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The antinociceptive activity of meptazinol depends on both opiate and cholinergic mechanisms

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1 Antinociceptive responses to meptazinol, morphine and oxotremorine and the effects of pretreatment with naloxone or scopolamine on these responses in mice and rats, were examined.

2 Meptazinol evoked larger increases in nociceptive thresholds in the mouse than in the rat, whereas morphine induced large increases in both species. Oxotremorine was both a more potent and a more effective antinociceptive agent in the mouse than in the rat.

3 Antinociceptive responses to meptazinol were consistently inhibited in animals pretreated with naloxone, whereas scopolamine attenuated the effects of meptazinol in some, particularly the mouse tail immersion test, but not in all of the procedures used.

4 Naloxone inhibited all antinociceptive responses to morphine, and scopolamine inhibited all responses to oxotremorine. However, there was no significant interaction between naloxone and oxotremorine or between scopolamine and various opioid analgesic agents.

5 These results indicate that meptazinol, unlike established opioid drugs, may induce antinociception by a dual action on opiate and cholinergic mechanisms.

Introduction

The pharmacological profile of meptazinol (*m*-[hexahydro-3-ethyl-1-methyl 1H azepin-3-yl]-phenol hydrochloride) is similar in many respects to that of established opioid drugs with dual agonist and antagonist properties (Goode & White, 1971; Stephens, Waterfall & Franklin, 1978). Thus meptazinol is an effective antinociceptive agent in animals and induces analgesia in man. It precipitates withdrawal signs in morphine-dependent animals and induces only very mild signs of dependence following chronic administration to rats and monkeys.

Unlike the majority of opioid agonist/antagonist analgesics, however, antinociceptive responses to relatively large doses of meptazinol are not fully attenuated in animals pretreated with naloxone. Also, although exhibiting a similar potency to pentazocine in antinociceptive tests, meptazinol is substantially less potent than pentazocine in displacing bound [^{3}H]-naloxone *in vitro* (Bill, Cowlrick, Fox, Todd, Ward, Wood & Wyllie, 1981). These and other deviations from the classical profile suggest that the antinociceptive activity of meptazinol might be due, at least in part, to an action on mechanisms other than those involving opiate receptors.

In contrast to opioid drugs in general, meptazinol potentiates the electrically-induced twitch response of the guinea-pig isolated ileum (Stephens *et al.*, 1978) suggesting that the induced release of acetylcholine from this preparation may be facilitated in the presence of meptazinol. As it is well-established that cholinomimetic agents exhibit antinociceptive activity in experimental animals (Hendershot & Forsaith, 1959; Leslie, 1969; Ireson, 1970) it seemed reasonable to propose that the antinociceptive effect of meptazinol might be due, in part, to a direct or indirect action on cholinergic mechanisms.

Methods

Female T/O strain mice (19–25 g) from Tuck and male albino Sprague-Dawley rats (120–160 g) from Charles River were housed in groups of 20 (mice) or 5 (rats) at an ambient temperature of 21–23°C on a 12 h light/dark cycle with free access to food and water.

All the following experiments were performed according to a balanced design and in such a manner that the observer was not aware of the treatment(s) each animal had received.

Dose-response determinations

A range of doses of meptazinol, morphine, pentazocine and oxotremorine were given subcutaneously to groups (8–10) of mice and rats to determine the relationships between dose and changes in response in the following antinociceptive procedures.

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Species	*Stimulus*	*Response*	*From method of:*
Mouse	Hot water (50°C)	Distinct tail flick	Benbasset, Peretz & Sulman (1959)
	Hot plate (55°C)	Drumming or licking feet	Woolfe & MacDonald (1944)
	Injection (i.p.) of phenylbenzylquinone (PBQ).	Number of abdominal writhes 5–15 m post PBQ	Hendershot & Forsaith (1959)
Rat	Hot water (50°C)	Distinct tail flick	Benbasset *et al.* (1959)
	Pressure to hind paw ('Analgesiometer' Ugo Basile, Milan)	Foot withdrawal or struggling	Randall & Sellito (1957)

The response thresholds (latency, pressure) or intensity (writhing frequency) in these and all subsequent experiments were measured 25–30 min after the injection of all the antinociceptive agents used except oxotremorine. Responses to oxotremorine were assessed 15–20 min post administration.

