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MSH and MIF-I in Animal Models of Tardive Dyskinesia

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DAVIS, K. L., A. J. KASTIN, B. A. BEILSTEIN AND A. L. VENTO. *MSH and MIF-I in animal models of tardive dyskinesia.* PHARMAC. BIOCHEM. BEHAV. 13(1) 37–40, 1980.—α-Melanocyte stimulating hormone (MSH) and MSH release inhibiting factor (MIF-I) were tested for their effects on animals with prior exposure to haloperidol. Such animals are known to have an augmented stereotypic response to dopamine agonists and have been used as an animal model of tardive dyskinesia. Both MSH and MIF-I increased the stereotypy that followed the administration of the lowest dose of apomorphine (0.125 mg/kg), suggesting that MSH and MIF-I might weakly increase dopaminergic transmission.

α-melanocyte-stimulating hormone (MSH) MSH release inhibiting factor (MIF) Tardive dyskinesia
Apomorphine Autoreceptor

α-MELANOCYTE-STIMULATING hormone (MSH) and MSH release inhibiting factor (MIF-I) have been found to affect dopamine related movement disorders in man. MSH aggravated the symptoms of Parkinson's disease and MIF-I reduced the rigidity and temor of patients with this disorder [1, 3, 7, 8 14, 15, 19, 20, 31]. The effect of MIF-I in patients with Parkinson's disease is consistent with the peptide's suppression of oxotremorine-induced tremor and potentiation of the effects of L-DOPA [6, 17, 18, 26, 28, 29, 30, 35], in rodents. However, there are a number of other clinical and preclinical reports that are more difficult to reconcile with the positive effects of MIF-I and opposite effect of MSH on patients with Parkinson's disease. For example, the action of α-MSH in potentiating L-DOPA-induced activity in mice would not predict its aggravation of the symptoms of Parkinson's disease. Furthermore, MIF-I has been observed to diminish L-DOPA-induced dyskinesia, although this finding has not been consistent [19,36]. Drugs improving the symptoms of Parkinson's disease are not known to also improve L-DOPA-induced dyskinesia. Finally, MIF-I in a dose comparable to that which potentiates L-DOPA-induced behavior in mice, may be associated with a transient reduction in the abnormal involuntary movements of patients with tardive dyskinesia [13].

If MIF-I increases striatal dopaminergic activity as the L-DOPA potentiation test suggests, it should aggravate the symptoms of patients with tardive dyskinesia. Thus, the ability of MIF-I to improve patients with Parkinson's disease, L-DOPA induced dyskinesia, and perhaps tardive dyskinesia cannot be simply explained on the basis of the drug's effect on dopaminergic transmission. However, the actions of MSH and MIF-I seem dose-dependent, and it is conceivable that different doses of these peptides could differentially alter dopaminergic activity. Consequently, an investigation of the effects of MIF-I on an animal model of tardive dyskinesia seems justified. Furthermore, since drugs that aggravate the symptoms of Parkinson's disease have been reported to reduce the abnormal movements of patients with tardive dyskinesia [22], MSH was also tested in an animal model of tardive dyskinesia.

METHOD

Animals

Naive albino male Sprague-Dawley rats weighing 180–200 g were housed in groups of five with free access to food and water, an ambient temperature of 21°C, and a controlled 12 hr on/12 hr off light/dark cycle.

Drug Administration

Solutions of apomorphine hydrochloride (Merck), haloperidol hydrochloride (McNeil), MSH and MIF-I were freshly prepared and administered. Dosages of apomorphine and haloperidol refer to the salts and all drug dosages were calculated for body weight of the animals. Weights were monitored weekly. All drugs were given between noon and 4:00 p.m.

Assessment of Stereotyped Behavior

Stereotyped behavior was assessed by two observers blind to the pretreatment regimen of the animals. Beginning

two minutes before the apomorphine injection and continuing for 60 minutes, the animals were rated for 45 second periods every 10 minutes. The assessment of stereotypy has been previously described [12]. Interrater reliability with this scale was high ($r>0.90$).

Assessment of Locomotor Activity

Immediately after injection, rats were replaced in the clear plastic cages (43×21.5×50 cm) in which they had been housed from the start of the study. Each cage was quadrisected by three photocells that recorded the number of times an animal crossed any of the beams.

Statistics

Unpaired *t*-tests and step-wise regression were used to determine differences between treatment groups.

Experiment 1: The Effect of MSH on the Animal Model of Tardive Dyskinesia

Thirty-five naive animals received daily subcutaneous (SC) injections of 0.5 mg/kg haloperidol for four weeks. One week after discontinuation of chronic haloperidol treatment, all animals were challenged with decreasing doses of apomorphine (1.0, 0.5, 0.25, 0.125 mg/kg SC) on four consecutive days. Each animal received only one dose per day in the described sequence. Fifteen of these rats received 100 μg/kg α-MSH dissolved in a diluent of 0.01 M acetic acid in normal saline by SC injection during the one week after discontinuation of haloperidol and the four days of challenge with apomorphine. Twenty more rats served as a control groups and received 1 ml/kg SC of diluent. Both MSH and saline were given 20 minutes before the injections of apomorphine.

