Br. J. Pharmac. (1985), **84**, 469–475

The effects of meptazinol in comparison with pentazocine, morphine and naloxone in a rat model of anaphylactic shock

P.M. Paciorek, M.H. Todd[1] & J.F. Waterfall[2]

Department of Pharmacology, Wyeth Institute of Medical Research, Huntercombe Lane South, Taplow, Maidenhead, Berkshire, SL6 0PH

1 The actions of meptazinol, pentazocine, morphine and naloxone on the cardiovascular changes accompanying anaphylactic shock were evaluated in ovalbumin-sensitized anaesthetized rats.

2 Pretreatment with meptazinol and pentazocine prevented the fall in mean arterial pressure associated with antigen challenge, whereas morphine and naloxone attenuated but did not completely prevent, this change.

3 None of the drugs significantly altered the antigen-induced decreases in heart rate.

4 All the drugs partially reversed the fall in mean arterial pressure when given after antigen challenge although the activity of naloxone was less marked.

5 Pretreatment with reserpine prevented the restoration of blood pressure by all drugs.

6 Additional experiments with meptazinol showed that pretreatment with phentolamine prevented its pressor action.

7 In pithed non-sensitized rats the frequency-pressor response curve to splanchnic stimulation was shifted to the left by meptazinol and shifted to the right by pentazocine, but the changes were small. Morphine and naloxone had no significant effects.

8 It was concluded that opioid mixed agonist-antagonists reverse the cardiovascular changes associated with anaphylactic shock. These effects appear to be mediated by facilitation of sympathetic neurotransmission.

Introduction

The opioid antagonist, naloxone, has no significant cardiovascular effects in normal animals or man (Holaday & Loh, 1981), but in various shock states it produces significant pressor responses, increases in cardiac output and prolongation of survival (Holaday & Faden, 1978; Curtis & Lefer, 1980; Reynolds *et al.*, 1980; Amir, 1982). There is some evidence that naloxone is effective clinically in endotoxic shock (Peters *et al.*, 1981). In contrast, morphine further decreases blood pressure in hypovolaemic shock and produces a severe metabolic acidosis, which can be fatal (Chasnow *et al.*, 1964).

Meptazinol, m-(3-ethyl-1-methyl-hexahydro-1H-azepin-3-yl)phenol hydrochloride is an opioid mixed agonist-antagonist which exhibits analgesic activity in animals and man (Stephens *et al.*, 1978). It has minimal effects on the cardiovascular system of normal animals (Rashid & Waterfall, 1979) but has recently been shown to elevate the blood pressure of rats subjected to hypovolaemic and endotoxic shock (Chance *et al.*, 1981; Paciorek *et al.*, 1983). Meptazinol has now been compared with pentazocine, morphine and naloxone in rats subjected to anaphylactic shock. A preliminary account of these experiments has been presented previously (Paciorek & Todd, 1982).

Methods

Anaphylactic shock model

Groups of 4 female Sprague-Dawley rats (200–250g) were immunized with ovalbumin ($10\,\mu g\,ml^{-1}$) in aluminium hydroxide gel (0.5 ml i.m. into each hind

[1]Present address: ICI Pharmaceuticals Division, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG.
[2]Author for correspondence.

limb) and with *Bordetella pertussis* (1×10^{10} killed organisms in 0.2 ml i.p.) as adjuvant. Eight days later rats were anaesthetized with a mixture of urethane (800 mg kg^{-1}) and chloralose (60 mg kg^{-1}) intraperitoneally and a cannula implanted in the left carotid artery. Blood pressure was recorded via a Statham P23 pressure transducer on a Grass Model 7 polygraph. Heart rate was derived from a tachograph triggered by the blood pressure signal. The trachea was intubated to aid spontaneous respiration and deep body temperature maintained at 37 ± 0·5°C using a heated blanket (Palmer). Mepyramine (0.1 mg kg^{-1} s.c.) was administered to all animals 10 min before the induction of shock to prevent bronchoconstriction. Reproducible cardiovascular shock was then achieved by slow i.v. administration of the antigen (ovalbumin, 0.05 mg kg^{-1}). Drugs or vehicle were administered either 5–15 min before or 30 min after induction of anaphylactic shock. Blood pressure and heart rate were monitored at 5 min intervals.