Drug interaction studies

In the following experiments, muscarinic antagonists or naloxone were given i.p. (or s.c. in those involving the writhing procedure) 10 min before the s.c. injection of the antinociceptive agents.

Interactions between antimuscarinic and antinociceptive agents The effects of pretreatment with scopolamine on the amplitude of antinociceptive responses to meptazinol, morphine and oxotremorine were examined in all of the mouse and rat procedures described above. Mice received various doses of scopolamine and rats received 2.5 mg/kg scopolamine before single doses of the antinociceptive agents selected, when possible, to induce responses of equal magnitude. Additional studies, involving the mouse tail immersion test only, included (a) the determination of the dose-response relationships for meptazinol in animals pretreated with 0.1 or 0.3 mg/kg scopolamine or vehicle, (b) the effects of atropine and atropine methyl nitrate on the response to 25 mg/kg meptazinol and (c) the effects of scopolamine (2.5 mg/kg) on the antinociceptive responses to buprenorphine, profadol, methadone, (+)-propoxyphene, codeine, pethidine and pentazocine.

Interactions between naloxone and antinociceptive agents The effects of naloxone on responses to meptazinol, morphine and oxotremorine in mice and rats were investigated in a series of experiments similar to those described involving scopolamine as the antagonist.

Two control groups, treated with vehicle plus vehicle and antagonist plus vehicle, were used in the majority of the interaction studies. The effects of the antagonists (% inhibition) were determined from $((VT\text{-}VV) - (AT\text{-}AV)/(VT\text{-}VV)) \times 100$, where the paired symbols represent mean responses to paired treatments; V = vehicle, A = antagonist and T = antinociceptive agent. The AV group was omitted from experiments involving scopolamine and various opioid drugs in the mouse tail flick test and in these instances VV was substituted for AV in the equation. Student's *t* test was used to test the significance of differences between AV and VV and between AT and VT. The ED_{50} values for the antagonists against single doses of antinociceptive agents were obtained by linear regression analysis. Data from the dose-response determinations in the absence and presence of antagonists were subjected to parallel line analysis.

Overt autonomic effects of oxotremorine

Groups of 6 mice and rats were treated with oxotremorine (0.02–0.4 mg/kg s.c.). Fifteen minutes later both the degree of salivation and of tremor were scored on a 4 point scale (absent, slight, moderate or marked). The total group score for each sign was expressed as a percentage of the maximum possible and then ED_{50} values were obtained by the method of Litchfield & Wilcoxon (1949).

Drugs

The drugs used in this study were: atropine methyl nitrate and atropine sulphate (Macfarlan Smith), buprenorphine hydrochloride (Reckitt and Colman), codeine phosphate (Macfarlan Smith), dextrop-

ropoxyphene hydrochloride (Lilly), meptazinol hydrochloride (Wyeth), methadone hydrochloride (Wellcome), morphine sulphate (Macfarlan Smith), naloxone hydrochloride (Endo labs), oxotremorine (Sigma), pentazocine base (Winthrop), pethidine hydrochloride (Macfarlan Smith), phenyl-*p*-benzoquinone (PBQ) (Kodak), profadol hydrochloride (Parke Davis), and scopolamine hydrobromide (Sigma).

All were suspended or dissolved in hydroxypropyl methyl cellulose (0.5% in distilled water) and administered in volumes of 10 ml/kg for mice and 2–5 ml/kg for rats. All of the doses shown in the text are expressed as the salts.

Results

Dose-response determinations

Meptazinol Figure 1 shows that meptazinol induced clear, dose-dependent antinociceptive responses in the mouse tail immersion, hot plate and writhing procedures (mean control ranges were 2.3–6.6 s., 6.3–9.1 s and 16–30 writhes/10 min respectively). Maximum responses in both rat tests (mean control ranges were 3.5–5.1 s for tail immersion and 140–200 g for paw pressure), however, were relatively small.

