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# ANTAGONISM OF 5-HYDROXYTRYPTAMINE RECEPTORS BY QUIPAZINE

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**1** The antagonist actions of quipazine on 5-hydroxytryptamine (5-HT) receptors have been investigated in the rabbit isolated superior cervical ganglion and on the rat isolated spinal cord and stomach strip.

**2** Changes in membrane potential induced by 5-HT or by the nicotinic agonist, 1,1-dimethyl-4-phenyl piperazinium (DMPP), were measured in the ganglion by the sucrose-gap technique. At ganglionic receptors, quipazine had little or no agonist activity, but greatly depressed depolarizations evoked by 5-HT but not depolarizations evoked by DMPP or trimethylammonium (TMA). Injections into the superfusion stream to the ganglion of 2 to 5 μmol quipazine in a small volume of Krebs solution prevented all subsequent responses to 5-HT. Superfusion of the ganglion with quipazine at a concentration of 1 μM produced complete blockade of responses to 5-HT in 3 of 6 ganglia and reduced responses by over 90% in 2 others; responses to DMPP were potentiated in amplitude and duration. Superfusion at a concentration of 0.1 μM depressed responses to 5-HT by 75% on average. The threshold concentration for the blocking action was around 0.01 μM, which depressed responses by 42% on average in 6 experiments (range 0 to 75%).

**3** 5-HT (1 μM or 100 μM) depressed the amplitude of the dorsal root potentials recorded from the isolated, hemisected cord of the neonate rat by 27 ± 5% (mean ± s.e. mean, $n = 14$) and by 45 ± 6% ($n = 14$), respectively. In the presence of quipazine (0.01 μM), 5-HT (1 μM or 100 μM) depressed the amplitude by 6 ± 2% ($n = 15$) and by 3 ± 1% ($n = 7$), respectively.

**4** Concentration-response curves of the contractions induced by 5-HT in the fundus of the rat stomach were obtained in the absence and presence of quipazine. Quipazine (1 μM) shifted the concentration-response curve to the right and depressed the maximum, suggesting a non-competitive mode of antagonism. $pI_{50}$ values were calculated in order to assess the antagonist activity of quipazine at rat fundus 5-HT receptors; the mean $pI_{50}$ was 6.91 ± 0.2 ($n = 6$).

**5** It is concluded that quipazine may be an effective antagonist at 5-HT receptors in various tissues.

## Introduction

The ganglion cells of the rabbit superior cervical ganglion (s.c.g.) are depolarized by 5-hydroxytryptamine (5-HT) acting on receptor sites which are distinct from those activated by nicotinic and muscarinic ligands (Wallis & Woodward, 1973; 1975; Wallis & North, 1978; Wallis, 1979). Because of their sensitivity to morphine, ganglionic 5-HT receptors are usually regarded as falling into that category of peripheral 5-HT receptor designated 'M' by Gaddum & Picarelli (1957) (see Trendelenburg, 1967). However, depolarization of the ganglion is not readily antagonized by morphine or by agents such as bromolysergic acid diethylamide (Brom-LSD), LSD, methysergide or picrotoxin unless concentrations of 10 to 100 μM are employed (Wallis & Woodward, 1973). Ganglionic 5-HT receptors display considerable specificity in response to a variety of indolealkylamines related to 5-HT (Wallis, 1979) and during the assessment of the agonist activity of some of these substances, 2-(1-piperazinyl) quinoline (quipazine, Figure 1) was tested. Quipazine has been reported to behave as an agonist at 5-HT receptors on various smooth muscle preparations (Hong & Pardo, 1968) and in the CNS (Rodriguez, Rojas-Ramirez & Drucker-Colin, 1973; Green, Youdim & Grahame-Smith, 1976).

This paper describes experiments in which the agonist and antagonist actions of quipazine on the ganglion were investigated. Preliminary experiments on the isolated spinal cord of the neonate rat showed quipazine also to have some antagonist activity at

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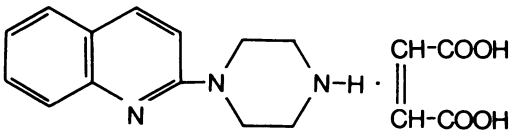


**Figure 1** Structure of quipazine, 2-(1-piperazinyl) quinoline maleate.

5-HT receptors in the CNS. Quipazine also antagonized contractions induced in the rat isolated stomach strip by 5-HT. A preliminary account of these findings has been presented to the British Pharmacological Society (Lansdown, Nash, Preston & Wallis, 1979).

