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Characterization of the effects of (±)-meptazinol, its individual enantiomers and N-methyl meptazinol on food consumption in the rat

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1 Both (±)-meptazinol (2 mg kg^{-1}) and levorphanol (1 mg kg^{-1}) produced hyperphagia over a 4 h period after intraperitoneal injection in free feeding rats during the daylight phase.

2 The individual (+)- and (−)-enantiomers of meptazinol (2 mg kg^{-1} i.p.) induced comparable increases in cumulative food intake.

3 N-methyl meptazinol (2–10 mg kg^{-1} i.p.), the quaternary analogue of meptazinol, produced no modification of food intake though it increased food consumption when injected intracerebroventricularly (10–100 μg per animal).

4 Meptazinol and levorphanol hyperphagia was abolished by 1 mg kg^{-1} doses (i.p.) of the opioid antagonists naltrexone, naloxonazine and (−)-Mr 1452 but not by its (+)-enantiomer Mr 1453 which is not effective as an opioid antagonist.

5 Intracerebroventricular administration of the δ-opioid receptor antagonist ICI 154,129 (10 μg per animal) suppressed meptazinol but not levorphanol hyperphagia.

6 It was concluded that meptazinol produces centrally mediated stereospecifically reversible hyperphagia through a μ-opioid receptor mechanism common to levorphanol, and also through δ-opioid receptor mechanism(s).

Introduction

Meptazinol (*m*-(3-ethyl-1-methyl-hexahydro-1-H-azepine-3-yl) phenol hydrochloride) is a novel analgesic agent which has been shown in both *in vitro* and *in vivo* studies to possess an activity profile which differs from that of classical opioids such as morphine. Thus, meptazinol has been postulated to act selectively at the high affinity μ_1-sites defined in receptor binding studies as being common to both morphine and the enkephalins (Spiegel & Pasternak, 1984). Furthermore, studies using both isolated tissues and conscious animals have suggested that meptazinol acts as a mixed agonist-antagonist at opioid receptors while also possessing some properties consistent with the stimulation of cholinoceptors (Ben-Sreti *et al.*, 1983; Bill *et al.*, 1983; Duchesne *et al.*, 1984; Cowlrick & Shepperson, 1985). In addition, meptazinol has only minor effects on the cardiovascular system, produces little or substantially less respiratory depression than morphine, and does not appear to induce physical dependence in laboratory animals (Spiegel & Pasternak, 1984; Cowlrick & Shepperson, 1985; Holmes & Ward, 1985).

There is now considerable evidence that agents acting as agonists at μ, κ and δ-opioid receptors increase food intake in non-deprived rats (for review see Morley *et al.*, 1983). In the current study, therefore, the mechanism of action of meptazinol-induced feeding was investigated by: firstly, comparing its effects on food consumption with those of the more traditional μ-agonist levorphanol; secondly, by comparing the appetitive effects of (±)-meptazinol with those of its resolved enantiomers and also with those of its quaternary analogue, N-methyl meptazinol; and thirdly, by examining the interactions between meptazinol or levorphanol and a variety of opioid antagonists with respect to ingestive behaviour. Some of the results presented in this communication have previously been reported in a preliminary form to the British Pharmacological Society (Jackson & Sewell, 1985a).

Methods

Animals and environment

Male Wistar rats (300–350 g), bred in the Welsh School of Pharmacy, were individually housed at 21 ± 1°C on a 12 h light-dark cycle (lights on 08 h 00 min–20 h 00 min) and randomly allocated into groups of six. Animals were allowed free access to tap water and to a powdered standard rat diet (Grain Harvesters Ltd., Wingham, Kent) both before and during experimentation.

Measurement of food intake

All procedures began at 10 h 00 min so that measurements were carried out during the daylight period when the food intake of control animals was minimal. Feedings jars were weighed at the time of administration of drug and thereafter at 1, 2 and 4 h to enable the calculation of mean group cumulative food intake (g kg^{-1} rat weight ± s.e.mean).

