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The effects of a new opioid analgesic, meptazinol, on the respiration of the conscious rat

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1 In the conscious rat arterial P_{CO_2} was measured as an index of respiratory status.

2 The opioid analgesic meptazinol (7.5–30 mg kg^{-1}) evoked small but significant increases in arterial P_{CO_2} which were attenuated by naloxone.

3 Meptazinol significantly reduced the increase in arterial P_{CO_2} evoked by morphine.

4 The respiratory depression induced by meptazinol, but not that induced by morphine, was enhanced by pretreatment with atropine.

5 The (+)-enantiomer, but not the (−)-enantiomer of meptazinol increased arterial P_{CO_2}. In contrast, only the (−)-enantiomer reduced the respiratory depressant effect of morphine.

6 It is proposed that the degree of respiratory depression induced by meptazinol is limited by its opioid antagonist and cholinomimetic properties.

Introduction

Meptazinol (*m*-(hexahydro-3-ethyl-1-methyl 1H azepin-3-yl)-phenol hydrochloride) is an effective analgesic in animals and man (Goode *et al.*, 1979; Jones, 1983). Previous studies have demonstrated that at equi-analgesic doses meptazinol has significantly less effect on respiration than some other opioid analgesics (Goode *et al.*, 1979). Various possible explanations have been put forward as to why meptazinol has little effect on respiration. It has been demonstrated, for example, that meptazinol binds selectively to the μ_1 opiate receptor, a receptor claimed to mediate analgesic effects, whilst having little affinity for the μ_2 receptor which is thought to mediate respiratory effects (Pasternak *et al.*, 1983).

Pharmacologically, meptazinol is claimed to be an agonist-antagonist capable of precipitating withdrawal symptoms in morphine-dependent rats. The analgesia evoked by meptazinol is partially reversed by naloxone, but in some experimental situations it is also partially reversed by anti-cholinergic agents (Bill *et al.*, 1983). This result suggests that there is a cholinergic component in the effects of meptazinol, and this is supported by the finding that meptazinol potentiates the twitch response to electrical stimulation of the guinea-pig isolated ileum (Stephens *et al.*, 1978). Following the finding that physostigmine reduces morphine-induced respiratory depression (Davidson *et al.*, 1981), either the cholinergic or the opioid antagonist effects of meptazinol, or both these properties, could account for its lack of effect on respiration.

The aim of this study was to examine the pharmacological properties of meptazinol in an attempt to evaluate their importance with regard to the respiratory effects of this compound.

Methods

Male Sprague-Dawley rats (150–200 g) supplied by Charles River were used throughout the study. The animals were anaesthetized with a 5% halothane in oxygen mixture, and maintained in a state of surgical anaesthesia with a 2% halothane mixture. A cannula filled with heparinised saline (125 units ml^{-1} in 0.9% saline) was placed in the right carotid artery, closed with a spigot, and exteriorized at the back of the neck. The preparation was allowed to recover from the effects of the operation for 24 h before any experiments were performed.

On the day of an experiment rats were placed in perspex restrainers 30 min before the experiment began; this was found to reduce the effects of stress due to handling and restraint. After this period a blood sample (100 µl) was withdrawn from the cannula and the arterial P_{CO_2} (mmHg) measured with a Corning

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168 pH/Blood Gas Analyser. Thereafter blood samples were taken at 10 min intervals for the duration of the experiment, a maximum of 12 samples being required.

Effect of opioid agonists on arterial P_{CO_2}

Three arterial blood samples were taken before the administration of saline (1 ml kg^{-1}, s.c.), morphine (7.5 mg kg^{-1}, s.c.), (±)-meptazinol (7.5, 15, 30 mg kg^{-1}, s.c.) or one of the enantiomers of meptazinol (30 mg kg^{-1}, s.c.). After dosing, blood samples were taken at 10 min intervals for 1 h.

