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Meptazinol has a similar agonist action on opioid receptors in field-stimulated mouse vas deferens and guinea-pig ileum

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1 The effects of the opioid receptor agonist RX783006 and of the opioid receptor partial agonist (+)-meptazinol have been examined on electrically induced twitch responses of the guinea-pig isolated ileum and of the mouse isolated vas deferens.

2 Log_{10} concentration-tissue state curves were determined for (+)-meptazinol and RX783006, alone, in combination and in the presence of naloxone (30 nM).

3 Analysis of these log_{10} concentration-tissue state curves using the null equations derived and tested in the preceding paper indicates that the opioid agonist action of (+)-meptazinol on mouse vas deferens is quantitatively similar to that on guinea-pig ileum.

4 The results also suggest that (+)-meptazinol acts as a functional antagonist on the guinea-pig ileum as well as on the mouse vas deferens.

5 The potency of (+)-meptazinol relative to RX783006 has been measured by an indirect method which should eliminate any functional antagonistic action of (+)-meptazinol. This method gives a relative potency of (+)-meptazinol in both tissues which is three to six times greater than that measured directly on guinea-pig ileum. This discrepancy may be due to experimental error but it may also indicate that direct measurements on guinea-pig ileum underestimate the agonist potency of this compound on opioid receptors.

Introduction

Although twitch responses produced by field stimulation of mouse vas deferens and of guinea-pig ileum are both inhibited by compounds that stimulate opioid receptors there has been debate as to whether the receptors in the two tissues are identical, (Sayre *et al.*, 1983; Goodall *et al.*, 1985). One compound which appears to show selectivity between the receptors in these tissues is the (+)-isomer of meptazinol which acts as an opioid agonist on guinea-pig ileum but not on mouse vas deferens. This difference could be due to a difference in the nature of the receptors, differences in receptor capacity or to the fact that (+)-meptazinol possesses other non-opioid actions which may vary from one tissue to another (Duchesne *et al.*, 1984). Classical methods for obtaining quantitative information from log_{10} concentration-response curves about the properties of the drug-receptor complexes are not valid in such circumstances. A new method of analysis was therefore developed which enables the affinity constant of an antagonist for its receptors to be estimated by comparing concentration-tissue state curves, even in the presence of functional interaction (Hughes & Mackay, 1985). When this method was used to estimate the affinity constant of meptazinol for the opioid receptors in mouse vas deferens, with RX783006 as the agonist and (+)-meptazinol as an antagonist, the value obtained was not significantly different from that obtained from experiments on guinea-pig ileum (Goodall *et al.*, 1985). However, when the concentration-tissue state curve to RX783006 in the presence of a fixed concentration of meptazinol was compared with that produced in the presence of the same fixed concentration of meptazinol and a fixed concentration of naloxone, the curves were distinctly non-parallel. This suggested that (+)-meptazinol might be acting as a sub-threshold agonist on the mouse vas deferens. The method developed previously for estimating the affinity constant of a competitive antagonist which also has functional interactant properties has now been exten-

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ded to give information about drugs which have both agonist and functional interactant actions (Goodall *et al.*, 1986, preceding paper). This method is now applied to deduce the agonist properties of (+)-meptazinol on mouse vas deferens and to compare the results with those obtained from guinea-pig ileum.

Methods

Guinea-pig isolated field-stimulated ileum

Male guinea-pigs (200–400 g) were stunned and killed by cervical dislocation. A 2 cm portion of ileum taken from 10 cm above the ileo-caecal junction was removed, cleared of adherent tissue, and mounted between two 5 mm coils of platinum wire (one above and the other below the tissue) in physiological saline (mM: NaCl 134, KCl 2.68, $CaCl_2$ 1.80, $MgSO_4$ 1.05, NaH_2PO_4 0.32, $NaHCO_3$ 11.9 and glucose 5.5; gassed with 5% CO_2 in O_2 and also containing mepyramine (0.1 μM) and hexamethonium (69 μM)). The temperature was maintained at 36°C and changes in length of the tissue in response to constant current electrical stimulation (300 mA, 2 ms duration, 0.1 Hz) were recorded isotonically (load 0.5 g). Reproducible responses to electrical stimulation were established after about 1 h.

