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Inhibition of native 5-HT3 receptor-evoked contractions in guinea pig and mouse ileum by antimalarial drugs

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A B S T R A C T
Quinine, chloroquine and mefloquine are commonly used to treat malaria, however, with associated gastrointestinal (GI) side-effects. These drugs act as antagonists at recombinant 5-HT3 receptors and modulate gut peristalsis. These gastrointestinal side effects may be the result of antagonism at intestinal 5-HT3 receptors. Ileum from male C57BL/6 mice and guinea pigs was mounted longitudinally in organ baths. The concentration–response curves for 5-HT and the selective 5-HT3 agonist 2-Me-5-HT were obtained with 5-HT (pEC\textsubscript{50}=7.57±0.33, n=12) more potent (P=0.004) than 2-Me-5-HT (pEC\textsubscript{50}=5.45±0.58, n=5) in mouse ileum. There was no difference in potency of 5-HT (pEC\textsubscript{50}=5.42±0.15, n=8) and 2-Me-5-HT (pEC\textsubscript{50}=5.01±0.55, n=11) in guinea pig ileum (P>0.05). Quinine, chloroquine or mefloquine was applied for 10 min and inhibitions prior to submaximal agonist application. In mouse ileum, quinine, chloroquine and mefloquine antagonised 5-HT-induced contractions (pIC\textsubscript{50}=4.9±0.17, n=7; 4.76±0.14, n=5; 6.21±0.2, n=4, correspondingly) with mefloquine most potent (P<0.05). Quinine, chloroquine and mefloquine antagonised 2-Me-5-HT-induced contractions (pIC\textsubscript{50}=6.35±0.11, n=8; 4.64±0.2, n=7; 5.11±0.22, n=6, correspondingly) with quinine most potent (P<0.05). In guinea-pig ileum, quinine, chloroquine and mefloquine antagonised 5-HT-induced contractions (pIC\textsubscript{50}=5.02±0.15, n=6; 4.54±0.1, n=7; 5.32±0.13, n=5) and 2-Me-5-HT-induced contractions (pIC\textsubscript{50}=4.62±0.25, n=5; 4.56±0.14, n=6; 5.67±0.12, n=4) with chloroquine least potent against 5-HT and mefloquine most potent against 2-Me-5-HT (P<0.05). These results support previous studies identifying anti-malarial drugs as antagonists at recombinant 5-HT3 receptors and may also demonstrate the ability of these drugs to influence native 5-HT3 receptor-evoked contractile responses which may account for their associated GI side-effects.

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1. Introduction

Enterochromaffin (EC) cells, within the epithelial layer of the gastrointestinal tract, release 5-HT and account for 90% of the body's store of 5-HT (Bueno, 2005). A variety of 5-HT receptors located on intestinal cells modulate peristalsis (Tuladhar et al., 2003, 1997, 2000) and secretion (Turvill et al., 2000). These include 5-HT\textsubscript{1A}, 5-HT\textsubscript{3}, 5-HT\textsubscript{4} and 5-HT\textsubscript{7} receptors (Hoyer et al., 2002). 5-HT\textsubscript{3} receptors play an important role in the excitability of the enteric nervous system, contributing to fast excitatory postsynaptic potentials in neurones of the myenteric and submucosal plexuses (Galligan, 2002, 2000; Michel et al., 2005). 5-HT\textsubscript{3} receptors are distributed throughout the human, guinea pig, rat and mouse intestine (Butler et al., 1990; Champaneria et al., 1992; Chetty et al., 2006, 2008; Gaddum and Picarelli, 1957; Kapeller et al., 2011), and play a pivotal role in modulating intestinal motility (Chetty et al., 2006; Liu et al., 2011; Mayer et al., 2006). Additionally, 5-HT\textsubscript{3} receptor antagonists such as ramosetron have been indicated for diarrhoea-predominant irritative bowel syndrome by blocking intestinal 5-HT\textsubscript{3} receptors (Lee et al., 2011).