The effects of antagonists on the response to opioid agonists

Three arterial blood samples were take prior to the administration of saline (1 ml kg^{-1}, s.c.). or atropine (3 mg kg^{-1}, s.c.). A further three samples were taken and then saline (1 ml kg^{-1}, s.c.), morphine (7.5 mg kg^{-1}, s.c.), (±)-meptazinol (30 mg kg^{-1}, s.c.), or one of its enantiomers (30 mg kg^{-1}, s.c.) was administered. Following dosing, arterial blood samples were taken at 10 min intervals for a further hour. In a second series of experiments either saline (1 ml kg^{-1}, via the tail vein) or naloxone (0.1 mg kg^{-1} via the tail vein) was given in place of atropine; meptazinol or morphine was then administered and the experiment conducted as above.

The effect of co-administration of opioid agonists on arterial P_{CO_2}

Three blood samples were taken prior to the co-administration of: saline (1 ml kg^{-1}) plus morphine (7.5 mg kg^{-1}), morphine (7.5 mg kg^{-1}) plus morphine (7.5 mg kg^{-1}), (±)-meptazinol (15 mg kg^{-1}) plus morphine (7.5 mg kg^{-1}), (+)-meptazinol (30 mg kg) plus morphine (7.5 mg kg^{-1}), or (−)-meptazinol (30 mg kg^{-1}) plus morphine (7.5 mg kg^{-1}). All drugs were given s.c. in a volume of 1 ml kg^{-1}. Following administration of the combination, arterial blood samples were taken for a further hour.

In a second series of experiments three blood samples were taken and then atropine (3 mg kg^{-1}, s.c.) was administered. Three more blood samples were taken and then a combination of morphine (7.5 mg kg^{-1}) plus saline, or morphine (7.5 mg kg^{-1}) plus meptazinol (15 mg kg^{-1}) was administered. Arterial blood samples were then taken for a further hour.

Statistics

Changes in arterial P_{CO_2} due to any of the treatments were assessed by calculating the change in each animal relative to the last control blood sample prior to drug administration. Each treatment group was then compared to its respective saline-treated control group by either nested analysis of variance (time-response curves), or unpaired t test (single measurements of responses). In the figures (*) denotes a significant difference ($P < 0.05$) compared to the control group.

Drugs

The following drugs were employed in this study: atropine sulphate (BDH), (±)-meptazinol HCl, (+)-meptazinol HCl, (−)-meptazinol HCl (Dept. of Chemistry, Wyeth Laboratories), morphine sulphate (Macfarlan Smith) and naloxone HCl (Endo Laboratories).