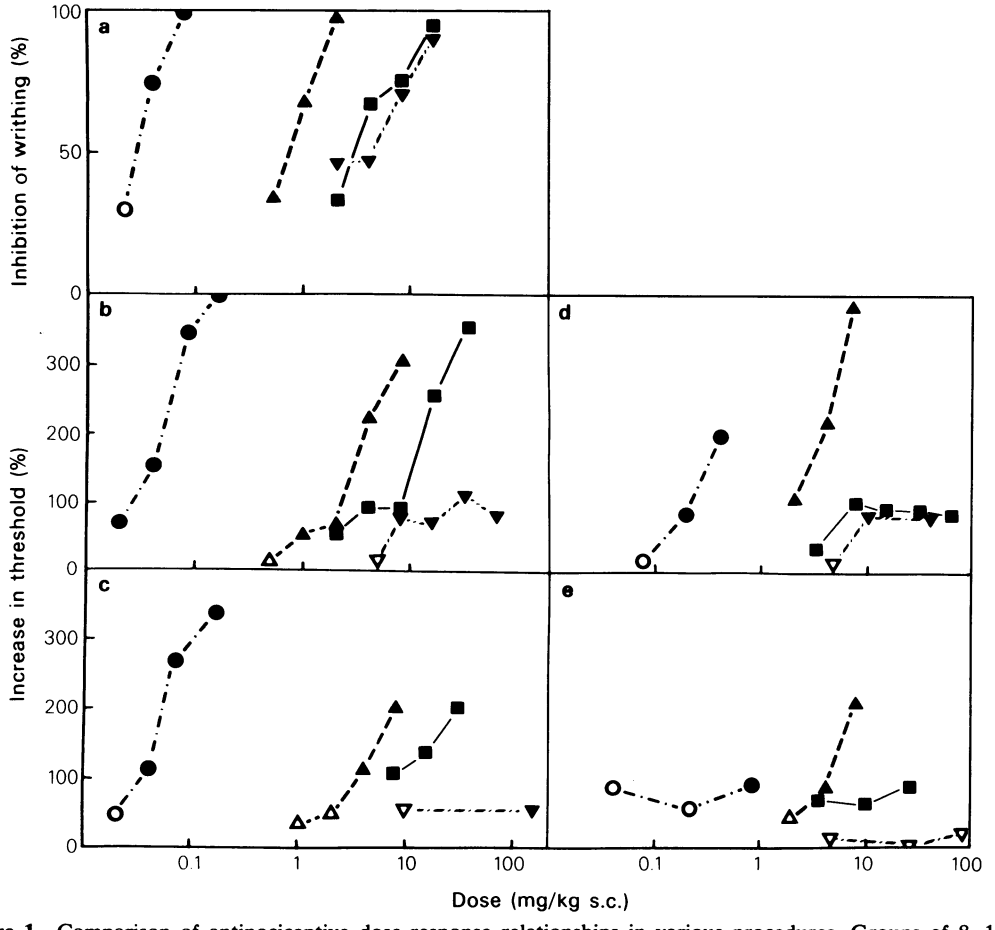

Figure 1 Comparison of antinociceptive dose-response relationships in various procedures. Groups of 8–10 animals were given meptazinol (■), morphine (▲), pentazocine (▼), oxotremorine (●) or vehicle s.c. Responses of mice to i.p. PBQ (a), tail immersion, 50°C (b), and hot plate, 55°C (c) and of rats to tail immersion, 50°C (d) and paw pressure (e) were recorded 30 min (15 min for oxotremorine) later. Mean responses of treated groups are expressed as % of appropriate controls. Open symbols, $P > 0.05$; closed symbols, $P < 0.05$.

Oxotremorine Oxotremorine also induced large responses in all three mouse tests (Figure 1). It was less potent in the rat than in the mouse tail immersion procedures and induced only small, variable increases in paw pressure thresholds.

Morphine Morphine was approximately five times as potent as meptazinol in all the mouse antinociceptive tests but, unlike meptazinol, it induced large dose-dependent responses in the rat (Figure 1).

Pentazocine The dose-response curves for pentazocine and meptazinol in the mouse writhing procedure were virtually identical. In all other tests, however, the maximum effect of pentazocine was small, rarely exceeding a doubling of control values. (Figure 1).

