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Biphasic Effects of MIF-1 and Tyr-MIF-1 on Apomorphine-Induced Stereotypy in Rats

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HARA, C. AND A. J. KASTIN. *Biphasic effects of MIF-1 and Tyr-MIF-1 on apomorphine-induced stereotypy in rats.* PHARMACOL BIOCHEM BEHAV **25**(4) 757–761, 1986.—The effects of several doses of MIF-1 and Tyr-MIF-1 (0.2, 0.5, 1.0 and 5.0 mg/kg, SC) on the stereotypic behavior induced by various doses (0.08, 0.2, 0.5, 1.0 and 2.0 mg/kg, SC) of apomorphine (APO) were tested in rats. MIF-1 increased the stereotypic behavior induced by 0.5 and 1.0 mg/kg of APO, but decreased the stereotypic behavior induced by 2.0 mg/kg of APO. Tyr-MIF-1 showed a biphasic effect similar to that exerted by MIF-1. The results suggest that the type of response to MIF-1 and Tyr-MIF-1 after APO is influenced by the activity of central dopaminergic neurons.

Peptides Apomorphine Dopamine Stereotypy Brain

MIF-1 (Pro-Leu-Gly-NH_2) has been shown to affect physiological and behavioral responses mediated by dopamine (DA). This tripeptide is active in the DOPA potentiation test [19, 20, 31, 32, 34], a model of tardive dyskinesia induced by chronic treatment with haloperidol [4, 6, 10], and rotational behavior induced by apomorphine (APO) in rats treated with 6-OHDA [26]. In addition, some clinical studies have shown that MIF-1 can ameliorate the symptoms of Parkinson's disease [2, 3, 14, 16, 33]. Thus, MIF-1 appears to interact with central dopaminergic systems.

Biochemical studies concerning the effects of MIF-1 on dopaminergic neurons, however, have produced inconsistent results [25, 27, 32]. Several factors may contribute to the conflicting results, including dose level and the use of acute or chronic treatment. Recently, we noticed that after single doses of MIF-1 (dose range: 0.2–5.0 mg/kg), an inverted-U shaped inhibition of haloperidol-induced catalepsy resulted [17]. Van Heuven-Nolsen *et al.* reported that the dose-response curves of the peptide on DA and norepinephrine utilization in rat limbic-forebrain nuclei were bell-shaped, and, in addition, the effects were evident after the lower doses only, not after the higher doses [34].

The structurally related Tyr-MIF-1 (Tyr-Pro-Leu-Gly-NH_2), an endogenous brain peptide [24, 36, 37], also showed an inverted U-shaped dose-response curve for haloperidol-induced catalepsy [17]. Although Tyr-MIF-1, like MIF-1, has been shown to antagonize the analgesia induced by opiates [15, 23, 24], the mode of action of Tyr-MIF-1 on central DA systems is unknown.

Accordingly, we examined the effects of single doses of MIF-1 and Tyr-MIF-1 on the stereotypy induced by the DA agonist APO in order to help clarify the mechanism of action of these peptides on central DA function.

METHOD

Animals

White, male rats were obtained from Charles River Laboratories (Boston, MA) and housed for at least 1 week before the experiment in a room with a 12:12 LD cycle (lights on at 0600 hr). The rats were allowed free access to food and water and were 11–12 weeks old at the beginning of the experiment. No animal was used more than once.

Procedure

The animals were transferred to the experimental room 24 hr before the experiment. The study was begun after the animals were adapted for 1 hr to the wire-mesh cages (30×30×30 cm) used for observation of the stereotypic behavior. The experiments were conducted between 0900–1200 hr to minimize the possible effect of circadian rhythm on DA function in the brain [28,29]. In addition, procedures on control and experimental groups were performed in parallel to reduce sources of variation. Ten min after treatment with APO, the animals were first rated for the degree of stereotypy for 30 sec and this was repeated every 10 min until the stereotypic behavior disappeared. The following rating scale was used: 0=absence of stereotypic behavior, 1=compulsive sniffing, 2=licking the floor or walls of the chamber at least once during the observation period, 3=biting the chamber at least once during the observation period, 4=compulsive continuous biting. This scoring system is capable of detecting a dose-response relationship for APO [29]. MIF-1, Tyr-MIF-1, or diluent were injected SC 10 min before the APO.

