

## EFFECTS OF MORPHINE, BUPRENORPHINE, PENTAZOCINE AND NALORPHINE ON ACQUISITION AND EXTINCTION OF ACTIVE AVOIDANCE RESPONSES IN RATS

N. SAHA, H. DATTA\* AND P. L. SHARMA

*Department of Pharmacology,  
Postgraduate Institute of Medical Education and Research,  
Chandigarh - 160 012*

( Received on April 25, 1990 )

**Abstract :** The effects of subcutaneous administration of morphine, buprenorphine, pentazocine and nalorphine were studied at two dose levels in rats (low dose  $\times$  10 and high dose  $\times$  20 of equivalent human dose) on the performance of active avoidance responses using a shuttle box. Pretraining injections of both doses of pentazocine and low dose nalorphine impaired acquisition on day 1 and day 2. Morphine and buprenorphine (at both dose levels) and high dose nalorphine did not affect the acquisition process. Post-training administration of morphine (high dose) and buprenorphine (both doses) delayed extinction of active avoidance responses. Low dose of morphine, high dose of pentazocine and both doses of nalorphine did not appreciably affect the extinction process. Mu opioid receptor agonists probably act as reinforcers to facilitate memory.

**Key words :** morphine                      buprenorphine                      pentazocine                      nalorphine  
active avoidance conditioning                      acquisition                      extinction                      rats

### INTRODUCTION

The possibility that the opioid peptides are involved in learning and memory has generated a lot of discussion and a number of studies in animals. Peripheral administration of low doses of opioid peptides has been shown to influence acquisition of new responses (1), extinction of previously learned responses (2), memory consolidation (3) and retrieval (4).

Results obtained in study of the influence of morphine on learning and memory have been conflicting. While relatively high doses of morphine improve retention of a one trial passive-avoidance situation (5,6), others found retention to be impaired (7,8).

Studies using opiate antagonists, have more uniform findings. Post-training administration of naloxone facilitated memory retention (9) while pretraining administration enhanced performance during acquisition (10). Post-training administration of naloxone and diprenorphine have

been reported to significantly improve spatial memory (11). Very few reports are available that describe the effects of mixed agonist-antagonist opiates on memory.

The present experiments were carried out to examine the effects of morphine and opiate mixed agonist-antagonists buprenorphine, pentazocine and nalorphine on acquisition and extinction of active avoidance responses.

### METHODS

Female (Wistar) rats 140-220 g and 90-120 days old were housed in groups of 6 and were maintained on standard laboratory chow and tap water, under 12-hours light and dark cycles.

A jumping-box was employed using a 5 sec buzzer as conditioning stimulus and buzzer plus an electric shock (1 mA) delivered to the grid on the floor of the cage for 5 sec as an unconditioned stimulus.

\*Corresponding Author

Rats were trained to avoid the foot shock by jumping from one compartment to another of the jumping box on hearing the buzzer (positive response). This was achieved by giving 10 trials with 30 sec intertrial interval between 8.00 and 12.00 hrs every day for 3 days. Effects of drugs on conditioned avoidance response (CAR) was noted 30 min after administration of the drugs on the 4th day. In each group the number of positive responders was noted and the mean number of avoidances per animal was calculated.

To study the effect on acquisition of CAR, the drugs were administered daily 30 min before the testing which was conducted each day for 3 days (12). Each animal was given 10 trials a day with a 30 sec inter-trial interval.

To study drug effect on extinction, the same procedure was followed except that the shock was omitted and the rats were subjected to 10 trials (with the usual inter-trial interval of 30 sec) on the 4th day, after 3 days of training. Rats that made seven or more avoidance responses during the first 10 extinction trials only were selected and were treated with saline or drug immediately and continued in the experiment for the extinction trials at 0.5, 2.5, 4.5, 6.5 and 8.5 hr after drug treatment (13). The study was carried out at a fixed time between 8.00 and 12.00 hrs.

Morphine, buprenorphine, pentazocine and nalorphine were administered (sc) at 10 times and 20 times of their equivalent human dose, on the nape of neck (volume 1 ml/kg). Control rats received normal saline only. Comparisons among groups in both acquisition and extinction tests were made by group analysis of variance followed by method of least significant difference.

