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Involvement of Brain Monoamines in the Stimulant and Paradoxical Inhibitory Effects of Methylphenidate

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Abstract

The significance of central noradrenergic, dop-aminergic and serotonergic neural systems for the locomotor stimulant effects of methylphenidate was investigated in the rat. In order to study the role of brain catecholamines, rats were pretreated with reserpine (2.5 mg/kg) followed 24 hrs later by treatment with α -methyltyrosine (25 mg/kg) or U-14,624 (75 mg/kg), a dopamine- β -hydroxylase inhibitor. In these experiments, methylphenidate stimulated motor activity was antagonized by α -methyltyrosine and enhanced after treatment with U-14,624, suggesting that release of newly synthesized dopamine is important to a locomotor stimulant action of methylphenidate. Evidence implicating brain serotonin in the actions of methylphenidate was obtained in rats pretreated with pargyline or p-chlorophenylalanine (PCPA). Administration of pargyline 1 hr prior to methylphenidate was found to reduce the locomotor activity induced by methylphenidate and this was antagonized by pretreatment with low doses of PCPA. Higher doses of PCPA caused a significant elevation of methylphenidate induced activity which could be reduced by 5-hydroxytryptophan. Destruction of serotonergic neurons with 5,7-dihydroxytryptamine also potentiated methylphenidate induced locomotion. These latter findings suggest that serotonergic fibers have an inhibitory function in brain. These results are discussed in relation to the possible mechanism by which methylphenidate may act in hyperkinesia.

Keywords

Methylphenidate; Locomotor Activity; 5-Hydroxytryptamine; Tyrosine Hydroxylase Inhibition; Dopamine- β -Hydroxylase Inhibition; p-Chlorophenylalanine; 5,7-Dihydroxytryptamine; 5-Hydroxytryptophan; MAO Inhibitors.

Much attention has been directed toward understanding the actions of those stimulant drugs found to be of value in the treatment of hyperkinetic syndrome (MBD) (Snyder and Meyerhoff, 1973). Of these drugs, *d*-amphetamine has been the most widely studied. From animal experiments, the stimulant effects of *d*-amphetamine have been suggested to be mediated through the indirect release of catecholamines (Weissman *et al.*, 1966; Hanson, 1966; Fibiger *et al.*, 1973; Von Voigtlander and Moore, 1973; Hollister *et al.*, 1974). Based upon such findings, Snyder and Meyerhoff (1973) have proposed that the therapeutic effectiveness of *d*-amphetamine in MBD was related to this action. These workers, however, did not provide an explanation for the paradoxical quieting effects of *d*-amphetamine in this syndrome.

Recently, several studies in animals have provided evidence that the neurochemical effects of *d*-amphetamine to induce motor activity (Neill *et al.*, 1972; Mabry and Campbell, 1973; Breese *et al.*, 1974b) and to increase rates of responding on a variable-interval schedule of reinforcement (Green and Harvey, 1974) are also influenced by central serotonergic fibers. In these latter studies, reduction of brain serotonin caused a marked enhancement of the stimulant properties of *d*-amphetamine, suggesting an inhibitory influence of serotonergic pathways. These findings subsequently led to the proposal that this serotonergic inhibitory action produced by *d*-amphetamine may have relevance to its therapeutic use in hyperkinesia (Breese *et al.*, 1974a, b).

Although methylphenidate is widely used in MBD (Millichap, 1968; Seger and Hallum, 1974), the basic neurochemical actions of methylphenidate have been less widely studied than those of *d*-amphetamine. The stimulatory properties of this drug have been proposed to be related to indirect release of catecholamines (Franklin and Herberg, 1974; Costall and Naylor, 1974) as well as direct actions on receptors (Thornburg and Moore, 1973; Costall and Naylor, 1974). In addition, a high dose of methylphenidate (100 mg/kg) has been reported to increase 5-HIAA content in rat brain without changing content of 5-hydroxytryptamine (Scheel-Krüger and Hasselager, 1974). The purpose of the present study was to examine the role of endogenous catecholamines in the action of methylphenidate and to determine if alterations in 5-hydroxytryptamine content in brain would influence methylphenidate-induced motor activity.

Methods

Male Sprague-Dawley rats (250–400 g) were housed in rooms with controlled lighting (10 hr light and 14 hr dark). Motor activity was recorded from activity cages with six photocell sensors mounted on the outer wall of a circular runway in a dark, soundproof room away from recording equipment (Breese *et al.*, 1974b). Counts were automatically recorded at 15 min intervals over a 2.5 or a 3 hr period. Animals were “habituated” to the chamber for 1 hr before receiving methylphenidate intraperitoneally.