Drugs and injections

The following drugs were used: (±)-meptazinol, the resolved (+)- and (−)-enantiomers of meptazinol and naloxonazine (courtesy of Wyeth); N-methyl meptazinol (synthesized by W. McCleary at the Welsh School of Pharmacy, UWIST); levorphanol tartrate (gift from Roche); naltrexone HCl (courtesy of Endo Laboratories); Mr 1452 and Mr 1453 [(−)-5,9-α-dimethyl-2-(3-furylmethyl)-2′-hydroxy-6,7-benzomorphan methane sulphonate and its (+)-isomer respectively; courtesy of Boehringer Ingelheim] and ICI 154,129 (N,N-bisallyl-Tyr-Gly-Gly-ψ-(CH_2S)-Phe-Leu-OH; gift from ICI Pharmaceuticals). All drugs were dissolved in sterile 0.9% NaCl with the exception of naloxonazine which was dissolved in 0.1 M NCl neutralised with $NaHCO_3$. Intraperitoneal injections were made in a dose volume of 1 ml kg^{-1}. Intracerebroventricular injections were made in a dose volume of 10 μl per rat through permanently indwelling cannulae implanted at least seven days before experimentation and according to a method previously described by Jackson & Sewell (1985b). The doses of all drugs were calculated as the salt. In interaction studies animals were injected with either meptazinol or levorphanol 30 min before the antagonist.

Statistical analysis

Statistical comparisons between mean group cumulative food intakes were made using the analysis of variance and Dunnett's *t* test.

Results

Effects of meptazinol and levorphanol on food consumption

Intraperitoneal meptazinol at a dose of 2 mg kg^{-1} (Figure 1a) and levorphanol (1 mg kg^{-1} i.p.; Figure 1b) both significantly increased food intake compared to the corresponding vehicle-treated controls over a simultaneous test period. The hyperphagic effects of these compounds became evident within the first hour after drug administration and were maintained over several hours so that the 4 h-cumulative food intakes of rats treated with either meptazinol (2 mg kg^{-1}) or levorphanol (1 mg kg^{-1}) remained significantly greater than the control values.

Higher doses of meptazinol (10–20 mg kg^{-1} i.p.) and levorphanol (10 mg kg^{-1} i.p.) did not produce any appreciable effects ($P > 0.05$) on food consumption. It was observed that animals injected with the larger dose of levorphanol exhibited overt signs of sedation which may well have interfered with any possible stimulation of ingestive behaviour.

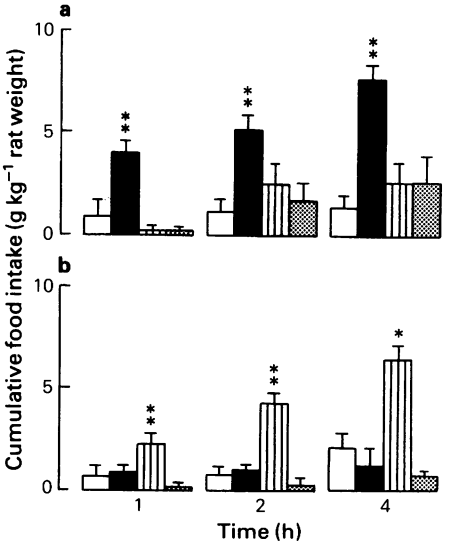

Figure 1 (a) Effect of meptazinol on cumulative food intake. Rats were injected i.p. with vehicle (open columns) or doses of meptazinol: 2 mg kg^{-1} (closed columns), 10 mg kg^{-1} (vertically-hatched columns), 20 mg kg^{-1} (stippled columns). (b) Effect of levorphanol on cumulative food intake. Rats were injected i.p. with vehicle (open columns) or doses of levorphanol: 0.1 mg kg^{-1} (closed columns), 1 mg kg^{-1} (vertically-hatched columns), 10 mg kg^{-1} (stippled columns). Significant differences from control values are indicated by $*P < 0.05$; $**P < 0.01$. Treatment groups contained 6 animals. Values are mean; vertical lines represent s.e.mean.

