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Short communication

INHIBITION OF "WET SHAKES" DURING MORPHINE ABSTINENCE BY AN ANTAGONIST OF OPIATE ANALGESIA

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An antagonist of morphine analgesia, N-cyclopropylmethylnorazidomorphine (CAM) inhibited the "wet shakes" appearing during spontaneous or nalorphine-precipitated morphine abstinence. CAM inhibited the pinna reflex more strongly than did morphine and selectively antagonized quipazine-induced head twitches; its inhibition of head twitches induced by 5-hydroxytryptophan or LSD seemed unspecific. The results suggest that the opiate receptors involved in the inhibition of some symptoms of morphine abstinence and of the pinna reflex differ from those involved in opiate analgesia.

"Wet shake" and head twitch inhibition
N-Cyclopropylmethylnorazidomorphine
Morphine abstinence syndrome
Drug-induced head twitches
Pinna reflex

1. Introduction

A dissociation of beneficial and habit-forming properties of opiates would be possible if different kinds of opiate receptors were involved in these two groups of actions of morphine and morphine-like compounds. The existence of more than one kind of opiate receptor has been postulated by Martin et al. (1976) and Knoll (1977) and Knoll et al. (1977). In the latter two papers it was proposed that there exist two kinds of opiate receptors, affected similarly by morphine, but differently by semisynthetic morphine derivatives, N-substituted azidomorphines. One of these compounds, N-cyclopropylmethylnorazidomorphine (CAM), was a particularly potent opiate agonist in some tests (e.g. isolated guinea pig ileum strip and mouse vas deferens preparations, inhibition of intestinal propulsion), while it strongly inhibited the analgesic action of morphine, as measured in four different tests. In this respect CAM was 2—4 times more potent than naloxone. CAM also antagonized the antitussive action of morphine and fentanyl-induced catatonia (Knoll, 1977; Knoll et al., 1977). Knoll and coworkers assumed that the actions of morphine mimicked by CAM were mediated through opiate A receptors, while those antagonized by CAM were mediated through opiate B-receptors. As it appeared that favourable actions of opiates were due to the stimulation of B receptors, it seemed interesting to find out whether A or B opiate receptors were involved in the phenomenon of opiate dependence. We attempted to do this by testing the effect of CAM on the morphine withdrawal syndrome, measured by the frequency of, so called, "wet shakes" (Martin et al., 1963).

Morphine also inhibits the pinna reflex (Corne et al., 1963) and the head twitches produced by compounds believed to stimulate serotonin receptors (Corne et al., 1963; Przegaliński et al., 1977). Therefore, we compared the action of morphine and CAM on the pinna reflex and the head twitches induced by an intraventricular injection of D,L-5-hydroxy-

tryptophan (5-HTP) or systemic administration of lysergide (LSD) or quipazine.

2. Materials and methods

Male Wistar rats, 160—220 g, were used throughout the experiment. The animals employed for the withdrawal studies were made tolerant to morphine by daily intraperitoneal injections (2/day) of increasing doses of morphine hydrochloride (Polfa), given according to the schedule of Bucket (1964) (from 40 mg/kg/day, increasing the dosage by 80 mg/kg/day) for 8 days. On the 9th day spontaneously appearing "wet shakes" were counted for 30 min, beginning 19.5 h after the last morphine injection (300 mg/kg). Afterwards, the withdrawal syndrome was augmented by an injection of nalorphine hydrochloride (Chinoin), 10 mg/kg i.p., and the "wet shakes" were counted for the next 90 min. The details of the injection procedure were published previously (Vetulani and Bednarczyk, 1977).

Rats used for studies with 5-HTP were prepared surgically, under light ether anesthesia, a day before receiving a freehand intraventricular injection of 40 μl of saline or 0.5 mg of 5-hydroxytryptophan (Sigma) dissolved in saline; the technique used has been described previously (Vetulani et al., 1972).

Lysergide hydrobromide (Spofa), quipazine maleate (courtesy of Miles Laboratories), N-cyclopropylmethylnorazidomorphine (CAM; gift of Professor J. Knoll of the Semmelweis University of Medicine, Budapest) and other drugs were given in a volume of 4 ml/kg i.p. Morphine was dissolved in distilled water, CAM in 0.005 N HCl, other drugs in saline solution. The pinna reflex was evoked by touching the external meatus of the ear with a plastic hair.

Morphine and CAM were given 30 min before the test (with the exception of the test for spontaneous morphine withdrawal, when counting of "wet shakes" was begun immediately after injection of CAM).

The ID_{50} of morphine and CAM in experiments other than those on the pinna reflex represents a median dose reducing by half the number of head twitches or "wet shakes" recorded throughout the observation period. As regards the pinna reflex, the ID_{50} values were calculated on the basis of the yes-or-no response. The values were calculated using the formulae of Litchfield and Wilcoxon (1949).

