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Effect of Morphine and Morphine-Like Drugs on Carbachol-Induced Fighting in Cats

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KRSTIĆ, S. K., K. STEFANOVIĆ-DENIĆ AND D. B. BELESLIN. *Effect of morphine and morphine-like drugs on carbachol-induced fighting in cats.* PHARMAC. BIOCHEM. BEHAV. 17(2) 371–373, 1982.—In the present experiments, morphine, methadone or pethidine was injected into the cerebral ventricle of the unanesthetized cat after fighting was induced with carbachol injected previously. The fighting evoked by carbachol was sensitive to the depressant action of morphine or pethidine but not to the depressant effect of methadone. The most likely explanation of the depressant effects of the former compounds is that they act on the postsynaptic receptors of central cholinergic neurons.

Morphine Morphine-like drugs Carbachol Intraventricular injections Fighting

CHOLINERGIC mechanisms in the brain have already been implicated in aggressive behavior [12, 14, 15]. For instance, it has been postulated that muscarinic cholinoceptive sites and cholinergic neurons participate in the occurrence of fighting produced by cholinomimetics injected into the cerebral ventricle of the unanesthetized cat [1, 2, 3]. Further, there is evidence that morphine and other narcotic analgesics affect central cholinergic mechanisms as well [2, 4, 8, 11, 16]. Therefore, it was of interest to investigate the effect of morphine, methadone and pethidine by injecting them into the cerebral ventricles of unanesthetized cat after fighting between two animals was induced by ICV injections of carbachol.

METHOD

Cats of either sex weighing 2.2 to 3.1 kg were used in these experiments. For injections into the left lateral ventricle, a Collison cannula [10] was implanted aseptically under sodium pentobarbitone (35–40 mg/kg IP) anesthesia into the skull through a hole which was drilled 7 to 8 mm from the stereotaxic zero line and 4–5 mm from the midline. The lower end of the cannula shaft was fitted with polyethylene tubing with a side opening 1 mm from its closed tip and positioned with the lumen towards the foramen of Monro. Dye studies post-mortem indicated that the injected material passed from the lateral ventricle into the third and fourth ventricles. Postoperatively, penicillin was administered intramuscularly. An interval of 5 days elapsed before the cats were used for the experiments.

The drugs injected into the cerebral ventricles were dissolved in pyrogen-free 0.9% NaCl solution. After each was warmed to 37°C it was injected by hand by a 1 ml syringe under aseptic conditions. The volume was 0.1 ml given over a period of 15 to 20 sec and washed with 0.1 ml of saline under the same conditions as the drugs. Thereafter, all the test animals were observed for a period of 4 hrs and intermittently for 24 hrs. In order to avoid the occurrence of tolerance, each cat was used only once in these experiments.

In this study, measures of fighting behavior were taken in a wire-mesh cage 110×130×150 cm. On the test day, before any behavior measure, cats were acclimated to the test environment for at least 1 hr before intracerebroventricular drug injection. Fighting was scored by two experienced observers, both of whom were blind with regard to the drug condition of the animals. The correlation coefficient for inter-rater reliability ranged consistently between 0.91 and 0.97.

The compounds used were: carbamylcholine chloride (carbachol), morphine hydrochloride, methadone hydrochloride (Heptanon, Pliva) and pethidine hydrochloride (Dolantin, Hoechst). The doses are expressed as the salt of the respective compound.

RESULTS

Carbachol and Behavior

In group-housed cats with each of 4–6 animals receiving intraventricular carbachol, the most impressive effect was a pattern of aggressive responses. Vocalization, miaowing, hissing and snarling as well as fighting, attacking, defense with paws and claws and biting were the main characteristics of this aggressive behavior. Restlessness, vocalization, tremor and slight mydriasis occurred with the smallest 5.0 μg dose of carbachol. When the dose of carbachol was raised to 30.0 μg, fighting, motor and autonomic responses occurred

