DOPAMINE D_4 RECEPTOR ACTIVATION COUNTERACTS NIGROSTRIATAL PATHWAY ACTIVATION BY MORPHINE: RELEVANCE IN DRUG ADDICTION.

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Morphine induces dopamine release in the caudate putamen (CPu), which promotes stereotyped behavior and habit learning for drug-seeking and –taking. Nigrostriatal pathway stimulation by morphine is due to a removal of tonic inhibition arising from SNr GABA interneurons on SNc dopaminergic neurons through the mu opioid receptor (MOR). Long-term morphine exposure produces a series of adaptations in SNc dopamine neurons, which affect neuron excitability and dopamine output to CPu. We have previously shown that dopamine D_4 receptor (D_4R) stimulation counteracts acute and chronic morphine-induced accumulation of several transcription factors in the CPu (Gago et al., 2011 Brain Res.). Since D_4R is expressed in the SNr (Rivera et al., Brain Res. 2003), we postulate that a functional D_4R-MOR interaction at the midbrain level could exists.

We have investigated the role of D_4R in the morphine-induced nigroestriatal dopamine metabolism in the rat brain using biochemical and immunohistochemical techniques. We also have studied the influence of D_4R on morphine-induced morphological changes in SNc dopamine neurons using both immunohistochemical and image analysis techniques. Finally, we examined a possible underlying mechanism of the D_4R-MOR interaction at the SN level using *in vitro* quantitative receptor autoradiography.

We have found that D_4R activation restores dopamine metabolism in the nigroestriatal pathway after acute morphine treatment and prevents morphine-induced rise of tyroxine hydroxylase and dopamine transporter. Rats receiving a continuous treatment of morphine (6 days) showed SNc dopamine neurons with smaller size and higher circularity index compared with the controls animals. These morphine-induced morphological adaptatives changes were prevented when a D_4R agonist (PD168,077) was administered at the same time with morphine. Autoradiographic studies demonstrated that the D_4R agonist reduce the affinity of MOR. The present study provides evidence for the existence of a fully blocking effect of the D_4R on the activation of dopaminergic nigroestriatal pathway by morphine.

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