Mouse isolated, field-stimulated vas deferens

Male mice (T.O. strain; 30–35 g) were stunned and killed by cervical dislocation. The whole vas deferens was removed, cleared of adherent tissue and mounted in physiological saline (mM: NaCl 128, KCl 5.63, $CaCl_2$ 2.16, NaH_2PO_4 1.19, $NaHCO_3$ 25, glucose 11.1, sucrose 13.1; gassed with 5% CO_2 in O_2). Changes in length of the tissue in response to constant current electrical stimulation (300 mA, 2 ms duration, 0.1 Hz) were recorded isotonically (load 0.5 g). Reproducible responses were established after about 45 min.

Experimental procedure

Log_{10} concentration-tissue state curves were obtained, the magnitude of the response to electrical stimulation being taken as a measure of tissue state. With guinea-pig ileum a concentration of agonist was applied every 15 min, allowed to equilibrate with the tissue for 3 min and then removed by washing. With mouse vas deferens the cumulative technique was used, increasing concentrations of agonist being added at 3 min intervals. When appropriate, (+)-meptazinol and/or the opioid antagonist naloxone were added to the physiological saline and allowed to remain in contact with the tissue for 2 min before agonists were added.

Analysis of results

For each experiment smooth curves were drawn by eye through the experimentally-determined points and equi-effective concentrations of agonist were read from the smoothed curves. These equi-effective agonist concentrations were substituted into the appropriate null equations to obtain values of parameters which should be characteristic of the drug-receptor system being studied.

The following null equations have been used, where K and f represent the affinity constants and intrinsic efficacies of the receptor-drug complexes indicated by the appropriate subscript. Square brackets are used to denote equi-effective molar concentrations of the molecular species indicated by the symbols within the brackets.

Method (a) Comparison of log_{10} concentration-tissue state curves of two agonists A and B which act on the same receptors (Mackay, 1966a, 1966b).

$$\frac{1}{[A]} = \frac{\psi_{AB}}{[B]} + I_{AB} \qquad (1)$$

where

$$I_{AB} = K_A (f_A/f_B - 1)$$

$$\psi_{AB} = f_A K_A / f_B K_B$$

Method (b) Comparison of log_{10} concentration-tissue state curves of agonist A with that of the same agonist in the presence of a constant concentration [B] of another agonist B (Mackay, 1966b; Kenakin & Black, 1978).

$$[A]' = L[A] + N \qquad (2a)$$

where

$$L = 1 + K_B[B]\{1 - f_B/f_A\} = 1 + (I_{AB}[B])/\psi_{AB} \qquad (2b)$$

and

$$N = -K_B f_B [B]/K_A f_A = -[B]/\psi_{AB} \qquad (2c)$$

Note that in order to be physically meaningful N must be <0.

Method (c) Comparison of the log_{10} concentration-tissue state curve for agonist A in the presence of a fixed concentration of agonist B with the curve for agonist A in the presence of the same concentration of B together with a fixed concentration of a pure competitive antagonist I.

The equi-effective agonist concentrations are designated $[A]_2$ and $[A]_3$ respectively. Agonist B may either act only on the receptors being studied or may also modify the state of the tissue in other ways.

$$[A]_3 = [A]_2P + Q \quad (3)$$

where

$$P = \frac{\psi_{AB}(1 + K_I[I]) + [B]\,I_{AB}}{\psi_{AB} + [B]\,I_{AB}}$$

and

$$Q = \frac{[B]\,K_I[I]}{\psi_{AB} + [B]\,I_{AB}}$$

Then $\psi_{AB} = [B]\,(P - 1)/Q$ and $I_{AB} = (1 + K_I[I] - P)/Q$.

