Effect of ($\pm$) N allylnormetazocine on one-trial inhibitory avoidance in CD1 mice: Lack of state dependency

CLAUDIO CASTELLANO

Istituto di Psicobiologia e Psicofarmacologia del CNR, Rome, Italy

Intraperitoneal administration of ($\pm$) N allylnormetazocine (SKF 10,047) (5.0 or 10.0 mg/kg of body weight) immediately posttraining in a one-trial inhibitory avoidance task significantly impaired retention of CD1 mice tested 24 h after training. Administration of SKF (5.0 or 10.0 mg/kg) prior to the retention test did not affect the retention performance of the mice given posttraining injections of saline or SKF (5.0 or 10.0 mg/kg). These findings indicate that the amnesic effects of posttraining injections of SKF are not due to induction of state dependency and, thus, are consistent with the view that SKF impairs retention in mice by interfering with memory storage, rather than retrieval, processes.

A number of researchers have studied in the recent years the behavioral effects of ($\pm$) N allylnormetazocine (SKF 10,047) (SKF), an opiate with an affinity for σ opioid receptors in a variety of animal species.

For example, it has been shown that, in the chronic spinal dog, SKF causes mydriasis, tachypnea, tachycardia, and mania, whereas morphine causes miosis, bradycardia, hypothermia, a general depression of nociceptive responses, and indifference to the environmental stimuli (Martin, Eades, Thompson, Huppler, & Gilbert, 1976). It has also been demonstrated that, in the rat, the μ opioid agonist morphine produces analgesia and stimulates locomotor activity, whereas SKF, lacking antinociceptive effects, stimulates locomotor activity and produces psychotomimetic effects (Iwamoto, 1981). Furthermore, impairment of acquisition of brightness discrimination, at doses that also increased movements between trials, have been observed in rats following SKF administration (Tang & Franklin, 1983). More recently, always in the rat, morphine, SKF, and some α agonists (U 50488 and ketocyclazocine) produced similar effects (comparable decreases in rates of responding) under a fixed-consecutive-number (FCN) schedule (Picker, Heise, & Dykstra, 1987). It must be also stressed that, in the same animal species, SKF produced dose-related decreases in accuracy of response rate in a fixed-ratio discrimination (Moerschbaecher, Devia, & Broklehurst, 1988). Moreover, in mice, SKF attenuated the marked suppression of motility (conditioned suppression) of animals placed in the same environment in which they had previously received an electric footshock (Nabeshima, Kamei, &

Kameyama, 1988). Finally, it must be stressed that SKF and phencyclidine (PCP), a potent anesthetic and psychotomimetic drug, exhibit many common pharmacological properties (see K. W. Jones, Bauerle, & DeNoble, 1990). In particular, SKF produces discriminative effects similar to those produced by PCP (Holtzman, 1980; Shannon, 1981) and displaces brain binding of ^3H -PCP (Zukin & Zukin, 1979; Jasinski et al., 1981).

Furthermore, it is likely that the behavioral effects shared by PCP and such opiates as SKF are mediated through nonopiate receptors (see Johnson & S. M. Jones, 1990, for a review). In a recent study, it has been shown that in the rat, the amnesic effect of posttraining SKF is due to its PCP-receptor binding activity (K. W. Jones et al., 1990).

It has recently been reported (Izquierdo, 1984) that the memory-impairing effects exerted by endogenous opioids, such as β endorphin and the enkephalins, can be attenuated by the administration of the same hormones shortly prior to the retention test. These findings have suggested that the retention impairment exerted by these hormones may be a consequence of a drug-induced state dependency. That is, these studies suggest that good retention performance may require a congruence of the animal's hormonal state during testing with that induced following training. On the other hand, it has been shown that the retention impairments induced by morphine (Castellano, 1975) and dynorphin (Introini-Collison, Cahill, Baratti, & McGaugh, 1987) are not due to a drug-induced state dependency (Castellano & McGaugh, 1989; Introini-Collison et al., 1987).

In the present research, the effects of SKF on memory consolidation were studied, and their eventual state dependency was assessed. CD1 mice were trained in a one-trial inhibitory avoidance task; the effects of posttraining administrations of SKF were investigated, and the effects on retention of posttraining SKF administration were com-

I thank Roberta Populin for her skillfull technical assistance. ($\pm$) N allylnormetazocine was kindly provided by the National Institute of Drug Abuse (Rockville, MD). Correspondence should be addressed to Claudio Castellano, Istituto di Psicobiologia e Psicofarmacologia, Via Reno, 1, 00198, Rome, Italy.

pared with those observed in mice treated with SKF both posttraining and prior to the retention test.

