according to the targets they innervate (Ford et al., 2006; Liss et al., 2005; Margolis et al., 2006). However, to date these studies have not provided an overall explanation of how the intrinsic properties of dopamine cells may mediate differences in firing patters of individual cells and the release of dopamine in various projection areas (Garris and Wightman, 1994).

In this issue of *Neuron*, Lammel et al. (2008) make an important step by examining how the properties of individual dopamine cells relate to the neural networks they reside within. By making use of retrograde tracers, they identify specific groups of projecting dopamine neurons. Through an exhaustive study, combining anatomical, electrophysiological, immunohistochemical, and laser-dissected individual mRNA-expression profiling based examinations, they identify two populations of mesocorticolimbic dopamine cells that segregate according to their projection targets.

The cell bodies of dopamine neurons that project to the medial prefrontal cortex (mPFC), medial accumbens shell, accumbens core, or amygdala originate in the medial posterior portion of the VTA. Dopamine cells that projected to the lateral shell of the NAc were only observed in more lateral portions of the VTA, partially overlapping with SNc cells that project to the dorsal striatum. These two groups of dopamine cells (mPFC, accumbens medial shell, and core and amygdala-projecting cells versus lateral shell and striatal-projecting cells) also varied in their expression levels of mRNA for key markers of dopamine cells. Markers included mRNA for tyrosine hydroxylase (TH), dopamine transporter (DAT), and vesicular monoamine transporter 2 (VMAT2). The abundance of these markers covaried in the two groups of neurons, being lower in the group of neurons located in the medial aspect of the VTA and higher in neurons that projected to the lateral aspect of the NAc shell and dorsal striatum. Thus, two broad groups of dopamine cells were defined based on both anatomical and biochemical characteristics.

The two groups of dopamine cells were further distinguished based on the intrinsic electrophysiological properties. Classical electrical properties of dopamine neurons in brain slice preparations include slow pacemaker firing, the presence of HCN

(h) channel-mediated, hyperpolarization-induced "sagging" of membrane potential, and a maximal firing rate of about 10 Hz (Grace and Bunney, 1984). Neurons that projected to the dorsal striatum and lateral shell of the NAc displayed these characteristics; however neurons in the medial aspect of the VTA were distinctly different: the group of cells projecting to mPFC, medial shell, core, and amygdala exhibited properties that distinguished them from the classically described properties of dopamine cells. These cells lacked the HCN channel-dependent sag in membrane potential, had a higher basal firing rate, and upon depolarization could sustain firing rates nearly twice that (20–30 Hz) of classically defined dopamine cells. The action potentials in this group of cells were also more prolonged and the following after-hyperpolarization was smaller than that observed in classically defined dopamine cells. Thus, two groups of dopamine cells were described that exhibit different anatomical, electrophysiological, and molecular properties.

A third unique group of dopamine cells was also identified. One hallmark of dopamine cells is the presence of D2 dopamine autoreceptors. Somatodendritic release of dopamine is known to activate D2 autoreceptors, resulting in a hyperpolarization of the membrane potential (Bjorklund and Lindvall, 1975; Lacey et al., 1987). In this study the dopamine neurons that projected to the mPFC were found to be unresponsive to the inhibitory effects of dopamine. With the combination of immunohistochemistry and single-cell RT-PCR, this group of mPFC-projecting cells was found to express low levels of both D2 receptors and the potassium channels (GIRK2) that mediate the dopamine-dependent inhibition. This observation provides the molecular and cellular results that confirm the original suggestion that dopamine cells projecting to the mPFC were markedly insensitive to dopamine (Chiodo et al., 1984).

The identification of two groups of mesocorticolimbic cells has important ramifications for unraveling the function of dopaminergic networks. Determining that subsets of cells express low DAT levels and high firing rates hints as to how these mesocorticolimbic neurons may mediate prolonged dopamine release observed at their targets (Garris and Wightman, 1994). Furthermore, determining that mesoprefrontal-projecting cells express low levels of D2 receptors and GIRK channels may explain the lack of dopamine autoinhibition in these cells, a property that allows them to maintain their high firing rates.

While recent work has also addressed differences in groups of projecting dopamine cells (Ford et al., 2006; Liss et al., 2005; Margolis et al., 2006), the exhaustive approach used by Lammel et al. defines groups of dopamine cells based on multiple criteria and is an important step toward furthering our understanding of the differences that exist within dopamine cells of the midbrain. Does this study signify the end in the search to relate intrinsic properties of dopamine neurons to their output? No, but it does mark a big step in the evolution of the understanding of the heterogeneity of cells within the VTA. The firing pattern of VTA dopamine cells is dependent on a mix of excitatory and inhibitory afferent inputs that arise from within and outside the VTA. A key extension will be to identify how the intrinsic properties of VTA dopamine cells mesh with the widely varied afferent inputs. Additionally, putting the role of novel, glutamateric VTA cells (Chuhma et al., 2004; Yamaguchi et al., 2007) into context within these dopaminergic circuits will prove a challenge in the future.

The work of Lammel et al., through their systematic identification of anatomical and intrinsic properties of mesocorticolimbic dopamine cells, reminds us of the importance of being able to distinguish the individual properties of different subgroups of dopamine cells if we wish to gain new insight into how dopamine modulates multiple behaviors.

REFERENCES

Bjorklund, A., and Lindvall, O. (1975). Brain Res. *83*, 531–537.

Bjorklund, A., and Dunnett, S.B. (2007). Trends Neurosci. *30*, 194–202.

Chiodo, L.A., Bannon, M.J., Grace, A.A., Roth, R.H., and Bunney, B.S. (1984). Neuroscience *12*, 1–16.

Chuhma, N., Zhang, H., Masson, J., Zhuang, X., Sulzer, D., Hen, R., and Rayport, S. (2004). J. Neurosci. *24*, 972–981.

Ford, C.P., Mark, G.P., and Williams, J.T. (2006). J. Neurosci. *26*, 2788–2797.

Garris, P.A., and Wightman, R.M. (1994). J. Neurosci. *14*, 442–450.

Grace, A.A., and Bunney, B.S. (1984). J. Neurosci. *4*, 2877–2890.

Ikemoto, S. (2007). Brain Res. Rev. *56*, 27–78.

Lacey, M.G., Mercuri, N.B., and North, R.A. (1987). J. Physiol. *392*, 397–416.

Lammel, S., Hetzel, A., Häckel, O., Jones, I., Liss, B., and Roeper, J. (2008). Neuron *57*, this issue, 760–773.

Liss, B., Haeckel, O., Wildmann, J., Miki, T., Seino, S., and Roeper, J. (2005). Nat. Neurosci. *8*, 1742–1751.

Margolis, E.B., Lock, H., Chefer, V.I., Shippenberg, T.S., Hjelmstad, G.O., and Fields, H.L. (2006). Proc. Natl. Acad. Sci. USA *103*, 2938–2942.

Yamaguchi, T., Sheen, W., and Morales, M. (2007). Eur. J. Neurosci. *25*, 106–118.