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BRIEF COMMUNICATION

Acute Administration of MIF-1 or Tyr-MIF-1 Inhibits Haloperidol-Induced Catalepsy in Rats

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HARA, C. AND A. J. KASTIN. *Acute administration of MIF-1 or Tyr-MIF-1 inhibits haloperidol-induced catalepsy in rats.* PHARMACOL BIOCHEM BEHAV 24(6) 1785–1787, 1986.—The effects of MIF-1 (Pro-Leu-Gly-NH_2) and Tyr-MIF-1 (Tyr-Pro-Leu-Gly-NH_2) on haloperidol-induced catalepsy were studied in order to examine the influences of both peptides on central dopaminergic function. In the first experiment, several variables were tested. It was found that the optimal effect was achieved with a dose of 1.0 mg/kg haloperidol injected SC an hour before testing for catalepsy and 1.0 mg/kg MIF-1 injected SC 30 min before testing. In the second experiment, Tyr-MIF-1 as well as MIF-1 were injected as single injections at four doses. Catalepsy was inhibited in an inverted U-shape dose-response relationship with the maximal effect of each peptide occurring at 1.0 mg/kg. The results indicate that when careful attention is given to dose, both MIF-1 and Tyr-MIF-1 can activate dopaminergic neuronal activity after acute administration.

MIF-1 Tyr-MIF-1 Haloperidol Catalepsy Peptides Tardive dyskinesia Dopamine

THE tripeptide Pro-Leu-Gly-NH_2 (MIF-1) is active in several animal models involving alterations of the dopaminergic systems. For example, in the 6-OHDA lesioned rotational model, MIF-1 significantly potentiated the behavioral response to apomorphine [9] as it did in an animal model of tardive dyskinesia induced by chronic administration of haloperidol [3]. MIF-1 also can potentiate the behavioral effects of DOPA [13]. In addition, the peptide can prevent the development of both behavioral and biochemical supersensitivity of dopamine receptors in the brain induced by the neuroleptic drug haloperidol [1].

These reports are consistent with the view that the neuropharmacological mechanism of action of MIF-1 in the brain involves an interaction with central dopaminergic systems. However, reports of the available evidence are not unanimous in support of this suggestion. As summarized by Van Heuven-Nolsen *et al.* [16] with respect to these conflicting results, several factors should be considered. These include dose level, acute or chronic treatment, route of administration (central or peripheral), single dose or multiple doses, the parameter being measured, and the treatment schedule.

Haloperidol-induced catalepsy is considered a useful model of the extrapyramidal motor disorders seen in humans as side effects of neuroleptic therapy, the mechanism probably being based on the blockade of postsynaptic dopamine receptors [12]. Although a single dose of MIF-1 has been found to potentiate central dopaminergic functions in the 6-OHDA lesioned rotational model [9] and haloperidol-induced tardive dyskinesia model [3], chronic treatment was reported to be necessary to attenuate the acute cataleptic response of haloperidol in rats [2]; a single dose was ineffective. In mice, neither the acute nor the chronic administration of MIF-1 was reported to affect the response [10].

Tyr-MIF-1 (Tyr-Pro-Leu-Gly-NH_2) is structurally related to MIF-1, but MIF-1 does not compete for its binding sites in brain [17] where it has been found by radioimmunoassay [6] and high performance liquid chromatography [8]. Tyr-MIF-1 acts as an opiate antagonist in the tail-flick test [7] and as an antidepressant in the water wheel test [5]. The influence of Tyr-MIF-1 on central dopaminergic function, however, has not been tested. Therefore, we examined the effects of acute administration of MIF-1 and Tyr-MIF-1 on haloperidol-induced catalepsy in order to clarify the mechanism of action of MIF-1 on central dopaminergic functions and to examine the effect of Tyr-MIF-1 on these functions.

