NEUROANATOMY

A split (mid)brain for dopamine

Dopamine is a versatile neurotransmitter that has a role in movement and many aspects of cognition. Lammel *et al*. have now characterized two types of neurons in the mesocorticolimbic dopamine system that are not only anatomically segregated, with non-overlapping axonal target regions, but that also have distinct molecular and functional properties. This structured diversity of the dopamine midbrain system might contribute to the multiplicity of dopamine functions in the CNS.

Dopamine pathways in the brain are generally divided into the well-characterized mesostriatal system, which originates in the substantia nigra pars compacta (SNc) and projects to the dorsal striatum, and the mesocorticolimbic system, which starts in the ventral tegmental area (VTA) and projects to the frontal cortex and limbic areas including the amygdala and the nucleus accumbens (NAc). By retrogradely tracing mesocorticolimbic dopamine neurons, the authors established that dopamine projections in the medial prefrontal cortex, the basolateral amygdala and the core and medial shell of the NAc originate in the medial posterior part of the VTA, whereas dopamine projections to the lateral shell of the NAc originate in the more lateral portions of the VTA and the medial part of the SNc.

Next, the authors characterized the molecular signatures of mesocorticolimbic neurons, looking particularly at genes that encode proteins that are involved in dopamine synthesis (tyrosine hydroxylase; TH), packaging (vesicular monoamine transporter 2; VMAT2) and reuptake (dopamine transporter; DAT). Again, two patterns emerged: dopamine projections originating in the medial posterior VTA had low DAT mRNA and protein levels relative to their levels of TH and VMAT2, whereas dopamine neurons running from the lateral VTA to the NAc lateral shell had higher DAT expression (as did mesostriatal neurons).

Whole-cell recordings in brain slices from adult mice revealed that VTA neurons projecting to the NAc lateral shell are 'classical', slow-firing dopamine neurons that resemble mesostriatal neurons. By contrast, dopamine neurons originating in the medial posterior VTA showed faster spontaneous discharge and, upon depolarization, fired in a sustained fashion at much higher maximal rates — electrophysiological properties that might contribute to the slow time course of dopamine signalling that is observed in, for example, the prefrontal cortex.

Finally, using perforated patch-clamp recordings, the authors showed that in the dual mesocorticolimbic dopamine system the mesoprefrontal neurons are unique: bath application of dopamine did not suppress activity in these neurons, whereas it did in all other recorded dopamine neurons. This appeared to be due to a lower expression of inhibitory D2 autoreceptors and their downstream target, G-protein-coupled K^+ channels, in mesoprefrontal neurons compared with mesolimbic neurons.

Abnormal midbrain dopamine levels have been associated with various disorders, including schizophrenia, addiction and ADHD. The discovery in this elegant study that there are multiple pathways within the mesocorticolimbic system might lead to the development of drugs or other treatments that specifically target these separate pathways and could thus avoid the side effects associated with the current non-specific dopamine-based treatments.

Leonie Welberg

ORIGINAL RESEARCH PAPER
Lammel, S. *et al*. Unique properties of mesoprefrontal neurons within a dual mesocorticolimbic dopamine system. *Neuron* **57**, 760–773 (2008)