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# MIF, TRH, and Simian Social and Motor Behavior

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CROWLEY, T. J. AND M. HYDINGER. *MIF, TRH and simian social and motor behavior.* PHARMAC. BIOCHEM. BEHAV. 5: SUPPL. 1, 79–87, 1976. – MSH-release-inhibiting factor (MIF) and thyrotropin-releasing hormone (TRH) both have been reported to modify mood and activity in man. These two hypothalamic peptides were given intramuscularly across a 1000-fold dose range to 5 juvenile male *M. nemestrina* monkeys living in a social group. Motor activity was recorded automatically, and an observer counted various social behaviors. MIF increased motor activity for up to 11 hr. It decreased quiet foraging behavior, but did not change behaviors of social interaction. TRH did not stimulate motor behavior; high doses strongly suppressed it and produced apparent somatic distress. TRH increased behaviors of quiet rest and association and decreased environmental exploration and low-intensity dominance behaviors. The lowest dose of TRH increased social play. Two monkeys showed repetitive, stereotyped behaviors even in baseline observations, and certain doses of TRH and MIF may have increased the frequency of these behaviors.

Peptides Monkeys Motor activity Animal behavior Ethology

TWO peptide compounds which occur naturally in the central nervous system of man and animals have been reported to modify human mood and activity. One of these peptides inhibits release from the pituitary of melanocyte-stimulating hormone in some assays (see [29]). This melanocyte-stimulating-hormone-release-inhibiting factor (MIF, l-prolyl-l-leucyl-glycinamide, also known as MSH-release inhibiting hormone, or MRIH-I) has behavioral effects similar to the antidepressant drugs in certain animal screening tests [29]. Moreover, in a group of 11 depressed patients, 7 reportedly improved significantly during MIF administration [14]. MIF, which is mildly to moderately effective as an anti-Parkinson agent [7, 16, 26], is also said to elevate mood and drive, or to provoke restlessness, in Parkinsonian patients [16].

The other compound, thyrotropin-releasing hormone (TRH, pyroglutamyl-histidyl-proline-amide, also referred to as thyrotropin releasing factor, lopremone, and protirelin) has been reported to have antidepressant properties [27, 43, 44, 55]. Even psychologically normal people reportedly responded to TRH with relaxation, euphoria, and a sense of increased energy [57]. In a study of 3 Parkinsonian patients, 2 were said to develop "a distinct feeling of well being" after TRH injections, although the drug did not improve motor symptoms [35]. However, numerous investigators also report that TRH is not an effective antidepressant [4, 8, 12, 13, 15, 18–21, 23, 34, 36, 54]. The initial suggestion that TRH might be useful in treating schizophrenia [56] has also been disputed [11].

But even within the negative reports are suggestions that TRH may alter behavior in subtle ways. The drug is said to have stimulant-like effects on the EEG and to increase the "drive for food, sex, work, and hobbies" [23]. After TRH injections a group of depressed patients showed "a slight decrease in tension, a transient and slight increase in energy, and an enhanced capacity to cope with feelings" [34].

Most clinically effective antidepressant drugs are believed to exert little effect on normal mood states; these peptides are of interest in part because they reportedly elevate mood in nonpsychiatric, as well as in clinically depressed, populations. Surprisingly, studies into the effects of these compounds on the affective or social behaviors of human beings have progressed with essentially no research into the drugs' effects on comparable behaviors in animals treated with TRH or MIF.

Recent reports from our laboratory [9,10] and elsewhere [17] have demonstrated some value in ethological analyses of drug-induced behavioral changes among group-living monkeys. Ethanol, methamphetamine, pentobarbital, morphine, and methadone alter the frequency of important social behaviors, such as those of dominance, submission, association, quiet rest, and sex. Certain clinically-observed drug effects may have been clarified by those studies. Since MIF and TRH were reported to elevate mood in normal as well as in depressed human subjects, it seemed useful to carefully quantify the drugs' effects on social and affective behavior in normal animals. A demonstration of modified affective behavior after exogenous administration of naturally occurring brain peptides could have important consequences, suggesting theoretical additions or alternatives to the widely accepted but increasingly complex [3] amine theories of affect. Accordingly, we have now examined the effects of TRH and MIF on the social and motor behaviors of members of a monkey group residing in our laboratory.

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## METHOD AND PROCEDURES

Animals were 5 sexually immature male *Macaca nemestrina* (Pigtail macaque) monkeys ranging from 20 25 months of age and from 2.2- 2.7 kg at the beginning of the study. One animal had been used about 15 months earlier in research on the behavioral and physiological effects of maternal separation [49]. For many months before the experiment, and throughout its duration, the animals lived in a room measuring 3.5 by 3 by 2.5 m with about 20 other male and female monkeys of comparable age; one sexually mature male was dominant in this group. The room, fitted with bars and shelves for climbing and a wire-mesh ceiling for brachiation, was lighted from 0700 to 1900 (± 10 min) and was maintained at a constant temperature of 24.4°C. Water was continually available, and Purina monkey chow biscuits and fruit were thrown to the group each morning. The floor of the room was covered with sawdust.

Each animal wore a leather vest with an attached 200 g motion-transducer/FM-transmitter backpack for 4 weeks before, and throughout, the experiment. These units provided continuous, telemetered counts of the steps and jumps of the animals.

