MORPHINE ANALGESIA AND ITS MODIFICATION BY DRUGS ALTERING SEROTONIN (5-HT) AND DOPAMINE LEVELS IN THE BRAIN

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Summary : Morphine analgesia in mice was significantly potentiated by pretreatment with 5-hydroxytryptophan (5-HTP), especially with higher dose of morphine. Morphine analgesia was antagonised by reserpine. With 1-dopa it was antagonised when the dose of morphine was minimal but with increased dosage of morphine, there was no significant effect.

Key words : Morphine analgesia

INTRODUCTION

Inspite of extensive studies on the mode of action of morphine analgesia and the central neurotransmitters involved, the issue is far from settled. 5-HT, noradrenaline and dopamine have been reported to be involved. The pharmacological agents like 5-hydroxytryptophan (5-HTP), 1-dopa, and reserpine which are known to affect the levels of biogenic amines in the central nervous system have been used for elucidation of the mode of action.

MATERIALS AND METHODS

The analgesic effect of morphine has been studied in mice using Eddy's Hot Plate, i.e. using thermal stimuli (3). The increase in the reaction time after morphine (with or without pretreatment) i.e. graded response method has been determined.

When the temperature of the hot plate was maintained at 55°C, each mouse was dropped into the chamber of the hot plate and the time taken for it to lick its front paws was noted. This reading was taken as the normal reaction time. Each mouse was subsequently injected with morphine and after 30 minutes the reaction time was similarly noted. Graded doses of morphine were used as shown below.

In the same manner, each group of mice was observed for normal reaction time, the reaction time after pre-treatment with each drug and again the reaction time 30 minutes after the combined effect with morphine in three graded doses.

Morphine was used in 3 different doses.

2.5 *mg/kg* body weight, 5.0 *mg/kg* body weight and 7.5 *mg/kg* body weight.

Doses of other drugs used :—

5-HTP 10 *mg/kg* 60 minutes prior, 1-dopa 20 *mg/kg* 30 minutes prior and reserpine 5 *mg/kg* 24 hours prior.

All doses were given by interaperitoneal route.

RESULTS AND DISCUSSION

5-HT and dopamine do not cross blood brain barrier. On the other hand 5-HTP and 1-dopa, the precursors of 5-HT and dopamine respectively cross the blood brain barrier and can effectively raise the concentration of these in the central nervous system. 5-HTP alone produced analgesia and significantly potentiated the effects of morphine, (Table I). The results are similar to those reported by Bhattacharya *et al.* (1).

TABLE I : Effect of morphine alone and in combination with drugs in mice.

Drugs & doses intraperitoneal	*Reaction time*		*Net increase after pre-treatment*	*Reaction time after morphine*	*Net increase*	*(±SE)*	*P value versus morphine*
	Before pretreatment	*After pre-treatment*					
Morphine 2.5 *mg/kg*	3.7 (30)			5.9	2.2	±0.18	<0.001
Morphine 5.0 *mg/kg*	2.8 (30)			5.3	2.5	±0.36	<0.001
Morphine 7.5 *mg/kg*	3.2 (30)			6.7	3.5	±0.26	<0.001
5-HTP 10 *mg/kg*	3.6 (20)	4.7	1.1				
5 HTP+Morphine 2.5 *mg*	3.6 (20)	4.7	1.1	6.9	2.2	±0.67	<0.01
5 HTP+Morphine 5.0 *mg*	2.2 (20)	5.1	2.9	13.6	8.5	±0.4	<0.001
5 HTP+Morphine 7.5 *mg*	2.9 (20)	5.1	2.2	35.7	30.6	±0.37	<0.001
1-dopa 20 *mg/kg*	4.5 (20)	7.0	2.5				
1-dopa+Morphine 2.5 *mg*	4.5 (20)	7.0	2.5	6.1	—0.9	±0.9	<0.7
1-dopa+Morphine 5.0 *mg*	4.7 (20)	6.7	2.0	8.4	1.7	±0.7	<0.3
1-dopa+Morphine 7.5 *mg*	3.1 (20)	5.1	2.0	6.9	1.8	±0.5	>0.05
Reserpine 5 *mg/kg*	3.0 (20)	3.1	0.1				
Reserpine+ Morphine 2.5 *mg*	3.0 (20)	3.1	0.1	5.1	2.0	±1.1	<0.1
Reserpine+ Morphine 5.0 *mg*	3.2 (20)	3.1	—0.1	5.6	2.4	±0.33	<0.01
Reserpine+ Morphine 7.5 *mg*	3.1 (20)	3.2	0.1	5.7	2.5	±0.26	<0.01

Number of mice used for each dose is shown in parentheses.

1-dopa pretreatment itself produced some analgesic effect but did not potentiate morphine analgesia rather it had indifferent effect. Bhattacharya *et al.* (loc cit) reported absence of potentiation of analgesia by use of 1-dopa. With a 5 *mg* dose of reserpine given 24 hours prior, no change in the reaction time was seen by reserpine alone. But observing the subsequent analgesic effects of morphine, it was apparent that the analgesia was significantly antagonised even with an increased dose of morphine, (Table I). Pletscher *et al.* (6) showed that reserpine reduced the level of endogenous 5-HT. Holzbauer and Vogt (4) showed that reserpine was also capable of releasing initially amines from their stores in the brain (subsequent depletion). The reduced 5-HT level by reserpine may thus explain its antagonistic effects on morphine analgesia. Similar findings have been reported by Bhattacharya *et al.* (loc cit), Bapat *et al.* (2), Schneider (7) and Tagaki *et al.* (8). Tenen (9) found that the analgesic effect of morphine was antagonised by p-chlorophenylalanine(P.C.P.A.) which is a 5-HT depletor. This is in consonance with our results which show that 5-HT potentiates morphine analgesia.

Since morphine analgesia was significantly potentiated by 5-HTP, antagonised by reserpine and was not affected by 1-dopa, it is reasonable to suggest that morphine analgesia is mediated through 5-HT receptors in the central nervous system.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the financial aid given by Armed Forces Medical Research Committee. The authors are grateful to Roche Products (Bombay) for a free gift of 1-dopa.

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