

● PERSPECTIVE

Dopamine regulation of striatal inhibitory transmission and plasticity: dopamine, low or high?

Basal ganglia are known for their involvement in motor control. This function is accomplished *via* the modulatory actions of different signalling molecules; one of these is dopamine (DA), which, besides regulating cognition and reward mechanisms, participates in the organization of motor programmes by filtering and selecting cortical commands on striatal synapses (Bromberg-Martin et al., 2010).

Modulatory actions of DA in the striatum are very well described in relation to corticostriatal inputs and glutamatergic release on GABAergic medium spiny neurons (MSNs), the projection cells of the nucleus (Cepeda et al., 1993). However, the nigrostriatal pathway's DA also ends at the striatal local GABAergic circuits made by synaptic inputs on MSNs, which come from axonal collaterals of other MSNs, as well as from GABAergic interneurons (Koos et al., 2004). These inhibitory influences shape MSNs activity, both of which DA modulates (Guzmán et al., 2003).

We recently reported that DA decreases the effect of inhibitory synapses between GABAergic interneurons on MSNs (Nieto-Mendoza and Hernández-Echeagaray, 2015); however, DA's effects on long-term synaptic plasticity induced in these synapses (GABAergic interneurons-MSNs) depend on the DA concentration and DA receptor subtype activation. High frequency stimulation at low DA concentrations produced mostly long-term depression (LTD), which was also favored in the presence of a D2 agonist, whereas a high concentration of DA favored the generation of long-term potentiation (LTP), which was associated with D1 receptor activation.

DA neurons normally display a tonic and slow-firing frequency that is correlated to low rates of DA release; however, high frequency firing of nigrostriatal cells is associated with increases in DA release in the striatum (Cachope and Cheer, 2014). Alterations in striatal DA physiological levels are associated with some neurodegenerative diseases. Low DA levels lead to motor impairments, such as tremors, stiffness or slowing of movement characteristics of Parkinson's disease (PD). On the other hand, increased DA levels have been observed in Huntington's disease (HD), which, besides movement alterations, is also associated with cognitive and psychiatric disorders (Cepeda et al., 2014).

We evaluated how the synaptic plasticity between GABAergic interneurons and MSNs was modified in mice treated with non-toxic doses of the mitochondrial inhibitor 3-nitropropionic acid (3-NP), a toxin used as a pharmacological model of striatal degeneration because it mimics some of the features of early stages of HD. The plasticity produced in slices from 3-NP-treated mice *in vivo* was similar to the LTP triggered under high levels of DA in healthy tissue slices. The D2 antagonist did not affect the LTP, but in the presence of the PKA inhibitor, it prevented LTP induction and generated LTD, suggesting that in a damaged striatum, D1/PKA signalling pathway play a preponderant role in the generation of LTP.

Sustained elevation of DA in the striatum causes motor dysfunction, as well as the selective degeneration of MSN (Cyr et al., 2002; Chen et al., 2013). It is known that 3-NP treatment increases DA levels in the striatum (Johnson et al., 2000), and therefore, LTP produced in the inhibitory synapses on MSN, which express D1 receptors, may result from an increase of DA levels in the striatum, modulating inputs of interneurons that largely project to the perisomatic area of MSNs. This occurs because 3-NP treatment reduces the number of spines and the thickness of the dendrites (Mendoza et al., 2014). The interneurons responsible for inhibition in the perisomatic area of MSNs are known to have a synaptic impact,

mainly on MSNs expressing D1 receptors (Gustafson et al., 2006). This inhibition is important because GABAergic LTP in MSNs that express D1 receptors may protect them from excitatory inputs from the cortex, and perhaps this is one of the reasons why these neurons are less damaged than are D2 expressing cells in the early stages of striatal degeneration.

What can we learn from this? Similar to with excitatory synaptic plasticity in the striatum, DA modulates inhibitory long-term synaptic plasticity. In addition, activation of D1 or D2 DA receptors favors LTP or LTD expression, respectively, while low DA concentration favors LTD through D2 receptor activation. Likewise, increments of DA levels or striatal degeneration promote LTP associated with D1 receptor activation. LTP in the inhibitory synapses on MSN expressing D1 receptors may prevent exacerbated activity of the direct pathway (D1), and perhaps, may also prevent uncontrolled movement in the early stages of striatal degeneration, while LTD in the inhibitory synapses will also disinhibit the indirect pathway (D2), promoting movement.

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