

**A COMPARISON OF THE CENTRAL NERVOUS SYSTEM  
STIMULATORY ACTIVITY OF VARIOUS ANOREXIANTS**

**Timothy J. Maher, Ph.D.**  
Assistant Professor of Pharmacology  
Massachusetts College of Pharmacy &  
Allied Health Sciences and  
Research Associate  
Massachusetts Institute of Technology  
Boston, Massachusetts

**Pfeiffer Pharmaceutical Sciences Laboratories  
Massachusetts College of Pharmacy &  
Allied Health Sciences  
179 Longwood Avenue  
Boston, Massachusetts 02115**

**February 6, 1984**

## INTRODUCTION

d-Amphetamine has long been used as an anorectic agent in man due to its ability to alter neurotransmitter release localized most probably within the lateral hypothalamus. A major problem with the use of this agent involves its ability to cause central nervous system (CNS) stimulation. Rats given sufficient doses of d-amphetamine (about 3-4 times as potent as the l isomer in causing CNS stimulation) experience restlessness, tremor, agitation and increased motor activity probably due to stimulation of the reticular activating system and higher brain centers such as the cortex. Whether dopamine or norepinephrine is the released neurotransmitter is not known at present.

A desirable characteristic of an anorectic agent would be its lack of CNS stimulatory activity. One way to quantitate CNS stimulatory activity is to measure locomotion in rats in an open-field apparatus. We have employed this technique to compare doses of amphetamine, phenylpropranolamine, d-norpseudoephedrine and methoxyphenamine that produce significant reductions (50% or more) in food intake in our rat anorectic screening model.

## MATERIALS AND METHODS

Groups of 5-7 male Sprague-Dawley rats weighing 250-400g (previously used for anorectic screening and not used in experiments for at least two weeks) were allowed free access to food and water. On the morning of the experiment animals received saline, d-amphetamine, phenylpropranolamine, d-norpseudoephedrine or methoxyphenamine intraperitoneally. All drugs were dissolved in saline and administered in a volume of 1 ml/kg body weight.

Drug groups were staggered throughout the day to control for diurnal variations in locomotion. Thirty minutes following injection each rat was placed in the middle of an open-field apparatus (kept in a separate testing room) and active motor behavior measured during the subsequent 10 min. period. The apparatus consisted of an opaque Plexiglas area of 70 x 70 cm, divided into 16 square fields and surrounded by walls 40-cm high. Holes of 2-cm diameter were drilled in the center of the squares adjacent to the walls and the apparatus elevated by about 2 cm to allow hole-poking. Locomotion (entering another field by at least 3/4 of the body) was used to determine the locomotor score. The test period was monitored and recorded with a video system and later displayed and scored.

Data were analyzed by a one way analysis of variance and a Newman-Keuls test. Significance was determined at the  $p < 0.05$  level in all experiments.

#### RESULTS

Rats receiving saline averaged approximately 100 square enterings per 10 min period and no diurnal variations or patterns were observed. The results of the first experiment are shown in Table 1. d-Amphetamine (2mg/kg) and methoxyphenamine (15mg/kg) both increased locomotion significantly ( $p < 0.05$ ). These doses produce significant reductions in food intake in rats as determined previously in our laboratory.

The second experiment employed anorectic doses of phenylpropanolamine (dl-norephedrine), d-norpseudoephedrine and methoxyphenamine. Both d-norpseudoephedrine (20 mg/kg) and methoxyphenamine (10 mg/kg) increased locomotor activity significantly ( $p < 0.05$ , Table 2) while phenylpropanolamine (20 mg/kg) failed to significantly change locomotor activity (there was a

slight decrease). These two experiments were combined and normalized to its appropriate control (saline) group and the results appear in Table 3.

The third experiment performed determined the dose-response relationships of methoxyphenamine in this system. Doses of 0, 5, 10, 15 and 20 mg/kg were employed and locomotion values appear in Table 4.

Significant increases in locomotor activity were detected with doses starting at 10 mg/kg.

#### DISCUSSION

These results indicate that doses of d-amphetamine, d-norpseudoephedrine and methoxyphenamine that produce an anorectic response in rats also cause an increase in locomotor activity, while a similar effective dose of phenylpropanolamine failed to alter this parameter. This work conforms to the findings in mice of Fairchild and Alles (J PET 158: 135-139, 1967) with respect to d-amphetamine, d-norpseudoephedrine and phenylpropanolamine (methoxyphenamine was not tested and actually the isomers of phenylpropanolamine were used rather than the racemate). If man behaves in a similar fashion to that seen in rats (this is true for d-amphetamine) one might expect to observe some degree of central nervous system stimulation with some doses of d-norpseudoephedrine and methoxyphenamine (methoxyphenamine has been reported to be abused by athletes for its stimulant properties [Lijec. Vjesn. 102 (5): 261-8, 1980.]), while possibly phenylpropanolamine will be without effect. Data in rats is important for differentiating the activities of compounds from one another and adds vital information to the scientific literature necessary for a starting point for safety and actions in man.