Experiment 2: The Effect of MIF-I on the Animal Model of Tardive Dyskinesia

Thirty naive animals were treated identically to the animals in Experiment 1 except that MIF-I was used instead of MSH. Fifteen animals were used as controls, and 15 animals received MIF-I (100 μg/kg).

Experiment 3: The Effect of Multiple Injections of MSH on Locomotor Activity Over Time

Five naive rats received daily injections of 100 μg/kg α-MSH SC for five days. Immediately after each injection, the animals were placed in the locomotor activity boxes. Activity was monitored for 60 minutes.

Experiment 4: The Effect of Various doses of MSH on Locomotor Activity

Ten doses of MSH were tested: 0, 20, 40, 60, 80, 100, 120, 140, 160 and 180 μg/kg. The six doses from 0–100 μg/kg inclusive were administered in a Latin Square design to ten naive rats. Ten additional rats were tested with both 120 μg/kg and 140 μg/kg on two consecutive days: five received 120 μg/kg the first day and 140 μg/kg the second day and the other five received 140 μg/kg the first day and 120 μg/kg on the second day. This same design was used to test 160 μg/kg and 180 μg/kg with ten more naive animals.

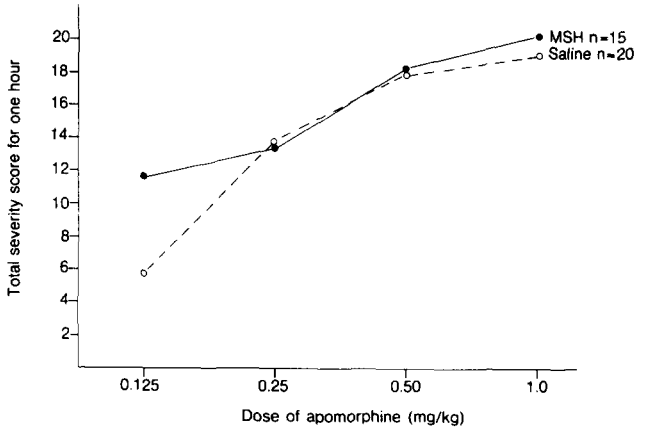

FIG. 1. The effect of MSH on apomorphine-induced stereotypy in animals pretreated with haloperidol.

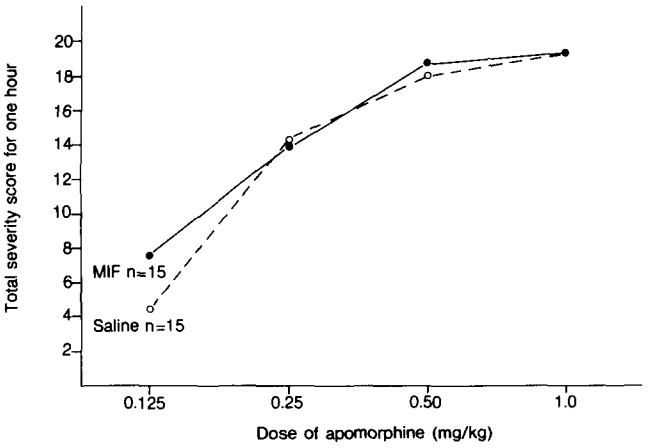

FIG. 2. The effect of MIF-I on apomorphine-induced stereotypy in animals pretreated with haloperidol.

RESULTS

Experiment 1

The effect of acute administration of 100 μg/kg of α-MSH on apomorphine-induced stereotypy in animals with a previous exposure to haloperidol is shown in Fig. 1. Statistical analyses demonstrated there was no significant difference in the severity of stereotypy between animals injected with MSH and control animals at all doses of apomorphine greater than 0.125 μg/kg. However, MSH seemed to exert its greatest effect at the lowest dose of apomorphine, 0.125 μg/kg ($p<0.01$ by unpaired *t*-test).

Experiment 2

The effect of acute administration of 100 μg/kg of MIF-I on apomorphine-induced stereotypy is shown in Fig. 2. As in Experiment 1, there was no significant difference between experimental and control animals on severity of stereotypic behavior at most doses of apomorphine. Again, as in Experiment 1, the greatest difference between MIF-treated and control animals was seen at the lowest dose of apomorphine, 0.125 μg/kg ($p<0.01$ by unpaired *t*).