Alternatively $L = K_I[I]/(P - 1)$ and $N = -Q/(P - 1)$.

Method (d) Use of the null equation shown below permits quantitation of the functional interactant properties of agonist B in terms of α_x, β_x and γ_x

$$\frac{[A]_2}{[A]_1} = \alpha_{21} + \beta_{21}[A]_2 + \frac{\gamma_{21}}{[A]_1} \quad (4)$$

where $[A]_2$ and $[A]_1$ are the equi-effective concentrations of agonist A in the presence and absence respectively of a fixed concentration of B. Then

$$\alpha_x = (\alpha_{21} + \beta_{21}N)/L$$
$$\beta_x = \beta_{21} \quad (5)$$

and

$$\gamma_x = (\gamma_{21} - N)/L$$

where L and N are defined by equations 2b and 2c. If there is no functional interaction then α_x is unity and β_x and γ_x are both zero. Equation 4 then reduces to equation 2a.

If values of ψ_{AB} and I_{AB}, or of L and N, have been estimated as described under method (c) then values for the functional interactant parameters α_x, β_x and γ_x can be estimated from the values of α_{21}, β_{21} and γ_{21} (Goodall *et al.*, preceding paper).

Where appropriate all estimates of parameters are expressed as mean ± s.e.mean with the number of observations (n) contributing to the mean value indicated in parentheses. Tests of statistical significance (t and t' tests) were carried out as described by Snedecor & Cochran (1967).

Drugs used

Hexamethonium bromide (Sigma), mepyramine maleate (Sigma) and naloxone hydrochloride (Sigma). (+)-Meptazinol hydrochloride was supplied by Wyeth Pharmaceuticals. Tyr-D-Ala-Gly-MePhe-$NH(CH_2)_2OH$ (RX783006) was obtained from Cambridge Research Chemicals, dissolved in oxygen-free water and stored at −70°C.

Results

The results of some of the experiments listed below have been reported, either qualitatively or quantitatively, in an earlier paper (Goodall *et al.*, 1985). They are presented again here and in most cases reanalysed because they are necessary for a clear appreciation of the more precise method now available for quantifying the actions of (+)-meptazinol on guinea-pig ileum and mouse vas deferens.

Guinea-pig ileum

Twelve experiments were carried out on guinea-pig ileum to compare the effects of the opioid receptor agonist RX783006 and (+)-meptazinol on the response to electrical stimulation. In each case (+)-meptazinol (0.5 to 10 μM) produced a small inhibition of the electrically induced twitch response, an effect compatible with a partial agonist action on opioid receptors. However, in only 5 experiments was the effect sufficiently great to allow construction of acceptable $\log_{10}$ concentration-tissue state curves. A typical example is shown in Figure 1. Equi-effective concentrations of RX783006 and of (+)-meptazinol were read from each pair of curves and analysed as described in Analysis of Results, method (a).

Experiments were also carried out on guinea-pig ileum to investigate the effect of a constant concentration of (+)-meptazinol, acting as a partial agonist, on

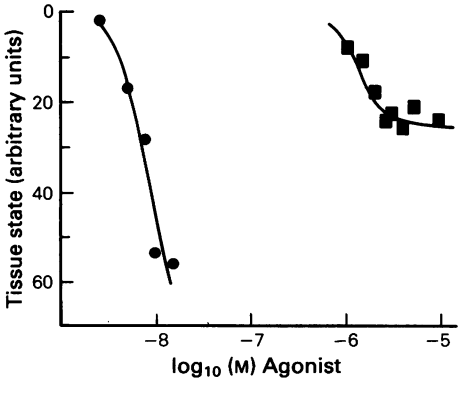

Figure 1 $\log_{10}$ concentration-tissue state curves for RX783006 (●) and for (+)-meptazinol (■) determined on the electrically-stimulated guinea-pig ileum preparation.

the $\log_{10}$ concentration-tissue state curve to RX783006. Concentration-tissue state curves were also obtained for RX783006 in the presence of (+)-meptazinol (5 μM) together with a fixed concentration (30 nM) of naloxone. The curves obtained from a typical experiment of this type are shown in Figure 2. Such curves were analysed as described under methods (b) and (c).

