EFFECTS OF HT-2157, A GALANIN-3 RECEPTOR ANTAGONIST, ON EXTRACELLULAR LEVELS OF 5-HT IN VARIOUS BRAIN REGIONS OF FREELY-MOVING RATS

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Galanin is a neuropeptide transmitter which has been shown to modulate central 5-hydroxytryptamine (5-HT) neurotransmission (Fuxe *et al.*, 1998; Kehr *et al*., 2002; Yoshitake *et al*., 2003) and has been implicated in depression (Weiss *et al*., 1998). In this study the effects of HT-2157 (1,3-dihydro-1-phenyl-3-[[3-(trifluoromethyl) phenyl]imino]-2H-indol-2-one), a selective Galanin-3 receptor antagonist (Blackburn *et al*., 2005), were examined on extracellular 5-HT levels in the frontal cortex, ventral hippocampus and cingulate cortex, using *in vivo* microdialysis. The serotonin selective reuptake inhibitor (SSRI), paroxetine, was used as a comparator. Male, Sprague-Dawley rats (250 – 350 g; Charles River, UK) were anaesthetised with isoflurane in an O_2/N_2O mixture and a concentric dialysis probe (manufactured in-house with Hospal membrane tip) was stereotaxically implanted into the rat brain. During a recovery period of at least 16 h food and water were available *ad libitum* and probes were continuously perfused with an artificial cerebrospinal fluid (Harvard Apparatus, UK) at a flow rate of 1.2 µl/min. Four basal samples (20 min interval) were collected prior to oral (po) administration of drug or vehicle. Dialysate 5-HT was quantified by reverse-phase HPLC with electrochemical detection. Values are mean ± SEM (n = 5-7) and statistical comparisons were made between drug- and vehicle-treated groups by one way ANCOVA with Dunnett's or Williams' test for multiple comparisons. HT-2157 (3, 10 and 30 mg/kg; 0.25% methylcellulose) evoked a significant, dose-dependent increase in frontal cortical 5-HT levels which was immediate (10 and 30 mg/kg) and sustained for at least 4 h post-drug. Maximal increases of 201 ± 89% (3 mg/kg), 1238 ± 393% (10 mg/kg) and 2424 ± 1090% (30 mg/kg) were observed (P<0.001) compared to vehicle-treated controls. HT-2157 (1 mg/kg) had no effect. Paroxetine (10 mg/kg) also resulted in an immediate and sustained increase in 5-HT levels, with a maximal rise of 1132 ± 381% (P<0.001). 5-HT in the ventral hippocampus was also significantly (P<0.001) increased following administration of HT-2157 at 10 mg/kg (461 ± 262%) and 30 mg/kg (824 ± 381%) and paroxetine at 10 mg/kg (863 ± 298%). HT-2157 (1 and 3 mg/kg) had no effect. In the cingulate cortex, HT-2157 significantly increased 5-HT levels by 61 ± 35% (3 mg/kg; P<0.05) and 472 ± 131% (10 mg/kg; P<0.001). HT-2157 (1 mg/kg) had no effect. Paroxetine (10 mg/kg) resulted in an increase of 436 ± 130% (P<0.001).

These data show that in the frontal cortex, ventral hippocampus and cingulate cortex, HT-2157 increased 5-HT levels in a dose-dependent manner. In both the frontal and cingulate cortex, the magnitude and time-course of effect of HT-2157 closely mirrored that of paroxetine, at the same dose (10 mg/kg), whereas in the ventral hippocampus HT-2157 displayed less efficacy than paroxetine (10mg/kg).

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