This study consisted of 3 experiments. Experiment 1

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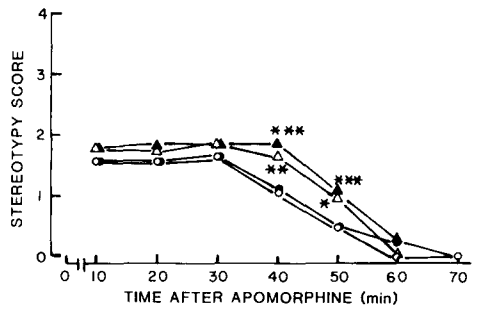

FIG. 1. Potentiating effect of MIF-1 on the stereotypy induced by 0.5 mg/kg of apomorphine. MIF-1 was injected SC 10 min before apomorphine. ○—○ diluent (n=12), ●—● MIF-1 0.2 mg/kg (n=12), △—△ MIF-1 0.5 mg/kg (n=12), ▲—▲ MIF-1 1.0 mg/kg (n=12). *$p<0.05$, **$p<0.01$, ***$p<0.001$: statistical difference from diluent.

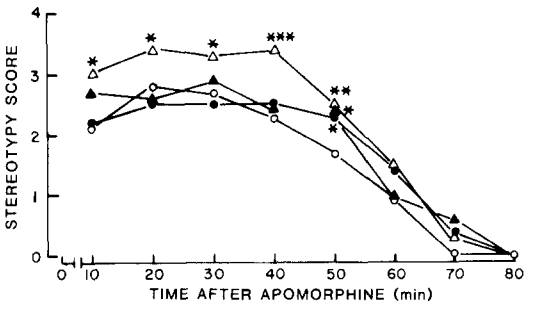

FIG. 2. Potentiating effect of MIF-1 on the stereotypy induced by 1.0 mg/kg of apomorphine. ○—○ diluent (n=12), ●—● MIF-1 0.2 mg/kg (n=12), △—△ MIF-1 0.5 mg/kg (n=12), ▲—▲ MIF-1 1.0 mg/kg (n=11). *$p<0.05$, **$p<0.01$, ***$p<0.001$: statistical difference from diluent.

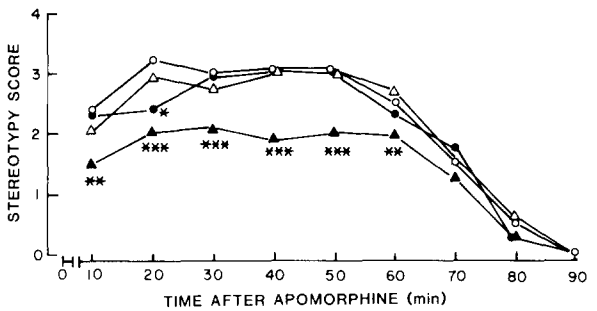

FIG. 3. Suppressive effect of MIF-1 on the stereotypy induced by 2 mg/kg of apomorphine. ○—○ diluent (n=12), ●—● MIF-1 0.2 mg/kg (n=12), △—△ MIF-1 0.5 mg/kg (n=12), ▲—▲ MIF-1 1.0 mg/kg (n=12). *$p<0.05$, **$p<0.01$, ***$p<0.001$: statistical difference from diluent.