An observer, looking into the room through a one-way window, counted the frequency of various social behaviors in the drug-treated subjects, recording them on a checklist. The count included associative behaviors, such as proximity to another animal, contact with another, receiving or providing grooming; rest behaviors, including upright and recumbent quiet resting or sleeping; dominance behaviors, including characteristic threat motions, brow jerks, displacements, food-stealing, bites, manual attacks, and pursuit; submissive behaviors, such as grimaces and lip-smacking, crouching, being displaced, defensive aggression, withdrawal, and flight; social play, rough and tumble play-fighting, which differs from true fighting in its lack of defensive aggression, submissive vocalization, crouching, or flight by either animal; environmental exploration of the window, the sawdust or other objects in the room; sexual behaviors of masturbation, anal exploration of females, and mounting, being mounted, or presenting (which may also be a dominance-submissive behavior for these animals); self-directed behaviors of biting, scratching, or auto-grooming; eating biscuits; and abnormal movements such as ataxic clumsy motions, tremor, or peculiar repetitive and stereotyped activity. Most of these behaviors have been described previously in detail for this species [33].

In this ethological technique, well-defined and objectively described behaviors [33] are actually counted; these are not mere ratings of "aggressiveness", "sexual interest", etc. Published reports from elsewhere [5], as well as unpublished data from our laboratory, have shown about 90 percent interobserver agreement in these behavioral frequency counts. In this study all observations were made by one person (MH).

Only one animal was treated per day. The animal was removed from the pen and received an intramuscular injection at about 0815. The monkey was then returned to the pen, and automatic recordings of motor activity began at 0830, continuing for the next 24 hr. Behavioral observations were made between 0830 and 0930, with food thrown into the pen at 0900. Observations were again made between 1030 and 1130 and between 1300 and 1400. The observer followed a rigid schedule, watching the subject for 15 sec and then recording data for 15 sec. Any behavior on the checklist was counted once if it occurred one or more times in any 15-sec observation. Scheduled rest breaks for the observer resulted in a total of 60 min of actual observation per day, together with 60 min for recording data.

Saline solutions provided 0, 0.01, 0.1, 1.0 or 10 mg/kg of either TRH or MIF in an injection volume of 1 - 2 ml. Solutions were mixed at the beginning of the experiment in multiple-dose, rubber-stoppered vials and were frozen when not in use. Each animal received each dose once in a counterbalanced, concurrent Latin square design which permitted evaluation of the two drugs during the same experimental period (July to September, 1975). No subject received injections more often than once per week. The observer injected the monkeys from the stock vials which were identified only by code numbers; she thus remained unaware of which drugs or doses were given on any day.

Drug effects upon the individual behaviors, or classes of behaviors (such as the class of dominance behaviors), were assessed by analyses of variance (ANOVA). Two-way analyses (5 animals × 5 doses) were applied to behaviors totaled across the three observation sessions of each day; three-way analyses (5 animals × 5 doses × 3 observation sessions) were also used to assess the time course of drug effects. Motor activity data were similarly evaluated by three-way analyses, using 5 animals × 5 treatments × $n$ hr (where $n$ = some number of hours following the drug treatment).

## RESULTS

### *MIF*

Figure 1 shows the time-course of motor activity of the 5 animals after the 5 doses of MIF. All 4 active doses of the drug stimulated motor activity in comparison to the saline injections. The 0.1 mg/kg dose produced the greatest stimulation. The elevation of motor activity persisted throughout the lights-on period, but may have peaked slightly 4 6 hr after the injections. Considering only the first 4 hr after drug administration, the 5 doses did not differ significantly in their effects on motor activity; but across the full 11 hr of postdrug, lights-on time, the motor effects of the 5 doses differed very significantly (three-way ANOVA, 5 animals × 5 doses × 11 hr; dose effect, $p<0.001$). This dose effect is shown more clearly in Fig. 2, which presents the total motor activity counts for the entire 11 hr following drug administration. There were no significant differences among doses in motor activity during the 12 hr of darkness, nor in the 1½ hr following drug administration. There were no significant differences among doses in motor activity during the 12 hr of darkness, nor in the 1½ hr after lights-on the next day.

There was no *de novo* production of repetitive stereotyped motor behaviors by MIF. However, 2 monkeys showed some stereotyped activity in baseline observations, perhaps as a result of early caging. One animal rapidly and repeatedly paced, upside down, in circles on the ceiling; the other habitually twisted his torso in a full circle while walking or running. Figure 3 shows that the stereotyped behavior increased considerably in one animal after MIF, 0.1 mg/kg, and in the other after 1.0 mg/kg. We could not statistically evaluate these changes.

MIF produced no vomiting, tremor, ataxia, nor other apparent side effects. Neither did the drug significantly alter the frequency of occurrence of any social behavior.