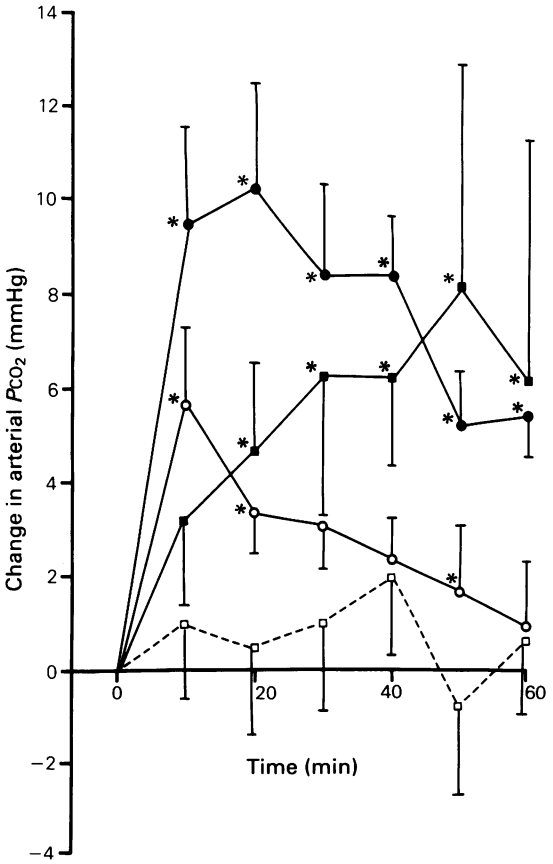

Figure 1 The effect of meptazinol on the arterial P_{CO_2} of the conscious rat. The arterial P_{CO_2} was measured at 10 min intervals for 1 h following the s.c. administration of saline, 1 ml kg^{-1} (□); or (±)-meptazinol, 7.5 mg kg^{-1} (○), 15 mg kg^{-1} (●) or 30 mg kg^{-1} (■). *Indicates a significant difference from the corresponding pre-dose control ($P < 0.05$, nested analysis of variance).

The doses referred to in the text correspond to the weight of the base of each compound. All drugs were made up in 0.9% saline and administered in a volume of 1 ml kg^{-1}.

Results

In order to ensure that all the blood gas parameters were within the normal range under our experimental conditions, predose measurements of P_{O_2} and pH were made in addition to P_{CO_2} in some rats. These measurements yielded mean values of ($n = 8$), pH = 7.49 ± 0.01, P_{O_2} = 96.6 ± 2.3 mmHg and P_{CO_2} = 36.5 ± 0.7 mmHg.

Effect of opioid agonists on arterial P_{CO_2}

Administration of saline (1 ml kg^{-1}, s.c.) had no significant effect on the arterial P_{CO_2} of the conscious rat (Figure 1). In contrast (±)-meptazinol (7.5,15,30 mg kg^{-1}, s.c.) significantly increased the arterial P_{CO_2} for at least 20 min following administration (Figure 1). The maximum increase in arterial P_{CO_2} evoked by 30 mg kg^{-1} meptazinol was not significantly different from that evoked by 15 mg kg^{-1}. The two enantiomers of meptazinol had markedly differing effects, a relatively high dose (30 mg kg^{-1}, s.c.) of the (−)-enantiomer had no effect on the arterial P_{CO_2}; in contrast, this dose of the (+)-

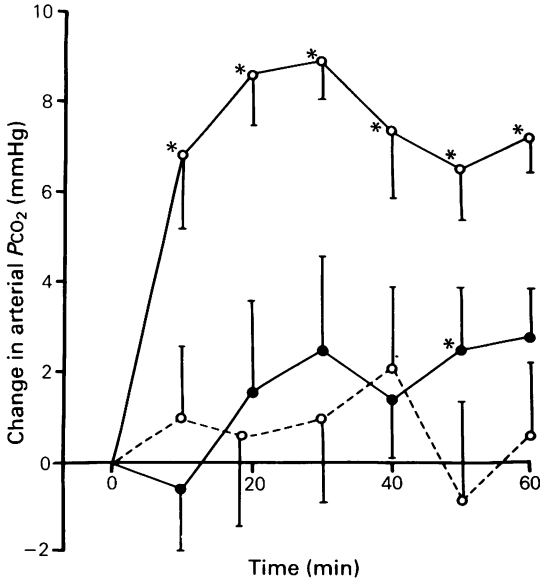

Figure 2 The effect of the two enantiomers of meptazinol on the arterial P_{CO_2} of the conscious rat. The arterial P_{CO_2} was measured at 10 min intervals for 1 h following the s.c. administration of saline 1 ml kg^{-1} (O--O), (+)-meptazinol 30 mg kg^{-1} (O—O), or (−)-meptazinol 30 mg kg^{-1} (●—●). *Indicates a significant difference from the corresponding pre-dose control ($P < 0.05$, nested analysis of variance).