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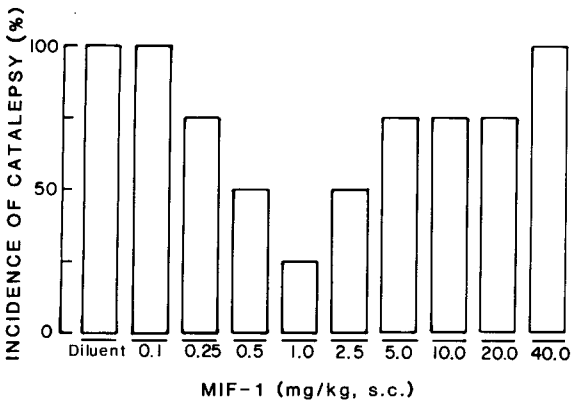

FIG. 1. Dose-response relationship of MIF-1 on haloperidol (1.0 mg/kg, SC)-induced catalepsy. MIF-1 was injected SC 30 min before the catalepsy test. Haloperidol was administered 1 hr before the test. Each group consisted of 4 rats.

METHOD

Animals

Male albino white rats (Charles River Laboratories, Boston, MA), 10–11 weeks old at the beginning of the experiment, were used. They were housed in the animal quarters for at least 1 week before the experiment in a temperature-controlled room (21±1°C) with 12:12 hr light-dark cycle (lights on at 0600 hr). They were allowed free access to food and water.

Procedure

The experiments were started after the animals were adapted under the same conditions in the experimental room for at least 24 hr. In order to minimize the possible effect of circadian rhythm on dopaminergic function in the brain [11], the experiments were conducted between 0900–1200 hr. Control and experimental groups were tested in parallel. Catalepsy was measured by a standard bar test and defined by the maintenance of the imposed posture of both frontal limbs over a horizontal steel bar for more than 30 sec in one of three trials [4]. Each rat was used only once, three trials being made in quick succession with a 60 second limit. All drugs were coded.

The present study consisted of two experiments. Experiment 1 was performed to evaluate the following variables: dose of MIF-1, dose of haloperidol, time after MIF-1 injection, and time after haloperidol injection. Based on these results, in Experiment 2, 1.0 mg/kg SC of haloperidol was administered 1 hr before the catalepsy test and MIF-1 and Tyr-MIF-1 were injected at doses of 0.1, 0.5, 1.0 and 5.0 mg/kg, SC 30 min before the catalepsy test.

Drugs

Haloperidol (Haldol, McNeil Pharmaceuticals, Fort Washington, PA) was diluted with 0.9% NaCl. MIF-1 and Tyr-MIF-1 were dissolved in diluent (0.9% NaCl acidified to 0.01 M with acetic acid). All drugs were administered in an injection volume of 1.0 ml/kg.

Statistical Analysis

Statistical evaluation was based on Fisher's exact probability test.

RESULTS

Experiment 1

In this study, only 1.0 mg/kg of haloperidol showed 100% incidence of catalepsy when 0.25, 0.5, and 1.0 mg/kg doses of the drug were administered SC and the catalepsy test was performed 1 hr later. When MIF-1 (1.0 mg/kg) was injected SC 30, 60, or 120 min before the catalepsy test, the incidence of catalepsy was lowest with the 30 min pretreatment. Therefore, MIF-1 was administered 30 min before the catalepsy test, and 1.0 mg/kg of haloperidol was injected 1 hr before the test in the subsequent studies. Figure 1 illustrates the dose-response effect of many doses of MIF-1 on haloperidol-induced catalepsy. MIF-1 blocked catalepsy induced by haloperidol in an inverted U-shaped dose-response relationship. The greatest inhibition by MIF-1 was obtained with the 1.0 mg/kg dose.

Experiment 2

Figure 2 illustrates the effects of a single dose of MIF-1 or Tyr-MIF-1 on haloperidol-induced catalepsy. Both peptides were effective. Again, an inverted U-shaped dose-response relationship was found. The 1.0 mg/kg dose of MIF-1 significantly reduced the incidence of catalepsy as compared with the effect of diluent ($p<0.05$). Tyr-MIF-1 reliably suppressed the incidence of catalepsy at doses of 0.5 mg/kg ($p<0.05$) and 1.0 mg/kg ($p<0.01$) as compared with diluent. On a molar basis, the rats received less Tyr-MIF-1 at each dose than MIF-1.