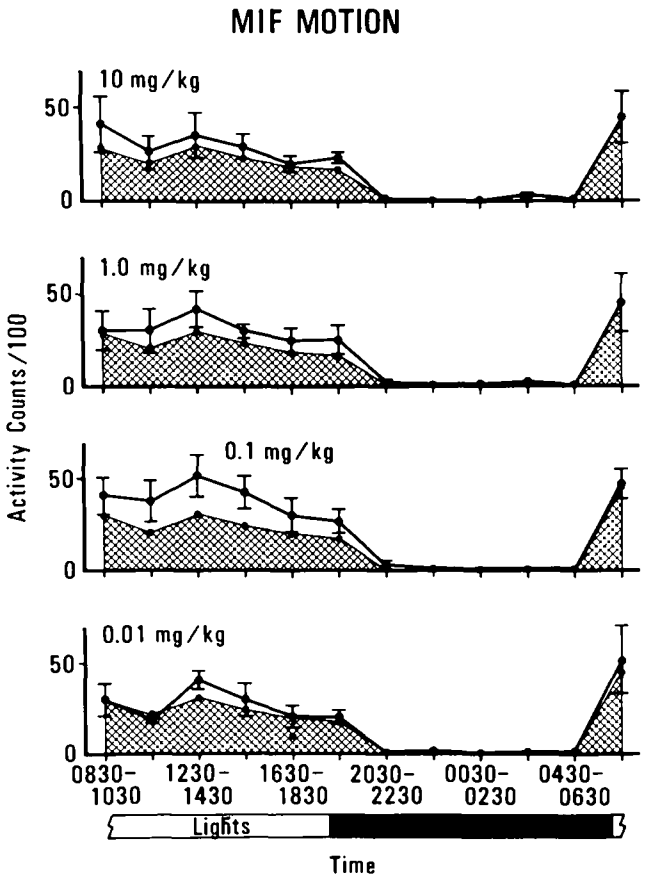


FIG. 1. Telemetered motor activity counts in 2-hr blocks for 5 monkeys after MIF injections (mean ± SEM). Counts after saline injections (shaded area) repeated in each panel. Bottom bar shows light dark period.

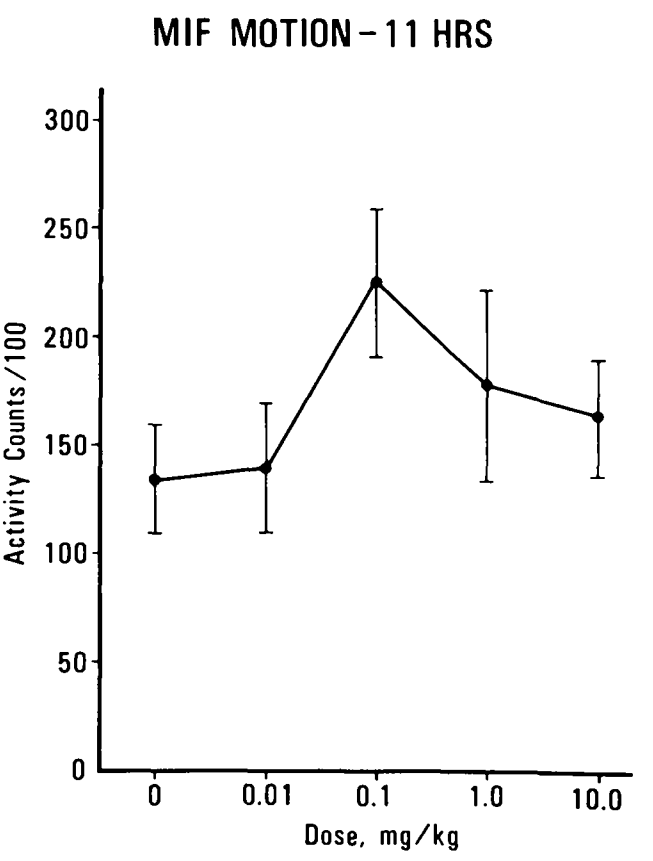


FIG. 2. Motor activity counts (mean ± SEM) during first 11 hrs after MIF injections, 5 monkeys. Dose on log scale.

The number of 15-sec intervals in which biscuits were eaten was not changed by the drug.

The general category, Environmental Exploration, appeared to be modified by MIF. Most of this effect was due to very large changes in the time which the subjects spent in sifting through the sawdust on the floor, apparently in search of minute bits of food. This is a rather quiescent behavior which occurs intermittently even in the presence of an ample supply of food bisquits. Figure 4 shows that under saline conditions this behavior occurred infrequently early in the day and increased later; in comparison to the saline condition the behavior occurred more frequently early in the day after MIF administration, but was much reduced later in the day (three-way ANOVA, 5 animals × 5 doses × 3 hr; dose effect, $p<0.008$). The lower doses of MIF were most effective in altering this behavior as the day progressed.