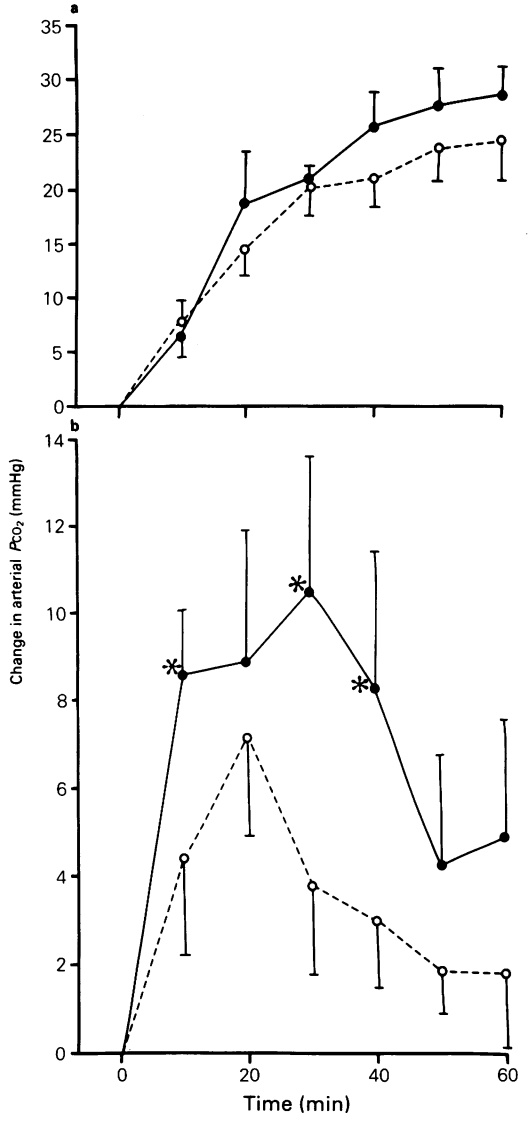

Figure 3 The effect of atropine on the respiratory depression evoked by morphine and meptazinol in the conscious rat. The arterial P_{CO_2} was measured at 10 min intervals for 1 h following the administration of: (a) morphine 7.5 mg kg^{-1} to rats pretreated with saline 1 ml kg^{-1} (O), or atropine 3 mg kg^{-1} (●); (b) meptazinol 30 mg kg^{-1} to rats pretreated with saline 1 ml kg^{-1} (O), or atropine 3 mg kg^{-1} (●). *Indicates a significant difference from the saline pretreated rats ($P < 0.05$, nested analysis of variance).