## Methods

### *Preparations*

*Rabbit s.c.g.* Superior cervical ganglia were removed from adult rabbits anaesthetized with urethane (1.25 to 1.5 g/kg i.v. as a 25% w/v solution) and prepared as described by Wallis, Lees & Kosterlitz (1975) for insertion into a sucrose-gap apparatus. In this version of the apparatus, the sucrose compartment is separated from adjacent chambers by rubber membranes (Kosterlitz & Wallis, 1966; Wallis *et al.*, 1975). Potential changes induced by 5-HT or other substances were amplified and displayed on a potentiometric chart recorder (Servoscribe R.E. 511. 20). Ganglia were superfused with Krebs solution at 20 to 22°C. To avoid the tachyphylaxis that follows superfusion of the tissue with a solution of 5-HT in an effective concentration, injections of 5-HT dissolved in a small volume of Krebs solution were made into the superfusion stream to the ganglion (Wallis & Woodward, 1975) or, in a few experiments, into the superfusion stream to the internal carotid nerve. 5-HT 0.2 μmol (81 μg) produces a depolarization approximately 2/3 maximum and this quantity was used to evoke a standard response. Reproducible responses could be obtained if the flow of Krebs solution to the ganglion was carefully controlled with the aid of a drop chamber and the rate of injection kept relatively constant at 1.5 ml/min.

*Rat spinal cord* Spinal cords were removed from neonate rats anaesthetized with ether. Rats 3 to 10 days old and of either sex were used. After decapitation, the entire vertebral column was rapidly removed and placed in a dish containing cool, oxygenated Krebs solution and urethane (50 mM). After laminectomy, the cord caudal to the cervical region was dissected free from the remainder of the vertebral column, taking care to cut all roots. The cord was then floated free and positioned on the floor of the dissecting dish so that it could be hemisected. The hemisected cord was mounted on a sloping, silver grid and superfused with a modified Krebs solution. A length of filter paper under the grid led the superfusion fluid away to a drainage chamber through which the preparation was earthed. A lumbar dorsal root was stimulated via a pair of Ag wire electrodes, using rectangular pulses just supramaximal and 0.2 ms in duration. The adjacent and caudal dorsal root was placed upon a non-polarizable wick electrode constructed by inserting an Ag/AgCl wire into an agar column containing a small wick at its tip. A second wick Ag/AgCl electrode made contact with the surface of the grid close to the cord. Both dorsal roots were lifted clear of the superfusion fluid and insulated with a mixture of paraffin and Vaseline applied through a syringe. The temperature was maintained at 20°C (±2°C).

Dorsal root potentials (DRP) were monitored on an oscilloscope, after amplification with an a.c. amplifier of time constant 1 s, which gave an accurate representation of the peak amplitude and reduced baseline drift to allow averaging. Responses were averaged by a Neurolog System (Digitimer Ltd.). Usually, the average of 8 responses was taken and displayed on a potentiometric chart recorder (Rikadenki B-034), with an adequate frequency response (full-scale deflection 0.25 s).

*Rat stomach strip* Adult rats were killed by cervical dislocation and exsanguination. A strip was cut from the fundus and suspended in a 10 ml organ bath at 37°C. The tissue was placed under a tension of 1 g and allowed to equilibrate for 1 h. In some experiments, hyoscine (0.1 μM) was added to the solution in an attempt to decrease the spontaneous activity of the strip. Identical responses to 5-HT were obtained in the presence and absence of hyoscine. The contraction of the muscle was recorded with a pendulum auxotonic lever (Paton, 1957) on a rotating drum, or on a chart recorder (Servoscribe R.E. 541.20) by connecting a strain gauge (Devices Type 2S.T.02) to the lever by a spring. 5-HT was added to the organ bath in not more than 0.4 ml Krebs solution and the contraction of the stomach strip allowed to develop for 90 s. The bath was then washed out and the muscle stretched for 30 s. The next addition of 5-HT was made 2 or 3 min later. When larger amounts of 5-HT were used longer intervals were found to be necessary. A slow flow of Krebs solution was maintained through the organ bath between each addition of 5-HT.