Drug interaction studies

Scopolamine alone did not consistently affect the

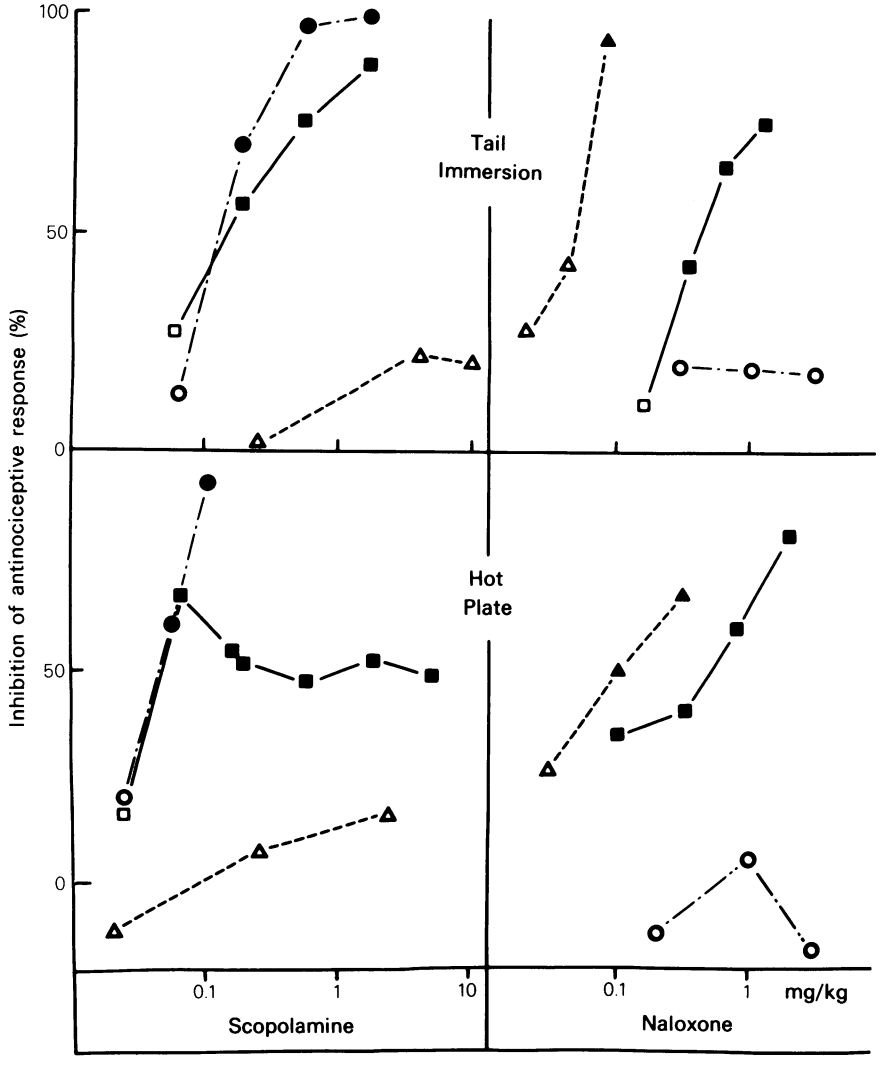

Figure 2 Inhibition of antinociceptive responses by naloxone and scopolamine. Groups of 10 mice received various doses of naloxone or scopolamine (i.p.) 10 min before antinociceptive agents or vehicle (s.c.). Responses recorded 30 min (15 min for oxotremorine) later. Graphs show % inhibition, calculated as described under Methods, of response to 25 and 20 mg/kg meptazinol (■), 5 and 6 mg/kg morphine (▲) and 0.064 and 0.12 mg/kg oxotremorine (●) respectively in tail immersion and hot plate tests. Open symbols, $P > 0.05$; closed symbols, $P < 0.05$ (significant inhibition).