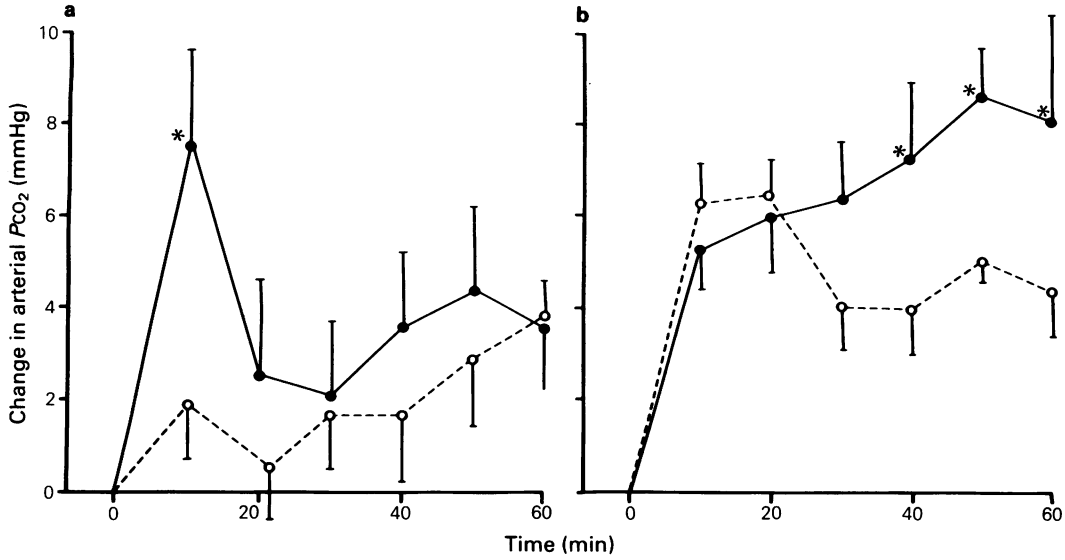

Figure 4 The effect of atropine on the respiratory depression evoked by the enantiomers of meptazinol in the conscious rat. The arterial P_{CO_2} was measured at 10 min intervals for 1 h following the administration of: (a) (−)-meptazinol 30 mg kg^{-1} to rats pretreated with saline 1 ml kg^{-1} (○), or atropine 3 mg kg^{-1} (●); (b) (+)-meptazinol 30 mg kg^{-1} to rats pretreated with saline 1 ml kg^{-1} (○), or atropine 3 mg kg^{-1} (●). *Indicates a significant difference from the saline pretreated rats ($P < 0.05$, nested analysis of variance).

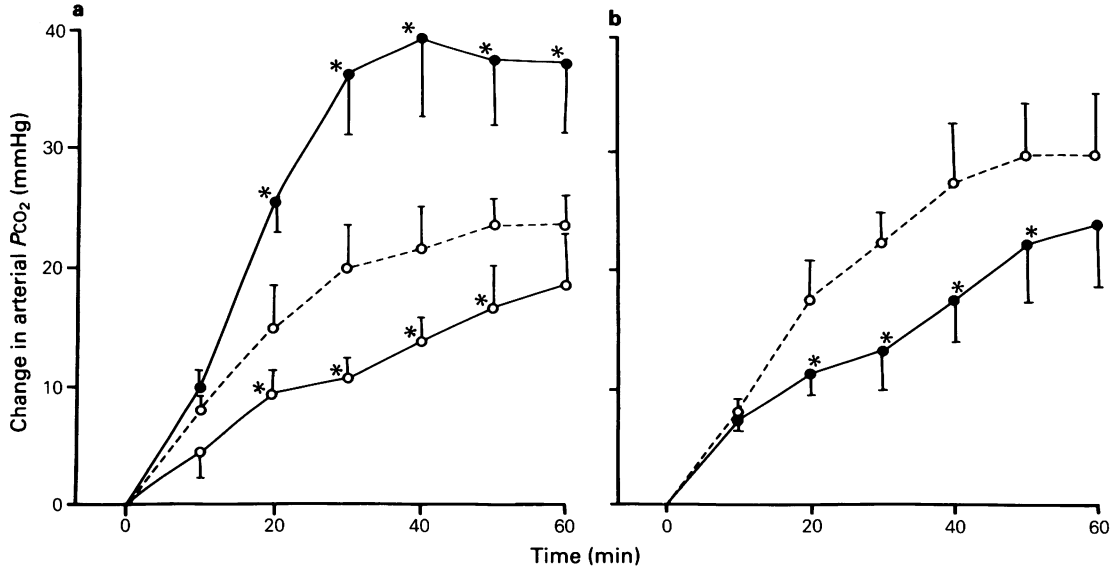

Figure 5 The effect of combinations of morphine and meptazinol on the arterial P_{CO_2} of the conscious rat. The arterial P_{CO_2} was measured at 10 min intervals for 1 h following the s.c. administration of a combination of (a) morphine 7.5 mg kg^{-1} plus saline 1 ml kg^{-1} (○--○); morphine 7.5 mg kg^{-1} plus morphine 7.5 mg kg^{-1}, (●—●); morphine 7.5 mg kg^{-1} plus meptazinol 15 mg kg^{-1} (○—○); or (b) the same morphine/saline (○--○), and morphine/meptazinol (●—●), combinations in animals pretreated with atropine (3 mg kg^{-1}, s.c.) 30 min before the administration of the combination. *Indicates a significant difference from the morphine + saline combination ($P < 0.05$, nested analysis of variance).

enantiomer evoked increases in arterial P_{CO_2} similar to those produced by 15 and 30 mg kg^{-1} of (±)-meptazinol (Figure 2).

