The analgesic and respiratory effects of meptazinol, morphine and pentazocine in the rat

P. G. GOODE, K. F. RHODES*, J. F. WATERFALL, *Wyeth Institute of Medical Research, Huntercombe Lane South, Taplow, Maidenhead, Berks. SL6 0PH, U.K.*

Meptazinol m-(3-ethyl-1-methylhexahydro-1H-azepin-3-yl) phenol hydrochloride is an opioid antagonist with analgesic actions in man (Paymaster 1976; Hedges et al 1977) and in animals (Goode & White 1971). A side effect of some analgesics of this type is respiratory depression (Martin 1967). We have used arterial blood oxygen tension (PO_2), carbon dioxide tension (PCO_2) and pH as indicators of respiratory status and compared the analgesic potency of the compounds with their respiratory depressant effects following intravenous administration to conscious rats.

For comparisons of analgesic potency a tail flick method based on that of Bonnycastle & Leonard (1950) was used with eight female rats (Charles River Albino, 100–200 g) in each dosage group. Before dosing, the time taken for each rat to flick its tail from a radiant heat source was measured to check that the animal showed a normal response to the stimulus. The rats were then dosed intravenously with 1 ml kg^{-1} of the drug solution or saline vehicle and their response times measured at 10, 20, 40 and 60 min after dosing. If the time taken for any drug-treated animals to respond was greater than the upper 99·9% confidence limit of the mean tail flick time for the saline control group, they were considered to be showing an analgesic response. The number of animals showing analgesia at each test interval for the whole experiment was totalled for each dosage group and the analgesic effect of each dose of drug was expressed as a percentage of the total possible analgesic responses. At least 3 dose levels were used for each determination. From the results a dose needed to produce a 50% level of response was determined for each drug from a best fit straight line plot of log-dose against percent-response, using the method of least squares.

Respiratory and cardiovascular studies were made in groups of five female rats (Charles River Albino, 330–450 g). The animals were anaesthetized with Fluothane (Imperial Chemical Industries Ltd) and cannulae placed in the left common carotid artery and external jugular vein. The cannulae were passed through the skin at the back of the neck. These procedures were carried out under aseptic conditions. At least 20 h were allowed for recovery from anaesthetic. For blood sampling animals were held in Perspex restrainers and 0·15 ml blood samples were removed from the arterial cannula via a 3-way stopcock. When samples were not being taken the arterial cannula was connected via the stopcock to a Bell and Howell pressure transducer (Type 422–0001) and heart rate and arterial pressure obtained from the trace of a Devices M2 pen recorder. At time zero animals received 1 ml kg^{-1} of saline or the same volume of drug solution via the venous cannula. Heparinized saline (0·3 ml of 125 IU ml^{-1}) was used to wash in the drug dose. Blood samples were taken at −10, −5, 5, 10, 15, 30, 45 and 60 min after dosing for

* Correspondence.

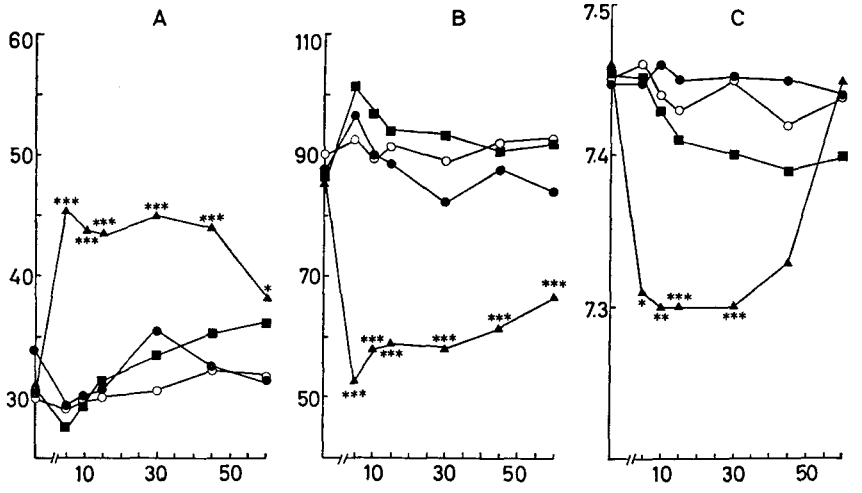

FIG. 1. The effects of 16 mg kg^{-1} meptazinol (■), 16 mg kg^{-1} pentazocine (●), 4 mg kg^{-1} morphine (▲) and saline vehicle (○) on:— (A) arterial blood PCO_2 (ordinate: mm Hg) (B) PO_2 (ordinate: mm Hg) and (C) pH (ordinate) of the conscious rat. Points on the ordinate were taken 5 min before dosing. Abscissa: time (min). * $P \leqslant 0{\cdot}05$, ** $P \leqslant 0{\cdot}01$, *** $P \leqslant 0{\cdot}001$.

estimation of blood gases and pH using a Radiometer BMS3MK2 blood micro system gas analyser. Heart rate and blood pressure were noted immediately before each blood sample was taken. Respiratory movements were recorded continuously on the pen recorder as the pressure trace of a pneumatic transducer (Narco Biosystems Inc) positioned between the thorax of the rat and the wall of the restrainer. Each animal received one dose of drug or vehicle only. The data underwent analysis of variance and treatment groups and saline controls were then compared at each time point by *t*-tests using the error mean square.