METHOD

Subjects

The subjects were 200 male CD1 mice (River Labs, Como, Italy), each weighing approximately 25 g. They were caged in groups of 8, with food and water available ad lib, and maintained on a 12-h light:dark cycle (lights on at 0700 h) at a constant temperature of 21°C for 2 weeks prior to the experiments.

Apparatus and Procedures

The step-through avoidance apparatus, similar to that previously described by Castellano, Pavone, and Puglisi-Allegra (1984), consisted of a 20×20×20 cm Lucite box with black walls and a grid floor. A long platform (12 cm long, 7.5 cm wide) extended from a small door (4×3 cm) in front of the box. The box was placed at the edge of a table with the platform extending out from the table. The inside of the box was dark. A 40-W lamp was positioned above the platform.

On the training trial, the mouse was placed on the platform facing away from the box. When the animal entered the box with all four feet the step-through latency was recorded, the entry was closed with a sliding door, and a footshock (0.7 mA, 1.0 sec, 50 Hz) was delivered. The mouse was then immediately returned to its home cage. For the retention test, 24 h later, the mouse was placed on the platform as in the training session and the step-through latency (maximum of 240 sec) was recorded. In all experiments, each group consisted of 8 mice. ($\pm$) N allylnormetazocine (SKF 10,047) (SKF) was dissolved in saline (0.9% NaCl) and injected i.p. in a volume of 10.0 ml/kg. Control groups received saline.

In the first set of tests, different groups of mice received i.p. injections of saline or SKF (2.5, 5.0, or 10.0 mg/kg) immediately

after training and saline 3 min prior to the retention test 24 h later. To determine whether the effect on subsequent retention varied with the training-treatment interval, additional groups were injected with saline or SKF (10 mg/kg) 120 min posttraining. To assess possible aversive effects of SKF injections, another group of mice did not receive footshock but was injected with SKF (10 mg/kg) immediately posttraining and tested 24 h later. To determine whether SKF affected response latencies at these times following injections, other groups of mice were injected with SKF (10 mg/kg), 30, 10, or 3 min prior to training without receiving footshock.

In the second set of tests, the effect of SKF administered prior to the retention test was examined. The mice were trained on the inhibitory avoidance task and given posttraining injections of either saline or SKF (5.0 or 10.0 mg/kg). Most of the groups were then given saline or SKF (5.0 or 10.0 mg/kg) 3 min prior to the 24-h retention test. Since it is possible that the presumed changes in brain state underlying posttraining state dependency may not be induced within 3 min, other groups received either saline or SKF (10 mg/kg) 10 or 30 min prior to the 24-h retention test.

RESULTS

As shown in Table 1, the retention latencies of the mice given the two higher doses of SKF (5.0 or 10.0 mg/kg) posttraining were significantly lower than were those of the saline controls. Retention was not affected by SKF (10.0 mg/kg) administered 120 min posttraining. Furthermore, in the mice not given footshock on the training trial the test latencies of the mice given posttraining SKF (10 mg/kg) did not differ from those of the saline controls. Finally, SKF did not affect initial step-through response latencies when administered 30, 10, or 3 min prior to training.

Table 1
Effect of SKF 10,047 on Step-Through Latencies

Treatment	Median	Interquartile Range
Retention Latencies (sec)		
Immediately Posttraining—3 min Pretest with Saline		
Saline	104.0	70.0–135.0
SKF		
2.5 mg/kg	99.0	75.0–133.0
5.0 mg/kg	51.0	32.0–60.0*
10.0 mg/kg	15.0	9.0–33.5*
Immediately Posttraining—No Footshock		
Saline	8.5	6.0–9.5
SKF		
10.0 mg/kg	8.5	7.5–9.5
120 min Posttraining		
Saline	105.0	75.0–127.0
SKF		
10.0 mg/kg	106.5	72.0–127.5
Initial Step-Through Response Latencies (sec)		
Prior to Training		
Saline		
3 min	6.5	5.5–8.0
10 min	7.0	4.0–9.0
30 min	7.5	5.0–10.0
SKF (10 mg/kg)		
3 min	7.0	5.0–9.5
10 min	6.5	5.0–8.5
30 min	6.5	4.5–9.0

Note— $n = 8$ mice per group. * $p < .002$ versus saline controls (Mann-Whitney U tests).