The effect of antagonists on the response to opioid agonists

Pretreatment of the preparation with an intravenous dose of naloxone (0.1 mg kg^{-1}) had no significant effect on the arterial P_{CO_2} ($P_{CO_2} = 36.5 \pm 1.4$ mmHg in saline pretreated controls, $n = 12$ and $P_{CO_2} = 37.0 \pm 2.0$ mmHg in naloxone-treated rats, $n = 10$). Following saline pretreatment, morphine (7.5 mg kg^{-1}, s.c.) or meptazinol (15 mg kg^{-1}, s.c.) significantly increased the arterial P_{CO_2} by 22.1 ± 6.3 and 6.3 ± 1.6 mmHg respectively; after naloxone pretreatment these increases were reduced to 5.7 ± 3.7 and 0.1 ± 1.6 mmHg respectively.

Atropine pretreatment had no significant effect on the arterial P_{CO_2} of the conscious rat ($P_{CO_2} = 38.8 \pm 0.14$ mmHg, following saline, $n = 24$ and 39.0 ± 0.56 mmHg following atropine pretreatment, $n = 24$). The increase in arterial P_{CO_2} evoked by morphine (7.5 mg kg^{-1}, s.c.) was not significantly affected by atropine (Figure 3a). In contrast the increase in arterial P_{CO_2} evoked by meptazinol (30 mg kg^{-1}, s.c.) was significantly enhanced following atropine (Figure 3b). The effect of atropine pretreatment on the respiratory depression evoked by the enantiomers appeared to be time-dependent. Atropine enhanced the degree of depression evoked by (−)-meptazinol at only the first sampling point (10 min) after administration of the opioid (Figure 4a). In contrast, the depression evoked by the (+)-meptazinol was enhanced at the 40,50 and 60 min time points following the administration of atropine (Figure 4b).

The effect of co-administration of opioid agonists on arterial P_{CO_2}

Co-administration of morphine (7.5 mg kg^{-1}) and saline evoked a significant increase in arterial P_{CO_2} (Figure 5a). A dose of 15 mg kg^{-1}, s.c. morphine (as a combination of two 7.5 mg kg^{-1} doses) evoked a significantly greater increase in arterial P_{CO_2} than that observed following the lower dose of morphine. In contrast, co-administration of morphine (7.5 mg kg^{-1}, s.c.) and meptazinol (15 mg kg^{-1}, s.c.) evoked an increase in arterial P_{CO_2} which was significantly less than that produced by the morphine (7.5 mg kg^{-1})/saline combination (Figure 5a). The effect of meptazinol on the response to morphine was also investigated in the presence of atropine. Pretreatment with atropine did not significantly alter the inhibition by meptazinol of the respiratory depression evoked by morphine (compare Figures 5a and 5b).

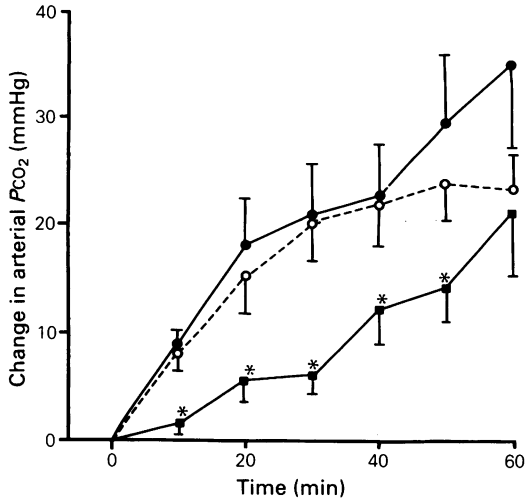

Figure 6 The effect of the enantiomers of meptazinol on the respiratory depression evoked by morphine in the conscious rat. The arterial P_{CO_2} was measured at 10 min intervals for 1 h following the administration of morphine 7.5 mg kg^{-1} plus saline 1 ml kg^{-1} (○), morphine 7.5 mg kg^{-1} plus (−)-meptazinol 30 mg kg^{-1} (■), or morphine 7.5 mg kg^{-1} plus (+)-meptazinol 30 mg kg^{-1} (●). *Indicates a significant difference from the morphine plus saline combination ($P < 0.05$, nested analysis of variance).

