THE HT-2157-INDUCED INCREASE IN EXTRACELLULAR 5-HT LEVELS IN THE FRONTAL CORTEX OF FREELY-MOVING RATS IS MODULATED BY 5 HT_{1A} RECEPTORS

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INTRODUCTION

HT-2157, a selective Galanin-3 receptor antagonist, has been shown to increase extracellular levels of 5-hydroxytryptamine (5-HT) in various brain regions (Rowley et al., 2005).

In this study the role of 5-HT_{1A} receptors in the HT-2157-induced increase in 5-HT levels was examined in the rat frontal cortex using 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.

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Between drug-treated groups by area under the curve analysis with one way ANOVA. Values are mean ± SEM (n = 7-8) and statistical comparisons were made with a post HT-2157 administration. Dialysate 5-HT was quantified by reverse-phase HPLC with electrochemical detection.

RESULTS

HT-2157 (10 mg/kg po) resulted in an immediate increase in extracellular cortical 5-HT levels which was sustained for up to 4 h post-drug administration with a maximum increase of 746 ± 141% compared to vehicle-treated controls (P<0.001). WAY 100 635 (0.3 mg/kg sc), administered 2 h after HT-2157, resulted in a small but significant (P<0.01) potentiation of the HT-2157-induced increase in 5-HT levels with a maximum rise in levels of 1113 ± 248%, compared to vehicle-treated controls (Figure 1A). Mean AUC: period 1 (0-120 min) HT-2157 alone = 18.5 fmol/20 µl; period 2 (120-240 min) HT-2157 + WAY 100 635 = 20.3 fmol/20 µl (P<0.01).

Paroxetine (10 mg/kg po) significantly increased cortical 5-HT levels for up to 4 h post-administration with a maximum increase of 758 ± 119% compared to vehicle-treated controls. WAY 100 635 and paroxetine or vehicle, WAY 100 635 and 8-OH-DPAT were administered 2 h and 1 h, respectively, after HT-2157 or paroxetine, via the subcutaneous (sc) route. Sample collection continued for 4 h post-HT-2157 administration. Dialysate 5-HT was quantified by reverse-phase HPLC with electrochemical detection.

Values are mean ± SEM (n = 7-8) and statistical comparisons were made between drug-treated groups by area under the curve analysis with one way ANCOVA.

Each data point represents mean ± S.E.M. (7-8 rats). The vertical arrows indicate administration of HT-2157, paroxetine or vehicle (0 min) and WAY 100 635 or saline (120 min). ††P<0.005, ††P<0.01: AUC analysis HT-2157 or paroxetine + WAY 100 635 compared to HT-2157 or paroxetine alone (ANCOVA).

SUMMARY AND CONCLUSIONS

These data show that the increases in cortical 5-HT levels evoked by HT-2157 and paroxetine were potentiated by the 5-HT_{1A} receptor antagonist, WAY 100 635.

The 5-HT_{1A} agonist, 8-OH-DPAT, attenuated the increase in 5-HT evoked by HT-2157. Similar effects have been observed on paroxetine-induced increases in 5-HT levels (Gundlah et al., 1997).

These data indicate that the rise in 5-HT evoked by HT-2157 was due, at least in part, to a mechanism dependent on neuronal firing.

REFERENCES


Rowley HL et al. (2005) Br J Pharmacol, (This meeting).

FIGURES

FIG. 1. Effect of WAY 100 635 on the (A) HT-2157- and (B) paroxetine-induced increase in cortical 5-HT levels

FIG. 2. Effect of 8-OH-DPAT on the HT-2157-induced increase in cortical 5-HT levels

Each data point represents mean ± S.E.M. (7-8 rats). The vertical arrows indicate administration of HT-2157, paroxetine or vehicle (0 min) and WAY 100 635 or saline (60 min). ††P<0.01: AUC analysis HT-2157 + 8-OH-DPAT compared to HT-2157 alone (ANCOVA).