The effects of MIF are summarized in Table 1. Although MIF very significantly increased motor activity and reduced quiet sawdust-sifting, its effects were nevertheless subtle. The constant and apparently purposeless activity seen in this species after methamphetamine administration [10] did not occur with MIF. Perhaps because the animals continued to rest intermittently and to engage in normal social behavior, the observer remained unaware of the drug's effects at the conclusion of the experiment; even

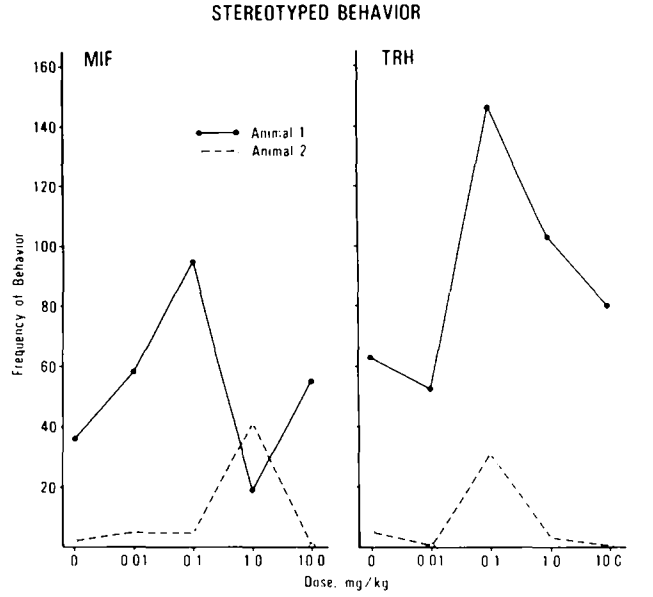


FIG. 3. Daily incidence of stereotyped motor behaviors in 2 susceptible monkeys at various doses of MIF and TRH. Dose on log scale.

TABLE 1

Significant Effects of MIF and TRH on Behavior

| Behaviors | Motor Activity | Stereotypy | Environmental Exploration | Quiescent Rest | Quiescent Associative | Total Hierarchical | Social Play |
|---|---|---|---|---|---|---|---|
| MIF | ↑ | ·? | ↓* | | | | |
| TRH | ↓ | ·? | ↓ | ↑ | · | ↓ | ↑† |

* Decrease in quiescent sawdust-sifting.
† Increase at lowest dose only.

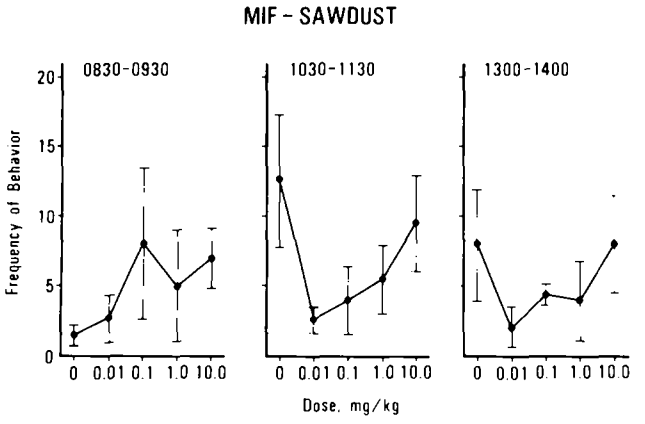


FIG. 4. Mean (± SEM) hourly frequency of sawdust-sifting behavior at 3 times after MIF administration. Dose on log scale.

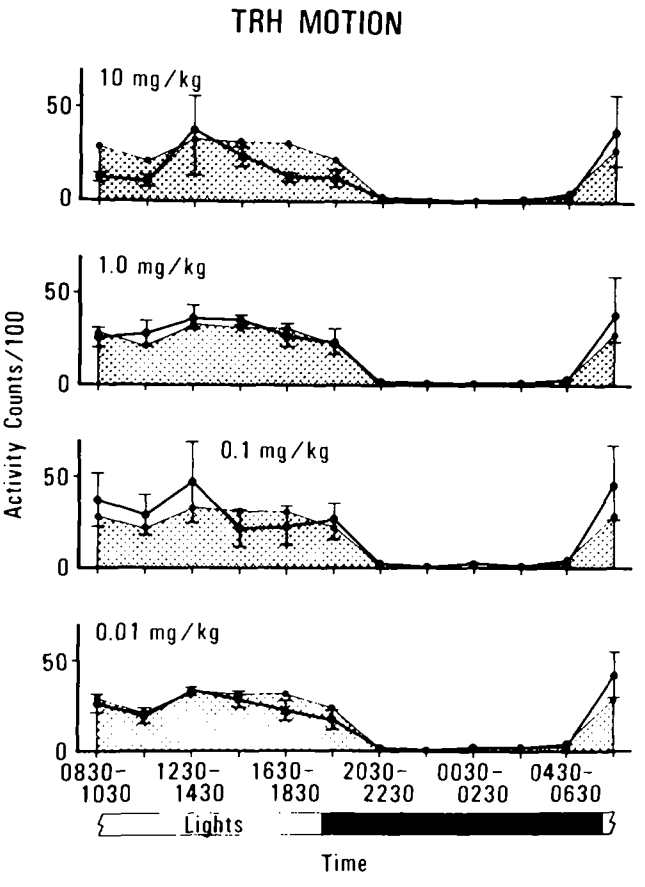


FIG. 5. Motor activity counts in 2-hr blocks for 5 monkeys after TRH injections (mean + SEM). Counts after saline injections (shaded area) repeated in each panel. Bottom bar shows light–dark period.

when she was informed of which vials were part of the MIF study, she could not identify those which contained active drug or saline.