*Assessment of antagonist potency* In the rat stomach strip dose-response curves to 5-HT in the absence or presence of quipazine suggested a non-competitive mode of antagonism and further experiments determined the molar concentration of quipazine

required to reduce the maximal response to 5-HT by 50%. The negative log of this molar concentration ($pI_{50}$) was used as a measure of antagonism (Barlow, 1964). In these experiments, the concentration of 5-HT producing a maximal response was first established and then the preparation exposed to increasing concentrations of quipazine; the maximal response to 5-HT was assessed periodically until it was established that no further reduction was occurring. Usually, the first concentration of quipazine tested was 0.1 μM. After prolonged equilibration a very small increase in the concentration of quipazine was sufficient to depress the maximal response to 5-HT by 50% or more. In experiments where the initial depression of the response was, say, 45% and the subsequent depression, say, 55%, the concentration of quipazine required to produce a 50% depression was assessed graphically.

*Solutions and drugs* All solutions were made up from distilled water passed subsequently through a deionizer. Krebs solution of the following composition (mM) was used in the experiments on rabbit ganglia and rat fundus: NaCl 118, KCl 4.75, $CaCl_2$ 2.54, $KH_2PO_4$ 1.2, $NaHCO_3$ 25, $MgSO_4$ 1.2 and glucose 11; it was gassed with 5% $CO_2$ and 95% $O_2$. The concentration of the sucrose solution superfusing part of the internal carotid nerve was 315 mM and taken to be isotonic. A modified Krebs solution of the following composition (mM) was used in experiments on rat spinal cord and gassed as before: NaCl 118, KCl 3.0, $CaCl_2$ 2.5, $NaHCO_3$ 25 and glucose 11. Magnesium ions were omitted from the solution as they are believed to interfere with certain depolarizing responses in the spinal cord (Evans, Francis & Watkins, 1977).

The drugs used were 5-hydroxytryptamine creatinine sulphate (Sigma), 1,1-dimethyl-4-phenyl piperazinium (DMPP) (Koch-Light), hyoscine hydrobromide (BDH), hexamethonium bromide (Sigma), trimethylammonium hydroxide pentahydrate (TMA) (Sigma), and 2-(1-piperazinyl) quinoline maleate (quipazine) (Miles Laboratories, Inc.).

## Results

*Action of quipazine at the superior cervical ganglion*

In 6 of 8 ganglia quipazine produced very small depolarizations whose amplitude was difficult to measure against the baseline noise. No response was obtained in 2 ganglia. The relative activity of quipazine expressed as a ratio of the molar quantity to the equipotent molar amount of 5-HT (Wallis, 1979) was around 240. Often as much as 2 to 5 μmol was required to produce a depolarization. In 7 ganglia following quipazine injections of between 2 and 5 μmol, there was a total blockade of subsequent responses to 5-HT, even when 10 times the normal amount of 5-HT (i.e. 2 μmol) was tested. However, depolarizations evoked by the nicotinic agonists, dimethylphenyl piperazinium (DMPP) or tetramethylammonium (TMA), were apparently undiminished in amplitude. In 6 other ganglia where the amount of quipazine injected was between 0.1 and 0.5 μmol, there was a total blockade of responses to 5-HT in 4 out of 6 experiments and in two experiments the responses to 5-HT were reduced by about 85%.

By superfusing the ganglion with a known concentration of quipazine, quipazine at a concentration of 0.1 μM was shown to reduce the responses to 5-HT, on average by about 75%, in 5 experiments (range 51 to 89%). Results from a representative experiment are shown in Figure 2a, b. Characteristically, the depolarizations elicited by 5-HT (Figure 2, a1) and DMPP (Figure 2, a2) were rapid and repolarization was followed by an after-hyperpolarization (see Lees & Wallis, 1974). After-hyperpolarizations evoked by DMPP were often relatively large in amplitude and often exceeded the preceding depolarization in magnitude. In earlier experiments (Wallis & Woodward, 1975) it was established that the responses remained relatively constant for several hours provided that a sufficient interval was left between each injection. Exposure of the ganglion to quipazine brought about a gradual reduction in the responses to 5-HT (Figure 2, a3, 4, 5, 7), which became less rapid in onset, longer in duration and the after-hyperpolarization disappeared. Quipazine did not produce a detectable change in resting membrane potential at this, or a ten-fold higher, concentration. This slow and progressive blockade of the response to 5-HT by quipazine was typical of its action on the ganglion and only after 2 h was blockade in this experiment maximal (Figure 2, a7). The time course of the blockade is shown in the graph (Figure 2b). In this and most other experiments on the ganglion, the sensitivity to 5-HT did not recover on washing the tissue with quipazine-free Krebs solution. However, responses to DMPP were unaltered by quipazine (Figure 2, a6, b) or slightly potentiated. The graph in Figure 2b shows this potentiation to disappear on washing.