The two enantiomers of meptazinol had markedly different effects on the response to morphine. Co-administration of morphine (7.5 mg kg^{-1}, s.c.) and (+)-meptazinol (30 mg kg^{-1}, s.c.) evoked an increase in arterial P_{CO_2} similar to that evoked by morphine alone. Co-administration of morphine (7.5 mg kg^{-1}, s.c.) and (−)-meptazinol however, significantly reduced the increase in arterial P_{CO_2} evoked by morphine (Figure 6).

Discussion

Meptazinol is an effective centrally acting opioid analgesic in animals and man. However, unlike many other opioid analgesics, meptazinol exhibits a remarkably low incidence or even absence of such typical side effects as constipation, miosis and respiratory depression. During the development of this compound two distinctive pharmacological properties have been identified which may explain this unusual but desirable profile. Firstly, meptazinol is considered to be an opioid agonist-antagonist, and secondly it exhibits certain cholinomimetic effects both *in vivo* and *in vitro* (Green, 1983; Duchesne *et al.*, 1984).

Using the conscious rat as a model we have investigated how the pharmacological properties of

meptazinol relate to its effects on respiration. In this study we have measured arterial PCO_2 as an index of respiratory status. This measure was used as the chemosensitive area of the medulla is highly sensitive to changes in arterial PCO_2, and it is signals from this centre that excite other respiratory centres resulting in changes in rate and depth of inspiration. In contrast, PO_2 has little effect on central chemosensitive centres, peripheral chemoreceptor sites being the main sensors for changes in this parameter. Although the central chemoreceptor area is very sensitive to hydrogen ions, these ions do not easily cross the blood brain barrier. Changes in the arterial pH therefore have considerably less effect on the chemosensitive area than PCO_2 (Guyton, 1976).

In the conscious rat, meptazinol evoked a small degree of respiratory depression measured as an increase in arterial PCO_2. This increase in PCO_2 was attenuated by pretreatment with a dose of naloxone which markedly reduced the respiratory depression evoked by morphine. This result suggests that the respiratory depression evoked by meptazinol is mediated by opiate receptors and that this effect is, therefore, a manifestation of the opioid agonist properties of this compound.

The degree of respiratory depression evoked by meptazinol increased as the dose was doubled from 7.5 to $15\,mg\,kg^{-1}$. A further doubling of the dose to $30\,mg\,kg^{-1}$ did not however result in any further increase in the degree of depression. As the maximum respiratory depression observed following meptazinol was markedly less than that evoked by the 'pure' agonist morphine it would appear that there are additional factors limiting the maximum effect of meptazinol.

Preliminary experiments with morphine revealed that a dose of $7.5\,mg\,kg^{-1}$ evoked a submaximal increase in PCO_2. This finding was confirmed by experiments in which the dose was increased to $15\,mg\,kg^{-1}$ (in the combination experiments) and a larger increase in PCO_2 produced. This experiment also demonstrated that the addition of two doses ($2 \times 7.5\,mg\,kg^{-1}$) of a 'full' opioid agonist result in a cumulative effect. Despite this finding, combination of a dose of $15\,mg\,kg^{-1}$ meptazinol with $7.5\,mg\,kg^{-1}$ morphine resulted in a smaller increase in PCO_2 than that evoked by this dose of morphine alone. This inhibitory effect of meptazinol could theoretically be due to either its cholinomimetic activity (see below), or an opioid antagonist property. The involvement of a cholinomimetic component was eliminated by pretreating the preparation with atropine. Under these conditions meptazinol still markedly reduced the respiratory depression evoked by morphine. This reduction of the effects of morphine therefore clearly demonstrates the opioid antagonist properties of meptazinol.