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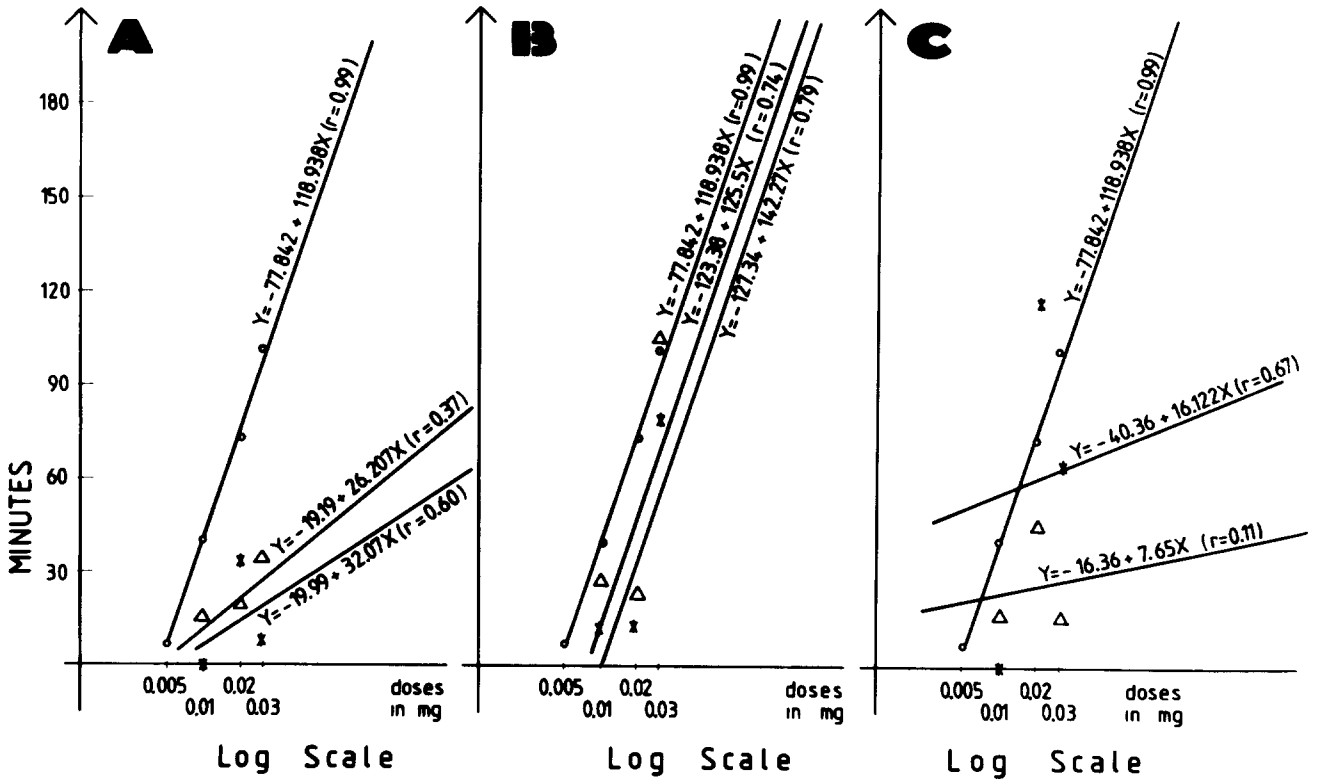

FIG. 1. Effect of morphine (A), methadone (B) and pethidine (C) on fighting response to carbachol. In A, B and C ○--○, various single doses of carbachol were injected into the cerebral ventricles of unanesthetized cats. In A △--△, morphine (0.2 mg) plus carbachol and *--* morphine (1 mg) plus carbachol. In B △--△ methadone (0.2 mg) plus carbachol and *--* methadone (1 mg) plus carbachol. In C △--△ pethidine (0.5 mg) plus carbachol and *--* pethidine (2 mg) plus carbachol. Ordinates = duration of fighting in minutes. Morphine, methadone and pethidine were injected into the cerebral ventricles of unanesthetized cats 15–20 minutes before intraventricular carbachol. Each symbol represents the mean of four experiments. Each cat was used only once for the experiment.

including mydriasis, salivation, piloerection, dyspnea, defecation, urination, scratching, circling, tremor, rigidity and weakness with adynamia. As shown in Figs. 1A, B and C, the fighting was dose-dependent.

