Serotonin-2A and -2C receptor modulation of the lateral habenula activity in the context of nicotine addiction: a neuroanatomical and electrophysiological study

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The aim of this dissertation was to investigate the role of the 5-HT_{2C} receptors (5-HT_{2C}Rs) in the modulation of the lateral habenular nucleus (LHb), under normal condition, and after acute and chronic nicotine treatment in rats. Due to the high homology between 5-HT_{2C}Rs and 5-HT_{2A}Rs, we studied both 5-HT receptors subtypes.
The expression of 5-HT_{2A}Rs and 5-HT_{2C}Rs in the LHb was investigated by immunohistochemical approach using mouse anti-5-HT_{2A}R/5-HT_{2C}R monoclonal antibodies. Immunohistochemical experiments showed a diffuse 5-HT_{2A}R and 5-HT_{2C}R immunolabelling in cell bodies and neuropil of the LHb. We show for the first time that 5-HT_{2A}Rs are expressed on LHb neurons, and are present in a similar proportion to 5-HT_{2C}Rs.
Standard single cell extracellular recordings were performed *in vivo* in anaesthetized rats. The effects of intravenous (i.v.) administration of different 5-HT_2R ligands on LHb neuronal activity were investigated: RO60-0175 (preferential 5-$HT_{2B/2C}$R agonist); lorcaserin (preferential 5-$HT_{2A/2C}$R agonist) and CP-809101 (selective 5-HT_{2C}R agonists); and TCB-2 (potent 5-HT_{2A}R agonist).
RO 60-01745 (5-640 µg/kg, i.v.) induced changes in 48% of the neurons treated, which responded with either an increase (18%) or a decrease (30%) in their firing rate. The change in firing activity was dose dependent, with maximum effects elicited towards the higher doses for both excitation and inhibition (+59 ± 22% and -56 ± 8%). Both effects were blocked by the administration of SB 242084, a selective 5-HT_{2C}R antagonist. Lorcaserin induced a significant increase in firing rate in 50% of neurons (+85 ± 23%), while CP 809101 administration affected 30% of neurons, increasing their firing rate (+29 ± 19%). SB 242084 reversed the CP 809101-induced increase in firing rate.
TCB-2 (5-640 µg/kg, i.v.) affected 79% of the neurons treated, which responded with either an increase (26%) or a decrease (53%) in their firing rate. The change in firing activity was dose dependant, with maximum effects elicited towards the higher doses (+118 ± 36% and -49 ± 10%). These effects were both reversed by the administration of MDL 11,939, a selective 5-HT_{2A}R antagonist.
Nicotine treatments altered the expression of 5-HT_{2A}R and 5-HT_{2C}R within the LHb. Acute nicotine treatment down-regulated 5-$HT_{2A/C}$R expression on the somata of LHb neurons, whereas chronic nicotine treatment up-regulated 5-HT_{2C}R expression. Acute nicotine treatment reduced the overall firing rate of LHb neurons and increased their irregularity in firing. Nicotine treatments were shown to attenuate the inhibitory response to RO 60-0175 administration, and the excitation response to TCB-2 administration.
Our data shows for the first time that both 5-HT_{2A}Rs and 5-HT_{2C}Rs bidirectionally modulate LHb neuronal output, with selective 5-HT_{2C}R agonists which are more likely to induce an excitation response, and the 5-HT_{2A}R agonists an inhibition response. These findings are important for their physiological relevance and for therapeutic intervention in the cessation of nicotine abuse and drugs of addiction in general.