Some rats were pretreated with reserpine (0.25 mg kg^{-1} i.p.) on days 5, 6 and 7 after immunisation to produce depletion of catecholamines (Huidobro-Toro & Musacchio, 1981) and were then used on day 8 as described above. Drugs were given only after the induction of shock in reserpinized animals. A further group of rats was given phentolamine (1.6 mg kg^{-1} i.v.) 25 min after antigen challenge followed by meptazinol (6 mg kg^{-1} i.m.) 5 min later.

Pithed rats

Female Sprague-Dawley rats (204–285g) were prepared with left femoral arterial and venous cannulae under halothane anaesthesia. Arterial blood pressure was recorded (Statham P23 pressure transducer, Grass Model 7 polygraph) and the trachea cannulated to facilitate mechanical ventilation (Palmer pump; 1 ml 100g^{-1} body weight). Three groups of 5 rats were pithed and prepared for electrical stimulation of the splanchnic bed as described by Gillespie & Muir (1967). Tubocurarine (1 mg kg^{-1} i.v.) was given to abolish skeletal muscle tremor. Stimulation parameters were 25 V, 0.5 ms pulse width (Grass SD9 stimulator). A stimulus frequency-pressor response curve was constructed using frequencies of 0.25–16 Hz. The animals were then dosed with drugs or vehicle and 15 min later a second frequency-response curve obtained. Three other groups of rats were pithed and bolus doses of noradrenaline (0.6 μg kg^{-1} i.v.) given until constant pressor responses were obtained. Dose-response curves to noradrenaline (0.01–5.12 μg kg^{-1}) were obtained before and 15 min after drug or vehicle administration.

Statistical analysis

Results were analysed by a nested analysis of variance (Snedecor & Cochran, 1980).

Drugs

Reserpine (Koch Light) was dissolved in a small quantity of benzyl alcohol and Tween 80, acidified with citric acid and made up to the required volume with distilled water. Meptazinol hydrochloride (Wyeth), phentolamine lactate (Sterling Winthrop), naloxone hydrochloride (Endo Labs Inc), morphine hydrochloride (McFarlan Smith) and phentolamine mesylate (CIBA) were administered in saline (0.9% w/v NaCl, 1 ml kg^{-1}). The high dose of meptazinol (17 mg kg^{-1} i.m.) and the single doses of morphine (3 mg kg^{-1} i.m.) and pentazocine (10 mg kg^{-1} i.m.) were equi-analgesic giving 80% inhibition of rat tail flick responses to radiant heat. The dose of naloxone (10 mg kg^{-1} i.v.) was that shown by Faden & Holaday (1979) to facilitate rapid recuperation of arterial pressure following haemorrhagic hypovolaemia.

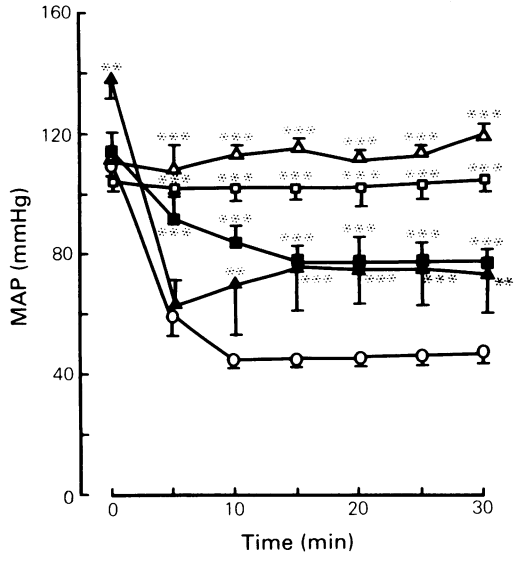

Figure 1 The effects of meptazinol, 17 mg kg^{-1} i.m. (△), pentazocine, 10 mg kg^{-1} i.m. (□), morphine, 3 mg kg^{-1} i.m. (■), naloxone, 10 mg kg^{-1} i.v. (▲) and saline vehicle, 1 ml kg^{-1} i.v. (○) pretreatment on the mean arterial pressure change (MAP) evoked by antigen challenge in ovalbumin-sensitized anaesthetized rats. $^{**}P < 0.01$, $^{***}P < 0.001$, different from vehicle group. The mean values are given in each case ($n = 4$) and vertical lines show s.e.mean.

