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**MEETING ABSTRACT**

**A6.1**
**Modulation of D<sub>2</sub> autoreceptors function in substantia nigra dopaminergic neurons: an in vitro electrophysiological approach**

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One of the main hallmarks of the dopamine (DA)-releasing neuronal population of the substantia nigra pars compacta (SNpc) is the presence of somato-dendritic D<sub>2</sub> autoreceptors, whose activation leads to opening of G protein-coupled inward rectifier K<sup>+</sup> (GIRK) channels and hence membrane hyperpolarization. The physiological importance of this auto-inhibition is implicitly understood by the fact that DA neurons firing is constantly controlled by tonic DA acting locally. Interestingly, the membrane hyperpolarization induced by prolonged DA exposure is subject to a time-dependent desensitization, such that neuronal firing may recover almost to control levels, in spite of persistent D<sub>2</sub> stimulation. This phenomenon, often referred as reversal of DA inhibition (RDI), is mostly observed in young animals. However, evidence exists that in Parkinson’s disease (PD) surviving adult DA neurons respond with RDI under prolonged DA. This may suggest a higher metabolic demand on the SNpc DA neurons population, due to the reduced auto-inhibition, that could exacerbate their progressive loss in PD. Moreover, RDI may dramatically blunt the efficacy of common pharmacological therapies aimed at increasing the DA tone in PD patients. With the aim to understand the cellular mechanisms underlying RDI, we have investigated DA neurons’ response to prolonged (>15 min) perfusion of DA 100 µM in midbrain slices from young (p12–15) mice. While a clear recovery of firing was observed with DA, the cells remained inhibited when the D<sub>2</sub> receptor was continuously stimulated with its agonist quinpirole (100 nM). Notably, if 100 µM DA was then added under quinpirole, their firing soon recovered as with DA alone. This strongly suggests that (1) DA as such is required for RDI, and (2) RDI is not due to the sole D<sub>2</sub> receptors stimulation. We then activated the GIRK channel through the converging GABA<sub>B</sub> receptor pathway by baclofen (300 nM), under D<sub>2</sub> receptor block with sulpiride (30 µM). No recovery from firing inhibition was observed under long exposure to baclofen (>15 min), however, if we then added 100 µM DA to baclofen and sulpiride, the cells resumed their activity. We thus propose the GIRK channel, rather than the D<sub>2</sub> receptor, as the main actor of RDI, whereby closure of the GIRK channel causes recovery from firing inhibition in spite of a continuous D<sub>2</sub> receptor stimulation. Implications for PD etiology and therapy will be discussed.

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