Table 1 Inhibition of antinociceptive responses by naloxone and scopolamine in the mouse (tail immersion test)

Procedure	*Analgesic agent*	*Dose* (mg/kg s.c.)	*Dose of antagonist* (mg/kg i.p.) *to reduce response by 50%* (ID_{50}) *Naloxone*		*Scopolamine*	
Tail immersion	Meptazinol	25	0.51	(0.3 −0.8)	0.16	(0.1 −0.2)
	Morphine	5	0.037	(0.03–0.05)	> 10	
	Oxotremorine	0.064	> 3		0.14	(0.1 −0.2)
Hot plate	Meptazinol	20	0.41	(0.09–1.0)	~ 0.05‡	
	Morphine	6	0.11	(0.07–0.2)	> 2.5	
	Oxotremorine	0.12	> 3		0.045	(0.04–0.05)
Writhing	Meptazinol	8	0.24	(0.1 −0.5)	> 2.5*	
	Morphine	2	0.028	(0.02–0.04)	> 2.5*	
	Oxotremorine	0.04	> 10		<< 0.5	

$n = 10$ per treatment group. Values in parentheses are 95% confidence limits (linear regression analysis).
‡ Maximum inhibition was approximately 50% (see Figure 2).
* Scopolamine alone caused significant reduction of writhing frequency but no sign of antagonism of responses to meptazinol or morphine at the dose shown.

response of mice or rats to the noxious stimuli used, except that of mice to the i.p. injection of PBQ (suppression of writhing, $ED_{50} = 1.0$ mg/kg). Naloxone alone was ineffective in all the procedures employed.

Antimuscarinic agents and meptazinol Low doses of scopolamine inhibited antinociceptive responses to 25 mg/kg meptazinol in the mouse tail immersion test in a dose-dependent manner (Figure 2). Pretreatment with 0.1 or 0.3 mg/kg scopolamine, however, caused a preferential attenuation of responses to doses of meptazinol > 16 mg/kg; the shift in the dose-response curve deviated significantly from parallelism (Figure 3). Atropine sulphate also markedly inhibited the response to 25 mg/kg meptazinol ($ED_{50} = 0.9$ mg/kg, 95% limits 0.2–1.9) but the maximum effect obtained with atropine methyl nitrate (28% inhibition at 2.5 mg/kg) was considerably smaller than that observed with the non-quaternary salt.

Scopolamine also significantly antagonized responses to meptazinol in the hot-plate test but the maximum inhibition achieved in this procedure was approximately 50% (Figure 2). The interpretation of the data from experiments involving PBQ was complicated by the antiwrithing activity of scopolamine itself. Nevertheless, as the response to 8 mg/kg meptazinol in mice given scopolamine (0.5–2.5 mg/kg) was always equal to, or greater than, that of mice given meptazinol alone, it was concluded that no inhibition was demonstrable.

The relatively small antinociceptive responses to meptazinol in the rat made the detailed evaluation of the effects of antagonists difficult. The effect of 20 mg/kg meptazinol in the paw pressure test, however, was markedly reduced (75%) in animals pretreated with 2.5 mg/kg scopolamine but no significant interaction was apparent in similar experiments utilizing the tail-immersion procedure (Table 3).

Scopolamine and oxotremorine All antinociceptive responses to oxotremorine were markedly inhibited in animals pretreated with scopolamine. The effective dose range of the antimuscarinic agent as an antagonist of oxotremorine in the mouse tail immersion and hot-plate procedures was similar to that as an antagonist of responses to meptazinol (Table 1). In contrast to the findings with meptazinol, however, low doses of scopolamine blocked responses to oxotremorine in both of these procedures (Figure 2) as well as in the PBQ-induced writhing test and the rat tail immersion test (Table 3). Oxotremorine failed to induce a sufficiently large or reproducible effect in the paw pressure procedure for any meaningful interaction studies to be undertaken.

Scopolamine and opioid drugs None of the antinociceptive responses to morphine in the mouse or rat were significantly modified in animals given 2.5 mg/kg scopolamine (Tables 1 and 3, Figure 2). Also, scopolamine failed to affect significantly the responses to any of the opioid drugs listed in Table 2 (mouse tail immersion test).

Naloxone and meptazinol Responses to meptazinol in all the mouse and rat antinociceptive procedures were inhibited in animals pretreated with naloxone (Tables 1 and 3, Figure 2). The doses of naloxone required to reduce the effects of meptazinol in the three mouse tests by 50% were in the range 0.25–0.5 mg/kg. In contrast to the effect of

Table 2 Effects of pretreatment with scopolamine (2.5 mg/kg i.p.) on antinociceptive responses to various analgesic drugs in the mouse (tail immersion test)

