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Inhibition by Lithium of β-Endorphin-Induced Psychomotor Excitation in Cats

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BELESLIN, D. B., R. SAMARDŽIĆ AND S. K. KRSTIĆ. *Inhibition by lithium of β-endorphin-induced psychomotor excitation in cats.* PHARMAC. BIOCHEM. BEHAV. 17(6) 1317–1320, 1982.—β-Endorphin injected into the cerebral ventricles of unanesthetized cats produced dose-dependent and long-lasting restlessness, locomotion, stereotyped sideways movements of the head, vacant staring, apprehension and flight accompanied with mydriasis and tremor. The most impressive features of the psychomotor excitation were the locomotion and the sideways movements of the head. Intracerebroventricular nalorphine prevented the psychomotor excitation caused by intracerebroventricular β-endorphin. Lithium chloride and lithium carbonate injected into the cerebral ventricles prevented and reversed the psychomotor excitation evoked by β-endorphin similarly injected. In cats showing spontaneous locomotor activity, intracerebroventricular lithium chloride also suppressed this activity. It is suggested that β-endorphin elicited psychomotor excitation by acting on central opiate receptors. However, the effect of lithium cannot be solely ascribed to an action on central opiate receptors and endogenous peptides. Since lithium affected the spontaneous as well as the β-endorphin-induced locomotion, it may be supposed that the cation suppressed the ongoing input activity at central locomotion activity levels.

β-Endorphin Opiate receptors Cats Lithium Nalorphine Psychomotor excitation

LITHIUM salts have long been known as valuable therapeutic and prophylactic agents against endogenous affective disorders. However, despite a growing number of reports, the mechanism by which lithium causes its therapeutically useful action is still not well understood. Most of the investigators have studied the effect of lithium on central monoaminergic functional activity [11,16]. Recent studies have led to the hypothesis that endogenous polypeptides, endorphins and enkephalins may play a role in the pathogenesis of psychomotor states [18] and that lithium alters the binding affinity of opiate agonists to central opiate receptors [1,15].

This study was designed to evaluate the effect of lithium salts on psychomotor excitation in cats elicited by β-endorphin in an effort to further characterize the possible involvement of endorphins in the pharmacological action of this psychoactive cation. For these experiments cats were selected in which intracerebroventricular β-endorphin is known to produce abnormal behavior identical to that which occurs after morphine is injected into the cerebral ventricles [2, 3, 8, 9, 12]. In addition, the effect of intracerebroventricular lithium chloride on spontaneous locomotor activity was investigated. The results of these experiments show that intracerebroventricular lithium can affect the spontaneous locomotor activity as well as the β-endorphin-induced psychomotor excitation in unanesthetized cats.

METHOD

In these experiments cats of either sex weighing between 2.1 and 3.8 kg were used. While the animals were under pentobarbital sodium (35–40 mg/kg IP) anesthesia, a hole was drilled and tapped 7 to 8 mm from the zero line and 4 to 5 mm from the midline. A Collison cannula, described by Feldberg and Sherwood [7], was then screwed aseptically into the skull. The lower end of the cannula shaft was made of polythene tubing with a side opening 1 mm from its closed tip and positioned with the lumen towards the foramen of Monro. Postmortem dye studies indicated that the injected material passed from the lateral ventricle into the third and fourth ventricle. Postoperatively, penicillin was administered intramuscularly. An interval of five days elapsed before the cats were used for the experiments.

The substances injected into the cerebral ventricles were dissolved in sterile, pyrogen-free 0.9% sodium chloride. These solutions were then injected by hand from a 1.0 ml syringe in a volume of 0.1 ml over a period of 15–20 sec and washed with 0.1 ml of saline under the same conditions. The injected animals were observed continuously for a period of four hr and intermittently for 24 hr. In order to avoid tolerance, each cat was used only once in these experiments.