Superfusion of the ganglion with a higher concentration of quipazine (1 μM) produced a total blockade of 5-HT responses in 3 of 6 ganglia, reduced responses by over 90% in 2 ganglia and by more than 75% in one ganglion. In 3 experiments concentrations of quipazine of 5 μM or more completely suppressed the response to 5-HT. Results from a representative experiment in which the ganglion was superfused with quipazine (1 μM) are shown in Figure 3a, b. Control responses elicited by 5-HT (Figure 3, a1) and DMPP (Figure 3, a2) were of comparable magnitude. In the

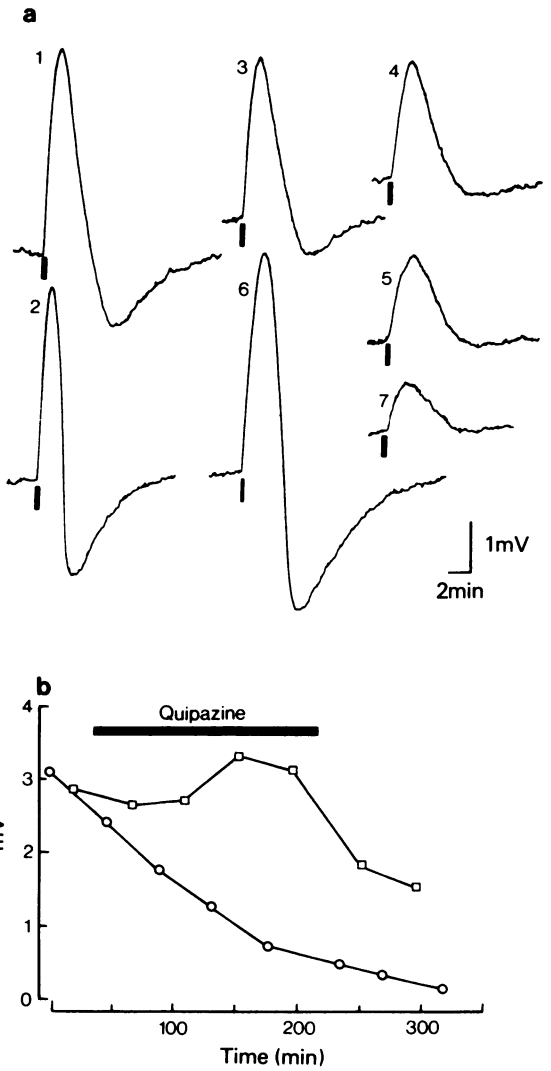


**Figure 2** The action of quipazine (0.1 μM) on ganglionic responses to 5-hydroxytryptamine (5-HT) or dimethylphenyl piperazinium (DMPP). (a) Chart records of changes in membrane potential induced by 5-HT or DMPP (0.2 μmol) injected during the periods indicated by the vertical black bars. The change in membrane potential is with respect to the potential preceding the vertical bar, which was taken as zero, ganglion depolarization upwards: (1) control response to 5-HT; (2) control response to DMPP; (3, 4, 5, 7) responses to 5-HT in the presence of quipazine for 11, 53, 95 and 141 min, respectively; (6) response to DMPP in the presence of quipazine for 118 min. (b) Amplitude of the depolarizations evoked by 5-HT (○) or DMPP (□) before, during and after exposure of the ganglion to quipazine. Ordinate scale: peak amplitude of the depolarization in mV; abscissa scale; time in min. The black bar indicates the period of exposure to quipazine.