Analgesic agent	*Dose* (mg/kg s.c.)	*Tail flick response latency in s* (mean ± s.e.mean) *Vehicle pretreatment*	*Scopolamine pretreatment*	*Inhibition* (%)
Vehicle	—	4.1 ± 0.3		
Morphine	5	13.8 ± 1.0	13.5 ± 0.7	3
Buprenorphine	0.25	14.5 ± 1.2	13.5 ± 0.6	10
Profadol	10	15.1 ± 1.0	13.2 ± 1.1	17
Vehicle	—	4.6 ± 0.5		
Methadone	4	11.6 ± 1.4	10.9 ± 1.4	9
d-propoxyphene	40	17.8 ± 2.2	15.2 ± 1.9	20
Codeine	30	11.2 ± 1.8	10.4 ± 1.3	12
Pethidine	30	12.6 ± 1.8	15.1 ± 1.6	− 31
Vehicle	—	3.1 ± 0.5		
Pentazocine	120	6.6 ± 0.5	5.8 ± 0.5	22
Vehicle	—	4.3 ± 0.3	4.4 ± 0.3	
Meptazinol	25	15.3 ± 1.5	5.9 ± 0.5	88***
Vehicle	—	3.3 ± 0.5		
Oxotremorine	0.064	20.1 ± 1.8	3.3 ± 0.5	100

$n = 10$. ***, $P < 0.001$.

Table 3 Effects of scopolamine (2.5 mg/kg i.p.) and naloxone (1 mg/kg i.p.) on antinociceptive responses in the rat

Second treatment	*Paw pressure* (g) *Vehicle pretreat*	*Naloxone pretreat*	*Tail flick latency* (s) *Vehicle pretreat*	*Naloxone pretreat*
Meptazinol (25)	363 ± 46	203 ± 0.29**	8.2 ± 0.6	5.4 ± 0.5**
Vehicle	194 ± 23	200 ± 15	4.3 ± 0.6	4.7 ± 0.6
Oxotremorine (0.4)			13.1 ± 1.1	13.8 ± 0.8
Vehicle			4.8 ± 0.3	4.1 ± 0.3
Morphine (4)	327 ± 45	214 ± 25*	16.9 ± 1.3	7.7 ± 1.1
Vehicle	160 ± 13	159 ± 10	4.1 ± 0.3	4.6 ± 0.5
		Scopolamine pretreat		*Scopolamine pretreat*
Meptazinol (25)	322 ± 32	180 ± 23***	11.3 ± 1.1	10.3 ± 1.9
Vehicle	165 ± 12	125 ± 9*	5.1 ± 0.5	4.0 ± 0.6
Oxotremorine (0.4)			11.1 ± 1.3	4.4 ± 0.7***
Vehicle			3.7 ± 0.4	3.3 ± 0.4
Morphine (4)	371 ± 67	406 ± 90	15.0 ± 1.9	16.8 ± 1.6
Vehicle	154 ± 20	131 ± 17	4.0 ± 0.3	3.7 ± 0.4

Each value shown is the mean ± s.e.mean.
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ compared with vehicle pretreated controls.
Values in parentheses show doses (mg/kg s.c.) of antinociceptive agents. $n = 10$, except scopolamine-meptazinol experiments where $n = 30$.