Table 2
Effect of SKF 10,047 Administered Posttraining and Prior to Retention Test

Treatment		Retention Latencies (sec)	
Posttraining (mg/kg)	Prior Retention Test (mg/kg)	Median	Interquartile Range
Saline	Saline: 3 min	104.0	70.0-135.0
Saline	Saline: 10 min	96.5	63.0-138.0
	Saline: 30 min	110.0	88.0-132.0
Saline	SKF(5): 3 min	106.5	67.5-137.5
Saline	SKF(10): 3 min	110.0	55.0-143.5
Saline	SKF(10): 10 min	106.0	64.5-132.0
Saline	SKF(30): 30 min	111.0	56.5-128.0
SKF(5)	SKF(5): 3 min	47.5	33.0-54.5*
SKF(5)	SKF(10): 3 min	41.5	32.0-52.5*
SKF(10)	SKF(5): 3 min	15.0	7.5-23.5*
SKF(10)	SKF(10): 3 min	22.0	14.5-27.5*
SKF(10)	SKF(10): 10 min	18.5	5.0-22.0*
SKF(10)	SKF(10): 30 min	13.0	9.0-28.5*

Note— $n = 8$ mice per group. * $p < .002$ versus saline, and $p < .002$ versus the group that received saline posttraining and the corresponding SKF dose pretesting (Mann-Whitney U tests).

As shown in Table 2, SKF administered prior to the retention testing did not affect the retention performance of the mice given saline injections posttraining. Furthermore, in all groups given posttraining SKF, the retention latencies of the mice given SKF prior to the retention test were comparable to those of the mice (shown in Table 1) given SKF posttraining and saline prior to the retention test.

DISCUSSION

Some points emerge from the results of the present research: (1) Posttraining administration of ($\pm$) N allyl-normetazocine (SKF 10,047) (SKF) impaired of retention in the CD1 mice; (2) SKF did not affect either response latencies when administered prior to training or retention of the unshocked controls when administered posttraining; (3) SKF did not affect retention when administered 120 min posttraining; and (4) administration of SKF 30, 10, or 3 min prior to the retention test did not attenuate the memory-impairing effect of the posttraining administration of the drug.

It must be considered that the fact that SKF was administered after training 24 h prior to the retention test (as well as the finding that administration of the drug prior to training or retention of the unshocked controls when administered posttraining did not affect the training response latencies) argues against any interpretation suggesting that the effects observed in the present research may be due to nonspecific drug influences on response latencies in this task. Moreover, SKF given prior to retention test had no effect on response latencies, suggesting lack of effect, at the doses used, on retrieval and/or performance. Finally, since SKF did not affect retention when administered 120 min posttraining, it is evident that its effects were time-dependent.

Point 4 above makes it clear that the present findings provide no support for the view that the retention-impairing effect (see Point 1) of posttraining administration of SKF is based on state dependency. On the con-

trary, these findings are consistent with the view that SKF impairs retention by impairing the processes underlying memory storage.

Previous researchers have found, in mice, morphine-induced retrograde amnesia and have shown that this effect was not due to induction of state dependency but to effects on the processes underlying memory storage (Castellano & McGaugh, 1989). Similarly, Introini-Collison et al. (1987) reported that, always in mice, the memory-impairing effects observed with dynorphin were similar to those observed with morphine, as well as with SKF, as in the present research. The evidence suggests that all of these treatments impair retention by interfering with memory storage processes. On the other hand, Izquierdo (1984) reported that the memory-impairing effects of beta endorphin and the enkephalins are reversed by treatment with the same substances prior to the retention test, suggesting the existence of state dependency.

Thus, the results of the present experiments, carried out with SKF 10,047, considered together with those obtained in previous studies with mice injected with morphine or dynorphin, suggest that, in this animal species, the effects of SKF, morphine, and dynorphin may involve physiological mechanisms different from those that are influenced by β endorphin and by the enkephalins.

Since, as has been pointed out, it is likely that the behavioral effects shared by PCP and such opiates as SKF are mediated through nonopiate receptors (see Johnson & S. M. Jones, 1990), further studies to be carried out with PCP will now be necessary to better clarify the present results.