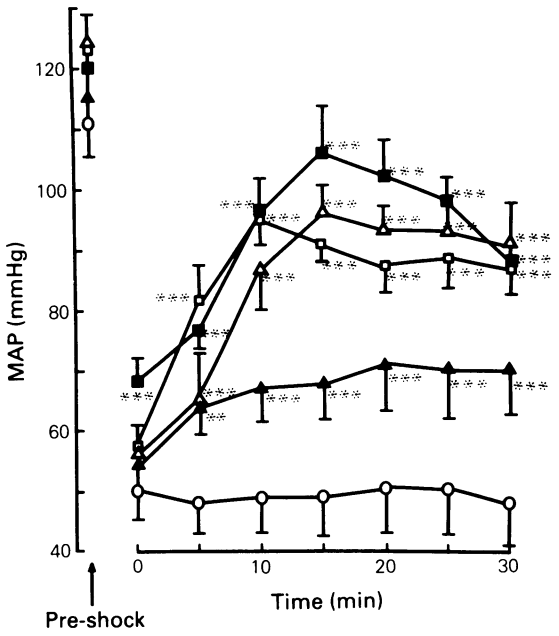

Figure 2 The effects of meptazinol, 17 mg kg^{-1} i.m. (Δ), pentazocine, 10 mg kg^{-1} i.m. (□), morphine, 3 mg kg^{-1} i.m. (■), naloxone, 10 mg kg^{-1} i.v. (▲) and saline vehicle, 1 ml kg^{-1} i.v. (○), on mean arterial pressure (MAP) when administered 30 min after the production of anaphylactic shock in anaesthetized rats. $^{**}P<0.01$, $^{***}P<0.001$, different from vehicle group. The mean values are given in each case ($n = 4$) and vertical lines show s.e.mean. Mean pre-shock values are shown on the top left of the figure.

Results

Anaphylactic shock model

Pretreatment studies When ovalbumin-sensitized rats were pretreated with saline vehicle (1 ml kg^{-1}), the antigen challenge produced a fall in mean arterial pressure (MAP) of 62 ± 3 mmHg 30 min after administration (Figure 1). Meptazinol (17 mg kg^{-1} i.m.) and pentazocine (10 mg kg^{-1} i.m.) prevented the fall in MAP at all time points compared with vehicle controls. Naloxone (10 mg kg^{-1} i.v.) partially attenuated the fall in MAP produced by the antigen and the effect was statistically significant when compared with the vehicle control group. Morphine (3 mg kg^{-1} i.m.) also significantly reduced but did not prevent the fall in MAP produced by ovalbumin ($P<0.001$) and at 30 min after antigen challenge MAP was 34 ± 15 mmHg below the pre-challenge level.

Animals pretreated with pentazocine and morphine had lower heart rates than those given vehicle. Heart rate was reduced by 52 ± 23 beats min^{-1} at 30 min after antigen challenge in vehicle control rats. The drug-treated groups exhibited small but variable changes in heart rates which were not significantly different from those of the control group (Table 1).

Post-shock studies Overall, antigen evoked a fall in MAP of 61 ± 3 mm Hg at 30 min after challenge. Subsequent administration of saline vehicle (1 ml kg^{-1}) had no further effect on blood pressure (Figure 2). Equi-analgesic doses of meptazinol (17 mg kg^{-1} i.m.), pentazocine (10 mg kg^{-1} i.m.) and morphine (3 mg kg^{-1} i.m.) significantly increased blood pressure at all time points compared with vehicle controls ($P<0.001$). The peak increases in blood pressure from values obtained after antigen challenge occurred at 15 min after dosing for meptazinol (39 ± 5 mm Hg) and morphine (38 ± 11 mm Hg) and at 10 min for pentazocine (38 ± 5 mm Hg) as shown in Figure 2. Naloxone (10 mg kg^{-1}) evoked a smaller pressor response which was also significantly different from the vehicle control group. The peak increase was 16 ± 5 mm Hg 20 min after dosing (Figure 2). None of the drugs completely reversed the blood pressure response to antigen challenge. Experiments using lower doses of meptazinol showed that 6 mg kg^{-1} was at least as effective as 17 mg kg^{-1} but, when the dose was reduced to 2 mg kg^{-1}, there was only a marginal response (Figure 3).