In this study, locomotor activity was measured in a wire mesh cage (110 × 130 × 150 cm). Before any activity was measured on the tested day cats were habituated for one hr

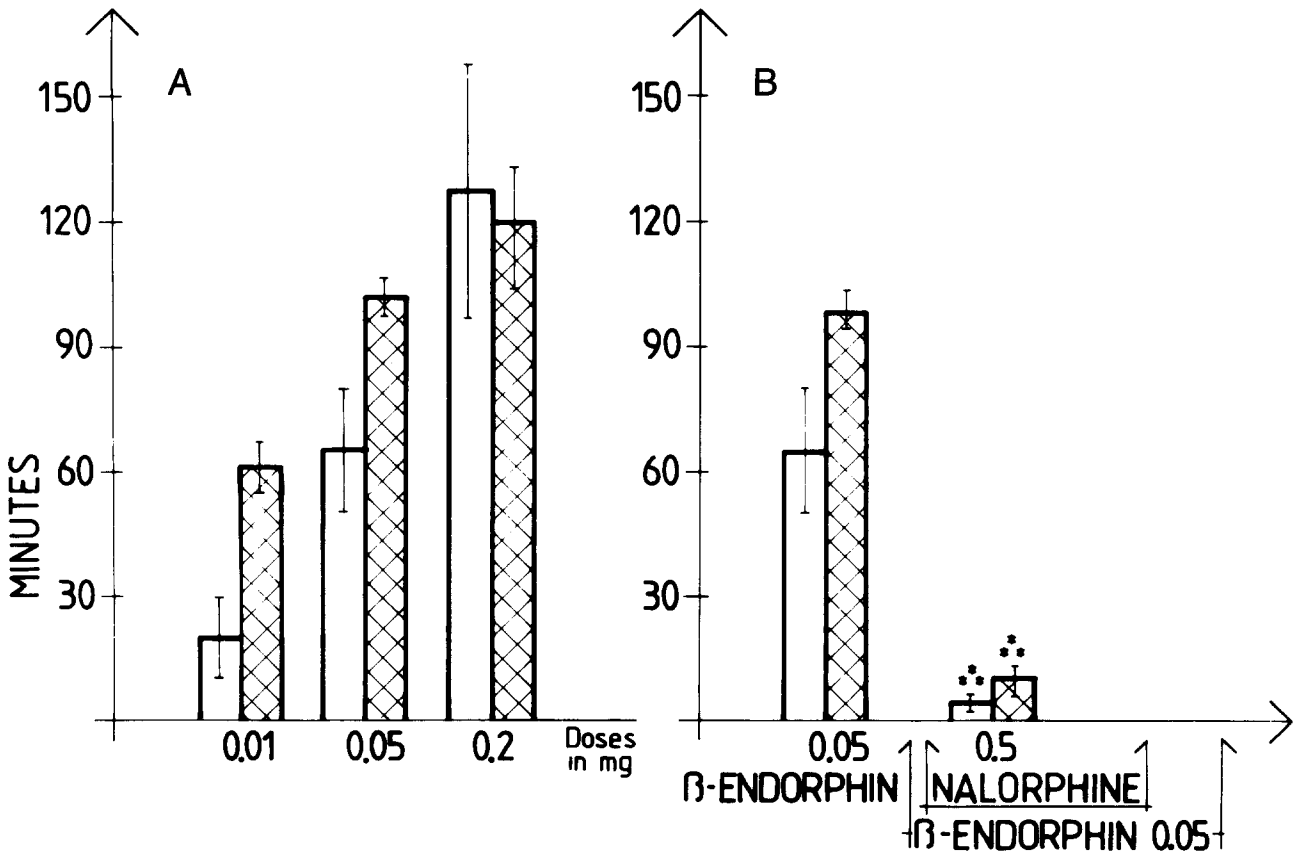

FIG. 1. Locomotion (open columns) and sideways movements of the head (cross-hatched columns) caused by β-endorphin injected into the cerebral ventricles of unanesthetized cats (A) and prevention of these symptoms by nalorphine similarly injected (B). Ordinates: duration of locomotion and sideways movements of the head in min. On abscissa in B the first two columns represent the control values for locomotion and sideways movements of the head evoked by intracerebroventricular β-endorphin. Between the arrows, nalorphine was injected into the cerebral ventricles of unanesthetized cats 15 to 20 min before β-endorphin similarly injected. Each column is the mean±SEM of four experiments. Each cat was used only once for the experiment. Statistical significance of differences from control values at $***p<0.001$ (Student t-test).

