INTRODUCTION

Galanin is a neuromodulator 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-f[3-(trifluoromethyl) phenyl]iminio]-2H-indol-2-one), a selective Galanin-3 receptor antagonist (Blackburn et al., 2005), on extracellular 5-HT levels in the frontal cortex, ventral hippocampus and cingulate cortex were examined in vivo microdialysis. The serotonin selective reuptake inhibitor (SSRI), paroxetine, was used as a comparator.

METHODS

Male, Sprague-Dawley rats (250–350g; Charles River, UK) were anaesthetised using isoflurane (5% to induce, 2% to maintain) in an O2/N2O mixture.

A concentric dialysis probe (manufactured in-house with Hospal membrane tip) was stereotaxically implanted into the prefrontal cortex (coordinates: AP: +3.2 mm; L: +/-0.9 mm; V: -4.2 mm). Coordinates are according to Paxinos and Watson (1986).

Rats underwent a recovery period of at least 16 h during which time 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 administration of drug or vehicle. Sample collection continued for 4 h post-drug administration. 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 Williams' multiple comparisons.

RESULTS

HT-2157 (3, 10 and 30 mg/kg) evoked a significant, dose-dependent increase in cortical 5-HT levels which was immediate (10 and 30 mg/kg) and sustained for at least 4 h post-drug (Figure 1). Maximal increases of 201 ± 89% (3 mg/kg) and 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 (Figure 2).

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; Figure 3).

SUMMARY AND CONCLUSIONS

These data show that in the rat 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 was less potent than paroxetine.

REFERENCES

Blackburn TP et al. (2005) ACNP Meeting Proceedings, P58.