The principal side effects of quinine, chloroquine and mefloquine include gastrointestinal disturbances such as nausea, vomiting, diarrhoea and constipation (Barrett et al., 1996; Fogh et al., 1988; White, 1992). This may be partially due to an interaction with receptors or ion channels expressed within the gut and the enteric nervous system. Quinine is known to block voltage-gated K\textsuperscript{+} channels (Schmalz et al., 1998) and chloroquine may indirectly modulate large Ca\textsuperscript{2+}-activated K\textsuperscript{+} channels (BK\textsubscript{Ca}) in the ileum (Jing et al., 2013). Quinine, chloroquine, and mefloquine have also been shown to act as antagonists at human and mouse recombinant 5-HT\textsubscript{3A} homo-oligomeric receptors expressed in Xenopus oocytes (Thompson et al., 2007; Thompson and Lummis, 2008).
Additionally, quinine, chloroquine and mefloquine can displace \([\text{H}^3]\text{granisteron} binding to mouse recombinant 5-HT3 receptors (Thompson et al., 2007) indicating that these anti-malarial drugs directly bind to the 5-HT binding site on the receptor. We hypothesise that these anti-malarial drugs, quinine, chloroquine and mefloquine will also act as antagonists at native 5-HT3 receptors in the small intestine, and by doing so may significantly attenuate 5-HT3-mediated contractions. In an attempt to investigate this hypothesis, we have utilised both mouse and guinea-pig isolated ileum preparations and examined the ability of the anti-malarial compounds, quinine, chloroquine and mefloquine to antagonise 5-HT and 5-HT3 mediated contractions. The rationale for using both mouse and guinea pig ileum being that the action of anti-malarial compounds at recombinant mouse 5-HT3A homooligomeric receptors has been evaluated previously (Thompson et al., 2007) and the guinea-pig 5-HT3A subunit (Lankiewicz et al., 2000) has a 85% sequence homology with its human counterpart with relatively similar agonist pharmacology to human recombinant 5-HT3A receptors (Belelli et al., 1995).

2. Materials and methods

2.1. Preparation of tissues

Male C57BL/6 mice (25–35 g; Charles River Laboratories, Margate, UK) were killed by cervical dislocation and the ileum was excised 2 cm before the ileo-caecal junction and placed in Tyrode’s solution (in mM: NaCl 137, KCl 2.7, CaCl2 1.8, MgCl2 1.0, NaH2PO4 0.42, NaHCO3 12.0, Glucose 5.5, pH 7.4). Segments of whole ileum (3–4 cm) were then carefully mounted longitudinally in 50 ml water jacketed organ baths containing Tyrode’s solution continuously aerated with 95% O2/5% CO2 and kept at 35–37 °C. The ileum segments were allowed to equilibrate for 30 min whilst mechanically attached to a force transducer with a resting tension of 0.5 g. The contractile responses were recorded by the force transducer and visualised by means of a chart recorder.

Portions of guinea pig ileum were obtained from adult male guinea pigs (200–300 g, Charles River, Laboratories, Margate, UK). The ileum was cut into 3.5–4 cm and mounted in a similar manner to that of mouse ileum. The tissues were equilibrated for 30 min followed by an initial application of acetylcholine (ACh; 1 μM) to establish the integrity of the tissue at the start of the experiment. All procedures involving animals were approved by the University of Kent Animal Welfare and Ethical Review Body in accordance with the UK Animals (Scientific Procedures) Act (1986).

2.2. Drugs

Acetylcholine, chloroquine, quinine (Sigma Aldrich, Poole, UK), 5-hydroxytryptamine hydrochloride (Tocris Bioscience, Bristol, UK), 2-methyl-5-HT (Tocris Bioscience, Bristol, UK) were dissolved in Tyrode’s solution. Mefloquine (Sigma Aldrich, Poole, UK) was dissolved in 50% dimethyl sulfoxide then diluted in Tyrode’s solution to a final dimethyl sulfoxide concentration of ≤ 0.3%. 5-HT and 2-methyl-5-HT were applied to the serosal layer of the ileum and responses recorded for 30 se which was sufficient for capturing the maximal contraction evoked from the drug. The Tyrode’s solution was then flushed and the organ bath filled with fresh Tyrode’s solution. The ileum was then maintained for 10 min prior to application of the next agonist concentration. For the anti-malarial (antagonist) compounds, application was also made to the serosal layer, however the ileum remained in contact with the anti-malarial compounds for 10 min. Following this 10 min interval, agonist was applied in the manner described above and the agonist evoked response recorded. The application of antagonists was not initiated until at least two agonist baseline responses (mm) in the absence of an antagonist did not differ greater than 5%.