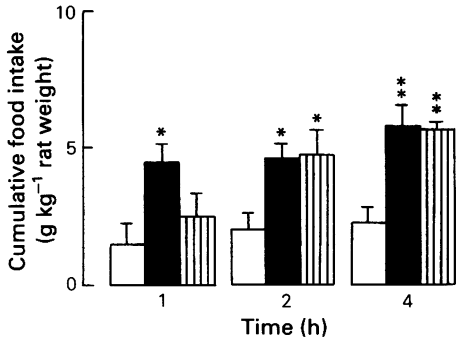

Figure 2 Cumulative food intake following i.p. administration of the enantiomers of meptazinol. Groups of 6 rats were injected: vehicle (open columns), (+)-meptazinol (2 mg kg^{-1}, closed columns), (−)-meptazinol (2 mg kg^{-1}, vertically-hatched columns). Significant increases over control levels are denoted by $*P<0.05$; $**P<0.01$. Values are mean; vertical lines represent s.e.mean.

Food intake studies with enantiomers of meptazinol

The dextro and laevo enantiomers of meptazinol (2 mg kg^{-1} i.p.) both significantly increased the intake of food during a 4 h observation period (Figure 2) and in this respect both isomers behaved like the parent compound. It was noted, however, that the appetitive effects of (−)-meptazinol were not apparent until the second hour of the trial although a corresponding dose of the (+)-isomer induced hyperphagia within the first hour after injection.

Food intake studies with peripherally and centrally administered N-methyl meptazinol

Animals injected with N-methyl meptazinol (2–10 mg kg^{-1} i.p.; Table 1a) did not eat significantly greater amounts ($P>0.05$) than vehicle-treated controls over the period of test. In addition, intraperitoneal administration of N-methyl meptazinol (2 mg kg^{-1}) did not produce any other obvious effects on behaviour. However, at 10 mg kg^{-1} i.p. there were signs of hind-limb muscle spasms and 'kicking' in two of the six animals in the test group while a 20 mg kg^{-1} i.p. dose of the quaternary analogue of meptazinol produced 100% mortality within 2 min of injection.

Intracerebroventricular injections of N-methyl meptazinol were administered over the dose range 1–100 μg per animal and no overt abnormal behavioural signs were recorded. It was noted that the 10 μg dose caused a significant increase in food consumption at 1 h, 2 h and 4 h although the highest dose (100 μg i.c.v.) did not produce significant hyperphagia until the second hour at which time its effect was comparable to the 10 μg dose (Table 1b).

Food intake studies following combined administration of opioid antagonists with either meptazinol or levorphanol

Naltrexone (1 mg kg^{-1} i.p.) significantly reversed the hyperphagia produced by either meptazinol (2 mg kg^{-1} i.p.; Figure 3a) or levorphanol (1 mg kg^{-1} i.p.; Figure 3b). In both instances there was a total reversal of hyperphagia to the intake levels of vehicle controls within the first and second hour though there appeared to be some recovery from the effects of the

Table 1 Cumulative food intake following (a) peripheral and (b) central administration of N-methyl meptazinol

	Cumulative food intake (g kg^{-1} rat weight)		
	Time (h)		
Treatment	1	2	4
(a) Vehicle (i.p.)	0.77 ± 0.52	0.95 ± 0.54	1.79 ± 1.26
N-methylmeptazinol (2 mg kg^{-1} i.p.)	0.85 ± 0.55	1.56 ± 0.73	2.52 ± 1.37
N-methyl meptazinol (10 mg kg^{-1} i.p.)	0.53 ± 0.43	0.72 ± 0.44	1.00 ± 0.45
(b) Vehicle (i.c.v.)	0.49 ± 0.31	0.57 ± 0.34	0.85 ± 0.37
N-methyl meptazinol (1 μg i.c.v.)	2.39 ± 0.43	2.67 ± 0.53	2.79 ± 0.54
N-methyl meptazinol (10 μg i.c.v.)	3.06 ± 0.87*	3.98 ± 0.89**	4.65 ± 0.44**
N-methyl meptazinol (100 μg i.c.v.)	2.49 ± 0.79	3.96 ± 0.85**	4.12 ± 0.88**

Values are mean ± s.e.mean.
Significant differences from control values are denoted by $*P<0.05$; $**P<0.01$. Treatment groups contained 6 animals.