Pentazocine lactate (Sterling Winthrop), morphine hydrochloride and meptazinol hydrochloride were used throughout.

The doses of analgesics producing a 50% response in the tail flick test were meptazinol (3·4 mg kg^{-1}), pentazocine (10·9 mg kg^{-1} by extrapolation) and morphine (1·0 mg kg^{-1}). The potencies of meptazinol and pentazocine relative to morphine were therefore 0·3 and 0·09 respectively. The largest doses of morphine, meptazinol and pentazocine tested (2, 8 and 8 mg kg^{-1} respectively) produced 81, 88 and 47% of the total possible analgesic response. These were used as the lower doses of the respiratory study and were considered to be approximately equianalgesic for morphine and meptazinol.

In the respiratory study morphine produced significant changes in PCO_2 (Fig. 1a) and PO_2 (Fig. 1b) indicative of respiratory depression at both 2 and 4 mg kg^{-1}, the effects being more pronounced at the higher dose.

Meptazinol and pentazocine produced no significant change in either gas tension at 8 or 16 mg kg^{-1} though some indication of increased PCO_2 was seen with the higher dose of meptazinol. In 3/5 rats which received 16 mg kg^{-1} meptazinol an additional blood gas measurement was made at 90 min. The mean PCO_2 of these animals fell from 37·3 mmHg at 60 min to 35·5 mmHg at 90 min. The only significant fall in pH was observed with 4 mg kg^{-1} morphine (Fig. 1c). Some reduction in pH was seen with 16 mg kg^{-1} meptazinol, but this was not significantly different from the saline control group. Meptazinol produced no significant effect on respiratory frequency at 8 or 16 mg kg^{-1} (Fig. 2a). The respiratory frequency of the 2 mg kg^{-1} morphine group was significantly higher than that of the saline group at 30 and 45 min after dosing. Pentazocine produced marked increases in respiratory frequency at both dose levels. No significant change in arterial pressure was seen with any of the analgesics (Fig. 2b). Heart rate was reduced by meptazinol at both 8 and 16 mg kg^{-1} (Fig. 2c) whereas pentazocine was without effect. Following the 2 and 4 mg kg^{-1} doses of morphine there was an initial slowing of heart rate (5 to 10 min after dosing) but at 60 min rate was significantly increased.

Convulsions were observed during the first 5 min after dosing in the rats which received 8 mg kg^{-1} pentazocine; this effect was more obvious at 16 mg kg^{-1}. Meptazinol at 16 mg kg^{-1} produced similar effects but morphine did not cause convulsions at the doses tested.

The results of this study show that meptazinol like the other opioid antagonist pentazocine had little respiratory depressant action in the conscious rat. A comparison of the effects of equianalgesic doses of morphine and meptazinol showed that meptazinol had little effect on respiratory status whereas marked effects were seen in the PO_2 and PCO_2 of the morphine treated animals. The ability of the opioid antagonists to produce anal-

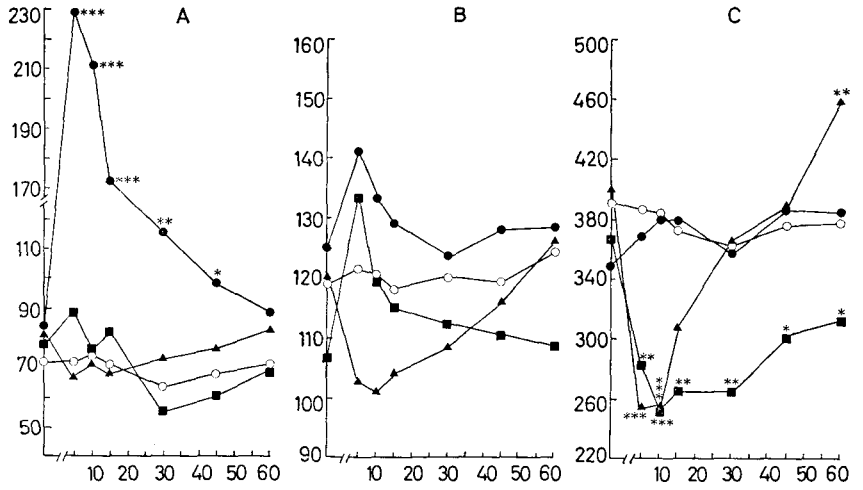

FIG. 2. The effects of 16 mg kg^{-1} meptazinol (■), 16 mg kg^{-1} pentazocine (●), 4 mg kg^{-1} morphine (▲) and saline vehicle (○) on:— (A) respiratory frequency (min^{-1}) (ordinate). (B) mean arterial pressure (mm Hg) (ordinate), and (C) heart rate (beats min^{-1}) (ordinate) of the conscious rat. Points on the ordinate were taken 5 min before dosing. Abscissa: time (min). * $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$.

