EFFECT OF RESERPINISATION ON POTENTIATION OF MORPHINE ANALGESIA BY EPHEDRINE IN RATS

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Summary: Pain thresholds were determined in the rats to test the analgesic effect of drugs. ED_{50} of morphine alone was 6.607 *mg/kg*. Simultaneous administration of ephedrine reduced the analgesic ED_{50} of morphine to 4.898 *mg/kg*. Reserpinisation antagonised the analgesic activity of morphine. But ephedrine was found to potentiate morphine analgesia, even in reserpinised rats.

Key words: morphine analgesia potentiation by ephedrine antagonism by reserpine

INTRODUCTION

Amphetamines are actively analgesic (4,5) and also potentiate addictive analgesics (1,6). Reserpine and tetrabenazine, which deplete brain catecholamines have been reported to antagonise morphine analgesia (2,8,9). Ephedrine, a sympathomimetic agent, which is structurally and functionally related to amphetamine was chosen for the present study to observe the effect on morphine analgesia in normal and reserpinised rats.

MATERIALS AND METHODS

Fifty albino rats of either sex weighing 90 to 130 *g* were selected. Bianchi and Franceschini's method (3) was used to produce pain. An artery clip, with its tips sheathed in rubber tubing, was applied to the root of the tail of a rat. Rats making continuous efforts to bite and dislodge the clip within 15 sec were given the drug. Animals not trying to remove the clip within 45 sec were considered to show "complete analgesia".

The rats were divided into 5 groups of 10 each. All the drugs were injected intraperitoneally. The doses of the drugs were so adjusted that each animal received the drug in a fixed volume of 0.5 *ml* of distilled water/ 100 *g* of body weight.

The following drugs were used: morphine sulphate (4,5,6,7 and 8 *mg/kg*) given 30 min before analgesic test, ephedrineh ydrochloride (30 *mg/kg*) given 30 min before analgesic test, and reserpine injection (5 *mg/kg*) given 24 hr before analgesic test. The doses are expressed in terms of salts.

Each group received the same dose of morphine throughout the experiment. Analgesia was always tested 30 min after injecting morphine. Analgesic ED_{50} was obtained by the log

dose-probit graphical method of Miller and Tainter (7). One week's interval was maintained between two sets of observations on the same group of animals.

A dose of ephedrine which increased the spontaneous motor activity (SMA) by the technique of Vad *et al.* (11) but was devoid of analgesic activity was chosen for the present work. Increase in SMA occured 15 min after injection of ephedrine and reached its maximum between 45 min and 60 min after injection of the drug.

The following sets of experiments were conducted :

(i) The analgesic activity of morphine; (ii) of morphine with ephedrine; (iii) of morphine in reserpine pretreated rats; and (iv) of morphine with ephedrine in reserpine pretreated rats.

RESULTS

The results have been summarised in Table I and Fig 1. The analgesic ED_{50} of morphine in these experiments was found to be 6.607 *mg/kg*. Ephedrine significantly

TABLE I: Effect of ephedrine and/or reserpine on morphine analgesia.

Morphine mg/kg	*% rats showing analgesia with morphine*			
	control	*with ephedrine*	*with reserpine*	*with reserpine and ephedrine*
4	10	30	0	20
5	20	50	0	40
6	40	70	0	60
7	60	80	10	80
8	70	90	20	90
ED_{50}	6.607	4.898	>8.0	5.495

($P<0.02$) reduced the analgesic ED_{50} of morphine to 4.898 *mg/kg*. Reserpine produced sedation and drowsiness and, when given alone, did neither produce analgesia nor hyperalgesia. Reserpine was found to markedly antagonise the analgesic activity of morphine. In reserpinised animals, 8 *mg/kg* of morphine produced analgesic activity only in 20% of animals. Administration of ephedrine and morphine in reserpinised rats antagonised the sedation produced by reserpine. Even in reserpinised rats, ephedrine was found to potentiate morphine analgesia. The analgesic ED_{50} of morphine which was more than 8 *mg/kg* in reserpinised rats was decreased to 5.495 *mg/kg* when ephedrine was also administered.

DISCUSSION

Many attempts have been made to correlate morphine analgesia with brain biogenic amine levels. Various drugs, known to cause changes in the brain contents of noradrenaline and 5-hydroxytryptamine, alter morphine analgesia (2,8,9,10).

Some sympathomimetic drugs are actively analgesic in animals (4,5) and also potentiate analgesia of addictive analgesics (1,6). But the involvement of adrenergic mechanisms in either morphine analgesia or indeed sympathomimetic analgesia has yet to be conclusively proved.

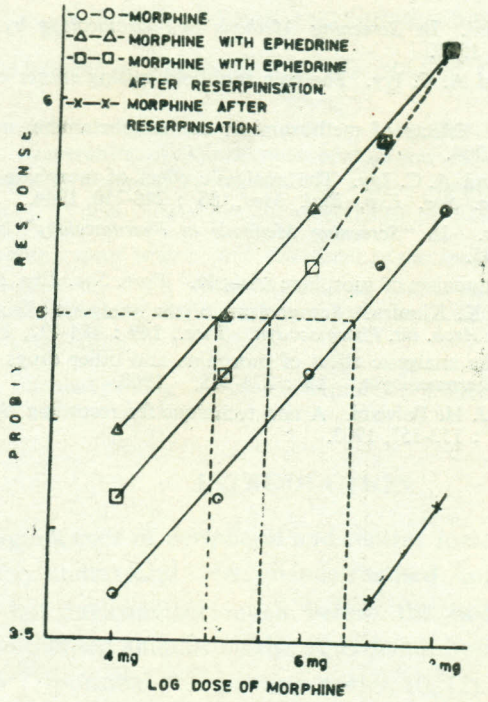

Fig. 1: Modification of morphine analgesia by ephedrine without and with reserpine.

In our study ephedrine, like amphetamine (6), potentiated morphine analgesia. Our finding that morphine analgesia can be antagonised by reserpine, is in accord with the literature reports (8,9). Further, even in reserpinised rats, ephedrine was found to potentiate morphine analgesia. This suggests that ephedrine potentiation of morphine analgesia is only partly and not wholly dependent on its central catecholamine releasing activity. The other action of ephedrine which might be responsible for the potentiation of morphine analgesia, is its direct CNS stimulant activity, which is independent of its adrenergic activity.

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