TABLE I

EFFECTS OF AMPHETAMINE AND METHOXYPHENAMINE ON LOCOMOTION IN THE RAT

<u>TREATMENT</u>	<u>DOSE (MG/KG)</u>	<u>N</u>	<u>LOCOMOTOR SCORE</u>
SALINE	-	7	109 ± 11
AMPHETAMINE	2	7	247 ± 17 <sup>*†</sup>
METHOXYPHENAMINE	15	7	197 ± 17 <sup>*</sup>

RATS WEIGHING 253-401g WERE ACCLIMATED TO OUR FACILITIES AND GIVEN FREE ACCESS TO FOOD AND WATER. ON THE DAY OF THE EXPERIMENT, RATS RECEIVED SALINE, AMPHETAMINE (2 MG/KG), OR METHOXYPHENAMINE (15 MG/KG) INTRAPERITONEALLY AND WERE TESTED FOR OPEN-FIELD LOCOMOTION WHILE BEING RECORDED WITH A VIDEO CAMERA. THE NUMBER OF GRID CROSSING PERFORMED IN A 10 MIN. PERIOD WAS DETERMINED AND CALLED THE LOCOMOTION SCORE. DATA WERE ANALYZED BY A ONE-WAY ANOVA AND A NEWMAN-KEULS TEST. \* P<0.05 DIFFERS SIGNIFICANTLY FROM SALINE, † P<0.05 SIGNIFICANTLY GREATER THAN METHOXYPHENAMINE.

TABLE 2

EFFECTS OF METHOXYPHENAMINE, PHENYLPROPANOLAMINE AND  
D-NORPSEUDOEPHEDRINE ON LOCOMOTION IN THE RAT

---

<u>TREATMENT</u>	<u>DOSE (MG/KG)</u>	<u>N</u>	<u>LOCOMOTOR SCORE</u>
SALINE	-	5	123 ± 13
METHOXYPHENAMINE	10	5	190 ± 14 *
• PHENYLPROPANOLAMINE	20	5	105 ± 26
D-NORPSEUDOEPHEDRINE	20	5	190 ± 19 *

---

RATS WEIGHING 253-491g WERE ACCLIMATED TO OUR FACILITIES AND GIVEN FREE ACCESS TO FOOD AND WATER, ON THE DAY OF THE EXPERIMENT, RATS RECEIVED SALINE, METHOXYPHENAMINE, PHENYLPROPANOLAMINE OR D-NORPSUEDOEPHEDRINE INTRAPERITONEALLY AND WERE TESTED FOR OPEN-FIELD LOCOMOTION WHILE BEING RECORDED WITH A VIDEO CAMERA. THE NUMBER OF GRID CROSSING PERFORMED IN A 10 MIN. PERIOD WAS DETERMINED AND CALLED THE LOCOMOTION SCORE. DATA WERE ANALYZED BY A ONE-WAY ANOVA AND A NEWMAN-KEULS TEST.

\*  $p < 0.05$  DIFFERS SIGNIFICANTLY FROM SALINE.

TABLE 3

EFFECTS OF ANOREXIANTS ON  
LOCOMOTION IN THE RAT

<u>TREATMENT</u>	<u>DOSE (MG/KG)</u>	<u>LOCOMOTOR SCORE</u> (PERCENT CHANGE FROM CONTROL)
SALINE	-	0
AMPHETAMINE	2	+127*
PHENYLPROPANOLAMINE	20	- 14
D-NORPSEUDOEPHEDRINE	20	+ 54*
METHOXYPHENAMINE	10	+ 54*
METHOXYPHENAMINE	15	+ 81*

GROUPS OF 5-7 MALE SPRAGUE-DAWLEY RATS WEIGHING 253-401 G WERE ACCLIMATED TO OUR FACILITIES AND GIVEN FREE ACCESS TO FOOD AND WATER. ON THE DAY OF THE EXPERIMENT, RATS RECEIVED SALINE, AMPHETAMINE, PHENYLPROPANOLAMINE, D-NORPSEUDOEPHEDRINE OR METHOXYPHENAMINE INTRAPERITONEALLY AND WERE TESTED FOR OPEN-FIELD LOCOMOTION WHILE BEING RECORDED WITH A VIDEO CAMERA 30 MIN. LATER. THE NUMBER OF GRID CROSSINGS PERFORMED IN A 10 MINUTE PERIOD WAS DETERMINED AND COMPARED TO THE SALINE GROUP (ONE-WAY ANOVA AND A NEWMAN-KEULS TEST)

\* P < 0.05 DIFFERS SIGNIFICANTLY FROM CONTROL.

TABLE 4

EFFECTS OF METHOXYPHENAMINE ON LOCOMOTION IN THE RAT

<u>TREATMENT</u>	<u>DOSE (MG/KG)</u>	<u>N</u>	<u>LOCOMOTOR SCORE</u>
SALINE	-	6	190 ± 11
METHOXYPHENAMINE	5	5	107 ± 9
	10	5	172 ± 14*
	15	5	142 ± 15*
	20	5	143 ± 13*

RATS WEIGHING 253-401g WERE ACCLIMATED TO OUR FACILITIES AND GIVEN FREE ACCESS TO FOOD AND WATER, ON THE DAY OF THE EXPERIMENT, RATS RECEIVED SALINE, OR METHOXYPHENAMINE (5, 10, 15 OR 20 MG/KG) INTRAPERITONEALLY AND WERE TESTED FOR OPEN-FIELD LOCOMOTION WHILE BEING RECORDED WITH A VIDEO CAMERA. THE NUMBER OF GRID CROSSING PERFORMED IN A 10 MIN. PERIOD WAS DETERMINED AND CALLED THE LOCOMOTION SCORE. DATA WERE ANALYZED BY A ONE-WAY ANOVA AND A NEWMAN-KEULS TEST.

\* $p < 0.05$  DIFFERS SIGNIFICANTLY FROM SALINE.