*TRH*

Figure 5 shows the time-course of motor activity following the 5 doses (including saline) in the TRH experiment. The most apparent effect is a marked suppression of motor activity at the highest dose of TRH, together with a tendency for the other doses to reduce activity some 8–12 hr after drug administration. Overall, the 5 activity curves differ significantly from one another across the first 4 hr, and across the first 11 hr, following TRH administration (three-way ANOVA's, 5 animals × 5 doses × 4 or 11 hr; dose effect, respectively, $p<0.002$ and $p<0.001$). The slight rises in activity at the start of the next day after administration (Fig. 5) are not statistically significant, and the drug did not significantly alter motor activity during the lights-out period. Figure 6, which sums the activity counts across these times, emphasizes that the major effect is to reduce motor activity at the highest dose.

The design provided that each animal would receive one saline injection as a control for TRH doses, and another as a control for MIF. The 11-hr motor activity curves following these two sets of saline administrations did not differ significantly from one another (three-way ANOVA, 2 treatments × 5 animals × 11 hr; treatment $p = 0.165$).

Figure 3 shows the post-TRH incidence of motor stereotypies in the two monkeys which occasionally exhibited such behaviors. The incidence increased considerably in both animals at 0.1 mg/kg. These results could not be evaluated statistically.

Shortly after the higher doses of TRH, the monkeys appeared to be ill for about 30 min. Four animals vomited after the 10 mg/kg dose, and two vomited after 1 mg/kg. Motor activity was grossly suppressed during this time; the animals sat quietly, hunched over (Fig. 7). This behavior had abated by the end of the first hour of observation. The monkeys were fed midway through that hour; Fig. 8 shows that the animals ate very little in that first hour after the highest dose of TRH. However, by the 1030–1130 observation the feeding after this dose exceeded that of the

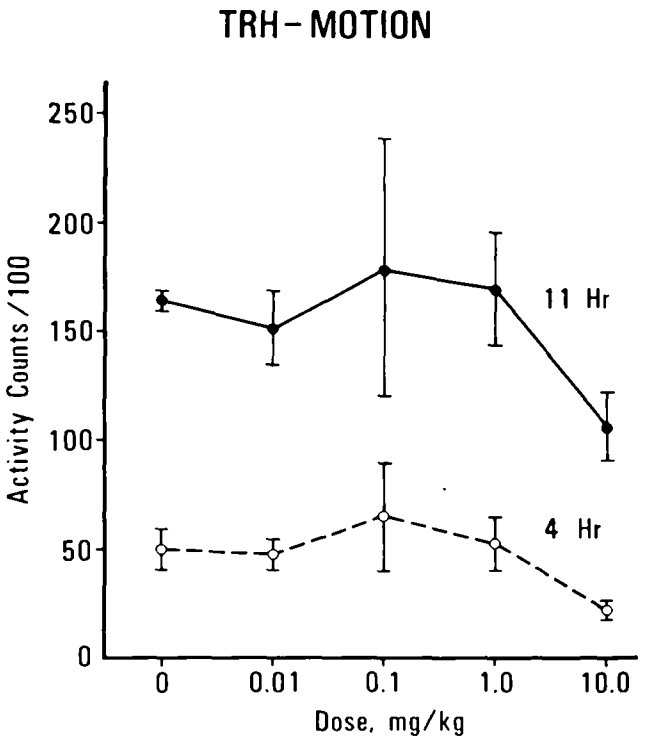


FIG. 6. Motor activity counts (mean + SEM) during first 4 hrs and first 11 hrs after TRH injections, 5 monkeys. Dose on log scale.

saline condition. These effects on feeding, while interesting, were not statistically significant. TRH may also have produced some pruritis; self-scratching increased about three-fold at the highest dose in the first hour (three-way ANOVA, 5 animals × 5 doses × 3 hr; dose effect $p<0.03$).

Several quiescent behaviors increased significantly after TRH. Perhaps in relation to the apparent somatic distress, rest behaviors – sitting or lying alone – increased with dose, especially in the first hour of observation (Fig. 9; three-way ANOVA, 5 animals × 5 doses × 3 hr; dose effect $p<0.023$). Quiescent associative behaviors – sitting quietly with others, grooming, etc. – generally increased with the highest dose, and also rose unexplainably from 1030–1130 after the 0.01 mg/kg dose. These dose effects were significant (Fig. 9; three-way ANOVA, 5 animals × 5 doses × 3 hr; dose effect $p<0.04$). Behaviors of environmental exploration declined after TRH (Fig. 10; dose effect $p<0.03$, three-way ANOVA). This whole class of behaviors declined in frequency; none was uniquely affected.

The higher doses of TRH also reduced the overall occurrence of "hierarchical" behaviors, the sum of the dominance and submissive behaviors which establish the dominance hierarchy within the group (dose effect; $p<0.044$, three-way ANOVA). This decline, which was confined to the first 2 observation sessions, was mainly due to a fall in low intensity dominance behaviors, such as threat movements, stares, brow jerks, and displacements (Fig. 10; $p<0.025$, three-way ANOVA). But despite these changes, there was no statistically significant change in the ratio of dominance to submissive behaviors, in the total of high- plus low-intensity dominance behaviors, nor in the total of submissive behaviors.

One active behavior did increase at the lowest dose of

FIG. 7. *M. nemestrina* (at left) in hunched-over posture after 0.1 mg/kg TRH. Animal wears vest and backpack transducer/transmitter.