## RESULTS

Figure 1 shows the effects of morphine and opioid agonist-antagonists on the CAR in rats. At the selected doses, none of the drugs had any major effect, when compared with the control group.

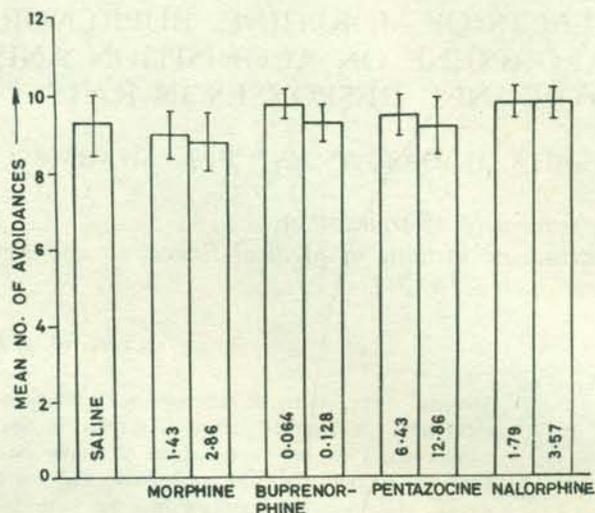


Fig: 1 Effects of various doses (mg/kg, in bars) of morphine buprenorphine, pentazocine and nalorphine on conditioned avoidance response, 30 min after their administration (sc) in trained rats.

Pentazocine (6.43 mg/kg and 12.86 mg/kg) and nalorphine (1.79 mg/kg) significantly reduced the initial acquisition process on day 1 and day 2 of the trial (Table I). However, on day 3, the values obtained in these groups were comparable with the saline treated group. Nalorphine at the higher dose (3.57 mg/kg), however, did not affect the

TABLE I: Effects of administration of morphine, buprenorphine, pentazocine and nalorphine on acquisition of active avoidance response in rats

Drug	Dose	No. of avoidances (Mean $\pm$ SD)		
		Day 1	Day 2	Day 3
Control	-	5.67 $\pm$ 1.97	7.67 $\pm$ 1.36	8.17 $\pm$ 1.72
Morphine	1.43	5.83 $\pm$ 2.22	7.80 $\pm$ 1.17	8.67 $\pm$ 1.20
	2.86	4.83 $\pm$ 0.98	7.67 $\pm$ 1.21	9.00 $\pm$ 0.89
Buprenorphine	0.064	5.00 $\pm$ 2.61	6.33 $\pm$ 2.8	8.00 $\pm$ 2.0
	0.128	6.00 $\pm$ 2.1	8.00 $\pm$ 0.63	8.83 $\pm$ 0.75
Pentazocine	6.43	2.00 $\pm$ 1.79*	4.00 $\pm$ 1.1*	8.17 $\pm$ 1.17
	12.86	1.83 $\pm$ 1.47*	4.16 $\pm$ 2.31*	8.00 $\pm$ 1.41
Nalorphine	1.79	3.17 $\pm$ 1.72*	5.30 $\pm$ 2.66*	8.00 $\pm$ 1.26
	3.57	3.63 $\pm$ 1.72	8.83 $\pm$ 1.17	9.50 $\pm$ 0.55

\*P < 0.05 in comparison with saline treatment (control) group  
n = 6 in each group.

TABLE II : Effects of administration of morphine, buprenorphine, pentazocine and nalorphine on extinction of active avoidance responses.