Table 1 Effects of meptazinol, pentazocine, morphine, naloxone and saline vehicle pretreatment on the heart rates of ovalbumin sensitized rats subjected to antigen challenge

	Heart rate (beats min^{-1})			
Pretreatment	*Pre-challenge*	*After antigen challenge*		
		10 min	*20 min*	*30 min*
Meptazinol (17 mg kg^{-1} i.m.)	420 ± 11	443 ± 10	433 ± 13	433 ± 14
Pentazocine (10 mg kg^{-1} i.m.)	355 ± 12	375 ± 15	370 ± 18	385 ± 22
Morphine (3 mg kg^{-1} i.m.)	385 ± 9	400 ± 24	370 ± 35	355 ± 35
Naloxone (10 mg kg^{-1} i.v.)	420 ± 12	403 ± 10	395 ± 10	408 ± 11
Saline (1 ml kg^{-1} i.v.)	440 ± 20	408 ± 46	390 ± 45	388 ± 40

Values shown are mean ± s.e.mean ($n = 4$).

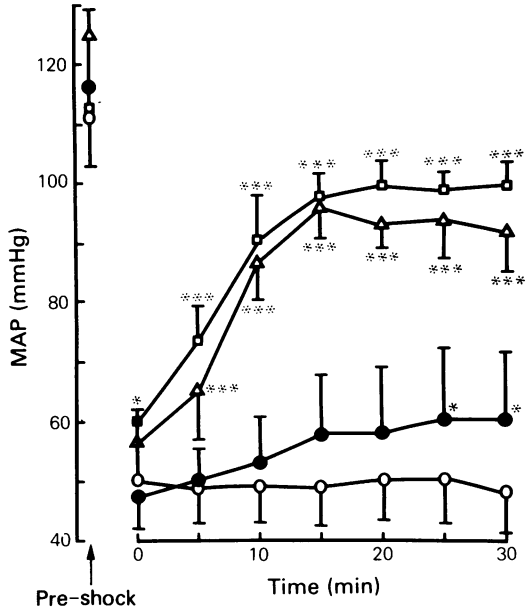

Figure 3 The effects of meptazinol, 2 mg kg^{-1} i.m. (●), 6 mg kg^{-1} i.m. (□), 17 mg kg^{-1} i.m. (△) and saline vehicle, 1 ml kg^{-1} i.v. (○), on mean arterial pressure (MAP) when administered 30 min after the production of anaphylactic shock in anaesthetized rats. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, different from vehicle group. The mean values are given in each case ($n = 4$) and vertical lines show s.e.mean. Mean pre-shock values are shown on the top left of the figure.

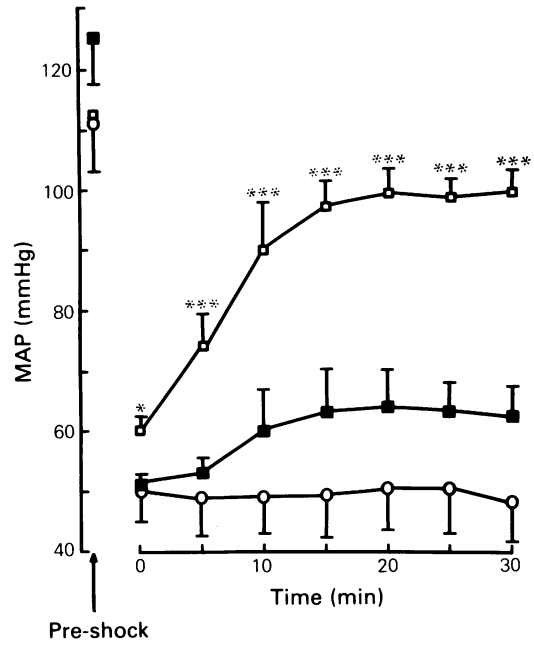

Figure 4 The effects of phentolamine (1.6 mg kg^{-1} i.v.) given 5 min before meptazinol (6 mg kg^{-1} i.m.) on the mean arterial pressure (MAP) in anaesthetized rats subjected to anaphylactic shock; (■) phentolamine pretreatment; (□) no pretreatment; (○) saline control (no meptazinol). *$P < 0.05$, ***$P < 0.001$, different from vehicle control group. The mean values are given in each case ($n = 4$) and vertical lines show s.e. mean.

