S01-04 - **5-HT$_{2C}$ RECEPTOR ACTIVATION INHIBITS STRESS-INDUCED INCREASE IN 5-HT TRANSMISSION: RELEVANCE TO THE EFFECTS OF ANTIDEPRESSANT DRUGS**

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Objectives: 5-HT$_{2C}$ receptors are well known to be involved in anxiety, but their implication in stress-induced changes of 5-HT transmission remained to be investigated. We thus assess the behavioral and neurochemical effects of 5-HT$_{2C}$ receptor activation in naïve and stressed mice, and after chronic paroxetine known to exert anxiolytic effects in humans.

Methods and results: The effects of the preferential 5-HT2C agonists m-chlorophenylpiperazine (mCPP) and RO60-0175, the selective 5-HT$_{2C}$ receptor antagonist SB242,084 and restraint-stress on anxiety-like behavior in mice were assessed using the social interaction test, while the neurochemical effects of these treatments on 5-HT turnover (5-HIAA/5-HT ratio) and extracellular 5-HT were determined using HPLC and microdialysis. Both mCPP and restraint-stress increased anxiety-like behavior in the social interaction test, and these effects were blocked by pretreatment with SB242,084. Restraint-stress increased 5-HT turnover in various brain areas, and this effect could be prevented by the 5-HT$_{2C}$ receptor agonist RO60-0175. Acute administration of SB242,084 potentiated the stress-induced increase in 5-HT turnover and blocked the inhibitory effect of RO60-0175. Microdialysis studies in frontal cortex revealed that RO60-0175 has an inhibitory effect on the stress-induced increase in extracellular 5-HT levels, but not on basal 5-HT levels. Chronic paroxetine prevented the anxiogenic effect of mCPP and prevented the inhibitory effect of RO60-0175 on restraint-stress-induced increase in 5-HT turnover.

Conclusions: These data strongly suggest that 5-HT$_{2C}$ receptor activation mediates the anxiogenic effect of stress. In addition, the anxiolytic action of long term treatment with SSRIs might be causally related to a clear-cut 5-HT$_{2C}$ receptor desensitization.

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