Pretreatment with atropine had no significant effect on the respiratory depression evoked by morphine, but enhanced that evoked by meptazinol. This result suggests that the cholinergic component reported to be present in the analgesic action of meptazinol (Bill *et al.*, 1983) is also evident in its respiratory effects. It has previously been reported that elevation of brain acetylcholine levels can overcome the respiratory depressant action of morphine (Weinstock *et al.*, 1981). It is possible, therefore, that the cholinomimetic effect of meptazinol may tend to limit the degree of respiratory depression that might otherwise be expected from its opioid agonist action.

Meptazinol is a mixture of two enantiomers which this study has shown to have markedly different effects on arterial PCO_2. The (+)-enantiomer significantly increased the arterial PCO_2 but this enantiomer had no significant effect on the response to morphine. In contrast, the (−)-enantiomer did not affect the arterial PCO_2 but significantly reduced the degree of respiratory depression evoked by morphine. This result is consistent with previous reports that the (−)-enantiomer is a more potent opioid antagonist than the (+)-enantiomer (Goode & White, 1971). Interestingly, both enantiomers are equipotent in analgesic tests suggesting that their analgesic agonist properties are similar (Goode & White, 1971). The differences in the effects of the enantiomers as analgesics and as respiratory depressants may support the hypothesis, first proposed by Martin *et al.* (1976), that the receptors mediating these two effects are different, since it would appear that the (−)-enantiomer can differentiate between them. An alternative explanation for the effects of the enantiomers may be proposed on the basis of their cholinergic properties. Duchesne *et al.* (1984), have reported upon the properties of meptazinol and its enantiomers in isolated tissue preparations and have confirmed the opioid agonist and antagonist properties reported by Goode & White (1971). In addition, Duchesne *et al.* reported that the (−)-enantiomer has a more pronounced cholinergic effect than the (+)-enantiomer. It is possible, therefore, that the opioid agonist effects of the (−)-enantiomer, which tend to depress respiration, are counterbalanced by its cholinergic effects. Clear evidence for the role of the cholinergic component was not seen in the experiments described in this paper, because although atropine enhanced the respiratory depression evoked by meptazinol, its effect on the enantiomers appeared to be time-dependent. It is likely that the nett effect of the enantiomers is the result of the balance of the opioid agonist, antagonist and cholinergic agonist properties.

The agonist and antagonist effects of meptazinol have not been observed in respiratory studies in some other laboratories. Recently, for example, it has been reported that meptazinol ($10\,mg\,kg^{-1}$, i.v.) had no

significant effect on arterial PCO_2 or PO_2 and did not affect the changes in these parameters evoked by morphine in the rat (Spiegel & Pasternak, 1984). There is no obvious explantion for the lack of effect of metazinol on blood gases in this study as the dose employed was within the dose range which evoked increases in PCO_2 in our study. The major difference in experimental protocol between these studies was that Spiegel and Pasternak used free, unrestrained, rats and in our study the rats were in perspex restrainers. These two methods may result in the rats being exposed to varying degrees of stress, a factor which has been suggested may alter the respiratory effects of some opioids (Ward & Takemori, 1983). The dose of morphine employed to assess the antagonist properties of meptazinol in these two studies was also different. This difference may be relevant in view of the apparent partial agonist activity of meptazinol. Classical receptor theory predicts that the nett response resulting from the compination of a full and a partial agonist will depend upon the dose of the full agonist (Goldstein *et al.*, 1973).

In summary, meptazinol evokes a weak respiratory depression in conscious rats. Pharmacological data indicate that the degree of this depression is limited by the cholinergic component of meptazinol's effects and its opioid antagonist properties.

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