2.3. Analysis of results

To construct the 5-HT and 2-me-5-HT agonist concentration-response curves, individual agonist-evoked contractile response heights (mm) were normalised to the maximal contraction height for each ileum. The mean normalised responses ± S.E.M. for each agonist concentration in a series were iteratively fitted using GraphPad Prism (version 6, Iowa, USA) to the non-linear regression equation

\[ y = E_{\min} + \left( E_{\max} - E_{\min} \right) \frac{(1 + 10^{\log I_{C_{50}} - \log C})}{1 + 10^{\log I_{C_{50}} - \log C}} \]

where \( E_{\min} \) is the baseline contraction, \( E_{\max} \) is the maximal agonist-evoked contraction, \( I_{C_{50}} \) is the concentration of the agonist required to produce 50% of the maximal contraction, \( L \) is the log of the agonist concentration and \( n_{H} \) is the Hill slope. Agonist potency was expressed as IC50 and pEC50 is the negative log of the IC50.

For antagonist experiments, baseline agonist response heights (mm) were measured and antagonist effects were measured as a % of the mean baseline agonist response for each ileum preparation. The relationships between increasing antimalarial (antagonist) concentration and % inhibition of agonist concentration-evoked contractions were iteratively fitted using GraphPad Prism (version 6, Iowa, USA) to the non-linear regression equation

\[ y = \frac{100}{1 + 10^{\log I_{C_{50}} - \log C}} \]

where IC50 is the concentration of the antagonist required to reduce to 50% of the agonist contraction, \( L \) is the log of the antagonist concentration and \( n_{H} \) is the Hill slope. Agonist potency was expressed as IC50 and pEC50 is the negative log of the IC50.

5-HT and 2-me-5-HT pEC50 were compared independently for mouse and guinea pig by a Student’s t-test, whilst pEC50 for each antagonist against 5-HT and 2-me-5-HT were compared by a one-way analysis of variance (ANOVA) followed by post-hoc analysis (Tukey’s t). Statistical significance was defined as \( P < 0.05 \).

3. Results

3.1. Mouse tissue

Both 5-HT and 2-methyl-5-HT were able to evoke concentration-dependent contractions in mouse ileum tissue 5-HT which was significantly more potent in its ability to induce contraction of the ileum than 2-methyl-5-HT (Fig. 1). Potency (expressed as pEC50) for 5-HT was 7.57 ± 0.33 (n=12), whilst potency for 2-methyl-5-HT was 5.45 ± 0.58 (n=5) (Table 1), which was significantly greater than potency for 5-HT when compared to the selective 5-HT3 agonist (Student’s t-test, t=3.36, df=15, \( P < 0.004 \)). With increasing concentrations, quinine was able to successfully antagonise 5-HT-induced (25 nM) contractions in mouse ileum (pIC50=4.9 ± 0.17, n=7, Fig. 2A) with complete block at 300 μM. Chloroquine also antagonised 5-HT induced contractions (pIC50=4.76 ± 0.14, n=5, Fig. 2B) as did mefloquine (pIC50=6.21 ± 0.2, n=4, Fig. 2C) (Table 2). A one-way analysis of variance revealed a statistically significant difference in the potency of the antimalarials to act as antagonists of the 5-HT mediated contractions \( F(2, 13) = 17.90, P < 0.001 \) with mefloquine acting as the most potent antagonist of 5-HT mediated contractions (Tukey’s t, \( P < 0.05 \)). A 10 min wash was sufficient to reinstate...
5-HT-evoked contractions following the highest concentration of either quinine or chloroquine, but not mefloquine. Quinine (pIC$_{50}$=6.35 ± 0.11, n = 8), chloroquine (pIC$_{50}$=4.64 ± 0.2, n = 7), and mefloquine (pIC$_{50}$=5.11 ± 0.22, n = 6) also successfully antagonised contractions evoked by the selective 5-HT$_3$ antagonist, 2-methyl-5-HT (10 μM) in mouse ileum (Fig. 3). Mefloquine was also able to successfully antagonise 2-methyl-5-HT-induced contractions with complete block at 100–300 μM. A one-way analysis of variance revealed a statistically significant difference in the potency of the antimalarials to act as antagonists of the 5-HT$_3$ mediated contractions [F(2, 18)=28.82, P < 0.0001] with quinine acting as the most potent antagonist of 5-HT$_3$ mediated contractions (Tukey's t, P < 0.05).