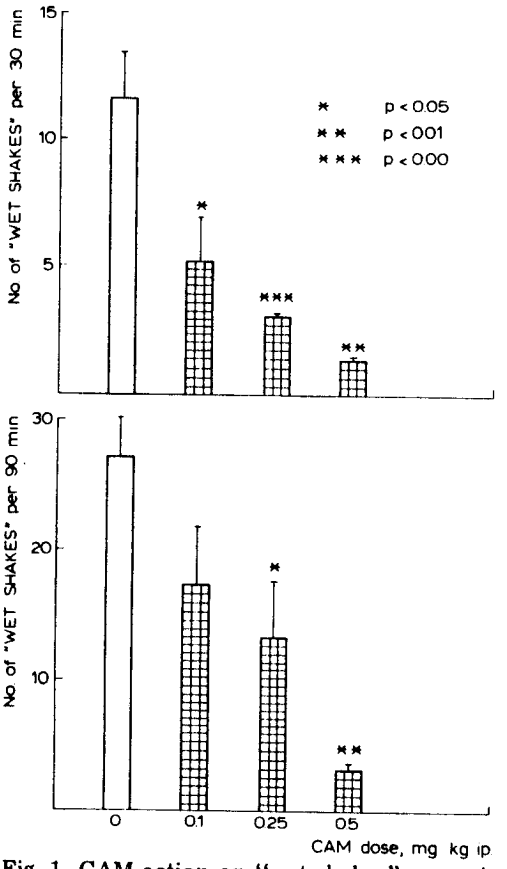

Fig. 1. CAM action on "wet shakes" appearing spontaneously 19.5 h after the last dose of morphine (300 mg/kg i.p.) in rats receiving increasing doses of morphine for 8 days (upper panel), and on "wet shakes" potentiated by nalorphine, 10 mg/kg i.p., injected to the same rats 30 min later (lower panel). CAM was given immediately before the first observation period (30 min before nalorphine). Each bar represents the mean (+ S.E.M.) of 6—10 results. P values refer to differences in the number of shakes in CAM-treated rats compared with animals receiving saline (t-test).

TABLE 1

Inhibition by morphine and N-cyclopropylmethylnorazidomorphine (CAM) of pinna reflex and head twitches induced by drugs.

The opiates were given i.p. × 30 min before the treatment inducing head twitches. The head twitches were recorded throughout the observation period, beginning immediately after the treatment. ID values were calculated (Litchfield and Wilcoxon, 1949) from graded responses (drug-induced head twitches) or quantal responses (pinna reflex).

Treatment inducing head twitches	Observation period (min)	ID_{50} (5% confidence limits) (mg/kg, i.p.)		(ID_{50} morphine)/(ID_{50} CAM)
		Morphine	CAM	
Pinna stimulation	Immediate response	9.30 (7.70—11.30)	0.94 (0.59—1.49)	9.9
5-HTP, 0.5 mg/rat, i.ventr.	90	8.75 (5.93—12.89)	0.69 (0.35—1.34)	12.7
LSD, 0.1 mg/kg, i.p.	15	1.38 (0.95—1.99)	0.54 (0.39—0.74)	2.6
Quipazine, 5 mg/kg, i.p.	40	3.04 (2.35—3.93)	0.003 (0.0006—0.0018)	894.1

3. Results

CAM inhibited, in a dose-dependent way, the development of body shakes during spontaneous and precipitated morphine withdrawal (fig. 1), the ID_{50} values being respectively 87 (28—270) and 178 (83—379) μg/kg. The inhibitory action of CAM may be considered specific, as these doses were approximately 5—11 times lower than the doses inhibiting the pinna reflex (table 1).

CAM inhibited the pinna reflex, being in this respect about 10 times more potent than morphine. The drug was also very potent in inhibiting the head twitches produced by quipazine. However, the ID_{50} doses of CAM with respect to the head twitches brought about by 5-HTP or LSD were within the range of doses inhibiting the pinna reflex (table 1).

4. Discussion

CAM antagonized the "wet shakes" appearing in the course of morphine withdrawal specifically: the antagonism was not due to either an inhibitory action on the pinna reflex, or to any possible specific antiserotonin effect (in fact our previous results (Vetulani and Bednarczyk, 1977) indicated that serotonin receptor blocking agents did not affect the morphine withdrawal syndrome). Most probably, the inhibitory effect of CAM was a result of its agonistic action on opiate receptors. This fact indicates that opiate A receptors are involved in the phenomenon of "wet shake", one of the abstinence symptoms in rats dependent on opiates. As the analgesic and antitussive actions of opiates result from stimulation of opiate B receptors (Knoll, 1977; Knoll et al., 1977), it seems that different types of opiate receptors are involved in beneficial effects of morphine-like drugs, and still different ones in the effects most severely limiting the medical use of opiates and causing the grave social problem of opiate addiction.

In fact, the earlier papers of Knoll (1973) and Knoll et al. (1974a, b) reported that some azidomorphines were very potent analgesic and antitussive agents, with negligible capacity to produce constipation and induce drug dependence. These azidomorphines now appear to be the opiates having a much higher affinity to opiate B than to opiate A receptors.

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