gesia with relatively little respiratory depression has previously been observed with, for instance, nalorphine (Keats & Telford 1966). The cardiovascular changes observed with meptazinol were notably a fall in heart rate with little change in arterial pressure and resembled those found with morphine in this study and with other analgesics of this type in the rat (e.g. Cowan et al 1977).

The convulsant effect of large doses of pentazocine has been reported both in animals and in man (Brogden et al 1973). It is possible that the large increase in respiratory frequency observed with pentazocine in these experiments could be a reflection of the convulsant effect and could tend to mask respiratory depressant changes in blood gases. It seems unlikely that a similar situation could exist with meptazinol as no change in respiratory frequency was observed with this drug and no signs of respiratory depression were seen at the lower, non-convulsant dose of meptazinol.

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Nuciferine and central glutamate receptors

D. R. CURTIS*, D. LODGE, J. C. BORNSTEIN, *Department of Pharmacology, John Curtin School of Medical Research, P.O. Box 334, Canberra City, ACT, 2601, Australia*

On the basis of theoretical considerations, and the result of in vivo and in vitro experimental studies, neuronal excitants chemically related to aspartate and glutamate appear to interact with different types of receptor site, some of which may interact with more than one class of agonist (Watkins 1978; Johnston 1979). The analysis of central excitant amino acid receptors is complicated, however, not only by regional and species differences and the difficulty of relating binding sites investigated under in vitro conditions to functionally significant receptors operating at synapses in vivo, but also by the probable innervation of many neurons by both aspartergic and glutamergic pathways (Curtis 1979). The degree of specificity of agonists and antagonists is thus of critical significance in both in vivo and in vitro investigations.

McLennan & Lodge (1979) have demonstrated that whereas the excitations of spinal interneurons and Renshaw cells (cats anaesthetized with pentobarbitone) by *N*-methyl-D- and -L-aspartate (NMDA, NMLA) and ibotenate were readily antagonized by D-α-aminoadipate (DαAA; Hall et al 1977; Biscoe et al 1977) and much less readily by L-glutamic acid diethylester (GDEE; Haldeman & McLennan 1972), excitations by L-glutamate and quisqualate were readily reduced by GDEE and much less so by DαAA. In contrast, excitation by kainate was almost insensitive to antagonism by GDEE and only slightly reduced by DαAA (see also Lodge et al 1978). A similar finding has been reported for rat thalamic neurons (McLennan & Hall 1978; Hall et al 1979). These and other observations suggest that whilst NMDA, NMLA and ibotenate may be selective agonists for L-aspartate receptors at which DαAA is an antagonist, L-glutamate and quisqualate may be more specific agonists than kainate for L-glutamate receptors which are antagonized by GDEE. On the basis of the reduction of certain synaptic excitations by GDEE (see Curtis 1979) these latter receptors may be those with which L-glutamate interacts as a synaptically released excitatory transmitter.

Recently Davies & Polc (1979) have reported that L-nuciferine (L-5,6-dimethoxyaporphine), previously found not to differentiate between the excitatory effects of L-glutamate and acetylcholine (ACh) on Renshaw cells in the rat (Duggan et al 1973) and cat (Curtis et al unpublished observations), depressed the excitation of feline Renshaw cells by ACh and kainate more than that by NMDA. Furthermore, the excitation of spinal interneurons by kainate was more sensitive to L-nuciferine than excitation by NMDA. This preferential reduction of excitation by kainate provides some support for proposed differences between receptors for NMDA and kainate, and for earlier proposals that L-nuciferine may selectively influence L-glutamate receptors in the cat cuneate nucleus (Hind & Kelly 1975), thalamus (Ben Ari & Kelly 1975; but see McLennan & Wheal 1976) spinal cord (Polc & Haefely 1977) and in the pigeon optic tectum (Felix & Frangi 1977).

In view of these results, the opportunity was taken to examine the selectivity of L-nuciferine as an antagonist of the excitation of spinal neurons by a range of excitant amino acids. The effects of 9-methoxyaporphine were also examined as this compound has previously been reported (as 2-methoxyaporphine; Curtis et al 1972) to diminish the effectiveness of both L-glutamate and L-aspartate as excitants of Renshaw cells more than that of acetylcholine, without distinguishing between excitation by the two amino acids. The experiments were performed on dorsal horn interneurons and Renshaw cells in lumbar segments of 5 spinal cats,

* Correspondence.