REFERENCES

- CASTELLANO, C. (1975). Effects of morphine and heroin on discrimination learning and consolidation in mice. *Psychopharmacologia*, **42**, 235-242.
- CASTELLANO, C., & MCGAUGH, J. L. (1989). Effect of morphine on one-trial inhibitory avoidance in mice: Lack of state-dependency. *Psychobiology*, **17**, 89-92.
- CASTELLANO, C., PAVONE, F., & PUGLISI-ALLEGRA, S. (1984). Mor-

- phine and memory in DBA/2: Effects of stress and of prior experience. *Behavioural Brain Research*, **11**, 3-10.
- HOLTZMAN, S. G. (1980). Phencyclidine like discriminative effects of opioids in the rat. *Journal of Pharmacology & Experimental Therapeutics*, **214**, 614-619.
- INTROINI-COLLISON, I. B., CAHILL, L., BARATTI, C. M., & MCGAUGH, J. L. (1987). Dynorphin induces task-specific impairment of memory. *Psychobiology*, **15**, 171-174.
- IWAMOTO, I. (1981). Locomotor activity and antinociception after putative mu, kappa and sigma opioid receptor agonists in the rat: Influence of dopaminergic agonists and antagonists. *Journal of Pharmacology & Experimental Therapeutics*, **217**, 451-460.
- IZQUIERDO, I. (1984). Endogenous state-dependency: Memory depends on the relation between the neurohumoral and hormonal states present after training and at the time of testing. In G. Lynch, J. L. McGaugh, & N. M. Weinberger (Eds.), *Neurobiology of learning and memory* (pp. 333-350). New York: Guilford.
- JASINSKI, D. R., SHANNON, H. E., CONE, E. J., VAUPEL, D. B., RISNER, M. E., MCQUINN, R. L., SU, T. P., & PICKWORTH, W. B. (1981). Interdisciplinary studies on phencyclidine. In E. F. Domino (Ed.), *PCP phencyclidine: Historical and current perspectives* (pp. 331-400). Ann Arbor, MI: NNP Books.
- JOHNSON, K. M., & JONES, S. M. (1990). Neuropharmacology of phencyclidine: Basic mechanisms and therapeutic potential. *Annual Review of Pharmacology & Toxicology*, **30**, 707-750.
- JONES, K. W., BAUERLE, L. M., & DENOBLE, V. J. (1990). Differential effects of and phencyclidine receptor ligands on learning. *European Journal of Pharmacology*, **179**, 97-102.
- MARTIN, W. R., EADES, C. G., THOMPSON, J. A., HUPPLER, R. E., & GILBERT, P. E. (1976). The effects of morphine- and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. *Journal of Pharmacology & Experimental Therapeutics*, **197**, 517-532.
- MOERSCHBAECHER, J. M., DEVIA, C., & BROKLEHURST, C. (1988). Differential antagonism by naltrexone of the effects of opioids on a fixed-ratio discrimination in rats. *Journal of Pharmacology & Experimental Therapeutics*, **244**, 237-246.
- NABESHIMA, T., KAMEI, H., & KAMEYAMA, T. (1988). A role played by sigma receptors in the conditioned suppression of motility in mice. *Psychopharmacology*, **94**, 515-520.
- PICKER, M., HEISE, W. J., & DYKSTRA, L. A. (1987). Evaluation of the effects of opioid agonists and antagonists under a fixed-consecutive-number schedule in rats. *Pharmacology, Biochemistry & Behavior*, **27**, 73-80.
- SHANNON, H. (1981). Evaluation of phencyclidine analogs on the basis of their discriminative stimulus properties in the rat. *Journal of Pharmacology & Experimental Therapeutics*, **216**, 543-551.
- TANG, A. H., & FRANKLIN, S. R. (1983). Acquisition of a brightness discrimination in the rat is impaired by opiates with psychotomimetic properties. *Pharmacology, Biochemistry & Behavior*, **18**, 873-877.
- ZUKIN, S. R., & ZUKIN, R. S. (1979). Specific ³H-phencyclidine binding in rat central nervous system. *Proceedings of the National Academy of Sciences, USA*, **76**, 5372-5376.

(Manuscript received December 20, 1990;
revision accepted for publication February 28, 1991.)