Role of central dopamine D3 and serotonin 2C receptors in the control of the mesoaccumbens dopaminergic pathway: implications for the treatment of depression

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The mesoaccumbens dopamine (DA) pathway, whose activity is functionally deficient in depressed states, is a key structure in mediating the neurochemical and behavioral effects of antidepressant drugs. Specifically, central DA-D3 receptors (D3R), which represent a target for new antidepressant agents, exert inhibitory controls on mesoaccumbens DA neurons. Also, D3R knock-out mice ($D3R^{-/-}$), which display increased DA extracellular levels in the nucleus Accumbens (NAc), are more sensitive to antidepressant drugs and exhibit reduced anxiety-like behaviour. The central serotonin$_{2C}$ receptor (5-HT_2CR), in keeping with its ability to inhibit the mesoaccumbens DA pathway, represents another major target for improved treatments of affective disorders. Several 5-HT_2CRs ligands have shown antidepressant-like activity in various behavioural models, although the mechanisms underlying their effects remain unclear. Thus, the mesoaccumbens DA pathway may serve as a common substrate in mediating the antidepressant effects of D3 and 5-HT2C compounds. The aim of this study was to asses this hypothesis by specifically identifying the relative contribution of D3Rs and 5-HT_2CRs in the control of mesoaccumbens DA pathway activity, as well as in the in depressive-like behaviors, by using D3R-/- and their wild-type (WT) littermates, treated (7 days) or not with several 5-HT2C ligands (the inverse agonist SB206553, the selective antagonist SB242084 or the combination SB242084 + SB206553) and tested in the tail suspention test (TST) after 8 weeks of exposure to the unpredictable chronic mild stress paradigm (UCMS). Stressed D3R-/- mice, tested in the TST, showed a decreased immobility time as compared to their wild type littermates ($p<0.01$). Wild type mice exposed to the UMCS and treated for the last 7 days of the experimental procedure with the 5-HT_2C inverse agonist SB206553 (2.5 mg/kg, i.p.), show a decreased immobility time in the TST as compared with their vehicle control group ($p<0.05$). Conversely, the same treatment with SB206553 increased the immobility time of D3R-/- as compared with their vehicle control group ($p<0.05$). Seven days of treatment with the 5-HT_2C antagonist SB242084 (1 mg/kg, i.p.) did not change the immobility time of both stressed D3R-/- and WT mice. Finally, the pre-administration (15 min before) of the 5-HT_2C selective antagonist SB242084 blocked the effect of the inverse agonist SB206553 in both stressed D3R-/- and WT mice. These data indicate that the effect of 5-HT_2C inverse agonist SB206553 in a depressive-like behavior may be changed by manipulating D3R function.