Morphine, Methadone, Pethidine and Behavior

Intraventricular injection of morphine (0.2–1.0 mg), methadone (0.2–1.0 mg) or pethidine (0.5–2.0 mg) also produced in 4–6 group-housed cats the responses of restlessness, apprehension, vacant staring, locomotion, pupillary dilatation and vomiting. The acute behavioral effects of methadone and pethidine, in addition to mydriasis and vomiting, were not as constant and much less intense than those of morphine. Tremor was caused only by morphine and methadone.

When the same doses of morphine (0.2–1.0 mg), methadone (0.2–1.0 mg) or pethidine (0.5–2.0 mg) were injected 15 to 20 min before the carbachol, the aggressive responses were affected by the depressant actions of morphine and pethidine, but not by methadone (Figs. 1A, B and C). Differences were statistically significant ($p \leq 0.01$) between the highest 30.0 μg dose of carbachol and those of small and high doses of morphine plus the highest dose of carbachol, as well as pethidine in the highest dose plus carbachol in the highest dose.

DISCUSSION

Fighting between cats occurred after intraventricular injection of carbachol but not following intraventricular morphine, methadone or pethidine. However, aggression consisting of violent motor excitement, vigorous movements or jumping in the cage, yowling, piloerection, clawing and biting of the cage has been observed in cats after parenteral administration of morphine [7]. In the present experiment, as well as those of Feldberg and Shaligram [9], intraventricular morphine elicited restlessness, apprehension, vacant staring, locomotion, mydriasis, tremor and vomiting.

An interesting finding of these experiments is that morphine and pethidine injected into the cerebral ventricle depressed the carbachol fighting behavior while methadone had no effect. Similarly, opiates such as morphine and etonitazene, but not methadone, induce a profound state of immobilization characterized by the absence of spontaneous movements when injected into the cerebral ventricles of rats [6]. However, in this investigation, methadone injected into the ventricle evoked less intense behavioral effects such as restlessness, apprehension, locomotion, mydriasis and vomiting. Thus, after intraventricular administration, methadone may not achieve a sufficient concentration in those brain structures which mediate aggressive responses.

In hemicholinium- and triethylcholine-treated cats, intra-

ventricular carbachol is reported not to induce fighting. However, choline administration into the cerebral ventricles of hemicholinium- and triethylcholine-treated cats restores the fighting after intraventricular carbachol [3]. Since the fighting produced by carbachol was sensitive to the depressant action of morphine and pethidine, it is possible that morphine and pethidine affect the central cholinergic mechanism involved in the aggressive behavior of the cat.

The question that arises concerns whether this effect of morphine and pethidine is due to their action on postsynaptic receptors or on acetylcholine release. The problem of attributing the depressant effect of morphine to the release of acetylcholine is complicated by the fact that morphine suppresses the release of acetylcholine from the brain of the anesthetized cat [2,11], but enhances it in the unanesthetized animal [13]. If morphine were to act by releasing acetylcholine, the fighting caused by carbachol should be potentiated. The most likely explanation of the depressant effects of morphine and pethidine on fighting, therefore, is that these drugs act on postsynaptic receptors of cholinergic neurons. Iontophoretic investigations reveal an atropine-like action of levorphanol in spinal neurons of the cat [8], and if this finding extends to morphine's effect, the depressant action of morphine on fighting should not be surprising. Iontophoretically given morphine usually reduces the stimulation of neurons by acetylcholine, norepinephrine and 5-hydroxytryptamine and may depress spontaneously active neurons in the central nervous system of the rat and cat [4, 5, 8]. In the present study, the correlation of morphine plus carbachol, and pethidine plus carbachol, showed little or no relationship suggesting that the action of the opiates may not be specific in nature.

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