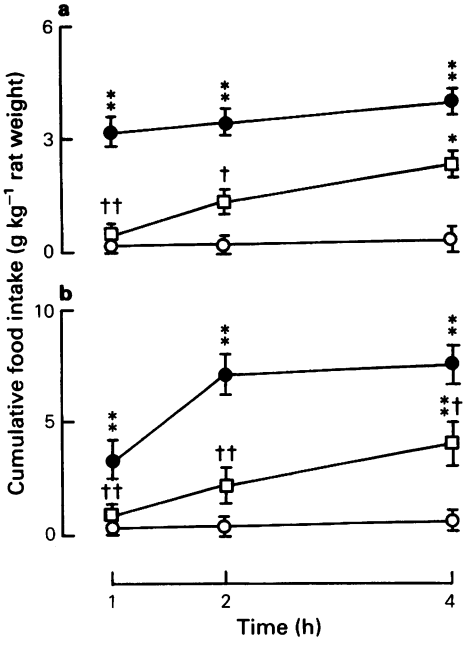

Figure 3 Inhibition of the hyperphagic response to (a) meptazinol (2 mg kg^{-1}) and (b) levorphanol (1 mg kg^{-1}) by naltrexone (1 mg kg^{-1}). Groups of 6 rats were injected i.p. with vehicle (○), meptazinol (a) or levorphanol (b) (●) or meptazinol plus naltrexone (a) or levorphanol plus naltrexone (b) (□). Significant differences from the vehicle-treated controls are indicated by $*P<0.05$; $**P<0.01$ and from the drug-treated controls by $\dagger P<0.05$; $\dagger\dagger P<0.01$. Values are mean; vertical lines represent s.e.mean.

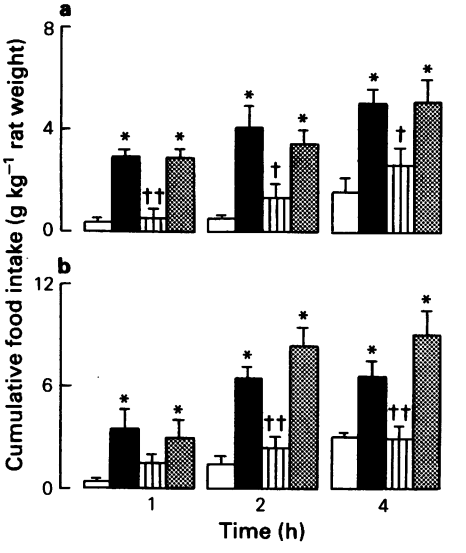

Figure 4 Effects of Mr 1452 (1 mg kg^{-1} i.p.) and its (+)-isomer Mr 1453 (1 mg kg^{-1} i.p.) on the food consumption induced by (a) meptazinol (2 mg kg^{-1} i.p.) and (b) levorphanol (1 mg kg^{-1} i.p.). Treatment groups ($n=6$) were injected: vehicle (open columns), meptazinol or levorphanol (closed columns), meptazinol or levorphanol plus Mr 1452 (vertically-hatched columns), meptazinol or levorphanol plus Mr 1453 (stippled columns). Significant differences from vehicle-treated controls are denoted by $*P<0.01$, and from the drug-treated control group by $\dagger P<0.05$; $\dagger\dagger P<0.01$. Values are mean; vertical lines represent s.e.mean.

opioid antagonist 4 h after administration since the cumulative food intakes were substantially greater than in the vehicle controls.