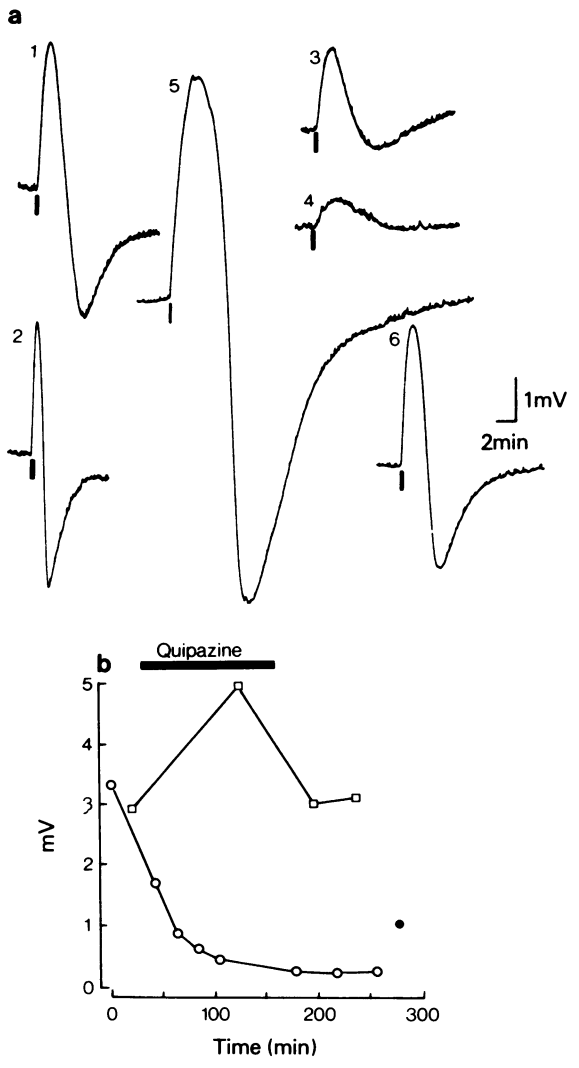


**Figure 3** The action of a higher concentration of quipazine (1 μM) on ganglionic responses to 5-hydroxytryptamine (5-HT) or dimethylphenyl piperazinium (DMPP). (a) Chart records of changes in membrane potential, induced by 5-HT or DMPP (0.2 μmol), as in Figure 2: (1) control response to 5-HT; (2) control response to DMPP; (3,4) responses to 5-HT in the presence of quipazine for 10 and 52 min, respectively; (5, 6) responses to DMPP in the presence of quipazine for 91 min and after superfusing with Krebs solution without quipazine for 76 min, respectively. (b) Amplitude of the depolarizations evoked by 5-HT (○) or DMPP (□) before, during and after exposure of the ganglion to quipazine. Ordinate scale: peak amplitude of the depolarization in mV; abscissa scale: time in min. The black bar indicates the period of exposure to quipazine. The closed circle (●) shows the response to an injection of a larger amount of 5-HT (2 μmol).

presence of quipazine at a concentration of 1 μM, the response to 5-HT declined in size more rapidly than in the presence of a concentration of 0.1 μM (cf Figures 3b and 2b). After 52 min, blockade was near maximal in this experiment (Figure 3, a4) and the depolarization evoked by 5-HT was small with a slow rate of rise. The response to DMPP, on the other hand, was not depressed but greatly potentiated in the presence of quipazine (cf Figure 3, a2, 5). The large after-hyperpolarization was particularly noticeable. The time course of these changes is shown graphically in Figure 3b. On washing out the quipazine the potentiation of the DMPP response was largely reversed (see also Figure 3, a6), but no recovery of the response to 5-HT was seen. The injection of 10 times the standard amount of 5-HT gave a somewhat larger response.

The threshold concentration for the blocking action of quipazine was around 0.01 μM and in 5 out of 6 experiments quipazine at this concentration caused a reduction in the depolarization evoked by 5-HT by 25 to 75%. However, in one experiment it had no effect. In the 6 experiments the mean reduction was 42%. This concentration of quipazine neither depressed nor potentiated the response to DMPP.

It has been shown that the non-myelinated axons leaving the ganglion in the internal carotid nerve may also be depolarized by 5-HT (Wallis, 1979). Although the magnitude of this depolarization varies considerably from preparation to preparation, the responses have a much faster time course than those evoked from the ganglion, probably because of the relative paucity of diffusion barriers. In 4 experiments the 5-HT-evoked depolarizations of non-myelinated fibres were suppressed by quipazine in comparable concentrations to those tested on the ganglion. In these experiments, there was some recovery of the responsiveness to 5-HT after prolonged washing, although this was never complete.