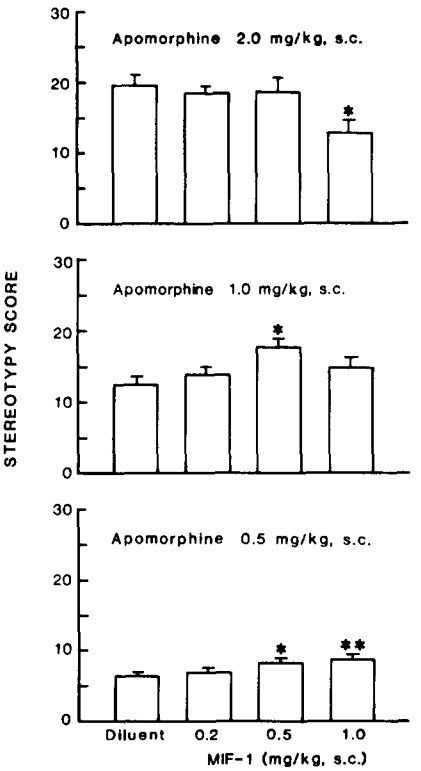

FIG. 4. Differential effects of MIF-1 on three doses of apomorphine. Each column represents the total score (±SEM) of stereotypy during the measured period. *$p<0.05$, **$p<0.01$: statistical difference from diluent.

examined dose-response relationships between APO and small doses of the tripeptide MIF-1. Experiment 2 confirmed the results obtained from Experiment 1 and examined the influence of a larger dose of MIF-1 on APO-induced stereotypy. Experiment 3 examined the influence of the tetrapeptide Tyr-MIF-1 on APO-induced stereotypy.

Drugs

APO (apomorphine-HCl obtained from Sigma) was dissolved in 0.9% NaCl and administered SC at the following doses: 0.08, 0.2, 0.5, 1.0 and 2.0 mg/kg. MIF-1 and Tyr-MIF-1 were dissolved in diluent (0.9% NaCl, 0.01 M acetic acid) and injected SC at doses of 0.2, 0.5, 1.0 and 5.0 mg/kg. Solutions of the peptides and diluent were coded so that the experimenter did not know their contents. The injection volume of all solutions was 1.0 ml/kg body weight.

Statistics

Data in each experiment were compared by analysis of variance (ANOVA) followed by Duncan's New Multiple Range Test (DNMRT).

RESULTS

Experiment 1

The doses of MIF-1 used in this part of the study performed in November/December were 0.2, 0.5 and 1.0 mg/kg. The doses of APO were 0.08, 0.5, 1.0 and 2.0 mg/kg.

Figure 1 illustrates the influence of MIF-1 on the stereotypy induced by 0.5 mg/kg of APO. MIF-1 significantly potentiated APO-induced stereotypy, $F(3,44)=3.91$, $p<0.05$. The time × treatment interaction was not significant. DNMRT indicated that 0.5 and 1.0 mg/kg of MIF-1 markedly enhanced the stereotypy at 40 and 50 min after the APM-treatment compared with diluent. MIF-1 did not induce any stereotypic behavior in rats treated with 0.08 mg/kg of APO, a dose of APO known not to elicit stereotypic behavior.

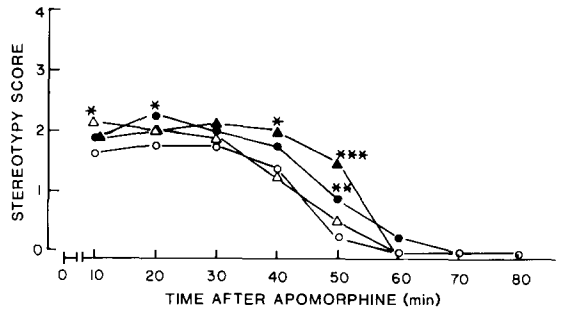

FIG. 5. Potentiating effect of MIF-1 on the stereotypy induced by 0.5 mg/kg of apomorphine. ○—○ diluent (n=8), ●—● MIF-1 0.5 mg/kg (n=8), △—△ MIF-1 1.0 mg/kg (n=8), ▲—▲ MIF-1 5.0 mg/kg (n=8). *$p<0.05$, **$p<0.01$, ***$p<0.001$: statistical difference from diluent.