prior to intracerebroventricular injections of drugs. The behavior of the animals was continuously under direct observation during the expriments. Locomotor activity was measured by visual counting of crossings made by the cat from one side of the cage to the other. Attempts were not scored. Locomotion and sideways movements of the head were scored by two experienced observers who were blind to the drug condition of the animals. The correlation coefficient for these checks ranged consistenly between 0.85 and 0.96.

The compounds used were: synthetic human β-endorphin, nalorphine bromide, lithium chloride and lithium carbonate. The doses of nalorphine and lithium refer to the salts and those of β-endorphin to the peptide.

RESULTS

Behavioral Effects of β-Endorphin

β-Endorphin (0.01–0.2 mg) injected into the cerebral ventricles of unanesthetized cats evoked restlessness, apprehension, stereotyped sideways movements of the head, locomotion, vacant staring and flight accompanied with mydriasis and tremor. The most impressive features of these phenomena were the locomotion and the sideways movements of the head.

After a short latency period of 5–15 min, the cat suddenly moved its head from side to side with ears extended, pupils maximally dilated and eyes wide open. Thereafter, the sideways movements of the head developed into a reaction of apprehension. The searching movements became more rapid. The cat usually withdrew a little and looked restless and frightened. It would then run away from some unknown threat, attempt to escape from the cage and ignore other cats without trying to attack or bite. Many cats appeared to be hallucinating: they would fix their gaze on a corner or a wall of the cage, stand stiffly and then back away abruptly. After impelling locomotion the cat would sit down suddenly or would stand stiffly with a vacant stare with pupils maximally dilated and eyes wide open. The periods of locomotion alternated with periods of sitting or standing which appeared at irregular time intervals.

The psychomotor excitation produced by intracerebroventricular injections of single doses of β-endorphin were dose-dependent and lasted from about 30–150 min. This is illustrated for locomotion and sideways movements of the