3.2. Guinea-pig tissue

5-HT (from 10 nM to 100 μM) and the selective 5-HT$_3$ agonist 2-methyl-5-HT (from 10 nM to 30 μM) produced concentration-dependent contractions in isolated guinea pig ileum. Potency (expressed as pEC$_{50}$) for 5-HT was 5.42 ± 0.15, whilst potency for 2-methyl-5-HT was 5.01 ± 0.55 with no statistical significant difference in potency between the two agonists (Student’s t-test, t = 0.619, df = 17, P = 0.544, Table 1). Increasing concentrations of quinine and chloroquine were able to antagonise submaximal 5-HT-induced contractions (pIC$_{50}$=5.02 ± 0.15, n = 6 and pIC$_{50}$=4.54 ± 0.1, n = 7, correspondingly) (Fig. 5A and B). Following a 10 min wash, 5-HT-evoked contractions were reinstated. In a similar manner, increasing concentrations of mefloquine also antagonised submaximal 5-HT contractions (pIC$_{50}$=5.32 ± 0.13, n = 5, respectively, Fig. 5C) (Table 3), however, 5-HT-evoked contractions could not be sufficiently restored in ileum treated with the maximal concentration of mefloquine (300 μM) following three successive washes (i.e., > 5 min). A one-way analysis of variance revealed a statistically significant difference in antagonist potency across the three anti-malarial compounds [F(2, 14)=8.874, P < 0.01] with chloroquine least potent in inhibiting 5-HT-induced contractions in the

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**Fig. 1.** (A) 5-HT (●) and 2-me-5-HT (○) induced contractions in mouse ileum. 5-HT (pEC$_{50}$=7.57 ± 0.33, n = 12) was more potent (Student’s t-test, t = 3.36, df = 15, P < 0.01) than 2-Me-5-HT (pEC$_{50}$=5.45 ± 0.58, n = 5). (B) 5-HT and 2-me-5-HT induced contractions in the guinea-pig ileum. Concentration-dependent contractions produced by 5-HT (pEC$_{50}$=5.42 ± 0.15, n = 8) and the selective 5-HT$_3$ agonist 2-Me-5-HT (5.01 ± 0.55, n = 11) were not significantly different (Student’s t-test, t = 0.619, df = 17, P = 0.544) in guinea pig ileum. Results are expressed as mean ± S.E.M.

**Fig. 2.** Quinine (●), chloroquine (○) and mefloquine (□) block 5-HT-induced contractions in isolated mouse ileum. Increasing concentrations of quinine (pIC$_{50}$=4.3 ± 0.17, n = 7), chloroquine (pIC$_{50}$=4.76 ± 0.14, n = 5) and mefloquine (pIC$_{50}$=6.21 ± 0.2, n = 4) were able to antagonise 5-HT induced contractions in mouse ileum, with mefloquine significantly more potent (Tukey’s t, P < 0.05). Results are expressed as mean ± S.E.M.

