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Quinine blocks 5-HT and 5-HT₃ receptor mediated peristalsis in both guinea pig and mouse ileum tissue

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Introduction. Quinine is commonly used to treat malaria; however one of the principal side effects is gastrointestinal disturbances (White, 1992). 5-HT₃ receptors modulate gut peristalsis (Chetty *et al.*, 2006), and, as quinine has been shown to act as a 5-HT₃ receptor antagonist (Thompson and Lummis, 2008) it is possible that these side effects result from actions at gut 5-HT₃ receptors. To address this question, we examined the ability of quinine to antagonise 5-HT and 5-HT₃ mediated peristalsis in guinea pig and mouse ileum.

Methods. Ileum was excised from male guinea pigs (200-300g) and C57BL/6 mice (25-35g) following cervical dislocation. Ileum segments (3-5 cm) were mounted in 50 ml organ baths containing Tryode's solution at 35-37 °C. Concentration-response curves were constructed for 5-HT and the selective 5-HT₃ agonist 2-Me-5-HT (non-cumulative doses). Quinine was pre-applied for 10 min and inhibition measured using agonist concentrations that elicited a submaximal response.

Results. Concentration-dependent contractions produced by 5-HT ($pEC_{50} = 5.45 \pm 0.17$, $n = 8$) and the selective 5-HT₃ agonist 2-Me-5-HT (5.01 ± 0.17 , $n = 11$) were not significantly different (Student's *t*-test, $t = 0.619$, $df = 17$, $p = 0.544$) in guinea pig ileum. Increasing concentrations of quinine were able to antagonise the activities of both 5-HT ($pIC_{50} = 5.03 \pm 0.2$, $n = 6$) and 2-Me-5HT ($pIC_{50} = 4.59 \pm 0.26$, $n = 4$). At mouse ileum, 5-HT ($pEC_{50} = 7.57 \pm 0.33$, $n = 9$) was more potent (Student's *t*-test, $t = 3.6$, $df = 12$, $p = 0.004$) than 2-Me-5-HT ($pEC_{50} = 5.45 \pm 0.58$, $n = 5$). Quinine antagonised both the 5-HT ($pIC_{50} = 4.87 \pm 0.31$, $n = 7$) and 2-Me-5-HT-induced ($pIC_{50} = 6.18 \pm 1.14$, $n = 4$) contractions.

Conclusions. These results support previous electrophysiological studies that identified quinine as an antagonist at recombinant 5-HT₃ receptors with IC_{50} values comparable with those reported here ($pIC_{50} = 4.87$, Thompson *et al.*, 2007). Further, we found that quinine completely blocked 5-HT induced contractions in mouse and guinea pig, raising the possibility that quinine targets other 5-HT receptors in the gut (e.g., 5-HT₄ receptors) and may influence intestinal function.

Chetty *et al.*, (2006). *Br.J.Pharmacol.*, 148; 112-141.

Thompson *et al.*, (2007). *Br.J.Pharmacol* 151; 666-667.

Thompson and Lummis, (2008). *Br.J.Pharmacol* 153; 1686-96. White, (1992). *BJCP*, 34; 1-10.