DISCUSSION

The present study showed that MIF-1 and Tyr-MIF-1 inhibited haloperidol-induced catalepsy in rats in an inverted U-shaped dose response relationship. This occurred with a single injection of each peptide. In mice, a single dose of MIF-1 and chronic pretreatment with MIF-1 were reported not to affect the acute cataleptic response of haloperidol [10]. In rats, acute administration of MIF-1 (20 and 40 mg/kg, SC) also was reported not to alter the intensity of the cataleptic response elicited by haloperidol, even though chronic MIF-1 treatment attenuated haloperidol-induced catalepsy [2]. The reason for the discrepancy between these reports and the present study may depend on the method used to measure catalepsy. These two papers [2,10] repeatedly tested catalepsy at several times in the same animals receiving higher doses (3.0 mg/kg) of haloperidol than in our study (1.0 mg/kg). Since the repeated testing of catalepsy is known to progressively increase the score for catalepsy even in normal saline-injected rats [14,15], the negative results of these papers might be explained by the increased level of catalepsy. Another reason for the discrepant results of at least one of the studies [2] may be the use of inappropriate doses of MIF-1. In the present study, MIF-1 showed an inverted U-shaped dose-response curve for the catalepsy (Figs. 1,2) with no effect at the higher doses. The negative study in rats [2] used high doses (20 and 40 mg/kg) of MIF-1. In contrast, the results from our study show that a single dose of 1.0 mg/kg MIF-1 can inhibit the acute cataleptic response of haloperidol.

Tyr-MIF-1 also inhibited induction of catalepsy by haloperidol in an inverted U-shaped dose-response relationship (Fig. 2). This effect of Tyr-MIF-1 on the catalepsy was simi-

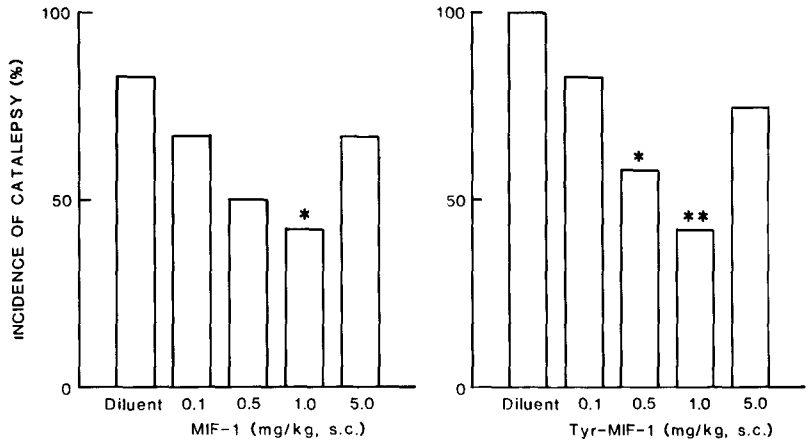

FIG. 2. Effects of a single dose of Tyr-MIF-1 as well as MIF-1 on haloperidol (1.0 mg/kg, SC)-induced catalepsy. Both peptides were administered SC 30 min before the catalepsy test. Haloperidol was injected 1 hr before testing. Each group consisted of 12 rats. $*p<0.05$, $**p<0.01$.

lar to that of MIF-1. Although the effects of Tyr-MIF-1 on central dopaminergic function is unknown, our results suggest that they may be similar to those of MIF-1.

In conclusion, we found that a single dose of either MIF-1 or Tyr-MIF-1 is capable of antagonizing haloperidol-induced catalepsy in rats, presumably by potentiating central dopaminergic function. As was first observed in 1971 [13], the response can follow an inverted U-shaped curve. Careful evaluation, therefore, must be made of dose-response relationships in such experiments.

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