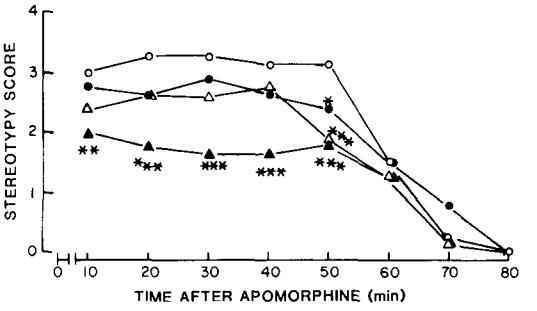

FIG. 6. Suppressive effect of MIF-1 on the stereotypy induced by 2.0 mg/kg of apomorphine. ○—○ diluent (n=8), ●—● MIF-1 0.5 mg/kg (n=8), △—△ MIF-1 1.0 mg/kg (n=8), ▲—▲ MIF-1 5.0 mg/kg (n=8). *$p<0.05$, **$p<0.01$, ***$p<0.001$: statistical difference from diluent.

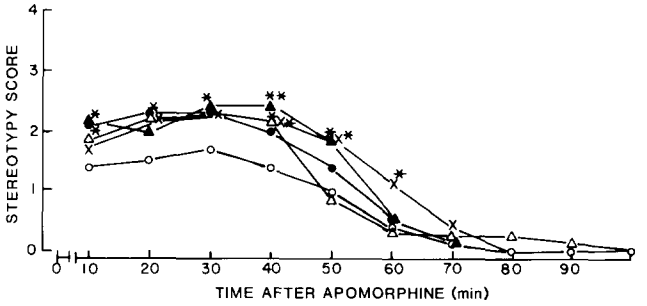

FIG. 7. Potentiating effect of Tyr-MIF-1 on the stereotypy induced by 0.5 mg/kg of apomorphine. ○—○ diluent (n=7), ●—● Tyr-MIF-1 0.2 mg/kg (n=7), △—△ Tyr-MIF-1 0.5 mg/kg (n=7), ▲—▲ Tyr-MIF-1 1.0 mg/kg (n=7), X—X Tyr-MIF-1 5.0 mg/kg (n=7). *$p<0.05$, **$p<0.01$: statistical difference from diluent.

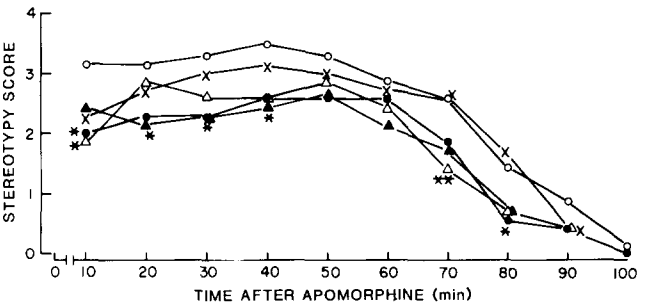

FIG. 8. Suppressive effect of Tyr-MIF-1 on the stereotypy induced by 2.0 mg/kg of apomorphine. ○—○ diluent (n=7), ●—● Tyr-MIF-1 0.2 mg/kg (n=7), △—△ Tyr-MIF-1 0.5 mg/kg (n=7), ▲—▲ Tyr-MIF-1 1.0 mg/kg (n=7), X—X Tyr-MIF-1 5.0 mg/kg (n=7). *$p<0.05$, **$p<0.01$: statistical difference from diluent.

Figure 2 shows the effect of MIF-1 on the stereotypy induced by 1.0 mg/kg of APO. ANOVA showed that although there was no main effect of treatment, the time × treatment interaction was statistically significant, $F(21,301)=1.64$, $p<0.05$. DNMRT indicated that 0.5 mg/kg of MIF-1 markedly potentiated the effect from 10 min through 50 min after the APO as compared with diluent. Doses of 0.2 and 1.0 mg/kg of MIF-1 also enhanced stereotypy at 50 min after APO.