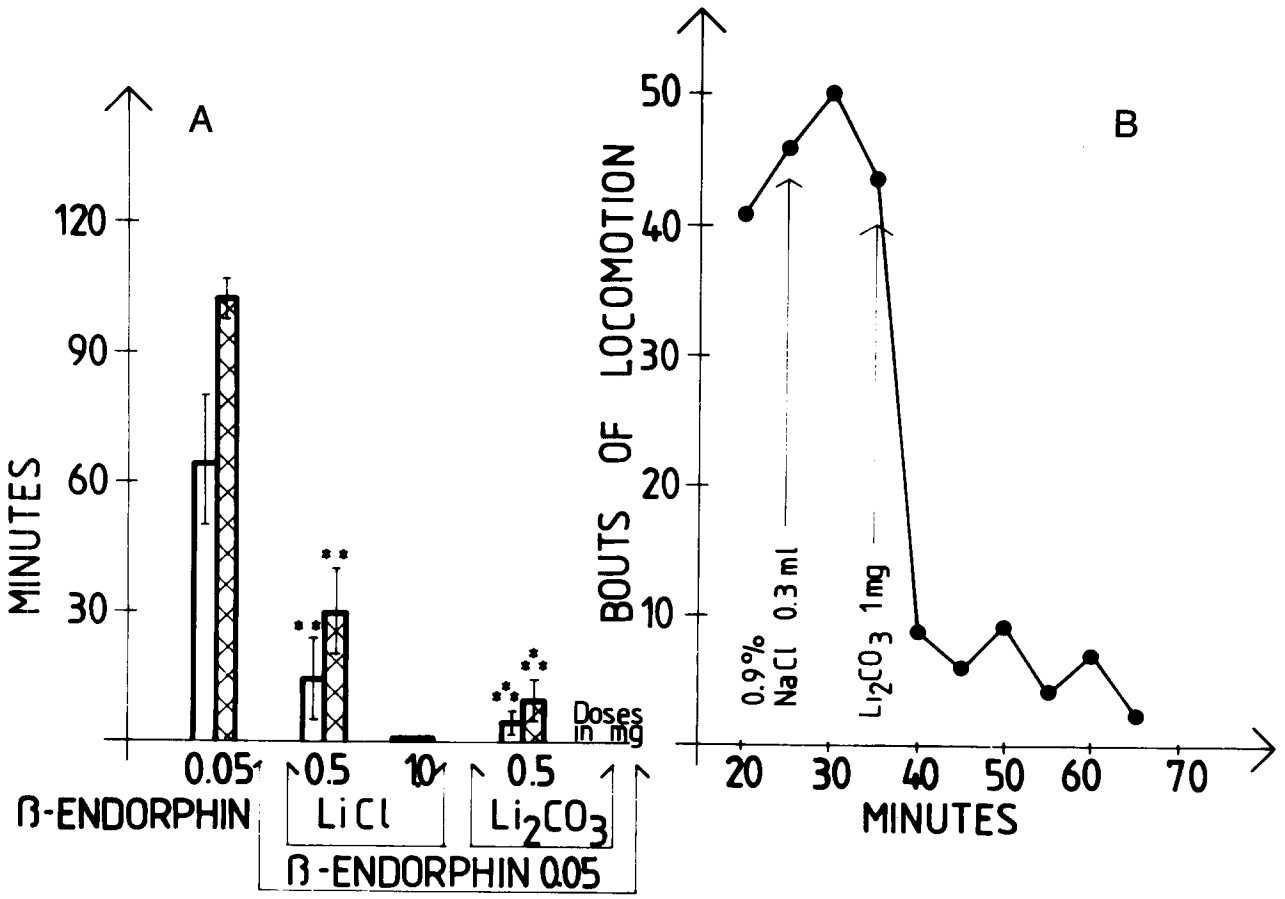

FIG. 2. The effect of LiCl and Li_2CO_3 on locomotion and sideways movements of the head caused by β-endorphin in unanesthetized cats. (A) Ordinate: duration of locomotion and sideways movements of the head in min. On abscissa in A, the first two columns represent the control values for locomotion (open columns) and sideways movements of the head (cross hatched columns) evoked by intracerebroventricular β-endorphin. Between the arrows LiCl and Li_2CO_3 were injected into the cerebral ventricles of unanesthetized cats 15 to 20 min before β-endorphin similarly injected. Each column is the mean±SEM of four experiments. Each cat was used only once for the experiment. Statistical significance of differences from control values at $^{**}p<0.01$ and $^{***}p<0.001$ (Student t-test). (B) A representative experiment of the effect of Li_2CO_3 on locomotion induced by β-endorphin in an unanesthetized cat. Consecutive 5 min activity counts were made at 10 min intervals. Ordinate: bouts of locomotion during each 5 min of a 10 min test. Abscissa: duration of locomotion in min.

head in Fig. 1A. Nalorphine (0.5 mg) injected into the cerebral ventricles 15–20 min before the peptide almost completely prevented the locomotion and the sideways movements of the head caused by the β-endorphin (0.05 mg) injection (Fig. 1B).

Lithium and Spontaneous Locomotor Activity

Since a group of five to six cats was kept in the cage for one hr prior to the actual scoring of spontaneous locomotor activity, the contribution of exploratory activity to the total counts was kept to a minimum. After one hr habituation only three out of 11 cats showed spontaneous locomotor activity. Consecutive five min activity counts were made at 10 min intervals for 120 min. During two subsequent 10 min intervals the locomotion ranged from two to six counts. Intracerebroventricular injections of 0.2 ml of 0.9% saline in the next 10 min interval did not change significantly the counts of spontaneous locomotion. However, when 10 min later lithium chloride in doses of 0.5 mg was injected into the cerebral ventricles, the spontaneous locomotor activity was suppressed.