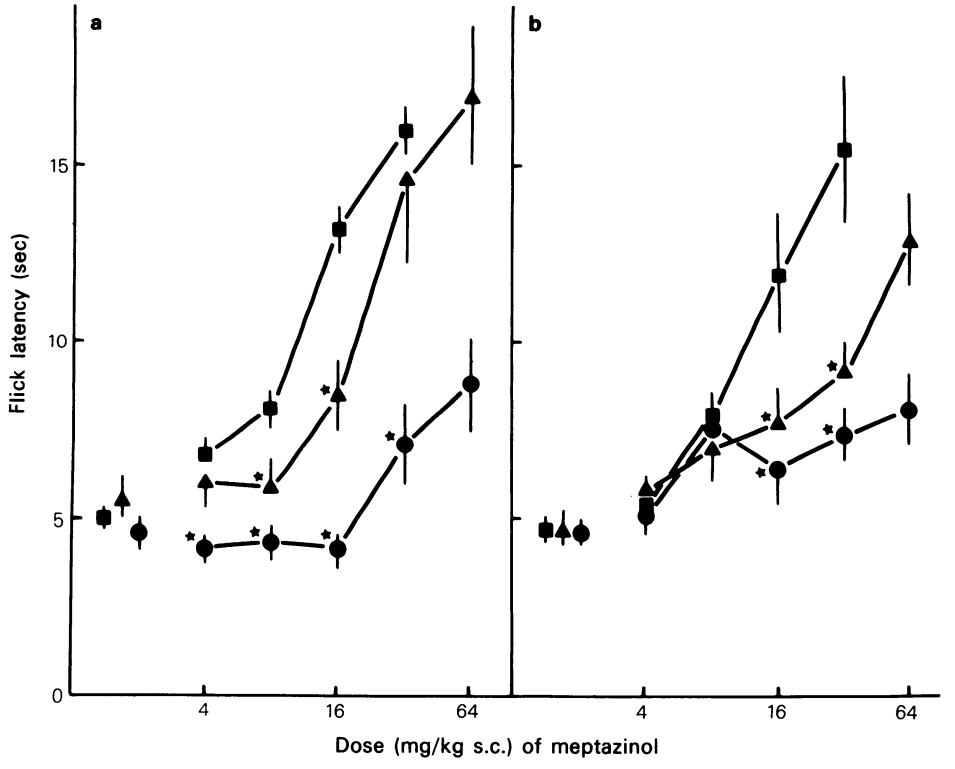

Figure 3 Dose-response relationship for meptazinol in the absence and presence of naloxone or scopolamine. Groups of 10 mice given 0.8 (▲) or 1.6 (●) mg/kg naloxone (a); 0.1 (▲) or 0.3 (●) mg/kg scopolamine (b) or vehicle (■) i.p. 10 min before meptazinol s.c. Responses to tail immersion (50°C) measured 30 min later. Shifts induced by scopolamine (but not those induced by naloxone) deviate ($P<0.05$ lower dose; $P<0.001$ higher dose) from parallelism. Vertical bars denote s.e. means.
* $P<0.05$ compared with control at same dose.

scopolamine, however, the shift in the dose-response curve to meptazinol induced by naloxone (mouse tail immersion test) did not deviate significantly from parallelism (Figure 3).

Naloxone and oxotremorine Pretreatment with naloxone (0.2–3 mg/kg to mice, 1 mg/kg to rats) did not significantly affect the responses to oxotremorine in the three mouse antinociceptive procedures (Table 1, Figure 2) or the rat tail immersion test (Table 3).

Naloxone and morphine Naloxone was a more potent antagonist (4–14× depending on the procedure) of antinociceptive responses to morphine than of responses to meptazinol in the mouse (Table 1, Figure 2). Also, 1 mg/kg naloxone markedly attenuated the effects of 4 mg/kg morphine in the rat (Table 3).

Overt autonomic effects of oxotremorine

Oxotremorine induced slight salivation and tremor in rats, but not in mice, at 0.02 mg/kg s.c. The ED_{50} values for salivation and tremor respectively were 0.04 and 0.08 mg/kg in the rat and 0.22 and 0.18 mg/kg in the mouse.

Discussion

Opioid drugs with mixed agonist and antagonist properties exhibit marked activity in mouse writhing tests but tend to be inactive or to show only weak activity in rodent antinociceptive tests involving heat as the noxious stimulus. In contrast, opioid drugs with predominantly agonist activity (at μ receptors) consistently induce pronounced changes in nociceptive

thresholds (Collier, Dinneen, Johnson & Schneider, 1968; Gray, Osterberg & Scuto, 1970; O'Callaghan & Holtzmann, 1975; Tyers, 1980). Although meptazinol behaved in a manner similar to that of established opioid partial agonists in the rat, the amplitude of responses to this agent in the mouse tail immersion and hot plate procedures was larger than that expected of a partial agonist. It is suggested that the reason for this unusual profile is that meptazinol affects two distinct central mechanisms, both of which are involved in the control of responses to noxious stimuli.

All of the results of the interaction studies between meptazinol and naloxone support the view that the former drug's mechanism of action involves an effect at opiate receptors. Although naloxone was a more potent antagonist of responses to morphine than of those to meptazinol, this is consistent with other evidence that partial agonists are less susceptible to naloxone challenge than are opioid agonists of the morphine type (Smits & Takemori, 1970). Also, the general profile of action of meptazinol *in vivo* resembles that of established agonist/antagonist analgesics (Stephens *et al.*, 1978) and recent ligand binding studies (M. D. Wood, personal communication) have shown that meptazinol has a moderate affinity for opiate (μ) sites.