**Fig. 3.** Quinine (●), chloroquine (○) and mefloquine (□) block 2-me-5-HT-induced contractions in isolated mouse ileum. Increasing concentrations of quinine (pIC$_{50}$=6.35 ± 0.11, n = 8), chloroquine (pIC$_{50}$=4.64 ± 0.2, n = 7) and mefloquine (pIC$_{50}$=5.11 ± 0.22, n = 3) were able to antagonise 2-me-5-HT induced contractions in mouse ileum, with quinine significantly more potent (Tukey’s t, P < 0.05). Results are expressed as mean ± S.E.M.
guinea pig ileum (Tukey’s t, P < 0.05). In addition, quinine (pIC50 = 4.62 ± 0.25, n = 5), chloroquine (pIC50 = 4.46 ± 0.14, n = 6) and mefloquine (pIC50 = 5.67 ± 0.12, n = 4) were able to block selective 5-HT3 receptor mediated contractions by antagonising submaximal 2-methyl-5-HT-evoked responses (10 μM) in a concentration dependent manner (Fig. 5). All but mefloquine were reversible within 10 min of wash. A one-way analysis of variance revealed a statistically significant difference in antagonist potency [F(2, 12) = 10.51, P < 0.01] with mefloquine acting as the most potent antagonist of 5-HT3 mediated contractions (Tukey’s t, P < 0.05).

4. Discussion

The main findings of the current investigation are that the antimalarial compounds quinine, chloroquine and mefloquine antagonise 5-HT-evoked contractions of both mouse and guinea-pig ileum. These drugs also antagonise 5-HT3 receptor mediated contractions. The ability of these drugs to significantly influence the activity of key intestinal modulators, such as 5-HT, may underlie or partially account for their associated GI side effects of these drugs.

5-HT and the selective 5-HT3 receptor agonist 2-me-5-HT produced concentration-dependent contractions in mouse and guinea-pig ileal tissue. The potency of 5-HT to produce contractions in guinea pig ileum tissue (pEC50: 5.42) is very similar to previous studies which reported potencies (pEC50) obtained in the presence of methysergide (e.g., 5.32, 5.38) (Butler et al., 1990; Eglen et al., 1990). The potency of the selective 5-HT3 agonist, 2-me-5-HT (pEC50: 5.01), was also very similar to previous reports (e.g., 5.4–4.91) (Butler et al., 1990, 1988; Eglen et al., 1990) adding validity to our investigation. Interestingly, 5-HT was significantly more potent as an agonist than 2-me-5-HT in producing contractile responses in mouse ileum, suggesting the possibility that a variety of 5-HT receptor subtypes may be responsible for 5-HT-evoked contraction in the mouse ileum. This is consistent with previous studies which report a greater potency for 5-HT in the mouse ileum compared to 5-HT application with 5-HT12,4,5,6,7 antagonism and 5-HT potency compared to 2-me-5-HT (Chetty et al., 2006).

The antimalarial compounds also blocked contractions evoked by 5-HT and 2-me-5-HT in mouse ileum. Interestingly, mefloquine was significantly more potent in antagonising 5-HT mediated contractions than either chloroquine or mefloquine. This pattern of antagonism is very similar to previous reports which found that mefloquine was significantly more potent in antagonising 5-HT-induced current responses in mouse recombinant 5-HT3A homooligomeric receptors (Thompson et al., 2007). However, when looking at the antagonism of 2-me-5-HT mediated contractions, we found that quinine was a significantly more potent antagonist. This difference may be due to expression native 5-HT3A and hetero-oligomeric receptor in the mouse gut (Matsumoto et al., 2013) which may be more sensitive to quinine antagonism than homooligomeric 5-HT3A receptors, although no studies of recombinant mouse 5-HT3A hetero-oligomers have been completed to date. What also must be considered is that the contractions would be mediated by native receptors which may possess different regulatory sites compared to recombinant receptors, as well as being modulated by different cellular machinery compared to expression systems such as Xenopus oocytes.

