Suggested Reference


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The STN-SNc hyperdirect pathway modulates dopaminergic neuron activity by inhibiting GABAergic inputs from the SNr via endocannabinoids

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Background

Endocannabinoids (eCB) are cannabis-like substances naturally produced in the brain where, amongst other functions, they modulate synaptic transmission (Hammond 2009). We have recently shown a novel modulatory mechanism of GABAergic transmission to the Substantia Nigra pars compacta (SNc) neurones which is initiated by metabotropic glutamate receptor (mGluR1) activation, and mediated by specific eCB, NADA (Freestone et al 2014). The source of glutamatergic input driving this eCB production is unknown. One possibility is the Subthalamic nucleus (STN) which provides a significant projection to the SNc and is a key component of the hyperdirect pathway (see box).

Aims

- To determine if the glutamatergic projection from the STN is responsible for driving eCB production in the SNc.
- Test if this projection modulates the GABAergic transmission from the Substantia Nigra pars reticulata (SNr) to the SNc.
- To compare the effect evoked by electrical and pharmacological stimulation of the STN and SNr.

Preservation of STN-SNc projection in brain slices

- Dye-filled processes (originating in the STN) seen in the SNc and SNr border regions
- Acute horizontal brain slice (250 µm; P15-21 rats)
- Whole-cell patch-clamp recording of GABAergic eIPSPs and eIPSCs evoked by SNr stimulation
- Electrical (bipolar) stimulation of the STN
- Pharmacological stimulation of the STN by ‘U’-tube application of carbachol

GABAergic transmission from SNr to SNc attenuated by prior electrical stimulation of the STN

- Previous studies have shown that electrical stimulation of the STN transiently attenuates (<1 s) GABAergic transmission from SNr neurons to dopaminergic SNc neurons (Flores et al 1996, Rosales et al 1994)
- The carbachol-induced attenuation of GABAergic transmission was prevented when mGluR1 or CB1 receptors were blocked
- Block of muscarinic receptor M3 with 4-DAMP (10 µM) also prevented the attenuation
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References

Sawaguchi T, et al 2012 AJP64: p355-357