In Fig. 3, the stereotypy induced by 2.0 mg/kg of APO was suppressed by MIF-1 rather than potentiated. ANOVA showed that MIF-1 significantly suppressed the stereotypy induced by 2.0 mg/kg of APO, $F(3,44)=3.21$, $p<0.05$. By DNMRT, 1.0 mg/kg of MIF-1 suppressed the stereotypy 10 min through 60 min after APO and 0.2 mg/kg of MIF-1 also suppressed it at 20 min.

Figure 4 summarizes the dose-response data. MIF-1 (1.0 mg/kg) suppressed the stereotypy induced by 2.0 mg/kg of APO but potentiated that induced by 0.5 mg/kg of APO. The effect of MIF-1 on the stereotypy induced by 1.0 mg/kg of APO, however, indicated an inverted U-shaped dose-response relationship.

Experiment 2

This study, performed three months later (February/March), re-tested the effects of 0.5 and 2.0 mg/kg of APO at doses of MIF-1 that were extended to 5.0 mg/kg. Different rats were used.

Figure 5 illustrates the effect of MIF-1 on the stereotypy induced by 0.5 mg/kg of APO. ANOVA showed no significant main effect of treatment, but the time × treatment interaction was statistically significant, $F(21,196)=2.06$, $p<0.01$. DNMRT showed that 5.0 mg/kg of MIF-1 potentiated stereotypy at 40 and 50 min after APO, 1.0 mg/kg of MIF-1 enhanced it at 20 and 50 min after APO, and 0.5 mg/kg of MIF-1 potentiated it at 10 min after APO.

Figure 6 shows the influence of MIF-1 on the stereotypy induced by 2.0 mg/kg of APO. Similar to Experiment 1, MIF-1 significantly suppressed the stereotypy induced by 2.0 mg/kg of APO, $F(3,28)=3.18$, $p<0.05$. The time × treatment interaction also was significant, $F(21,196)=2.39$, $p<0.01$. DNMRT indicated that 0.5 mg/kg of MIF-1 significantly suppressed stereotypy 10 through 50 min after APO compared with diluent, and 0.5 and 1.0 mg/kg MIF-1 inhibited it at 50 min after APO.

Experiment 3

This study, performed in May/June, examined the influence of Tyr-MIF-1 on the stereotypy induced by 0.5 and 2.0 mg/kg of APO. Doses of Tyr-MIF-1 used in this study were 0.2, 0.5, 1.0 and 5.0 mg/kg. ANOVA showed no main effect of treatment on the stereotypy induced by 0.5 mg/kg APO

(Fig. 7) or 2.0 mg/kg APO (Fig. 8). However, DNMRT indicated that Tyr-MIF-1, like MIF-1, enhanced stereotypy induced by 0.5 mg/kg of APO and suppressed that induced by 2.0 mg/kg of APO. With 0.5 mg/kg APO, 5.0 mg/kg of Tyr-MIF-1 potentiated stereotypy induced at 40 through 60 min, 1.0 mg/kg of Tyr-MIF-1 potentiated it at 10 and 30 min through 50 min, 0.5 mg/kg of Tyr-MIF-1 potentiated it at 30 min, and 0.2 mg/kg Tyr-MIF-1 potentiated it at 10 and 20 min after APO.

By contrast, the stereotypy induced by 2.0 mg/kg of APO was suppressed by 1.0 mg/kg of Tyr-MIF-1 20 through 40 min after APO. The stereotypy induced by 2.0 mg/kg APO was also suppressed by 0.5 mg/kg of Tyr-MIF-1 at 10 and 70 min and by 0.2 mg/kg of Tyr-MIF-1 at 10 and 80 min.