The values of ψ_{AB} and I_{AB} obtained by applying all three methods to guinea-pig ileum are summarised in Table 1.

The results obtained by method (b) assume that (+)-meptazinol has no functional interactant effect on guinea-pig ileum. However, the same data can also be analysed to see whether any functional interactant effects might be present, by using method (d) with estimates of ψ_{AB} and I_{AB} obtained in other ways. The results of such calculations, carried out for the individual experiments and using individual values of ψ_{AB} and I_{AB} obtained by method (c), are summarised in Table 2. Similar calculations were made using mean values of ψ_{AB} and I_{AB} obtained in various ways (Table 4).

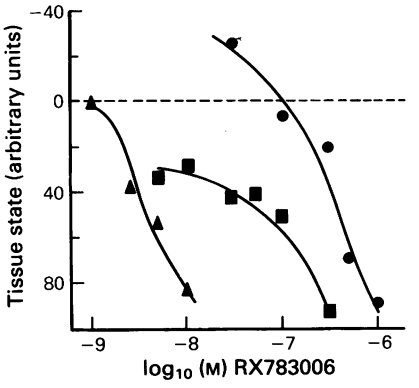

Figure 2 Log_{10} concentration-tissue state curves determined on the electrically-stimulated guinea-pig ileum preparation for RX783006 alone (▲), in the presence of (+)-meptazinol (5 μM; ■), and in the presence of (+)-meptazinol (5 μM) and naloxone (30 nM) together (●).

Mouse vas deferens

A series of experiments was carried out to obtain log concentration-tissue state curves for RX783006 alone, in the presence of a fixed concentration of (+)-meptazinol (5 μM) and in the presence of the same concentration of (+)-meptazinol together with a fixed concentration of naloxone (30 nM). Curves obtained in a typical experiment of this type are shown in Figure 3. The equi-effective concentrations read from curves obtained for RX783006 alone and in the presence of (+)-meptazinol fitted equation 4 with β_{21} effectively zero. The data were therefore analysed to obtain values of α_{21} and γ_{21} which are shown in Table 3. On the same tissues, comparison of curves obtained for RX783006 in the presence of (+)-meptazinol (5 μM) with those obtained in the presence of the same concentration of (+)-meptazinol together with naloxone (30 nM) provided indirect estimates of ψ_{AB} and I_{AB} by use of method (c). These indirect estimates are shown in Table 3 and their mean value is included in Table 1 for an overall comparison of values obtained on guinea-pig ileum and mouse vas deferens. For each tissue the individual estimates of ψ_{AB} and I_{AB} were then used to calculate values of α_x and γ_x as described in Analysis of Results method (d). The results of these calculations are also shown in Table 3. Finally, values of α_x and γ_x were calculated with values of ψ_{AB} and I_{AB} obtained by other methods (Table 4).

Table 1 Comparison of values of ψ_{AB} and I_{AB} obtained for RX783006 (A) relative to (+)-meptazinol (B) by various methods on guinea-pig ileum and mouse vas deferens

	Guinea-pig ileum			*Mouse vas deferens*		
Method	ψ_{AB}	$I_{AB} \times 10^{-6}$ M	$(I_{AB}/\psi_{AB}) \times 10^{-6}$ M	ψ_{AB}	$I_{AB} \times 10^{-6}$ M	$(I_{AB}/\psi_{AB}) \times 10^{-6}$ M
(a)	144 ± 30	110 ± 15	1.19 ± 0.62	—	—	—
(b)	67.7 ± 18.5	302 ± 109	4.65 ± 1.90	—	—	—
(c)	42.9 ± 15.0	41.2 ± 9.7	1.46 ± 0.39	24.1 ± 8.9	31.2 ± 14.8	1.02 ± 0.34

