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The interaction of H_3 ligands with 5-HT_3 receptors in NG108-15 cells

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Recently, binding studies by Leurs et al. (1995) have established that the H_3 agonist imetit and the H_3 antagonists thioperamide and iodophenpropit can displace the selective 5-HT_3 receptor ligand [^{3}H]-GR65630 from rat cortex membranes. In addition, these workers have shown that iodophenpropit and thioperamide are 5-HT_3 receptor antagonists and imetit is a potent 5-HT_3 agonist in the guinea pig ileum. Some of these compounds may therefore, have the capacity to interact with ligand gated ion channels. These aspects of their pharmacology have not been investigated using electrophysiological techniques.

In the present study, the patch clamp technique was used to investigate the influence of H_3 receptor ligands on macroscopic 5-HT_3 receptor-mediated currents in cultured undifferentiated NG108-15 hybrid cells. Agonist-induced currents were recorded from cells voltage clamped at a membrane potential of -80mV. Agonists were applied using a motor-operated SF-77 fast-step perfusion system (Warner Instruments) for 5 seconds and the applications were repeated every 90 seconds to avoid desensitization.

The 5-HT activated inward current rapidly desensitised. Currents were inhibited by low concentrations of d-tubocurarine or tropisetron and showed saturation with increasing concentration (EC_{50}=3.0±0.1μM;n_H= 3.1±0.5; n=5). Imetit exhibited weak partial agonist activity at the 5-HT_3 receptor (EC_{50}=11.8μM; n_H= 2.3±0.9; n=7). These inward currents were inhibited by both d-tubocurarine and tropisetron. Imetit responses, unlike 5-HT induced currents, were slow to desensitise and at a high concentration demonstrated a degree of agonist block.

The H_3 antagonists iodophenpropit and thioperamide did not generate inward currents but were able to inhibit 5-HT responses with an IC_{50} of 1.57±0.3μM(n=5) and 13.7±3.5 μM (n=9) respectively. Increasing concentrations of thioperamide shifted the log concentration response curve for 5-HT to the right whilst at the same time depressing the maximal response, indicating a non-competitive antagonism of 5-HT. Many noncompetitive antagonists have been shown to channel block and consequently increase the apparent rate of receptor desensitisation.

Analysis of the kinetics of 5-HT responses showed a rapidly activating current (rise time 100ms±10ms; n=6) that underwent a biexponential desensitisation (τ_f=570ms ±40ms; τ_s = 6.21s±0.75s; n= 6). In the presence of thioperamide the rate of activation of the 5-HT induced current was markedly slowed (rise time = 340ms±0.01ms; n=6;$p<0.05$), this appeared to obscure the rapid phase of desensitisation, and decreased the time constant of the slow phase (τ_s = 3.75s±0.4s; n= 6; $p<0.05$). These data are consistent with thioperamide acting as a non-competitive antagonist and imetit acting as a weak partial agonist at the 5-HT_3 receptor.

Leurs et al. (1995) Br.J.Pharmacol.,116, 2315-2321