In reserpinized rats, antigen challenge produced a mean fall in MAP of 39 ± 1 mmHg at 30 min after administration. Subsequent administration of saline vehicle had no effect on MAP. Meptazinol, pentazocine, naloxone and morphine had no significant effects on MAP in reserpinized animals.

Phentolamine (1.6 mg kg^{-1} i.v.) administered 25 min after the antigen challenge prevented the pressor effect of meptazinol (6 mg kg^{-1} i.m.) given 5 min later to ovalbumin sensitized rats (Figure 4).

Antigen challenge evoked a mean decrease in heart rate of 38 ± 8 beats min^{-1} 30 min after dosing

Table 2 Effects of meptazinol, pentazocine, morphine, naloxone and saline vehicle on the heart rates of rats when given 30 min after the induction of anaphylactic shock

Treatment		*Heart rate* (beats min^{-1})				
		Pre-antigen	*30 min post antigen*	*Post drug*		
				10 min	20 min	30 min
Meptazinol	2 mg kg^{-1} i.m.	413 ± 22	393 ± 27	380 ± 14	410 ± 14	420 ± 13
Meptazinol	6 mg kg^{-1} i.m.	430 ± 29	373 ± 17*	400 ± 25	428 ± 20	408 ± 22
Meptazinol	17 mg kg^{-1} i.m.	413 ± 9	375 ± 7*	408 ± 15	425 ± 10	440 ± 12
Pentazocine	10 mg kg^{-1} i.m.	395 ± 24	350 ± 47***	365 ± 47**	378 ± 39*	365 ± 26***
Morphine	3 mg kg^{-1} i.m.	423 ± 9	388 ± 23	398 ± 21	413 ± 17	398 ± 18
Naloxone	10 mg kg^{-1} i.v.	428 ± 6	380 ± 15*	375 ± 23*	390 ± 11	408 ± 9
Saline	1 ml kg^{-1} i.v.	433 ± 19	413 ± 20	405 ± 18	408 ± 14	418 ± 15

Values shown are mean ± s.e.mean ($n = 4$).
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, significantly different from saline vehicle control group (nested analysis of variance).

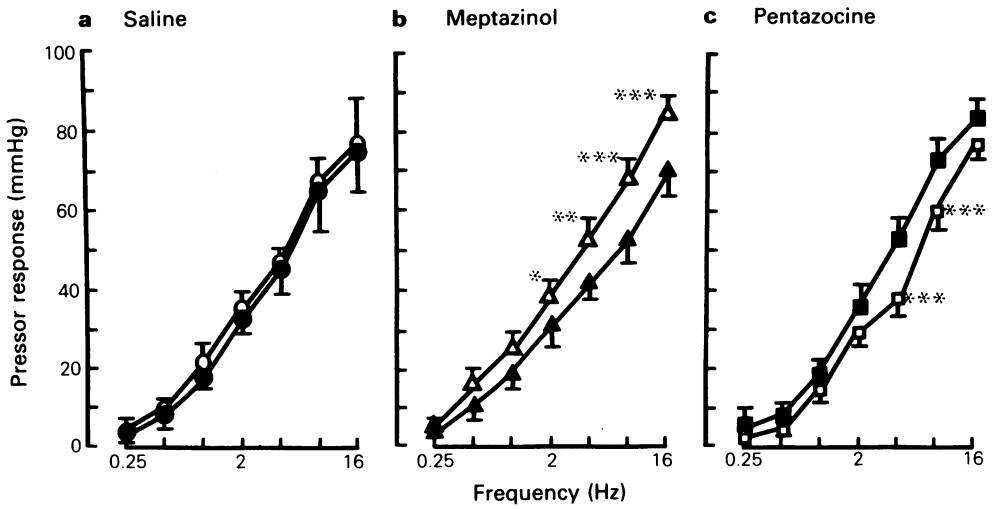

Figure 5 The effect of (a) saline vehicle, 1 ml kg^{-1} i.m., (b) meptazinol, 17 mg kg^{-1} i.m., (c) pentazocine, 10 mg kg^{-1} i.m. on the frequency-pressor response curve to electrical stimulation of the splanchnic bed in pithed rats. Closed symbols denote effects before, and open symbols effects 15 min after, drug or vehicle treatment. The mean values are given in each case (n = 5) and vertical lines show s.e.mean.