Drug	Dose	No. of avoidances (Mean $\pm$ SD)					
		0 hr.	0.5 hr	2.5 hr	4.5 hr	6.5 hr	8.5 hr
Saline		8.67 $\pm$ 1.2	6.33 $\pm$ 2.25	4.83 $\pm$ 0.75	3.00 $\pm$ 1.26	1.50 $\pm$ 0.83	0.33 $\pm$ 0.51
Morphine	1.43	8.17 $\pm$ 1.47	7.00 $\pm$ 1.79	5.83 $\pm$ 2.32	4.83 $\pm$ 2.13	3.33 $\pm$ 1.96	1.83 $\pm$ 1.94
	2.86	9.33 $\pm$ 1.03	8.67 $\pm$ 1.50	8.00 $\pm$ 1.67*	7.00 $\pm$ 2.40*	5.67 $\pm$ 2.73*	3.00 $\pm$ 2.60*
Buprenorphine	0.064	8.83 $\pm$ 1.17	8.17 $\pm$ 2.70	7.17 $\pm$ 2.85	7.83 $\pm$ 2.56*	6.50 $\pm$ 2.07*	2.67 $\pm$ 1.05*
	0.128	8.33 $\pm$ 1.36	7.33 $\pm$ 2.87	6.50 $\pm$ 2.50	7.33 $\pm$ 2.06*	5.50 $\pm$ 1.87*	2.83 $\pm$ 1.60*
Pentazocine	6.43	7.50 $\pm$ 0.84	4.33 $\pm$ 1.97	2.17 $\pm$ 1.7*	0.50 $\pm$ 0.54*	0.33 $\pm$ 0.51	0.17 $\pm$ 0.41
	12.86	8.40 $\pm$ 1.22	6.67 $\pm$ 2.25	2.50 $\pm$ 2.4	1.67 $\pm$ 1.5	1.17 $\pm$ 0.75	0.67 $\pm$ 0.82
Nalorphine	1.79	8.33 $\pm$ 0.82	5.83 $\pm$ 2.22	3.67 $\pm$ 2.73	2.50 $\pm$ 1.9	1.83 $\pm$ 1.17	1.00 $\pm$ 1.27
	3.57	8.83 $\pm$ 1.33	6.33 $\pm$ 2.50	3.83 $\pm$ 2.00	2.83 $\pm$ 2.4	1.67 $\pm$ 1.21	0.67 $\pm$ 0.82

\*p <0.05 in comparison with control (saline) group.

n = 6 in each group.

learning process, Morphine (1.43 and 2.86 mg/kg) and buprenorphine (0.064 and 0.128 mg/kg) did not influence the acquisition of CAR on any of the 3 days.

Morphine (2.86 mg/kg) and buprenorphine (0.064 and 0.128 mg/kg) significantly delayed extinction. Though the drugs had little effect at 0.5 hr, morphine (2.86 mg/kg) produced significantly different avoidance values after 2.5 hr and buprenorphine after 4.5 hr and the difference persisted till the last trial.

Pentazocine (6.43 mg/kg) enhanced extinction at 2.5 and 4.5 hr only but not later. Low dose morphine (1.43 mg/kg), high dose pentazocine (12.86 mg/kg) and nalorphine (1.79 and 3.57 mg/kg) did not affect the extinction process.

## DISCUSSION

In the present study, neither dose of morphine influenced the acquisition of CAR. Post-training administration of 2.86 mg/kg of morphine as well as buprenorphine (0.064 and 0.128 mg/kg) significantly delayed extinction. The finding is in contrast to the observations made by Izquierdo (8), who reported that low post-trial doses of morphine impaired retention of a shuttle-box avoidance task. However, post-trial administration

of morphine has been shown to improve retention of one trial passive avoidance situation (5).

There is paucity of reports on effects of mixed agonist-antagonists on learning and memory. We now report that pentazocine and low doses of nalorphine adversely affected acquisition though not on day 3 and that pentazocine (low dose) enhanced extinction.

Of the pure antagonists, naloxone (0.3 mg/kg) improved performance during acquisition and also enhanced retention. Naloxone at a dose of 0.1 and 3 mg/kg did not influence these parameters in an earlier study (10).

At the selected doses, none of the drugs per se produced any effect on CAR in rats. However, only higher doses of morphine (10 mg/kg) have been reported to disrupt continuous avoidance behaviour in rats (14). Thus, the impaired performance in rats treated with pentazocine and nalorphine (0.179 mg/kg) were not due to acute effects of these drugs on the execution of CAR, but probably due to effects on memory processing.