The increased food intake induced by either meptazinol (2 mg kg^{-1} i.p.) or levorphanol (1 mg kg^{-1} i.p.) was reduced by Mr 1452 (1 mg kg^{-1} i.p.) to levels which did not significantly differ from vehicle controls (Figure 4). However, the suppressive effects of Mr 1452 on levorphanol hyperphagia did not attain levels of significance until the second hour of the trial due to the delayed emergence of the full feeding response to this agonist compound. In contrast, Mr 1453 (1 mg kg^{-1} i.p.) did not modify the hyperphagia produced by meptazinol or levorphanol at any time period after drug treatment.

Naloxonazine (1 mg kg^{-1} i.p.) effectively blocked the food intake induced by hyperphagic doses of both meptazinol (Figure 5a) and levorphanol (Figure 5b) for the full 4 h duration of the test period. Thus, animals injected with meptazinol or levorphanol plus the opioid antagonist ate similar amounts to the vehicle-treated controls.

In contrast to the above findings, although the selective δ-antagonist ICI 154,129 (10 μg per animal i.c.v.) significantly attenuated the hyperphagia induced by meptazinol over the 4 h trial (Figure 6a), it had no apparent effects on levorphanol-induced food intake (Figure 6b). Consequently, animals treated with levorphanol plus ICI 154,129 consumed similar quantities of food to the group given levorphanol alone at the 1, 2 and 4 h readings.

In relation to the above observations concerning antagonism of opioid-induced food intake, we have previously demonstrated that the doses of naltrexone, Mr 1452 and ICI 154,129 used in the present study have no inherent effects on baseline feeding levels during the light phase (Jackson & Sewell, 1984a; 1985c). Furthermore, naloxonazine (1 mg kg^{-1} i.p.) did not appear to possess any intrinsic effects on appetite during the daylight period since the 4 h-

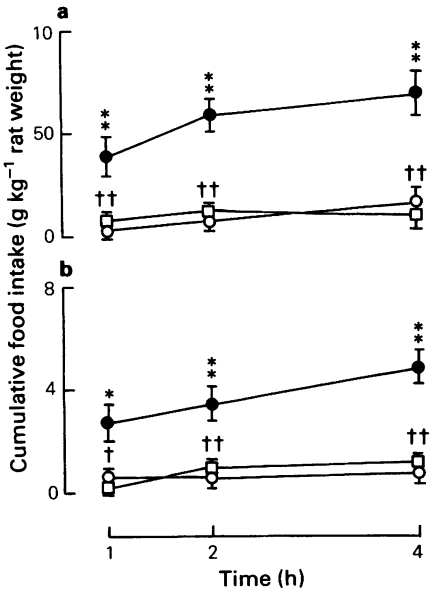

Figure 5 Antagonism of the feeding induced by (a) meptazinol (2 mg kg^{-1}) and (b) levorphanol (1 mg kg^{-1}) by the opioid antagonist naloxonazine (1 mg kg^{-1}). Groups of 6 rats were injected i.p. with vehicle (○), meptazinol (a) or levorphanol (b) (●) or meptazinol plus naloxonazine (a) or levorphanol plus naloxonazine (b) □). Significant differences from vehicle-treated controls are indicated by $*P<0.05$; $**P<0.01$ and from the drug-treated controls by $\dagger P<0.05$; $\dagger\dagger P<0.01$. Values are mean; vertical lines represent s.e.mean.

