ELECTROPHYSIOLOGICAL EVIDENCE FOR 5-HT_{2C} RECEPTOR-MEDIATED CONTROL OF 5-HT CELL FIRING IN THE ANAESTHETISED RAT

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The role of 5-HT_1 autoreceptors in feedback regulation of central 5-hydroxytryptamine (5-HT) neurones is well established. Emerging data suggest that 5-HT neurones may also be controlled by the 5-HT_{2C} receptor subtype. Specifically, 5-HT_2 receptor agonist administration was reported to inhibit the firing of 5-HT neurones in the rat dorsal raphe nucleus (DRN) *in vivo*, an effect partially blocked by the 5-$HT_{2B/C}$ receptor antagonist SB 206553 (Boothman *et al*., 2003). More recently it was found that the putative selective 5-HT_{2C} receptor agonist, WAY 161503, inhibited 5-HT cell firing, an effect reversed by the selective 5-HT_{2C} receptor antagonist, SB 242084 (Boothman *et al.*, 2006). The present study extended this pharmacological analysis using the 5-HT_{2C} receptor agonists, RO-60-0175 and *m*-chlorophenylpiperazine (mCPP) (Nilsson, 2006).

Male Sprague-Dawley rats (280-300 g) were anaesthetised with chloral hydrate supplemented with saffan. Extracellular recordings of DRN 5-HT neurones were made using stereotaxically implanted single barrel glass electrodes (2 M NaCl, 2 % pontamine sky blue, 10-16 MΩ). 5-HT neurones were identified using specific electrophysiological and pharmacological criteria (Boothman *et al*., 2003). After 3 min baseline recording, rats (6-7 per group) were injected i.v. with WAY 161503, RO-60-0175 or mCPP in accumulating doses given at 2 min intervals (0.125, 0.25, 0.5, 1.0 mg kg^{-1}). SB 242084 (1.0 mg kg^{-1}) was injected 2 min after the final dose, usually followed by the 5-HT_{1A} agonist, 8-OH-DPAT (10 μg kg^{-1}). Firing rate was determined for the final min of each post-drug interval (Spike2 software). Agonist and antagonist effects were analysed statistically using 1-way ANOVA with Dunnett's test *post-hoc* (versus pre-drug values) and Student's paired t-test (versus last dose of agonist), respectively.

WAY 161503 caused a dose-related inhibition of 5-HT cell firing to 4 % of pre-drug levels ($P<0.0001$), and this effect was reversed by SB 242084 in each case ($p<0.05$). RO-60-0175 also caused a dose-related inhibition of 5-HT cell firing ($P<0.001$) to 20 % of pre-drug levels, and this effect was reversed by SB 242084 in each case ($p<0.05$). mCPP caused a dose-related inhibition of 5-HT cell firing in 4 out of 7 cells recorded ($P<0.01$). For inhibited cells, mCPP reduced firing to 6 % of pre-drug levels and the effect was reversed by SB 242084 ($p<0.05$). The 3 cells that did not respond to mCPP were inhibited by 8-OH-DPAT.

In summary, these data show that the 5-HT_{2C} receptor agonists WAY 161503, RO-60-0175 and mCPP each inhibit the firing of rat DRN 5-HT neurones *in vivo*, and that this effect is reversed by the selective 5-HT_{2C} receptor antagonist SB 242084. The lack of sensitivity of some 5-HT neurones to mCPP may reflect a partial agonist or non-specific action of this drug (Nilsson, 2006). These findings add further support to the hypothesis that 5-HT_{2C} receptors participate in the feedback regulation of central 5-HT neurones.

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