TRH. Social play occurred more frequently after 0.01 mg/kg (Fig. 11, $p<0.027$, three-way ANOVA). This dose did not affect motor activity very much; Fig. 5 shows that activity was about equal until 1430 after either saline or the 0.01 mg/kg dose of TRH.

Most of these TRH-induced changes in social behavior were transient; i.e., they were statistically demonstrable only in three-way ANOVA's which considered hour-by-hour changes across the 3 hr of observation, and several were confined only to the first or second observation period. A two-way ANOVA (animal × dose), which considered the 3 hr in combination, revealed only one significant dose-related effect, the increase in associative behaviors ($p<0.033$).

Table 1 reviews the major behavioral effects of the drugs and shows that, while MIF generally increased activity, TRH generally reduced it.

## DISCUSSION

### *MIF*

In this study the tripeptide, MIF, was administered intramuscularly in a thousand-fold dose range to monkeys. MIF is active in mice after oral, intravenous, subcutaneous, or intraperitoneal administration [39], and oral doses in

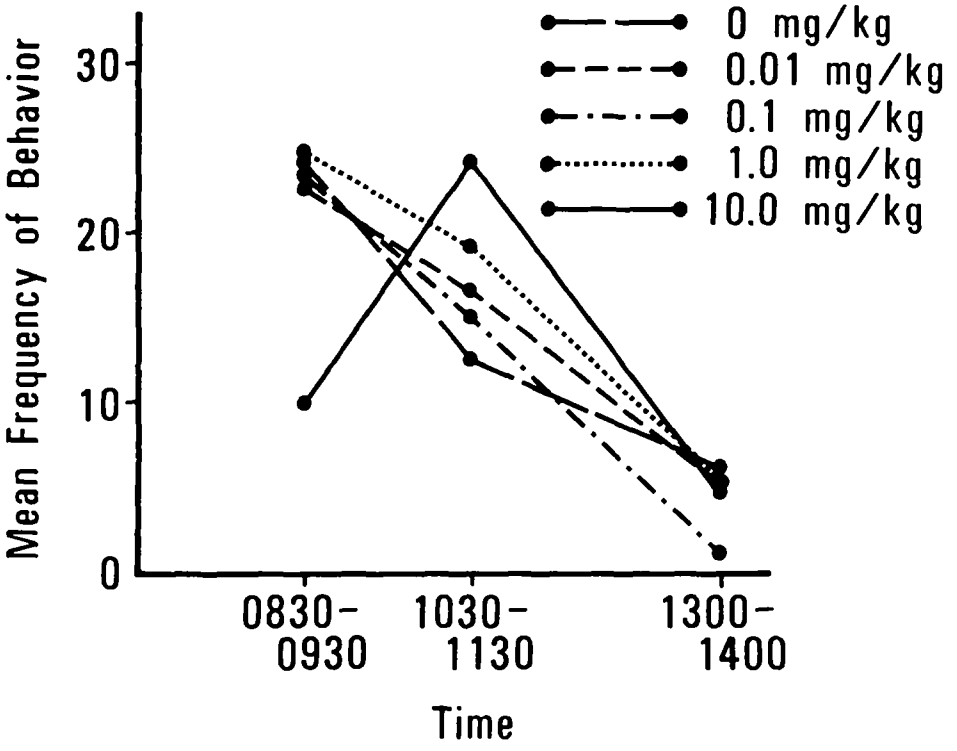


FIG. 8. Mean hourly frequency of biscuit-eating in 5 monkeys after TRH administration, 5 doses.

monkeys after deserpidine-induced sedation [42]. A wide dose range was examined, for in rodents measurable effects reportedly occur between 0.1 mg and 40 mg/kg [22,39]. Human subjects have taken up to 30 mg in intravenous infusions [7,16] or 50 60 mg per day in repeated, oral doses [14,26]. Thus, the doses used here span part of the range used with rodents and bracket the range used with human beings.

MIF very significantly altered the behavior of monkeys in this study. Differences in motor activity after the various doses did not attain statistical significance during the first 4 hr following the injections, but examination of the 11 hr period after the injections showed at least slight activity increases with all MIF doses, and a rise of nearly 75 percent after 0.1 mg/kg. This finding during prolonged recordings may indicate why Kastin, *et al.* [28], were unable to show increased motor activity in rats after MIF; they measured activity for only 3 min beginning 15 min after drug administration. The duration of motor stimulation by MIF is surprising, since the drug's half-life in the blood stream of rats is under 10 min [48]. Presumably, the material exerts CNS effects long after plasma levels have become negligible.

Despite clear evidence of motor stimulation, the monkeys showed remarkably little behavioral disturbance after MIF. Rest behaviors continued to occur without significant change, and dominance, submission, biscuit eating, grooming, and other behaviors persisted unaltered. The monkeys less frequently sifted through the sawdust on the floor, foraging for bits of food; this behavior also declines during methamphetamine stimulation [10].

Methamphetamine consistently causes bizarre, repetitive, stereotyped motor behaviors in this species [10]. Two monkeys which routinely showed stereotypies probably had more of these behaviors after certain doses of MIF, but the drug produced no stereotypies *de novo* in the other 3 monkeys. MIF reportedly induces stereotyped behavior in cats [37], and may cause dyskinesias in some l-DOPA treated Parkinsonian patients [7].