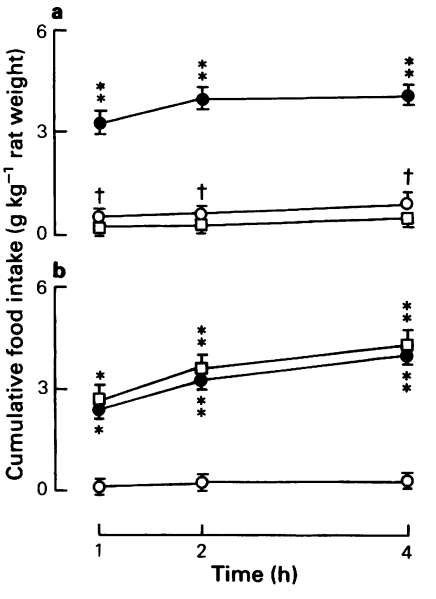

Figure 6 Effect of ICI 154,129 (10 μg i.c.v.) on the food intake induced by (a) meptazinol (2 mg kg^{-1} i.p.) and (b) levorphanol (1 mg kg^{-1} i.p.). Rats were treated with vehicle (○), meptazinol or levorphanol (●), meptazinol plus the δ-antagonist (a) or levorphanol plus the δ-antagonist (b) (□). Significant differences from the control values are indicated by $*P<0.05$; $**P<0.01$. Significant antagonism of the meptazinol response by ICI 154,129 is indicated by $\dagger P<0.01$. Treatment groups contained 6 animals. Values are mean; vertical lines represent s.e.mean.

cumulative food intake of rats treated with this dose of antagonist was 0.34 ± 0.09 g kg^{-1} rat weight compared to a corresponding control value of 0.29 ± 0.10.

Discussion

Meptazinol and levorphanol both stimulated daytime free feeding. Previous work has demonstrated that even more highly specific μ-opioid agonists such as [D-Ala^2, NMe-Phe^4, Gly-ol]-enkephalin also display similar hyperphagia (Jackson & Sewell, 1985d). Moreover, the μ-mixed agonist-antagonist levallorphan (Wood, 1982) also initiates food intake during the day (Jackson & Sewell, 1986) which is consistent with the concept of μ-mediated hyperphagia.

The finding that levorphanol was apparently devoid of hyperphagic activity at the highest dose may be ascribed to the onset of its depressant effect. This does not explain the lack of effect of meptazinol at higher doses since there was no sedation during the period of recorded food intake. It is relevant however that meptazinol possesses opioid antagonist actions, particularly at higher doses when it may precipitate withdrawal signs in morphine-dependent monkeys (Stephens *et al.*, 1978) or rats (Goode & White, 1971). Opioid antagonists also inhibit food intake in some experimental models (see Morley *et al.*, 1983; Sanger, 1983) so it is tenable that the lack of high-dose meptazinol hyperphagia in this study is the functional product of inherent opioid agonist and antagonist properties.

Both enantiomers of meptazinol produced analogous increases in food intake which is unexpected because the hyperphagic element of another opioid agonist, tifluadom, is specific to its opioid-selective (+)-enantiomer (Jackson & Sewell, 1984a). However, both meptazinol enantiomers are opioid agonists on μ-receptors in the guinea-pig ileum (Duchesne *et al.*, 1984) and both are equipotent in analgesic tests

(Goode & White, 1971) which illustrates their agonist properties and corroborates their matching hyperphagic effects in this study.

N-methyl meptazinol produced an increase in food consumption after intracerebroventricular but not peripheral administration. Thermoregulatory effects of this compound also emerge only after central injection (Ben-Sreti *et al.*, 1985). Thus, it is postulated that these dual feeding and temperature responses are mediated centrally because it is widely assumed that polar quaternarized opioid molecules do not readily cross the blood-brain barrier. However, other factors such as differences in receptor affinity exist between some opioids and their quaternary analogues (Brown & Goldberg, 1985) and this may account for our findings. The peripheral toxic effects of N-methyl meptazinol did not appear until higher doses than those displaying hyperphagia to the tertiary form of meptazinol. Therefore it can be argued that there was no masking of potential hyperphagia via peripheral toxicity in the case of the quaternary analogue. Furthermore, the central mediation of meptazinol hyperphagia may be reconciled with other supraspinal effects since transection at the spinal level completely eliminates the antinociception induced by meptazinol in the tail-flick test (Spiegal & Pasternak, 1984).

