5-HT_{2C} RECEPTOR-DEPENDENT MODULATION OF MIDBRAIN DOPAMINE NEURON ACTIVITY IN VIVO: IMPLICATIONS FOR THE TREATMENT OF DEPRESSION

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Several studies, focusing on the role of central serotonin2C receptors (5-HT_{2C}Rs) in the regulation of midbrain dopamine (DA) neurons, have highlighted their potential for improved treatments of DA-related disorders (depression, schizophrenia, drug abuse). Specifically, the mesoaccumbens DA pathway, originating from the ventral tegmental area (VTA) and projecting to the nucleus accumbens (NAc) plays an important role in mediating cognitive, rewarding and affective functions. In vivo studies indicate that 5-HT_{2C}Rs exert tonic/phasic inhibitory controls on NAc DA release, involving both endogenous 5-HT and 5-HT_{2C}R constitutive activity (CA). Intracranial microinjection studies, assessing their influence on DA-dependent behaviours, led to the conclusion that the mesoaccumbens DA pathway undergoes distinct regional regulations by 5-HT_{2C}Rs, and that NAc-5-HT_{2C}Rs may exert excitatory controls on NAc DA release. Thus, the mesoaccumbens DA pathway may undergo functional opposite controls by 5-HT_{2C}Rs in the VTA (inhibition) and NAc (excitation). Thus, the present study was aimed to determine the relative contribution of VTA- and NAc-5-HT_{2C}Rs in the control of NAc DA release. Experiments were performed using *in vivo* microdialysis coupled with HPLC-ECD in halothane-anesthetized rats, given peripheral and/or intracranial microinjections of selective 5-HT_{2C}R ligands (SB242084, SB243213: antagonists; SB206553: inverse agonist; Ro60-0175: agonist).Intra-VTA injection of SB242084 or SB243213 (0.1-0.5 µg/0.2 µl) and intra-NAc infusion of SB242084 (0.1-1 µM) significantly blocked the decrease in accumbal DA outflow induced by the intraperitoneal (i.p.) injection of 3 mg/kg Ro60-0175. The increase in DA release induced by SB206553 (5 mg/kg, i.p.) was blocked by the intra-NAc infusion of SB242084, but unaltered by its intra-VTA injection. At variance with their systemic effects, local injection of 5-HT_{2C}R antagonists has no influence on basal DA release. The obtained results show that both VTA- and NAc-5-HT_{2C}Rs participate in the inhibitory control exerted by central 5-HT_{2C}Rs on NAc DA release, and that the NAc may serve as a major site for the effect of 5-HT_{2C}R CA. Considering the effects of peripheral administration of 5-HT_{2C}R antagonists, they also indicate that tonic inhibition of DA neurons may result from a composite response involving 5-HT_{2C}Rs located within multiple brain areas (VTA, NAc, prefrontal cortex). Finally, 5-HT_{2C}R-dependent excitatory controls reported in behavioural studies may result from actions on NAc-DA transmission, occurring independently from changes of DA release itself.