The mechanism for these actions of MIF is of interest. MIF, and probably other compounds (*cf.* review [30]) present in the hypothalamus, inhibit the release of melanocyte-stimulating hormone (MSH) from the pituitary in some conditions. Injected, radiolabelled MIF is concentrated against a gradient in pineal and pituitary, to a lesser extent in hypothalamus, but perhaps not in cerebral cortex [48]. MIF's behavioral effects in part could be secondary to its effects on pituitary MSH, for MSH clearly modifies neurobehavioral function. MSH injections induce high-voltage theta activity in the rat EEG [52], may have similar effects in women [32], and alter evoked response in man [31]. MSH appears to enhance attention in rats [50,51] and man [31].

Apart from effects possibly mediated through MSH, MIF also may have direct actions on brain function. Since MSH is produced in the pituitary, hypophysectomy eliminates MSH responses to MIF. Nevertheless, MIF injections modify the behavior of hypophysectomized mice pretreated with l-DOPA or oxytremorine, and so these drug interactions apparently are not mediated by MSH [40,41]. Thus, it seems likely that MIF alters brain functions directly, in addition to any MSH-mediated effects.

Whatever its mechanism of action, MIF appears to be a subtle but potent, long-acting stimulant in young *M. nemestrina*. Over a broad dose range it produces essentially no unusual social behavior and no grossly apparent somatic distress. Chase, *et al.* [7], reported some drowsiness among Parkinsonian patients receiving MIF, but our findings are much closer to those of Fischer, *et al.* [16], who stated

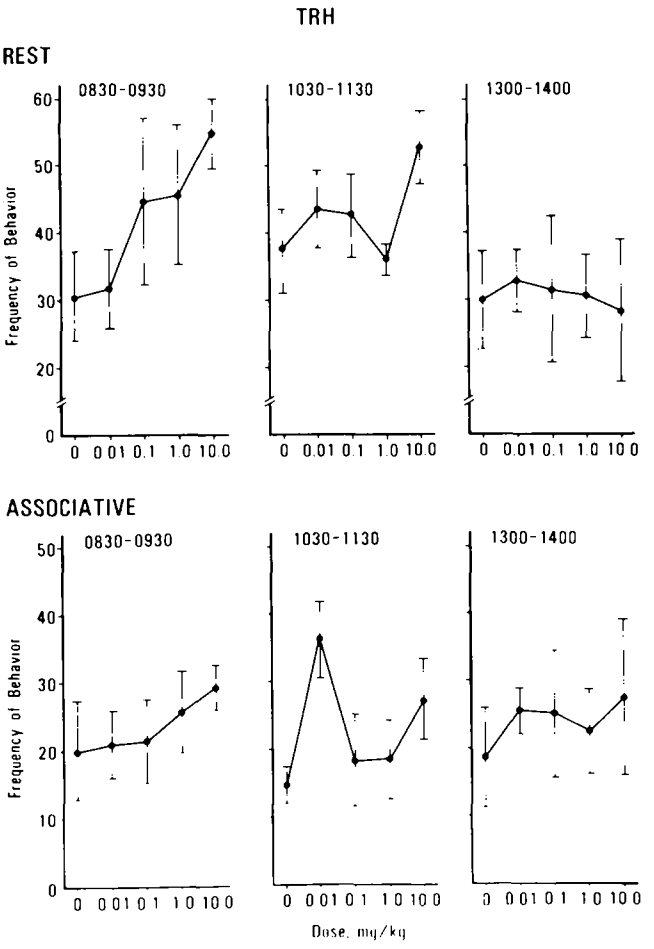


FIG. 9. Mean (+ SEM) hourly frequency of rest and associative behaviors at 3 times after TRH administration. Dose on log scale.

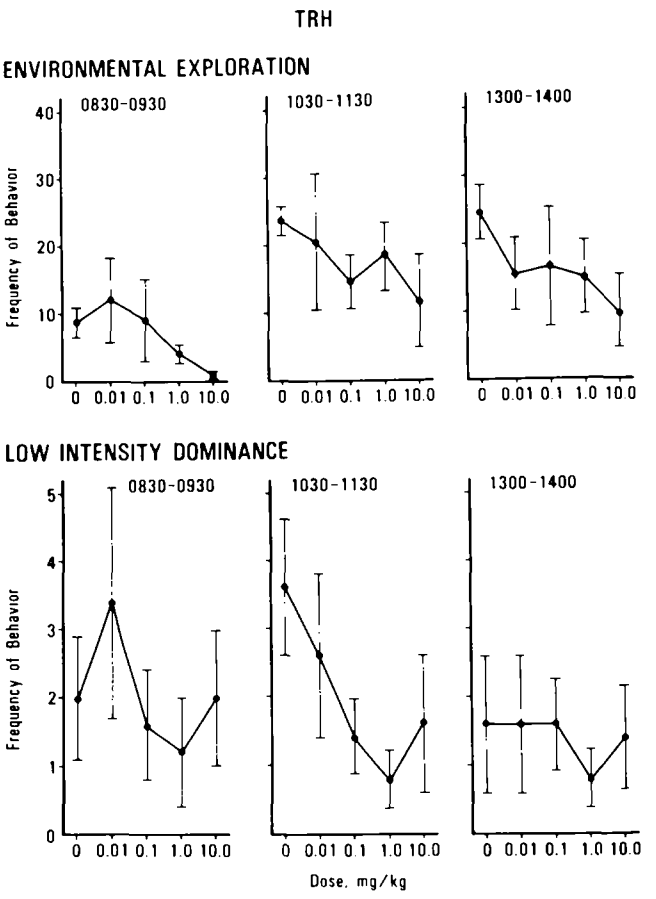


FIG. 10. Mean (+ SEM) hourly frequency of environmental exploratory and low-intensity dominance behaviors after TRH administration. Dose on log scale.