The antimalarial compounds quinine, chloroquine and mefloquine were also able to antagonise both 5-HT and selective 5-HT3 receptor evoked contractions in guinea pig ileal tissue. Interestingly, the antagonist action of the antimalarial compounds on native receptors expressed in tissue is very similar to previous reports of antagonist action of antimalarial compounds on recombinant receptors. Thompson et al. (2007, 2008) expressed human and mouse recombinant 5-HT3 receptors in Xenopus oocytes and measured 5-HT3 receptor-mediated inward current responses via two-electrode voltage clamping. As with the current study, both quinine and mefloquine antagonised agonist induced responses with complete block at 100–300 μM, remarkably similar to the present results from native receptors expressed in guinea-pig tissue. The rank order of antagonist potency of 5-HT3 receptor mediated contractions in guinea pig ileum, with mefloquine significantly more potent than quinine or chloroquine, was extremely similar to the antimalarial antagonism of current responses mediated by recombinant human 5-HT3A hetero-oligomers reported by Thompson and Lummis (2008). Based on previous studies, it is likely that the native receptors expressed in the guinea pig ileum are hetero-oligomeric receptors, and the biophysical profile of native 5-HT3 receptors is similar to that of human 5-HT3A hetero-oligomers (Zhou and Galligan, 1999). This may explain the similar antagonist profile observed in this study.
It was noted that for guinea-pig and mouse ileum experiments, the antimalarial compounds were able to block contractions induced by the non-selective agonist 5-HT. As there are other 5-HT receptors expressed within the intestine (e.g., 5-HT₁A, 5-HT₂ and 5-HT₇) and these receptors may also induce or influence contractile responses, it raises the question as to whether quinine and mefloquine also have affinity for other 5-HT receptors in addition to 5-HT₃. Receptor binding experiments and subsequent docking studies conducted by Thompson et al. (2007) indicated that the antimalarial compounds quinine and chloroquine will most likely dock at the 5-HT binding site on the 5-HT₃ receptor. This may be due to the molecular similarity with these compounds and 5-HT. It is plausible that these antimalarial compounds may also bind to the 5-HT docking site at other 5-HT receptors thus potentially act as antagonists at other 5-HT receptors. This may in part explain the complete block of 5-HT induced contractions following pre-application of quinine.

Other possible factors influencing the results may be downstream receptor interaction and/or channel blockade by the antimalarial drugs. It is known that 5-HT₃ receptors can be expressed presynaptically on parasympathetic and sympathetic afferents to the gut causing release of ACh (Fox and Morton, 1990), which in turn elicits contractions of longitudinal muscle via activation of muscarinic ACh receptors. As quinine is known to act as a blocker of voltage-activated currents and muscarinic activated potassium channels (Dresviannikov et al., 2006), it is plausible that the effects observed may have been influenced in part by a blockade of these channels by quinine. Mefloquine is also known to block K⁺ channels. However it would be anticipated that a blockade of K⁺ channels would result in excitation, rather than an inhibition of contractile responses. It was noted during the experiments that following the initial application of quinine at 100–300 nM, there was a clear contraction with no responses at higher doses (data not shown). These observations would be consistent with potassium channel blockade leading towards excitation and contractile responses rather than a straightforward inhibition of the contractions. It is not clear that the results can be explained as simply a downstream blockade of muscarinic receptor activated cation channels. Both quinine and mefloquine completely antagonised 5-HT induced contractions, which may indicate an antagonism at 5-HT₃ receptors, as well as 5-HT₂ and 5-HT₅ receptors. It is known that 5-HT₂ induced contractions are not influenced or dependent upon cholinergic receptor activation or inhibition. Therefore this would imply that the effects of quinine and mefloquine observed upon 5-HT induced contractions cannot be due exclusively to an interaction at muscarinic receptor activated channels.

It should be noted that this study has focused exclusively on isolated intestinal tissue preparations. The antimalarial drugs may have direct central effects. Ondansetron, a selective 5-HT₃ antagonist and antiemetic drug, produces its antiemetic effect by blocking peripheral 5-HT₃ receptors on vagal afferents and brain 5-HT₃ receptors expressed in the medullary chemoreceptor zone (Gan, 2005). It is plausible that the antimalarial drugs would act at the same central 5-HT₃ receptors producing an antiemetic effect. Mefloquine has the ability to cross the blood brain barrier (Baudry et al., 1997). However, quinine and chloroquine cannot easily cross the blood brain barrier (Hagihara et al., 2000; Silamut et al., 1985) and this would be expected to impede any possible antiemetic effects by these drugs by acting at central 5-HT₃ receptors.