When transmission through the ganglion was examined in 4 experiments by observing compound action potentials evoked by a supramaximal stimulus to the cervical sympathetic trunk every minute, superfusion for up to 60 min with quipazine (1 μM) had no apparent effect on the ability of the ganglion to transmit action potentials.

*Action of quipazine on the spinal cord*

In the isolated, hemisected cord of the neonate rat, 5-HT has a depressant action on dorsal root potentials (DRPs) evoked by stimulation of an adjacent dorsal root (Figure 4). The DRP is thought to reflect depolarization of the primary afferents (Eccles, Eccles & Magni, 1961) and may be the basis for presynaptic inhibition in the cord (see Schmidt, 1971). The response (Figure 4a) consists of a rapid component, the dorsal root reflex and a slow negative wave, the DRP. In some experiments, as can be seen from the specimen results of Figure 4, the dorsal root reflex became more pronounced as the experiments continued. The amplitude of both components was depressed by 5-HT (1 μM) (Figure 4b) and this effect was reversed on washing. At a higher concentration (100 μM), a more rapid and profound depression of the response was observed (Figure 4e). The average reduction of the DRP by 5-HT (1 μM) was 27 ± 5% (mean ± s.e. mean, $n = 14$) and by 5-HT (100 μM) was 45 ± 6% ($n = 14$). In some experiments superfusion of the cord with quipazine (0.01 μM) itself led to some reduction in DRP amplitude (Figure 4h). In 13 of 22 applications on 9 cords, quipazine (0.01 μM) had no effect on DRP amplitude and in the remainder caused a slight reduction; the average reduction was 5 ± 2% ($n = 22$). After the cord had been superfused with quipazine (0.01 μM) for at least 10 min, the depressant action of 5-HT was very much reduced or abolished (Figure 4i). DRP amplitude recovered to control levels on washing (Figure 4j). In the presence of quipazine (0.01 μM), 5-HT (1 μM) depressed DRP amplitude by 6 ± 2% ($n = 15$), while 5-HT (100 μM) depressed DRP amplitude by 3 ± 1% ($n = 7$). No depression by 5-HT was observed in 4 experiments in which the cord was superfused with a higher concentration of quipazine (1 μM).

*Action of quipazine on the fundus of the rat stomach*

Even though smooth muscle receptors to 5-HT may be substantially different from those on neurones, it was thought worthwhile to attempt a preliminary quantitative analysis of the antagonist properties of quipazine on a tissue that would allow this. The rat stomach strip preparation was shown by Vane (1957) to be extremely sensitive to indolealkylamines.

In 8 preparations, dose-response curves to 5-HT were obtained in the presence and absence of quipazine (0.01 μM). This concentration had a variable effect, causing a slight potentiation of the responses to lower concentrations of 5-HT in 2 experiments and a depression of the maximum response to 5-HT in 7. An unequivocal shift of the dose-response curve to the right was only seen in 2 experiments. At a higher concentration of quipazine (1 μM) the effect was more pronounced and more consistent. In Figure 5, pooled data from 11 preparations have been used to construct the dose-response curve to 5-HT in the absence and presence of quipazine. The $ED_{50}$ value for 5-HT is 0.09 μM ($pD_2 = 7.05$). In 5 of these experiments, following the exposure of the fundus to quipazine (1 μM) for at least 30 min, the 5-HT dose-response curve was shifted to the right and the maximum response considerably depressed. This depression was not surmountable by higher concentrations of 5-HT.

