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INCREASED DOPAMINE TRANSMISSION IMPAIRS BEHAVIORAL FLEXIBILITY AND SYNAPTIC PLASTICITY

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In addition to its key roles in motor and reward systems, brain dopamine (DA) has also been implicated in integrative functions contributing to adaptive behaviors such as attention, learning and memory, which processing involved the plastic changes of synaptic strength. Since the first formal evidence for Long Term Plasticity mechanism (LTP) in the Hippocampal Formation (HF), the phenomenon of synaptic plasticity has been described in various brain areas. It is appealing to consider that this is particularly true for brain regions that receive DA inputs, including the striatum and the frontal cortex being those most studied beside the hippocampus.
We have observed, using mice lacking the dopamine transporter (DAT) which constitute a unique genetic model of persistent functional hyperdopaminergia, a **strong deficit of LTD** and an enhancement of LTP in the CA1 region of hippocampal slices. This finding suggests that the augmentation of endogenous dopamine by DAT knockout modulates the plastic property of bidirectional synaptic plasticity by inducing a metaplastic shift in the HF. This deficit of LTD can be reversed by the D2 antagonist haloperidol, whereas the LTP increase is not altered. In the same animals, we observed a major impairment of cued-learning in the Morris watermaze, as well as more subtle, but solid, deficits in the spatial learning. These **deficits of behavioral flexibility** are reversed using haloperidol. Finally, in control animals, the direct blockade of the DAT using GBR12935, can reproduce the LTD and the behavioral deficits, indicating that they are not a consequence of developmental changes.

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