DISCUSSION

MIF-1/Tyr-MIF-1 have been found to exert an inverted U-shaped dose-response relationship in various studies since first described in 1971 [5, 11, 12, 15, 21, 23, 31, 34, 35]. Recently, we found that single doses of MIF-1 and Tyr-MIF-1 also suppressed haloperidol-induced catalepsy in a similar inverted U-shaped dose-response pattern [17]. Some evidence for inverted U-shaped dose-response relationships of MIF-1 and Tyr-MIF-1 was also observed in the present study with APO-induced stereotypy. On a molar basis, each animal that had been injected by weight (mg/kg) received relatively less Tyr-MIF-1 than MIF-1; this raises the possibility that at least at the low dose of APO (0.5 mg/kg) Tyr-MIF-1 may be more effective than MIF-1.

The results were generally consistent in the three main experiments, but variation was observed. Since the studies were performed in a temporary building not containing the fine environmental control now available to us, differences in such factors as temperature, humidity, and noise might have influenced the results. It is also possible that seasonal variables may have been responsible. The experiments were performed in three periods spanning an eight month period. The endogenous rhythm of dopamine receptor binding, measured with ^{3}H-spiroperidol in rat striatum and dextrobutaclamol, has been reported to vary greatly at different times of year [28].

More evident was the biphasic response to MIF-1 and Tyr-MIF-1 for APO-induced stereotypy that reflected the dose of APO. That is, the stereotypic response induced by a low dose of APO was potentiated by the peptides whereas the response induced by a high dose of APO was suppressed. This suggests that the effect of these peptides on APO-induced stereotypy is limited by the dose of APO used. Although the mechanism of this biphasic effect of MIF-1 and Tyr-MIF-1 is unclear, at least two possible explanations should be considered. The first is that MIF-1 and Tyr-MIF-1 indirectly regulate DA neuronal activity. The second is that the effects of these peptides result from actions on different DA-containing brain loci.

Concerning the first possibility, APO mimics the intrinsic activity of endogenous DA at DA-receptor sites [30]. The stereotypic behavioral patterns induced by DA agonists in rats can be differentiated into at least two components; sniffing generally occurs at lower doses of drug whereas gnawing, biting and licking usually occur at higher doses [7,8]. The development of these behavioral patterns has been linked with the function of the striatum [1,9]. In the present study, the stereotypy reflected this dose-response relationship of APO [29]. Since neither MIF-1 nor Tyr-MIF-1 elicited any behavioral changes by themselves, the peptides might influence striatal DA neuronal activity which in turn may be correlated with the stereotyped behavioral pattern induced by APO.

Concerning the second possibility, studies involving electrolytic lesions of the brain have suggested a differential involvement of the DA-containing mesolimbic areas with the mediation of the different stereotypic components in rats. Lesions placed in the nucleus amygdaloideus centralis have been shown to selectively abolish the stereotypic motor patterns of gnawing, biting, and licking induced by APO and other stereotypic agents, while lesions placed in the tuberculum olfactorium and nucleus accumbens septi more effectively reduced the stereotypic sniffing or head and limb movements [7,8]. Therefore, the biphasic effect of MIF-1 and Tyr-MIF-1 found in the present study may depend on the characteristic responsiveness of various brain loci to the peptides. This also appears to be supported by the findings that MIF-1 decreased DA utilization in the nucleus caudatus and the globus pallidus while increasing it in the nucleus dorsomedialis [34].

In addition, it has been shown that MIF-1 and Tyr-MIF-1 can act as opiate antagonists since these peptides block the antinociceptive actions of opiates [13, 15, 22–24, 37, 38]. Naloxone, the non-peptide opiate antagonist, can both attenuate and augument APO-induced behavior, and has been suggested to exert presynaptic as well as postsynaptic activity on the brain DA system [18].

In conclusion, the effects of MIF-1 and Tyr-MIF-1 on APO-induced stereotypy can result in an inverted U-shaped dose-response relationship. The biphasic stereotypic effect of either potentiation or suppression exerted by these peptides appears to reflect DA activity as influenced by the dose of APO.

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