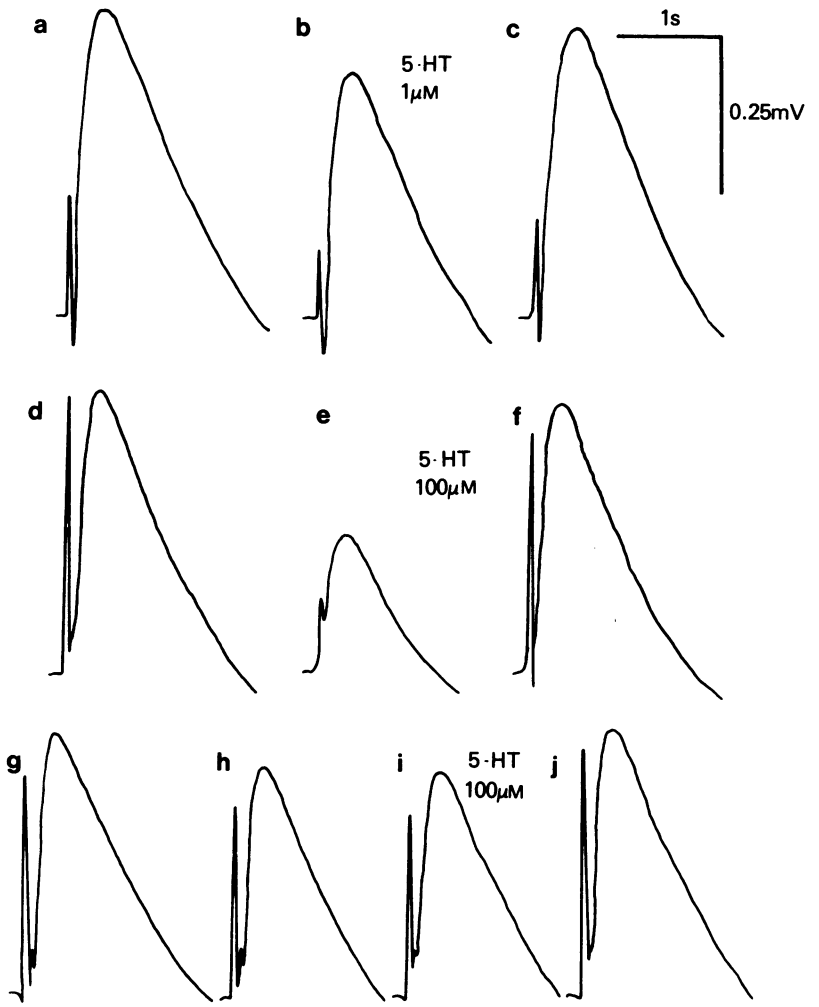


**Figure 4** The effect of 5-hydroxytryptamine (5-HT) and quipazine on dorsal root potentials (DRP) recorded from the rat isolated spinal cord. Chart records of the electronic average of 8 responses, dorsal root depolarization upwards, evoked by stimulation of an adjacent dorsal root: (a, d, g,) control responses; (b) on exposure to 5-HT (1 μM) for 12 min; (c) 10 min after returning to Krebs solution; (e) on exposure to 5-HT (100 μM) for 7 min; (f) 31 min after returning to Krebs solution; (h) on exposure to quipazine (0.01 μM) for 6 min and (i) for 15 min plus 5-HT (100 μM) for 9 min; (j) 24 min after returning to Krebs solution.

A non-parallel shift of the dose-response curve could be due to a non-competitive mode of antagonism. The $pI_{50}$ value for quipazine in 6 experiments was found to be $6.91 \pm 0.2$ ($n = 6$). Often 1 h was required for equilibrium to be reached.

## Discussion

The results suggest that quipazine may be an effective antagonist at 5-HT receptors in various tissues. However, no quantitative measure of antagonism was made at the ganglion because it is technically impracticable to repeat dose-response curves (Wallis & Woodward, 1975), or in the cord where the response is a complex and prolonged synaptic potential, probably generated across two or more synapses (Schmidt, 1971). To date, we have found no other compound as effective as quipazine in antagonizing the ganglionic depolarizing action of 5-HT. Morphine, for instance, the classical antagonist at 'M' tryptamine receptors (Gaddum & Picarelli, 1957), is relatively ineffective.