TABLE 1

EFFECT OF CHRONIC ADMINISTRATION OF α-MSH (100 μg/kg) ON LOCOMOTOR ACTIVITY

Day	Total locomotor activity $\bar{X}$ SEM
1	297.6 ± 45.7
2	234.2 ± 35.9
3	244.4 ± 13.9
4	304.0 ± 48.8
5	242.6 ± 46.8

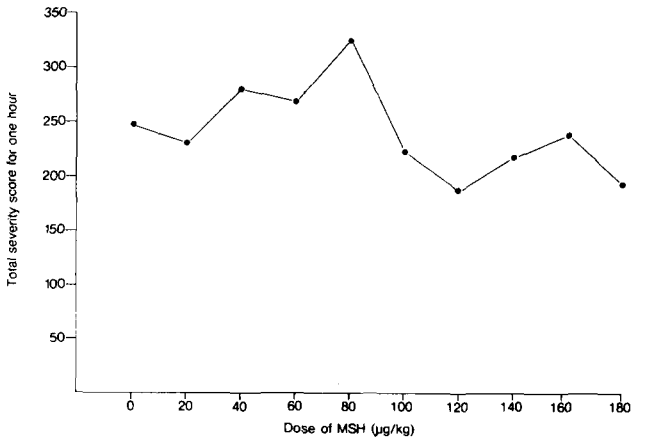

FIG. 3. The effect of MSH on locomotor activity.

Experiment 3

Statistical analyses of the data from animals injected for five days with MSH to determine the effects of chronic administration of MSH on locomotor activity revealed no significant increase or decrease in locomotor activity on any day. The results are shown in Table 1.

Experiment 4

Figure 3 shows the results of various doses of MSH on locomotor activity. As indicated by this graph, there was no monotonic dose-response to MSH, but there did appear to be a maximum response at 80 μg/kg MSH and a minimum response at 120 μg/kg MSH. A single F value for all doses of MSH was obtained by pooling the sums of squares and error terms from separate analysis done on each group in this experiment. This analysis, done over all doses, did not indicate any significant differences in this study.

DISCUSSION

MIF-I and α-MSH did not suppress apomorphine-induced stereotypy in animals with a previous long-term exposure to haloperidol. In contrast, choline chloride, a drug with some efficacy in diminishing the abnormal involuntary movements of tardive dyskinesia [10, 11, 16, 33], is known to decrease the severity of apomorphine-induced stereotypy in rats with a previous exposure to haloperidol [12]. Thus, the results from this model would not seem to indicate a role for either MSH or MIF-I in low doses as an effective treatment for patients with tardive dyskinesia.

However, apomorphine-induced stereotypy was augmented by MIF-I and α-MSH after the administration of the lowest dose of apomorphine (0.125 mg/kg). This effect is consistent with the reported action of both of these brain peptides to potentiate L-DOPA-induced locomotion in mice.

It is also in agreement with the demonstration that a similar dose of MIF-I produced stereotypy in cats [25]. Yet, in two other investigations, MIF-I in doses up to 20 mg/kg had no effect on apomorphine-induced stereotypy [9,23]. The apparent discrepancy between these two investigations and the present results are probably a function of the larger doses of apomorphine employed in these studies. The present experiment found augmentation of stereotypy only after a dose of 0.125 mg/kg apomorphine. MIF-I had no effect in the stereotypy induced by 0.25 mg/kg, 0.50 mg/kg, or 1.0 mg/kg. Thus, according to the present results, MIF-I would not be expected to have an effect on stereotypy induced by large doses of apomorphine. The investigations in which MIF-I did not augment apomorphine-induced stereotypy utilized 2.5 to 5.0 mg/kg of apomorphine [9,23]. The fact that MIF-I could augment apomorphine-induced stereotypy after 0.125 mg/kg of apomorphine suggests that both MIF-I and MSH may enhance dopaminergic neuronal activity. However, this effect is so weak that it may only become apparent in animals with dopamine receptors made supersensitive by long-term haloperidol pretreatment or 6-hydroxydopamine [24].

It has been shown that low doses of amphetamine, apomorphine, and L-DOPA inhibit the firing rate of dopaminergic neurons [4]. The behavior sequela of this action of low dose apomorphine (0.05 mg/kg) is to decrease locomotor activity below basal levels in mice [5]. The effects of small doses of dopaminergic agents to inhibit dopaminergic activity, diminish locomotor activity, and even improve the symptoms of schizophrenia [32,34], have been attributed to stimulation of a negative feedback circuit activated by dopamine agonists and located presynaptically.

The weak augmentation in dopamine activity suggested by the effect of MSH on the animal model of stereotypy raises the possibility that MSH might also have "autoreceptor" activity. Hence, the action of various doses of MSH on locomotor activity was tested. At no dose of MSH was locomotor activity significantly decreased below basal levles, in agreement with a previous study using only one dose [21]. Thus, there was no indication that MSH was exerting an "autoreceptor" effect comparable to that seen with a low dose of apomorphine. Nor did these doses of MSH significantly increase locomotor activity above basal levels. However, it should be noted that these effects are usually best demonstrated in mice, whereas the studies reported here used rats.

In conclusion, these results raise the possibility of a weak, direct or indirect, interaction of α-MSH and MIF-I with dopaminergic transmission. This possibility deserves renewed attention in models sensitive to relatively small changes in dopaminergic activity.

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