Each parameter value is a mean ± s.e.mean, based on 5 results.
The various methods involve comparison of pairs of $\log_{10}$ concentration-tissue state curves measured on the same piece of tissue: (a) for RX783006 and for (+)-meptazinol; (b) for RX783006 and for RX783006 with a fixed concentration (5 μM) of (+)-meptazinol; (c) for RX783006 with a fixed concentration (5 μM) of (+)-meptazinol and for RX783006 with the same fixed concentration of (+)-meptazinol and a fixed concentration (30 nM) of naloxone.

Table 2 Indirect estimates of various parameters from individual experiments on field-stimulated guinea-pig ileum

	Curve 3 cf curve 2					*Curve 2 cf curve 1*			
Experiment number	P	$Q \times 10^7 M^{-1}$	ψ_{AB}	$I_{AB} \times 10^{-6} M$	$(I_{AB}/\psi_{AB}) \times 10^{-5} M$	α_{21}	$\gamma_{21} \times 10^8 M^{-1}$	α_x	$\gamma_x \times 10^8 M^{-1}$
1	2.56	2.40	34.4	44.4	12.9	10.6	−22.8	1.42	−1.11
2	1.82	7.50	5.5	15.3	27.9	27.7	− 3.8	1.85	5.85
3	2.35	3.10	21.8	35.3	16.2	12.5	−6.5	1.37	1.81
4	5.07	2.28	89.3	36.1	4.0	(61.4)*	(−10.3)*	(20.3)*	(−1.56)*
5	2.78	1.40	63.6	75.1	11.8	15.6	−8.5	2.3	−0.10
Mean values	2.93	3.34	42.9	41.2	14.6	16.6	−10.4	1.73	1.61
± s.e.mean	±0.55	±1.07	±15.0	±9.7	±3.9	±3.8	±4.2	±0.21	±1.54

The values of ψ_{AB} and I_{AB} are for RX783006 relative to (+)-meptazinol.
The ratio I_{AB}/ψ_{AB} is an estimate of the affinity of (+)-meptazinol for its receptors.
The $\log_{10}$[RX783006] vs. tissue state curves were: curve 1: RX783006 alone; curve 2: RX783006 in the presence of (+)-meptazinol (5 μM); curve 3: RX783006 in the presence of (+)-meptazinol (5 μM) and naloxone (30 nM).
In all cases β_{21} was taken to be zero and K_I for naloxone $0.41 \times 10^9 M^{-1}$.
*The figures in parentheses were *not* included in the estimation of these means and standard errors.

Discussion

Since ψ_{AB} and I_{AB} contain the quantities f_A, f_B, K_A and K_B they should be characteristic of the receptor system being studied. The results summarised in Table 1 show that for guinea-pig ileum, the value of ψ_{AB} obtained by method (c), which should be free of any functional interactant component, is less than that obtained by either of the other two methods. However the values of ψ_{AB} and I_{AB} obtained on guinea-pig ileum using method (c) are statistically significantly different only from the values obtained directly by method (a) ($P < 0.05$). The values of these parameters estimated using method (c) on guinea-pig ileum are not significantly different from those estimated on mouse vas deferens by the same method. The agonist actions of (+)-meptazinol on field-stimulated guinea-pig ileum and mouse vas deferens, assessed by a method which should eliminate complications due to functional interaction, are therefore indistinguishable.

In experiments carried out on rat jejunum, in which carbachol, hexyltrimethylammonium and atropine were used to test the validity of method (c), estimates obtained for ψ_{AB} were about half the value of those measured directly (Goodall *et al.*, 1986). This discrepancy was assumed to be due to spontaneous changes in tissue sensitivity with time. In the present experiments the indirect estimate is only one third to one sixth of the directly measured value. It may be that the spontaneous changes in tissue sensitivity are greater in these studies on the opioid receptors in field-stimulated guinea-pig ileum and mouse vas deferens. However it is also possible that the discrepancy is due to a functional interactant effect of (+)-meptazinol not only on mouse vas deferens but also on guinea-pig ileum. If the value of ψ_{AB} obtained by method (c) is accurate, then the potency of (+)-meptazinol relative to RX783006 would be 3 to 6 times greater than indicated by its direct action on guinea-pig ileum.