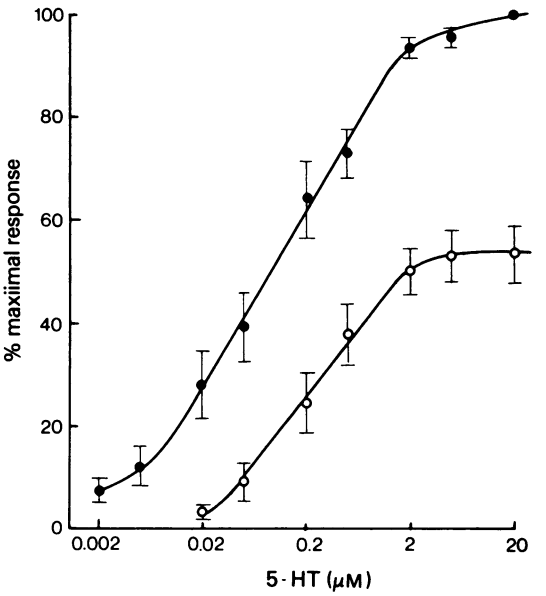


**Figure 5** Effects of quipazine on contractions of the rat fundus induced by 5-hydroxytryptamine (5-HT). (●): Control concentration-response curve to 5-HT, pooled data from 11 experiments; (○): concentration-response curve to 5-HT in the presence of quipazine (1 μM), pooled data from 5 experiments, Each point shows the mean and the vertical line the s.e. mean. Ordinate scale: magnitude of contraction as a percentage of the maximal response; abscissa scale: concentration (μM) of 5-HT in the organ bath.

Cyproheptadine was shown by Wallis & North (1978) to discriminate between 5-HT applied iontophoretically onto single ganglion cells and acetylcholine released intrinsically to evoke a synaptic potential; in sucrose-gap experiments, it is not very selective in antagonizing depolarizations evoked by applied 5-HT compared to those evoked by DMPP. Preliminary experiments suggest that metoclopramide, which was reported by Fozard & Mobarok Ali (1978) to antagonize 5-HT actions on the terminals of adrenergic neurones, is effective at the ganglion; at a concentration of 1 μM, depolarizations evoked by 5-HT were reduced in amplitude, but to a lesser extent than in the presence of the same concentration of quipazine.

The apparent potentiating action of quipazine on responses to DMPP, which was frequently observed when the concentration of blocking agent was 1 μM, cannot at present be explained. The action of quipazine on the depolarization of the ganglion by 5-HT was in general not surmountable by larger amounts of 5-HT; it was inferred that the maximal response was depressed. Further, the blockade was not reversed during superfusion with quipazine-free Krebs solution for periods as long as 3 h. In contrast, the potentiating action of quipazine on depolarizations evoked by DMPP was readily reversed on washing out the blocking agent, suggesting this may be due to a secondary action unrelated to blockade of 5-HT receptors.

The nature and the site of 5-HT receptors within the spinal cord is obscure. It is usually assumed that the DRP reflects a depolarization of the primary afferent fibres. This is probably generated via a polysynaptic path in the Substantia gelatinosa involving, perhaps, two interneurones in series (Réthelyi & Szentágothai, 1969). There is some evidence that a descending bulbospinal pathway, consisting of neurones which release 5-HT, may converge onto the neural mechanism generating primary afferent depolarization, either synapsing with interneurones or with the afferent terminals themselves (Proudfit & Anderson, 1974). Thus, it is possible that intrinsic 5-HT is released within the relevant area of the spinal cord, although it is unclear whether it is an excitatory or an inhibitory transmitter. 5-HT in the superfusion fluid had a depressant action on the DRP, as did quipazine itself in a few experiments. The most obvious effect of quipazine on this tissue was to prevent the depressant action of 5-HT.

The fundus strip from the rat stomach displayed a high sensitivity to 5-HT, the $pD_2$ value obtained being similar to that reported by Görlitz & Frey (1973). Quipazine shifted the dose-response curve to the right and depressed the maximum. This kind of non-parallel shift might be expected from an antagonist acting in a non-competitive manner. In experiments designed to assess the potency of quipazine as an antagonist of 5-HT receptors of the stomach strip in which sufficient time was allowed for equilibration of the blocking agent with the receptors, the negative log of the mean molar concentration causing a 50% depression of the maximal response evoked by 5-HT was 6.91.

There were indications that in all three tissues quipazine may be a partial agonist, for it had a very weak depolarizing action at the ganglion, displayed some 5-HT-like activity in a proportion of experiments on the spinal cord, and on the rat fundus in concentrations of 0.01 μM displaced the lower end of the dose-response curve to the left in a minority of experiments. It can be concluded that, at least in these tissues, quipazine appears to be a weak partial agonist with potent antagonist properties.

It is interesting that Hong & Pardo (1966) failed to note the antagonist properties of quipazine in their studies on a variety of smooth muscle preparations which did not include the rat fundus. Quipazine was a potent stimulant of the uterus, aorta, nictitating membrane, intestine, trachea and urinary bladder. How-

ever, in the guinea-pig ileum, at least, a rapid tachyphylaxis developed so that only one concentration of the drug could be tested.

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