Lithium and Behavioral Effects of β-Endorphin

Lithium chloride (0.5–1.0 mg) and lithium carbonate (0.5 mg) were injected into the cerebral ventricles 15 to 20 min before intracerebroventricular administration of β-endorphin (0.05 mg). In the experiments illustrated in Fig. 2A, lithium salts injected before β-endorphin greatly reduced or prevented the appearance of locomotion and lateral movements of the head. In a typical experiment, an intracerebroventricular injection of 0.3 ml of 0.9% NaCl had no effect, but lithium carbonate in a dose of 1.0 mg greatly reduced the locomotor activity caused by β-endorphin (0.05) injected similarly (Fig. 2B). In addition, lithium salts injected intracerebroventricularly prevented or reversed restlessness, apprehension, vacant staring and flight caused by β-endorphin.

Since there is no solid evidence on the behavioral effect of the volume injected into the cerebral ventricles of the unanesthetized cat, in control experiments 0.3 ml of 0.9% saline was used instead of 0.2 ml (0.1 ml of dissolved drug plus 0.1 ml of 0.9% NaCl for wash-in). Intracerebroventricular injection of 0.3 ml of 0.9% NaCl into the cerebral ventricle of

three unanesthetized cats did not produce any visible behavioral, autonomic or motor change.

DISCUSSION

Sedation, muscular rigidity and immobility similar to a cataleptic state have been described in rats following intraventricular administration or microinjection into the periaqueductal gray of β-endorphin [4]. In contrast, β-endorphin injected into the cerebral ventricle of the cat evoked restlessness, apprehension, lateral movement of the head, vacant staring and impelling locomotion accompanied by pupillary dilatation and tremor. The same behavioral syndrome was obtained when β-endorphin was infused into the third ventricle or injected into the cerebral ventricles of unanesthetized cats [2, 3, 8, 9, 12]. However, β-endorphin evokes stimulation of locomotor activity when infused into the ventral tegmental area in the rat [17]. It follows then that even within the same species, the site of administration determines the behavioral action.

As shown in these experiments, the psychomotor excitation caused by an acute injection of β-endorphin into the cerebral ventricles of unanesthetized cats could be prevented or reversed by an acute intracerebroventricular administration of lithium. Moreover, in the present investigation it was found that lithium injected intracerebroventricularly abolished also the spontaneous locomotor activity in cats. These findings are not surprising since it is already known that lithium salts can depress the spontaneous motor activity as well as drug-induced hyperactivity in rodents [5, 13, 14].

In the present experiments the psychomotor excitation was antagonized by nalorphine and this appears to be a direct result of an action on central opiate receptors. The question then arises as to how lithium blocks psychomotor excitation, especially the locomotion caused by β-endorphin. Since lithium decreases the binding affinity of opiate agonists to brain opiate receptors [1,15], the ability of lithium to decrease the high affinity binding of β-endorphin to brain opiate receptors may account at least in part for the findings of the present study. Alternatively, other modes of action of lithium are equally possible. For instance, acute or short-term lithium treatment can reduce the amount of noradrenaline for interaction at receptor sites [11,16]. In this connection it should be mentioned that an opiate-dopamine interaction is involved in the psychomotor excitation evoked by morphine in cats [6] as well as for the locomotor activation induced by β-endorphin in the rat [17]. Thus, the action of this cation on more than one putative neurotransmitter may account for the psychopharmacological effect of lithium. Since lithium affects the spontaneous as well as the β-endorphin-induced locomotor activity, it is possible that the cation suppresses the ongoing input at sites mediating central locomotor activity.

Finally, the reported interaction between lithium, nalorphine and β-endorphin may be of clinical interest. That is, a recent study has shown that naloxone administered to manic or schizophrenic patients relieved at least temporarily some of the pathological symptoms [10].

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