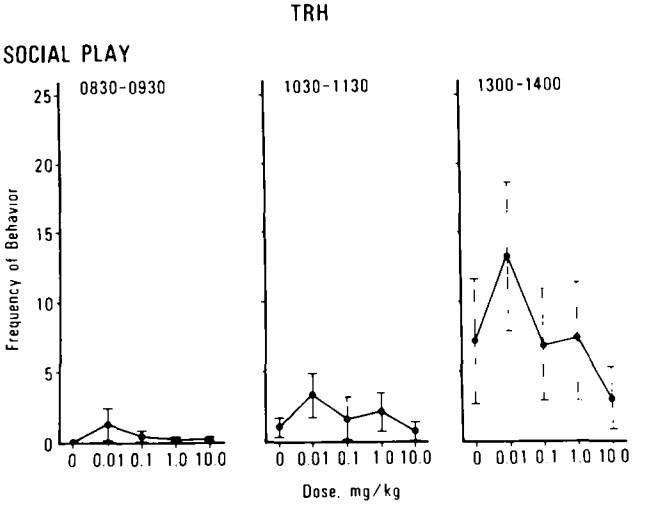


FIG. 11. Mean (+ SEM) hourly frequency of social play at 3 times after TRH administration. Dose on log scale.

that MIF's modest amelioration of Parkinsonism was probably due to "the central stimulating effect of MIF beneficially changing mood, drives and reaction to stimuli". Predictions of drug actions in psychiatric patients from studies in presumably healthy animals must be made with great caution. But if MIF is tested in psychiatric populations its apparent stimulant effect may suggest a possible value in adult anergic, or childhood stimulant-sensitive, disorders. We might also note that stimulant drugs which cause animal stereotypies usually have worsened schizophrenia.

*TRH*

TRH is a tripeptide which occurs in relatively high concentration in the hypothalamus; smaller concentrations, but larger total amounts, are found elsewhere throughout the cerebrum [5, 24, 38]. The cerebral distribution of TRH generally parallels that of the catecholamines [58].

This study examined the behavioral effects in monkeys of intramuscular TRH injections across a thousand-fold dose range. The compound is biologically active in adult human beings after intramuscular [2], intravenous [45,47], and oral [46] administration, producing in each instance prompt release of TSH and prolactin from the pituitary, followed by a release of triiodothyronine ($T_3$) and thyroxine ($T_4$) from the thyroid. Similar endocrine effects occur in young monkeys [25].

Our monkeys were repeatedly injected with TRH, sometimes as often as weekly. But it appears unlikely that cumulative endocrine effects altered our results. $T_3$ and $T_4$

rise dramatically in human beings during prolonged oral administration of TRH, but they return to baseline levels within 1 week when the treatment is stopped [46]; $T_3$ and $T_4$ elevations in man after single doses of TRH are of even briefer duration [46].

TRH had little behavioral effect in the present study unless the drug was given in high doses which produced vomiting, together with a general suppression of eating, motor activity, environmental exploration and hierarchical behaviors. Transient nausea is also commonly reported among human subjects receiving the drug [1].

Most of the observed effects were of brief duration, although motor suppression persisted for many hours after the highest dose, and even the lower doses may have reduced motor activity some 8–12 hr after their administration. "Extensive fatigue" was also noted in a few human subjects 6–10 hours after TRH injections [1]. The failure of TRH to enhance motor activity in these primates was surprising, for intraventricular injections of TRH reportedly activate rats [53]. It does appear that TRH, 0.1 mg/kg, increased motor stereotypies in the two animals which sometimes demonstrated these behaviors.

Our monkeys did show a small but significant increase in social play at the lowest dose of TRH. Thus, we are unable to conclude that the drug has no stimulating properties in primates. This small increase in an active social behavior after a low dose, coupled with a pervasive suppression of active behaviors at higher doses, suggests that dose may be of considerable importance in determining the behavioral effects of TRH. But we must emphasize that the low-dose, TRH-induced increase in social play was slight. This modest change in monkeys would not appear to parallel the suggestion that TRH generally increases the "drive for food, sex and work" [23] in man. Our results certainly do not parallel the report of elevated mood and activity in normal women receiving TRH: "Subject 3 said she felt like dancing down the hall . . . subject 10 did dance down the hall" [57]. But that stimulant effect of TRH in normal human subjects remains in contention; it has been reported that 2.5–160 mg of TRH taken orally in single doses, or 30 mg orally per day for 8 days, has no effect on mood [46]. The latter report would appear to indicate that TRH in man, as in our monkeys, has at best minor effects on drive, activity levels, social behaviors, or affect.

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