# DOPAMINE $D_4$ RECEPTOR COUNTERACTS MORPHINE-INDUCED CHANGES IN M OPIOID RECEPTOR SIGNALING IN THE STRIOSOMES OF THE RAT CAUDATE PUTAMEN.

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Morphine is one of the most potent analgesic drugs used to relieve moderate to severe pain. After long-term use of morphine, neuroadaptive changes in the brain promotes tolerance, which result in a reduced sensitivity to most of its effects with attenuation of analgesic efficacy, and dependence, revealed by drug craving and physical or psychological manifestations of drug withdrawal. The mu opioid receptor (MOR) is critical, not only in mediating morphine analgesia, but also in addictive behaviors by the induction of a strong rewarding effect. We have previously shown that dopamine $D_4$ receptor ($D_4R$) stimulation counteracts morphine-induced activation of dopaminergic nigrostriatal pathway and accumulation of Fos family transcription factors in the caudate putamen (CPu).

In the present work, we have studied the effect of $D_4R$ activation on MOR changes induced by morphine in the rat CPu on a continuous drug treatment paradigm, by analyzing MOR protein level, pharmacological profile, and functional coupling to G proteins. Furthermore, using conditioned place preference and withdrawal syndrome test, we have investigated the role of $D_4R$ activation on morphine-related behavioural effects.

MOR immunoreactivity, agonist binding density and its coupling to G proteins are up-regulated in the striosomes by continuous morphine treatment. Interestingly, co-treatment of morphine with the dopamine $D_4$ receptor ($D_4R$) agonist PD168,077 fully counteracts these adaptive changes in MOR, in spite of the fact that continuous PD168,077 treatment increases the [$^3$H]DAMGO $B_{max}$ values to the same degree as seen after continuous morphine treatment. In addition, the administration of the $D_4R$ agonist counteracts the rewarding effects of morphine, as well as the development of physical dependence. The present results give support for the existence of antagonistic functional $D_4R$-MOR receptor-receptor interactions in the adaptive changes occurring in MOR of striosomes on continuous administration of morphine and preventing morphine-related behaviour.

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