(n = 28). The antigen-induced bradycardia varied between animals and so the absolute values for heart rate differed significantly between some treatment groups after challenge (Table 2). Following subsequent drug or vehicle administration there was a tendency for heart rate to rise to the values recorded before antigen challenge.

Pithed rats

Electrical stimulation of the splanchnic bed in pithed rats evoked a frequency-dependent pressor response which was not modified by saline (1 ml kg^{-1}) pretreatment (Figure 5a). Meptazinol (17 mg kg^{-1} i.m.) produced a small but significant shift to the left of the frequency-pressor response curve (Figure 5b), whereas pentazocine evoked a slight shift to the right (Figure 5c). Morphine (3 mg kg^{-1} i.m.) and naloxone (10 mg kg^{-1} i.v.) had no effect. The same doses of meptazinol and pentazocine did not modify the dose-pressor response curve to intravenous noradrenaline.

Discussion

When administered before antigen challenge, equi-analgesic doses of meptazinol and pentazocine were equally effective in preventing the characteristic fall in blood pressure, whereas the protective effect of morphine was smaller. All three agents were approximately equi-effective, however, in reversing the hypotension associated with anaphylactic shock. Although naloxone showed pressor effects in these studies, it was the least effective of the agents tested in preventing the fall or reversing the cardiovascular changes accompanying anaphylactic shock. The dose-response curve for meptazinol appeared to be relatively steep, a dose of 6 mg kg^{-1} being as effective as 17 mg kg^{-1} in increasing the blood pressure of shocked rats, whereas a dose of 2 mg kg^{-1} showed only borderline activity.

It seems likely that the pressor effects of these drugs are mediated, at least in part, via the sympathetic nervous system since they were all ineffective in reversing the cardiovascular changes induced by anaphylactic shock in rats that had been treated with reserpine before antigen challenge. Further studies with meptazinol alone support involvement of the sympathetic nervous system, as pretreatment with phentolamine also prevented its pressor action on the shocked circulation. Previously, *in vitro* studies (Bill *et al.*, 1981) have shown that meptazinol increases neurotransmitter release both in rat isolated atria and in vas deferens, and Paciorek *et al.* (1983) have shown that basal and K^+-stimulated release of noradrenaline from rat cortical synaptosomes was increased in a concentration-dependent manner by meptazinol. The other agents used in this study also interact with neurotransmitters. Morphine increases central noradrenaline release, synthesis and turnover (Way & Shen, 1971; Smith & Sheldon, 1973) and an increase in plasma catecholamine levels has also been seen with pentazocine (Tammisto *et al.*, 1971). Faden *et al.* (1981) have shown that following spinal cord transection, the reversal of the accompanying hypotension by naloxone is blocked by domperidone and the administration of naloxone is accompanied by a rise in the

circulating plasma dopamine concentration. Also, Schadt & York (1981) found that in hypovolaemic rabbits phentolamine partially inhibited the rise in blood pressure induced by naloxone, suggesting that the effects of naloxone are sympathetically mediated.

Whilst there is substantial evidence for an interaction of these drugs with the sympathetic nervous system, the experiments done in pithed rats suggest that the direct release of transmitter from sympathetic nerve endings is unlikely to be the predominant action of these compounds in the shocked animal. Thus, for meptazinol a maximum increase in blood pressure of 15 mmHg was detected in the pithed rat whereas pressor responses of 40 mmHg were recorded with the same dose after anaphylactic shock. In addition, the direct release of noradrenaline cannot account for the pressor actions of pentazocine, morphine and naloxone, none of which potentiated the electrically evoked pressor responses in the pithed rat. Indeed, morphine has been shown to reduce noradrenaline release from postganglionic sympathetic nerve endings of the cat nictitating membrane (Cairnie *et al.*, 1961).