Examination of Figures 2 and 3 shows that there is qualitative evidence in favour of the idea that (+)-meptazinol is showing functional antagonistic actions

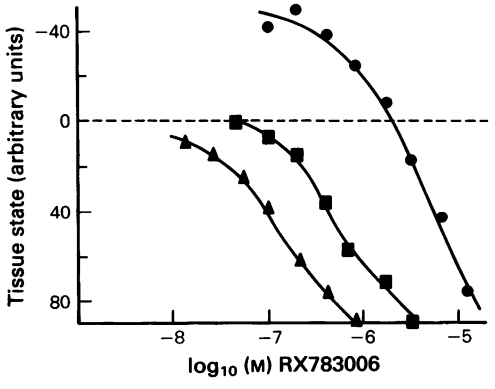

Figure 3 $\log_{10}$ concentration-tissue state curves determined on the electrically-stimulated mouse vas deferens preparation for RX783006 alone (▲), in the presence of (+)-meptazinol (5 μM; ■), and in the presence of both (+)-meptazinol (5 μM) and naloxone (30 nM) together (●).

Table 3 Indirect estimates of various parameters from individual experiments on field-stimulated mouse isolated vas deferens

	Curve 3 cf curve 2					*Curve 2 cf curve 1*			
Experiment number	P	$Q \times 10^7\,M^{-1}$	ψ_{AB}	$I_{AB} \times 10^{-6}\,M$	$(I_{AB}/\psi_{AB}) \times 10^{-5}\,M$	α_{21}	$\gamma_{21} \times 10^8\,M^{-1}$	α_x	$\gamma_x \times 10^8\,M^{-1}$
1	2.06	1.7	31.7	67.3	21.2	3.71	1.3	0.32	1.5
2	2.82	6.2	14.7	16.9	11.5	5.39	59.9	0.80	13.9
3	6.79	32.1	9.0	2.0	2.2	4.38	5.9	2.08	29.1
4	4.10	16.4	9.5	5.6	5.9	7.20	20.1	1.82	18.4
5	3.08	1.9	55.6	54.7	9.8	7.33	3.4	1.24	2.1
Mean values	3.77	11.7	24.1	29.3	10.1	5.60	18.1	1.25	13.0
± s.e.mean	±0.82	±5.8	±8.9	±13.3	±3.2	±0.73	±11.0	±0.32	±5.2

The value of ψ_{AB} and I_{AB} are for RX783006 relative to (+)-meptazinol.
The ratio I_{AB}/ψ_{AB} is an estimate of the affinity of (+)-meptazinol for its receptors.
The $\log_{10}$[RX783006] vs. tissue state curves were: curve 1: RX783006 alone; curve 2: RX783006 in the presence of (+)-meptazinol (5 μM); curve 3: RX783006 in the presence of (+)-meptazinol (5 μM) and naloxone (30 nM).
In all cases β_{21} was taken to be zero and K_I for naloxone $0.41 \times 10^9\,M^{-1}$.