Various hypotheses have been put forward in an attempt to explain the effects of morphine on memory processing. Izquierdo (8) reported that low doses of morphine inhibit memory and

postulated the existence of opiate-amnesia receptors. It was stated that morphine in low doses, interacts specifically with one type of receptor (probably  $\mu$ ) and these receptors are involved in the process of impaired memory retention. In the present study, morphine and buprenorphine ( $\mu$  receptor partial agonist) delayed extinction and had no effect on acquisition process. This observation is in contradiction to the above postulate.

The other hypothesis (5) states that reinforcers facilitate memory processing. It has been shown that post-trial application of various reinforcers

like food enhances acquisition (15). It has been argued that injections of morphine acted as reinforcers. This theory seems to be more consistent with the results presented in this paper as morphine and buprenorphine delayed extinction though they did not effect acquisition. However, the mechanism of enhanced extinction caused by pentazocine (6.43 mg/kg) is a matter of conjecture. It is possible that the psychotomimetic and dysphoric effects of pentazocine (16) may have acted as a negative reinforcer. However, it is difficult to explain why pentazocine (12.86 mg/kg) and nalorphine having similar dysphoric properties did not influence the extinction.

## REFERENCES

1. Rigter H, Hannan TJ, Messing RB, et al. Enkephalins interfere with acquisition of an active avoidance response. *Life Sci* 1980; 26: 337-345.
2. DeWied D, Kovaes GL, Bohns B, VanRee JM, Greven HM. Neuroleptic activity of the neuroleptic  $\beta$ -LPH 62-77 (des-tyr<sup>1</sup>- $\gamma$ -endorphin; DT $\gamma$ E). *Eur J Pharmacol* 1978; 49: 427-36.
3. Izquierdo I, Paiva ACM, Elisabetsky E. Post-training intraperitoneal administration of leu-enkephalin and beta-endorphin causes retrograde amnesia for two different tasks in rats. *Behav Neural Biol* 1980; 28: 246-50.
4. Izquierdo I. Effect of Bendorphine and naloxone on acquisition, memory and retrieval of shuttle avoidance and habituation learning in rats. *Psychopharmacology* 1980; 69: 111-15.
5. Mondadori C, Waser PG. Facilitation of memory processing by post-trial morphine: possible involvement of reinforcement mechanism? *Psychopharmacology* 1979; 63: 279-300.
6. Staubli U, Huston JP. Avoidance learning enhanced by posttrial morphine injection. *Behav Neural Biol* 1980; 28: 487-90.
7. Castellano C. Dose dependent effects of heroin in memory in two inbred strains of mice. *Psychopharmacology* 1980; 67: 235-39.
8. Izquierdo I. Effect of naloxone and morphine on various forms of memory in the rat: Possible role of endogenous opiate mechanisms in memory consolidation. *Psychopharmacology* 1979; 66: 199-203.
9. Izquierdo I, Graudenz N. Memory facilitation by naloxone is due to release of dopaminergic and  $\beta$ -adrenergic systems from tonic inhibition. *Psychopharmacology* 1980; 67: 265-68.
10. Fulginiti S, Cancela LM. Effect of naloxone and amphetamine on acquisition and memory consolidation of active avoidance responses in rats. *Psychopharmacology* 1983; 79: 45-48.
11. Gallagher M, King RA, Young NB. Opiate antagonists improve spatial memory. *Science* 1983; 221: 975-976.
12. Roy RK, Uppal RP. Neurobehavioral effects of katamine. *Ind J Exp Biol* 1986; 24: 292-95.
13. LeMoal M, Koob GF, Koda LY, et al. Vasopressor receptor antagonist prevent behavioral effects of vasopressin. *Nature* 1981; 291: 491-93.
14. Shannon HE. Stimulation of avoidance behavior by buprenorphine in rats. *Psychopharmacology* 1983; 80: 19-23.
15. Huston JP, Mondadori C. Reinforcement and memory: a model (Proceddigns). *Act Nerv Super* 1977; 19: 17-19.
16. Hamilton RC, Dundee JW, Clark RS, Loan WB, Morrison JD. Studies of drugs given before anesthesia XIII. pentazocine and other opiate antagonists. *Br J Anesth* 1967; 39: 647-56.