In contrast to the relatively consistent effects of naloxone, the action of scopolamine on responses to meptazinol differed substantially according to the antinociceptive test and species used. Although these differences may seem enigmatic it is possible to argue that meptazinol affects a central cholinergic mechanism in addition to its effect on opiate receptors. The results obtained with the cholinomimetic agent, oxotremorine, have an important bearing on this suggestion.

The observation that oxotremorine induced antinociceptive effects agrees with previous findings (Leslie, 1969; Ireson, 1970) but in this study it was both more potent and induced more substantial changes in nociceptive thresholds in the mouse than in the rat. This was not simply a reflection of an overall lower potency in the rat because signs of parasympathetic stimulation were recorded with lower doses of oxotremorine in the rat than in the mouse. Thus, significant antinociceptive activity was recorded with doses of oxotremorine that induced virtually no overt signs of cholinergic activity in the mouse, but only doses that caused marked salivation and tremor were effective in the rat. With these differences in mind it is reasonable to expect that any antinociceptive effect of meptazinol mediated via a cholinergic mechanism in the mouse, would supplement that due to its opioid agonist action, whereas a similar action in the rat might not. This seems the most obvious explanation of why much larger changes in response thresholds to heat stimuli were induced by meptazinol in the mouse than in the rat and why these effects, like those induced by oxotremorine, were markedly inhibited in mice pretreated with scopolamine. The relatively poor inhibitory activity of atropine methyl nitrate, which does not readily penetrate the CNS, suggests that the site of the relevant cholinergic mechanism, as in the case of oxotremorine (Ireson, 1970), is within the CNS.

In contrast to its action in other antinociceptive procedures in the mouse, scopolamine failed to modify responses to meptazinol in the writhing procedure. It seems pertinent to note, however, that scopolamine also failed to inhibit the small responses to 8 mg/kg meptazinol in the tail immersion test. This dose of meptazinol almost blocked the writhing response, but induced only a slight increase in tail-flick latency. These observations suggest that the threshold dose of meptazinol to affect opiate receptors in the mouse is somewhat smaller than that required to affect cholinergic machanisms. Thus, full inhibition of the writhing response to PBQ would seem to be achieved at a dose of meptazinol that affects only (or predominantly) opiate receptors whereas doses sufficient to induce moderate increases in tail-flick latencies affect both opiate and cholinergic processes.

The low amplitude of the maximum antinociceptive response to meptazinol in both rat procedures made the detailed quantification of the effects of putative antagonists considerably more difficult in this species than in the mouse. Nevertheless, clear antagonism by naloxone was demonstrated in both tests. The inability of scopolamine to inhibit responses to meptazinol in the rat tail immersion procedure in contrast to its marked effect in the paw pressure test, was particularly difficult to explain since, in the mouse, the most pronounced inhibitory effect of scopolamine was recorded in the former procedure. The differences in the effectiveness of oxotremorine between species may be relevant but the reason why scopolamine should antagonize responses to meptazinol in one rat procedure and not the other remains obscure.

The relevance of cholinergic mechanisms to the antinociceptive action of established opioid drugs has been a matter of debate. Thus, Pedigo, Dewey & Harris (1975) reported that the antinociceptive activity of acetylcholine (i.c.v.) in the mouse was antagonized by narcotic antagonists and concluded that morphine might be affecting central muscarinic sites. Ireson (1970), however, considered that cholinomimetic agents produce their antinociceptive effect by an action on a centrally-sited muscarinic receptor whereas morphine and nalorphine do not. The evidence that morphine-like drugs modify the

release of neurotransmitters, including acetylcholine (e.g. Jhamandas, Phillis & Pinsky, 1971; Lees, Kosterlitz & Waterfield, 1971) is substantial. Nevertheless, the lack of cross antagonism between peripherally administered opioid and cholinomimetic drugs reported by Ireson and confirmed in this study strongly suggests that the two classes of drugs affect responses to noxious stimuli via essentially different neural mechanisms.

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