Powerful inhibitory action of mu opioid receptors (MOR) on cholinergic interneuron excitability in the dorsal striatum

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Cholinergic interneurons (ChIs) of dorsal striatum play a key role in motor control and in behavioural learning. Neuropeptides regulate cholinergic transmission and *mu* opioid receptor (MOR) activation modulates striatal acetylcholine release. However, the mechanisms underlying this effect are yet uncharacterized. Here, we examined the electrophysiological responses of ChIs to the selective MOR agonist, DAMGO {[D-Ala2-MePhe4-Gly(ol)5] enkephalin}. We observed a robust, dose-dependent inhibition of spontaneous firing activity (0.06−3 μM) which was reversible upon drug washout and blocked by the selective antagonist D-Phe-Cys-Tyr-D-Trp-Orn-Thr-Pen-Thr-NH_2 (CTOP) (1 μM). Voltage-clamp analysis of the reversal potential of the DAMGO effect did not provide univocal results, indicating the involvement of multiple membrane conductances. The MOR-dependent effect persisted in the presence of $GABA_A$ and ionotropic glutamate receptor antagonists, ruling out an indirect effect. Additionally, it depended upon G-protein activation, as it was prevented by intrapipette GDP-β-S. Because D2 dopamine receptors (D2R) and MOR share a common post-receptor signalling pathway, occlusion experiments were performed with maximal doses of both D2R and MOR agonists. The D2R agonist quinpirole decreased spike discharge, which was further reduced by adding DAMGO. Then, D2R or MOR antagonists were used to challenge the response to the respective agonists, DAMGO or quinpirole. No cross-effect was observed, suggesting that the two receptors act independently.

Our findings demonstrate a postsynaptic inhibitory modulation by MOR on ChIs excitability. Such opioidergic regulation of cholinergic transmission might contribute to shape information processing in basal ganglia circuits, and represent a potential target for pharmacological intervention.