

**DOPAMINE AND THE REGULATION OF MOVEMENTS
- SIGNIFICANCE OF NIGRAL AND STRIATAL DOPAMINE RELEASE
IN NORMAL, HEMIPARKINSONIAN AND DYSKINETIC RATS**

Akademisk avhandling

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av

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Avhandlingen baseras på följande arbeten:

- I:** **Andersson DR**, Nissbrandt H and Bergquist F. Partial depletion of dopamine in substantia nigra impairs motor performance without altering striatal dopamine neurotransmission. *Eur J Neurosci.* 2006 Jul;24(2):617-24.
- II:** **Andersson DR**, Bergquist F and Nissbrandt H. Motor activity-induced dopamine release in the substantia nigra is regulated by muscarinic receptors. *Submitterat manuskript, 2009.*
- III:** Lindgren HS*, **Andersson DR***, Lagerkvist S, Nissbrandt H and Cenci MA. Serotonergic modulation of striatal and nigral dopamine release in a rat model of L-DOPA-induced dyskinesia *Manuskript, 2009.* *delat första författarskap



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Abstract

DOPAMINE AND THE REGULATION OF MOVEMENTS - SIGNIFICANCE OF NIGRAL AND STRIATAL DOPAMINE RELEASE IN NORMAL, HEMIPARKINSONIAN AND DYSKINETIC RATS

Introduction: The nigrostriatal dopamine (DA) containing neurones are a pivotal component in the basal ganglia, a network that regulates movement. Degeneration of these neurones causes the cardinal symptoms of Parkinson's disease (PD). In addition to releasing DA from terminals in the striatum, these neurones also release DA from cell bodies and dendrites in the substantia nigra (SN). Although, somatodendritic DA release is known to influence motor performance, the mechanisms for this regulation needs to be clarified. PD is predominantly treated with L-DOPA, a precursor of DA. After 4-6 years of L-DOPA-treatment, approximately 40 % of the PD patients develop side effects in the form of abnormal involuntary movements. The reasons for these abnormal movements are not yet fully elucidated, but they are believed to be induced by large pulsatile fluctuations of DA following L-DOPA administration. **Methods and observations:** By use of simultaneous nigral and striatal microdialysis combined with motor performance testing, we demonstrate that nigral somatodendritic DA release exerts its influence on motor performance without affecting striatal terminal release. We also show that somatodendritic DA release can functionally compensate for disturbances in striatal DA release and thus partially maintain motor ability. Furthermore, local nigral application of the muscarinic antagonist scopolamine amplifies a previously described motor activity-related increase in somatodendritic DA release, and this amplification partially restores motor performance ability in 6-OHDA-hemilesioned rats. By combining dual probe microdialysis with a rat model of L-DOPA-induced dyskinesias, we demonstrate that the amount of DA formed and released from a given dose of L-DOPA is larger in rats that express dyskinesias than in rats that do not. Furthermore, our data indicate that the larger DA peak in dyskinetic compared to non-dyskinetic animals reflects a denser serotonergic innervation in the former group. We also show that 5-HT autoreceptor agonists attenuate extracellular DA concentrations following L-DOPA and reduce dyskinesias. **Conclusions:** The results in this thesis indicate that the principal role of somatodendritic DA release is to modulate basal ganglia output on the level of the substantia nigra, and not to regulate terminal release in the striatum. Moreover, our findings indicate that the amount of DA formed from an L-DOPA dose is the main cause of dyskinesias in rats, and also lend support to previous findings identifying striatal 5-HT neurones as the source of L-DOPA-derived DA.

Keywords: dopamine, substantia nigra, striatum, L-DOPA, dyskinesias, serotonin