on both guinea-pig ileum and mouse vas deferens. In both tissues a potentiation of the twitch response by (+)-meptazinol is revealed by addition of naloxone. Tables 2 and 3 show the results of calculations carried out to explore this problem quantitatively. In each experiment the values of ψ_{AB} and I_{AB} were estimated by method (c) and these values were used to estimate values of α_x and γ_x for the same tissues by method (d). In the case of the mouse vas deferens (Table 3) the values of α_x and γ_x were 1.25 ± 0.32 and $(13.0 \pm 5.2) \times 10^{-8}$ M respectively. Applying the same method to results obtained on guinea-pig ileum (Table 2) the values for α_x and γ_x were 1.73 ± 0.21 and $(1.61 \pm 1.54) \times 10^{-8}$ M. In comparing these figures it is worth noting that generally the magnitude of γ_x has a greater effect on the maximum response obtainable than does the magnitude of α_x. It will be seen from these figures that the low values of ψ_{AB} and I_{AB} estimated by method (c) are compatible with a lower degree of functional antagonism on guinea-pig ileum than on mouse vas deferens. It will also be noticed that the values of γ_x for mouse vas deferens are consistently positive, whereas both positive and negative values are obtained from guinea-pig ileum. This variability in γ_x in the case of the ileum might explain the fact that an appreciable number of these tissues gave poor, though detectable, maximal responses to (+)-meptazinol alone.

The values of ψ_{AB} and I_{AB} used in deriving the values of α_x and γ_x discussed above were obtained with method (c). It is reasonable to ask what the situation would be if these values were in error. The results of calculations carried out to try to answer this question are shown in Table 4. While considering these results it should be kept in mind that values of α_x greater than unity and positive values of γ_x correspond to functional antagonism. Conversely values of α_x less than unity and negative values of γ_x indicate synergism. It will be seen (Table 4) that using mean values of ψ_{AB} and I_{AB} measured directly on guinea-pig ileum, the functional interactant effects of (+)-meptazinol required to fit the data for guinea-pig ileum would be a mixture

Table 4 Comparison of values of the functional interactant parameters α_x and γ_x obtained indirectly on guinea-pig ileum and mouse vas deferens, for different assumed values of ψ_{AB} and I_{AB}

Assumed values		*Guinea-pig ileum*		*Mouse vas deferens*	
ψ_{AB}	$I_{AB} \times 10^{-7}\,M$	α_x	$\gamma_x \times 10^8\,M^{-1}$	α_x	$\gamma_x \times 10^8\,M^{-1}$
144.0	11.0	3.44 ± 0.80 (4)	−1.44 ± 0.88 (4)	1.16 ± 0.15 (5)	4.48 ± 2.27 (5)
42.9	4.12	2.86 ± 0.66 (4)	0.22 ± 1.46 (4)	0.97 ± 0.13 (5)	5.12 ± 1.88 (5)
24.1	3.12	2.22 ± 0.52 (4)	1.39 ± 0.57 (4)	0.75 ± 0.10 (5)	5.20 ± 1.47 (5)

ψ_{AB} and I_{AB} are for RX783006 relative to (+)-meptazinol.
All values are mean ± s.e.mean with number of observations in parentheses.

of antagonism due to α_x and synergism due to γ_x, the latter being quantitatively more important. On the other hand, these same values of ψ_{AB} and I_{AB} indicate antagonism on mouse vas deferens due to γ_x. The use of mean values of ψ_{AB} and I_{AB} estimated by method (c) on ileum and vas deferens to obtain, in turn, mean values of α_x and γ_x for both tissues gives numerical values somewhat different from those presented in Tables 2 and 3 but does not change the essential pattern which is that the lower values of ψ_{AB} are more consistent with a functional antagonistic effect of (+)-meptazinol on guinea-pig ileum. By contrast, all the sets of values of ψ_{AB} and I_{AB} used to calculate the results in Table 4 would require (+)-meptazinol to act as a functional antagonist on mouse vas deferens.

In summary, the values of ψ_{AB} and I_{AB} measured for RX783006 relative to (+)-meptazinol by a method that eliminates complications due to functional interaction with other systems, are not significantly different on mouse vas deferens and guinea-pig ileum. The values obtained by this method are however significantly lower than those measured directly on guinea-pig ileum. The discrepancy may be due to experimental error but it could also be explained if the potency of (+)-meptazinol relative to RX783006 is actually three to six times greater than it appears to be when their actions are compared directly on the field-stimulated guinea-pig ileum.

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