One feature of this study was the relatively weak pressor activity of naloxone compared with meptazinol, pentazocine and morphine. Other authors have shown that naloxone is an effective agent in raising blood pressure and facilitating recovery from haemorrhagic (Curtis & Lefer, 1980), endotoxic (Holaday & Faden, 1978), hypoglycaemic (Huidobro-Toro & Musacchio, 1981) and traumatic shock following spinal cord injury (Faden *et al.*, 1981). Naloxone has also been found to improve survival in mice following anaphylactic shock (Amir, 1982).

Although central opioid receptors have been implicated in the pathophysiology of shock, the relatively poor activity of naloxone in the present study may indicate the involvement of other systems. For example, thyrotropin releasing hormone, but not naloxone, is effective in raising blood pressure following induction of anaphylactic shock in conscious guinea-pigs (Lux *et al.*, 1983). It is interesting that in the current experiments both the opioid mixed agonist-antagonists and even the relatively pure agonist morphine were more effective pressor agents than naloxone. Morphine is known to release histamine (Feldberg & Paton, 1951) and thus might be expected to potentiate the hypotension in a shock model which relies on the release of endogenous autacoids to lower blood pressure (Sanyal & West, 1958). As all the experimental animals in the current study were pretreated with mepyramine, the hypotensive effect of morphine would be obscured. None of the opioids have been found to stabilize mast cells or to have any influence on immunological mechanisms, suggesting that there is no direct involvement by any of the agents used in this study on the antigen-antibody reaction mediating anaphylactic shock.

The heart rate changes induced by the drugs were, in general, small and variable. Rats pretreated with pentazocine and morphine before antigen challenge had lower heart rates than the vehicle-treated group, a consequence of the previously reported bradycardia induced by these drugs in anaesthetized animals (Rashid & Waterfall, 1979).

In conclusion, meptazinol is an effective agent for preventing or reversing the hypotension associated with anaphylactic shock in rats. Previous studies have shown that meptazinol also reverses the cardiovascular changes associated with haemorrhagic and endotoxic shock (Chance *et al.*, 1981, Paciorek *et al.*, 1983) without compromising vital organ flow (Chance & Waterfall, 1982) whereas its cardiovascular effects in normal animals and man are minimal (Stephens *et al.*, 1978). The results for meptazinol in anaphylactic shock extend and support the rationale for its use in shock states and suggest that it interacts with the autonomic nervous system to produce its effects. The exact site or sites of action remain to be determined.

References

AMIR, S. (1982). Opiate antagonists improve survival in anaphylactic shock. *Eur. J. Pharmac.*, **80**, 161–162.

BILL, D., COWLRICK, I.S., FOX, J., TODD, M.H., WARD, P.J., WOOD, M.B. & WYLLIE, M.G. (1981). Does meptazinol bind to opiate receptors? *Br. J. Pharmac.*, **74**, 866P.

CAIRNIE, A.B., KOSTERLITZ, H.W. & TAYLOR, D.W. (1961). Effect of morphine on some sympathetically innervated effectors. *Br. J. Pharmac.*, **17**, 539–551.

CHANCE, E., TODD, M.H. & WATERFALL, J.F. (1981). A comparison of the cardiovascular effects of meptazinol, morphine and naloxone in haemorrhagic shock in rats. *Br. J. Pharmac.*, **74**, 930P.

CHANCE, E. & WATERFALL, J.F. (1982). Effects of meptazinol and naloxone upon regional blood flow in rats subjected to haemorrhagic hypotension. *Br. J. Pharmac.*, **77**, 526P.

CHASNOW, E.A., SMALL H.S., HENRY, J.H., PAPPER, E.M. & NAHAS, G.G. (1964). The effect of morphine, meperidine and thiopental in hypovolaemic shock. *Surgery*, **55**, 567–573.

CURTIS, M.T. & LEFER, A.M. (1980). Protective actions of naloxone in haemorrhagic shock. *Am. J. Physiol.*, **239**, H416–H421.

FADEN, A.I. & HOLADAY, J.W. (1979). Opiate antagonists; a role in the treatment of hypovolaemic shock. *Science*, **205**, 317–318.

FADEN, A.I., JACOBS, T.P., FEUERSTEIN, G. & HOLADAY, J.W. (1981). Dopamine partially mediates the cardiovas-

cular effects of naloxone after spinal injury. *Brain Res.*, **213,** 415–421.