In conclusion, the present findings present an inhibition of both 5-HT and 5-HT₃ receptor-mediated contractions in both guinea-pig and mouse ileum tissue by the antimalarial drugs quinine, chloroquine and mefloquine. These results strongly suggest that these antimalarial drugs will directly interact and influence physiological function in the gut and may inhibit or disrupt normal contraction reflex responses at high concentrations. It is possible that the GI side-effects reported for these compounds may partially be the result of antagonist action at 5-HT₃ receptors.

**Table 1**

<table>
<thead>
<tr>
<th>Agonist</th>
<th>EC₅₀ (µM)</th>
<th>pEC₅₀ (± S.E.M.)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mouse ileum tissue</strong></td>
<td></td>
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<tr>
<td>5-HT</td>
<td>27.12</td>
<td>7.57 (± 0.33)</td>
<td>12</td>
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<tr>
<td>2-me-5-HT</td>
<td>3.5</td>
<td>5.45 (± 0.58)</td>
<td>5</td>
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<tr>
<td><strong>Guinea pig ileum tissue</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>5-HT</td>
<td>3.8</td>
<td>5.42 (± 0.15)</td>
<td>8</td>
</tr>
<tr>
<td>2-me-5-HT</td>
<td>9.7</td>
<td>5.01 (± 0.55)</td>
<td>11</td>
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</table>

**Table 2**

Inhibition of agonist evoked contractions in isolated mouse ileum by antimalarial compounds.

<table>
<thead>
<tr>
<th>Antimalarial</th>
<th>IC₅₀ (µM)</th>
<th>pIC₅₀ (± S.E.M.)</th>
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<tr>
<td><strong>Inhibition of 5-HT-evoked contractions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinine</td>
<td>12.5</td>
<td>4.9 (± 0.17)</td>
<td>7</td>
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<tr>
<td>Chloroquine</td>
<td>17.6</td>
<td>4.76 (± 0.14)</td>
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</tr>
<tr>
<td>Mefloquine</td>
<td>0.62</td>
<td>6.21 (± 0.2)</td>
<td>4</td>
</tr>
<tr>
<td><strong>Inhibition of 2-me-5-HT-evoked contractions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinine</td>
<td>0.44</td>
<td>6.35 (± 0.11)</td>
<td>8</td>
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<tr>
<td>Chloroquine</td>
<td>22.9</td>
<td>4.64 (± 0.2)</td>
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<tr>
<td>Mefloquine</td>
<td>7.85</td>
<td>5.31 (± 0.22)</td>
<td>6</td>
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</tbody>
</table>

**Table 3**

Inhibition of agonist evoked contractions in isolated guinea pig ileum by antimalarial compounds.

<table>
<thead>
<tr>
<th>Antimalarial</th>
<th>IC₅₀ (µM)</th>
<th>pIC₅₀ (± S.E.M.)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhibition of 5-HT-evoked contractions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinine</td>
<td>9.46</td>
<td>5.02 (± 0.15)</td>
<td>6</td>
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<tr>
<td>Chloroquine</td>
<td>28.71</td>
<td>4.54 (± 0.1)</td>
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<tr>
<td>Mefloquine</td>
<td>4.78</td>
<td>5.32 (± 0.13)</td>
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<tr>
<td><strong>Inhibition of 2-me-5-HT-evoked contractions</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Quinine</td>
<td>24</td>
<td>4.62 (± 0.25)</td>
<td>5</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>27.48</td>
<td>4.56 (± 0.14)</td>
<td>6</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>2.15</td>
<td>5.67 (± 0.12)</td>
<td>4</td>
</tr>
</tbody>
</table>

**Author contribution**

SPK conceived the principal question and designed the experiments.

SPK and SSW wrote the manuscript.

SPK, JW, MCK, SM, MAA, & IDB conducted the experiments.

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References


