The implications of 5-HT2 receptor subtypes in the anxiolytic-like effects of paroxetine in the mouse four plate test

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The effects of the selective serotonin reuptake inhibitor (SSRI), paroxetine (0.25-8 mg/kg) administered intraperitoneally (i.p.) potently augmented the number of punished passages accepted by mice in this paradigm for the doses of 2 to 8 mg/kg. The magnitude of increase was comparable to that seen after alprazolam (0.25 mg/kg) administration. The effects of paroxetine (8 mg/kg) were not reversed by the selective 5-HT2C receptor antagonist, RS 10-2221 (0.1 and 1 mg/kg) or the selective 5-HT2B/2C receptor antagonist SB 206553 (0.1 and 1 mg/kg), at doses which lack an effect when administered alone. In contrast, the selective 5-HT2A receptor antagonist, SR 46349B (0.1 and 1 mg/kg) completely abolished the paroxetine-induced increase in punished passages. It is thus postulated that 5-HT2A receptors play a role in the effects of paroxetine in this model of anxiety. The co-administration of selective 5-HT2A, 2B, 2C receptor agonists (DOI 0.06 and 0.25 mg/kg; BW 723C86 0.5 and 2 mg/kg and RO 60-0175 0.25 and 1 mg/kg) respectively, was subsequently investigated. The effects of sub-effective doses of paroxetine (0.25 and 1 mg/kg) were potentiated by 5-HT2 receptor agonists challenge. These results indicate that the co-administration of 5-HT2 receptor agonists with paroxetine may provide a powerful tool for enhancing the clinical efficacy of this SSRI.
amygdala, and the central gray (1). Some of these brain areas are clearly involved in the regulation of anxiety. However, it is not known the possible role of sigma ligands on anxiety modulation. Therefore, this study was designed to examine the effects of acute treatment with SKF 10047, a sigma-1 selective agonist, on anxiety tested in the elevated plus maze. For this purpose, male mice of the OF:1 strain were used. Animals were randomly allocated to one control group receiving saline and three experimental groups receiving SKF 10047 (2, 4 and 8 mg/kg, ip) injections. Tests were performed 30 min after injections. The elevated plus maze used in our experiment was designed according to the test developed by Lister (2) in mice. At the beginning of the test, each naïve mouse was placed in the central area of the maze with its head facing an open arm. The following behavioral parameters were recorded during 5 min using a Sony V8 camera: (a) total time in open arms; (b) total time in closed arms; (c) total time in central area; (d) number of open arms entries; (e) number of closed arms entries; and (f) rearings. Behavioural analysis was performed by a trained experimenter who was unaware of treatment of the groups. As statistical analysis, nonparametric Kruskall-Wallis and Mann-Whitney U-tests were used. SKF 10047 (4 and 8 mg/kg) produced a significant reduction in the number of entries in open arms, as well as in the time spent in this area, as compared with the control group (p<0.05), without depressing motor activity. These results suggest that SKF 10047 could exhibit an anxiogenic-like profile in the elevated plus-maze test in male mice. Further investigations are needed to determine the generality of present findings to other test situations.

References

P.3.043 Dopamine transporter density changes of basal ganglia with SSRI treatment in OCD patients

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It has been suggested that dopamine as well as serotonin is associated with the pathophysiology of obsessive-compulsive disorder (OCD). We investigated the DAT density of the basal ganglia using iodine-123 labelled N-(3-iodopropyl-2-yl)-2fi-carbomethoxy-4fi-fluorophenyl) toluene ([123I]IPT) single-photon emission tomography (SPET) in patients with OCD before and after serotoner reuptake inhibitors (SSRI) treatment and evaluated the activity of the presynaptic dopamine function in patients with OCD. Ten patients with OCD before and after treatment and nineteen normal control adults were included in the study. We performed brain SPET 2 h after the intravenous administration of [123I]IPT and carried out both quantitative and qualitative analyses using the obtained SPET data, which were reconstructed for the assessment of the specific/non-specific dopamine transporter (DAT) binding ratio in the basal ganglia. We then investigated the correlation between the severity scores of OCD symptoms changes assessed with the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) and the specific/non-specific DAT binding ratio of the basal ganglia. Patients with OCD after treatment showed a significantly decreased specific/non-specific DAT binding ratio in right basal ganglia compared with the state before treatment. No significant correlation was found between the total scores changes of the Y-BOCS during treatment and the specific/non-specific DAT binding ratio of the basal ganglia. These findings suggest that the dopaminergic neurotransmitter system of the basal ganglia in patients with OCD could play an important role in the pathophysiological mechanism of OCD.

The underlying mechanisms by which physical or psychological stress causes neurodegeneration are still unknown. We have demonstrated that inducible nitric oxide (NO) synthase (iNOS) is expressed in brain cortex after immobilisation stress and that its overexpression accounts for the accumulation of oxidative/nitrosative mediators. Among the mechanisms involved in this process, a role for glutamate and cytokines (particularly tumour necrosis factor-factor, TNF-α) have been proposed. Of particular interest is the issue of whether the intensity and/or persistency of stress causes mood disorders such as depression and neurodegeneration and whether such changes are reversible or not. Now we sought to determine whether repeated exposure to immobilisation stress lead to persistent oxidative status in rat brain. Several groups (n=6) of young adult male Wistar rats were immobilised during 6 hours every day during 7 or 14 days (S7, S14) to induce stress. Cerebral cortices were obtained immediately after the last session of stress or 20 h later. Stress increases Ca2+-independent NOS activity after 7 or 14 days (control: 1.69±0.10; S7: 58.53±9.88; S14: 89.13±11.02 pmol citrulline/min/mg protein; – both P<0.05 vs control). This enzymatic activity returns to basal 20 h after S7 (0.95±0.1; P>0.05 vs control), but not after S14 (5.90±0.09; P<0.05 vs control). Similarly, stress increases malondialdehyde (MDA, an indicator of lipid peroxidation) accumulation in cortex after S7 and S14 (control: 0.0095±0.001; S7: 0.0157±0.004; S14: 0.0199±0.01 nmol/mg prot; – both P<0.05 vs control). MDA levels return to basal 20 h after S7 (0.0092±0.001; P>0.05 vs control), but not after S14 (0.0149±0.01; P<0.05 vs control). In order to elucidate the possible mechanisms involved in this short-term persistency of oxidative status, we have determined brain levels of TNF-α. Interestingly, TNF-α levels did not increase after S7 nor 20 h after S7, but increases after S14 (control: 23.6±3.2; S14: 29.6±2.8 pg/mg protein, P<0.05), and 20 h after S14 (30.0±3.2 pg/mg protein, P<0.05 vs control). These findings indicate that TNF-α accounts for stress-induced persistency of iNOS expression and MDA accumulation after 14 days of repeated exposure, supporting a possible neuroprotective role for specific blockers of the TNF-α effects or release in this situation. * CM supported by FAPESP and Fundo Bunka-Banco Sumitomo