FELDBERG, W. & PATON, W.D.M. (1951). Release of histamine from skin and muscle in the cat by opium alkaloids and other histamine liberators. *J. Physiol.*, **114,** 490–509.

GILLESPIE, J.S. & MUIR, T.C. (1967). A method for stimulating the complete sympathetic outflow from the spinal cord to blood vessels in the pithed rat. *Br. J. Pharmac.*, **30,** 78–87.

HOLADAY, J.W. & FADEN, A.I. (1978). Naloxone reversal of endotoxin hypotension suggests a role of endorphins in shock. *Nature*, **275,** 450–451.

HOLADAY, J.W. & LOH, H.H. (1981). β-Endorphins. In *Hormonal Proteins and Peptides.* ed. Choh Hao Li, Vol. X, pp. 203–291. New York: Academic Press Inc.

HUIDOBRO-TORO, J.P. & MUSACCHIO, J.M. (1981). Naloxone reversal of insulin-induced hypotension in reserpine pre-treated rats. *Arch. Int. Pharmacodyn. Thér.*, **251,** 310–321.

LUX, W.E., FEUERSTEIN, G. & FADEN, A.I. (1983). Thyrotropin-releasing hormone reverses experimental anaphylactic shock through non-endorphin-related mechanisms. *Eur. J. Pharmac.*, **90,** 301–302.

PACIOREK, P.M. & TODD, M.H. (1982). A comparison of the cardiovascular effects of meptazinol and naloxone following anaphylactic shock in anaesthetized rats. *Br. J. Pharmac.*, **76,** 245P.

PACIOREK, P.M., TODD, M.H. & WYLLIE, M.G. (1983). Restoration of mean arterial pressure in endotoxic shock by meptazinol; contributions from lysosomal membrane stabilisation, opiate antagonism and noradrenaline release. *Biochem. Pharmac.*, **32,** 877–881.

PETERS, W.P., JOHNSON, M.W., FRIEDMAN, P.A. & MITCH, W.E. (1981). Pressor effects of naloxone in septic shock. *Lancet*, **1,** 529–532.

RASHID, S. & WATERFALL, J.F. (1979). Cardiovascular actions of meptazinol in comparison with pentazocine and morphine. *Gen. Pharmac.*, **10,** 459–464.

REYNOLDS, D.G., GURLL, N.J., VARGISH, T., LECHNER, R.B., FADEN, A.I. & HOLADAY, J.W. (1980). Blockade of opiate receptors with naloxone improves survival and cardiac performance in canine endotoxic shock. *Circ. Shock*, **7,** 39–48.

SANYAL, R.K. & WEST, G.B. (1958). Anaphylactic shock in the albino rat. *J. Physiol.*, **142,** 571–584.

SCHADT, J.C. & YORK, D.H. (1981). The effects of autonomic blockade on the response to naloxone in conscious rabbits made hypotensive by haemorrhage. *Fedn. Proc.*, **40,** 522.

SMITH, C.B. & SHELDON, M.I. (1973). Effects of narcotic analgesic drugs on brain noradrenergic mechanisms. In *Agonist and Antagonist Actions of Narcotic Analgesic Drugs.* ed. Kosterlitz, H.W. pp. 164–175. Baltimore: University Park Press.

SNEDECOR, G.W. & COCHRAN, W.G. (1980). *Statistical Methods.* 7th Edition. Ames: The Iowa State University Press.

STEPHENS, R.J., WATERFALL, J.F. & FRANKLIN, R.A. (1978). A review of the biological properties and metabolic disposition of the new analgesic agent, meptazinol. *Gen. Pharmac.*, **9,** 73–78.

TAMMISTO, T., JAATTELA, A., NIKKI, P. & TAKKI, S. (1971). Effects of pentazocine and pethidine on plasma catecholamine levels. *Ann. Clin. Res.*, **3,** 22–29.

WAY, E.L. & SHEN, F.H. (1971). Effects of narcotic analgesic drugs on specific systems: catecholamines and 5-hydroxytryptamine. In *Narcotic Drugs: Biochemical Pharmacology.* ed. Clouet, D.H. pp. 229–253. New York: Plenum Press.

(Received June 27, 1984.
Revised September 6, 1984.
Accepted October 5, 1984.)