Meptazinol and levorphanol stimulation of food intake was effectively attenuated by the opioid antagonists naltrexone and (−)-Mr 1452. In contrast, the (+)-benzomorphan enantiomer, Mr 1453, which is not only inactive as an opioid antagonist but also ineffective in reducing food intake in deprived rats (Sanger *et al.*, 1981), did not suppress either meptazinol or levorphanol-induced food consumption. These findings confirm the involvement of opioid receptors in meptazinol and levorphanol-hyperphagia and establish the stereoselective reversibility of these ingestive responses by opioid antagonists.

Naloxonazine is a long-lasting selective inhibitor of high affinity [^{3}H]-dihydromorphine binding (μ_1) sites in brain homogenates (Hahn & Pasternak, 1982). Similarly, meptazinol displaces ^{3}H-opioid ligand binding and though it is not potent in this respect, the multiphasic nature of full competition curves suggests that it also has higher affinity at the μ_1-designated site (Spiegel & Pasternak, 1984). Moreover, in pharmacological studies the antinociceptive action of meptazinol is clearly antagonized by naloxonazine in rats and mice (Spiegel & Pasternak, 1984). These findings are therefore consistent with our data that meptazinol hyperphagia is reversed by naloxonazine.

On the basis that naloxonazine reduces opioid antinociception but not respiratory depression (Ling *et al.*, 1985) it has been implied tha there are different receptor mechanisms for these actions, there being an involvement of μ_1-sites in opioid analgesia but not in the latter effect. Furthermore, comparison of the activity of morphine, metkephamid and [D-Ala^2-D-Leu^5]-enkephalin (DADL) has indicated a role for μ_2 rather than δ systems in respiratory depression (μ_2 referring to the low affinity sites for morphine described in receptor binding studies; Wolozin & Pasternak, 1981). In light of this suggestion it is pertinent that meptazinol itself does not possess substantial respiratory depressant activity (Goode *et al.*, 1979; Spiegal & Pasternak, 1984; Cowlrick & Shepperson, 1985) and since, like levorphanol it induces naloxonazine-reversible hyperphagia, it could be hypothesized that its effects on food intake involve a μ_1 mechanism which is common to levorphanol. Moreover, when given intravenously at higher doses than those currently employed, naloxonazine reduces free-feeding and food-deprivation induced ingestive behaviour in its own right and this again is thought to be mediated through μ_1-sites (Simone *et al.*, 1985).

Endogenous enkephalins have been implicated in the regulation of appetite after reports that central injections of enzyme-resistant enkephalin analogues increase food consumption in freely-feeding rats (McLean & Hoebel, 1980; Tepperman *et al.*, 1981; Tepperman & Hirst, 1983; Jackson & Sewel, 1985b) though inhibitors of enkephalin enzyme degradation do not substantially modify food intake (Jackson & Sewell, 1985e). ICI 154,129 has been reported to act as a selective antagonist at δ-opioid receptors in both *in vitro* and *in vivo* studies (Gormley *et al.*, 1982; Shaw *et al.*, 1982). It is therefore relevant that this δ-antagonist and its analogue ICI 174,864 both decrease nocturnal food intake in non-deprived rats and this is further evidence in favour of a modulatory role for an enkephalinergic/δ-receptor system in feeding behaviour (Jackson & Sewell, 1985b).

We have now shown that a low dose of ICI 154,129 suppresses meptazinol- but not levorphanol-induced food intake. Furthermore, the same dose of ICI 154,129 selectively antagonizes the hyperphagia induced by DADL but not that induced by μ- and κ-agonists (Jackson & Sewell, 1984b).

In conclusion, meptazinol increases food intake through central μ-opioid receptors in a stereospecifically reversible manner. Additionally, these appetitive effects may also involve either indirect and/or direct δ-receptor mechanisms and in this respect meptazinol hyperphagia differs from that of the traditional μ-agonist levorphanol. It is also noteworthy that in other *in vivo* experiments, naloxonazine is active not only at μ- but also at δ-receptor sites in the central nervous system (Dray & Nunan, 1984) and this substantiates our findings regarding meptazinol hyperphagia and its suppression by both ICI 154,129 and naloxonazine.

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