Dopamine D_4R restores morphine-induced impairment of adult neurogenesis in the subventricular zone

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In the adult mammalian brain, neuroblasts from the subventricular zone (SVZ) migrate along the rostral migratory stream into the olfactory bulb, where they differentiate and synaptically integrate to contribute with the maintenance of the olfactory function. It has been established that endogenous as well as exogenous opioid signalling affects proliferation in adult brains. In fact, chronic administration of morphine reduces adult neurogenesis in SVZ although its implication in addiction has not yet been clarified. On other hand, dopamine has been also identified as a regulatory factor of adult neurogenesis as dopaminergic cells from the substantia nigra compacta project toward the dorsal SVZ whereas the ventral tegmental area innervates the ventral SVZ. Previous results demonstrated that morphine increases striatal dopamine signaling, which is restored by the specific stimulation of dopamine D_4 receptor (D_4R). The mechanisms by which D_4R counteracts morphine effects is not completely understood, but the existence of a D_4R-MOR heterodimer in the striosomes of the caudate putamen has been proposed . However, it is unknown how this interaction could affect both the adult neurogenesis and olfaction.

In the present work, we have studied the effects of a chronic treatment with morphine alone or in combination with a D_4R agonist (PD168,077) on adult neurogenesis occurring in the SVZ. Furthermore, the impairment or improvement of odorants discrimination has also been analyzed.

Using immunohistochemical techniques, we found that chronic treatment with morphine increases dopamine signalling in the SVZ and promotes a depletion of cell proliferation, affecting both neural and glial precursors. These effects were counteracted by the coadministration of morphine with the D_4R agonist. The present results support for a critical role of the D_4R to prevent morphine effects in the SVZ.

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