Drug Treatments

Some rats were injected with 2.5 mg/kg reserpine (s.c.) 24 hrs before receiving 75 mg/kg U-14,624, 25 mg/kg α -methyltyrosine, or vehicle. These animals were then tested with 5 mg/kg methylphenidate 1 hr later. In addition, methylphenidate was also administered to rats pretreated with various monoamine oxidase inhibitors, *p*-chlorophenylalanine (PCPA), or 5,7-dihydroxytryptamine (5,7-DHT). The PCPA (200 mg/kg) was suspended in a 0.5% methylcellulose solution and administered orally for 1 day or 2 successive days to reduce serotonin (Koe and Weissman, 1966). The methylphenidate (10 mg/kg) was administered 24 hrs after the last dose of PCPA. Some rats that received PCPA were given 5-hydroxytryptophan (75 mg/kg) 1 hr before methylphenidate. The 5,7-DHT (200 μ g) was administered intracisternally in 25 μ l of saline containing 0.5 % ascorbic acid 30 min after pargyline (50 mg/kg, i.p.) to destroy serotonergic fibers (Baumgarten *et al.*, 1973; Breese and Cooper, 1975). Animals were examined 10 days after treatment. Rats were given methylphenidate 1 hr after receiving pargyline, tranlylcypromine, nialamide, clorgyline, iproniazid, or pheniprazine.

Drugs

Methylphenidate HCl and reserpine were furnished by Ciba-Geigy Corp., Summit, N.J. The 5,7-dihydroxytryptamine and α -methyltyrosine were purchased from Regis Chemical Company (Chicago, Ill.). *P*-Chlorophenylalanine was kindly supplied by Pfizer Inc. (Groton, Conn.). The pargyline, (Abbott Laboratories, North Chicago, Ill.), pheniprazine (Lakeside Laboratories, Milwaukee, Wis.), tranlylcypromine (Smith, Kline and French Lab., Philadelphia,

Pa.), iproniazid (Hoffmann LaRoche Laboratories, Nutley, N.J.), nialamide (Pfizer Inc., Groton, Conn.) and clorgyline (May and Baker, LTD, Dagenham) were all gifts. The L-5-hydroxytryptophan was purchased from H & H Bulk Biochemical (Los Angeles, California). The U-14,624 (1-phenyl-3-[2-thiazolyl]-2-thiourea) was purchased from Aldrich Chemical Co. (Milwaukee, Wis.).

Biochemical Measures

Determinations of brain norepinephrine, dopamine, and serotonin were carried out as previously described (Breese and Traylor, 1970).

Statistics

Statistical comparisons between groups were made with either Students's or Dunnett's *t* test (Two tailed probability values are reported). Correlational analyses were performed by multiple regression and partial correlation.

Results

Effects of α -Methyltyrosine and U-14,624 on Methylphenidate-induced Locomotor Activity in Reserpinized Rats

While the effects of *d*-amphetamine-induced motor activity have been intensively studied (Weissman *et al.*, 1966; Creese and Iversen, 1973; Hollister *et al.*, 1974), less information concerning the neurochemical mediation of methylphenidate-induced locomotor activity was available. For that reason, the effects of methylphenidate were tested in reserpinized rats treated with either α -methyltyrosine to inhibit synthesis of both catecholamines or U-14,624 to inhibit synthesis of norepinephrine (Fig. 1). Following treatment with α -methyltyrosine, methylphenidate-induced locomotion was drastically reduced, suggesting that the response elicited after reserpine treatment was related to release of newly synthesized catecholamines. Treatment with the dopamine- β -hydroxylase inhibitor, U-14,624, did not antagonize the increased locomotion caused by methylphenidate, but rather produced a significant elevation in locomotor activity. Although Thornburg and Moore (1973) did not observe a significant increase in methylphenidate-stimulated activity in *mice* after U-14,624, this latter observation deserves further investigation with regard to a possible inhibitory role for norepinephrine in rats. Regardless, these findings seemed to implicate dopaminergic pathways in the mediation of the increased activity induced by methylphenidate.

Effect of PCPA and 5,7-DHT on Methylphenidate-induced Motor Activity

In order to search for possible involvement of serotonergic fibers in the action of methylphenidate, methylphenidate was administered to rats following treatment with either PCPA or 5,7-DHT. The increase in motor activity induced by this drug was found to be markedly enhanced following these treatments (Fig. 2). This potentiation of methylphenidate-induced stimulation produced by PCPA was subsequently found to be significantly antagonized by 5-hydroxytryptophan ($P < 0.05$; Table 1). The effect of these various treatments on brain monoamines is shown in Table 1.

Effect of Pargyline on Methylphenidate-Induced Motor Activity

In accord with experiments with *d*-amphetamine (Breese *et al.*, 1974b), administration of pargyline (50 mg/kg) also significantly reduced the locomotor response induced by methylphenidate (Fig. 3). This reduced response included a decrease in peak activity as well as in total activity during the 3 hr period following drug administration. At a higher dose of methylphenidate (10 mg/kg), pargyline pretreatment did not produce a significant reduction in the locomotor response to methylphenidate (Table 2). The degree of inhibition of

methylphenidate-induced locomotor activity could also be altered if the dose of pargyline were varied (Table 3, top).

Effect of PCPA on Pargyline Reduction of Methylphenidate-Stimulated Motor Activity

If the inhibition of methylphenidate-induced motor activity by pargyline were due to brain serotonin, pretreatment with PCPA should reverse this inhibition. Fig. 4 indicates that 24 hrs after a single dose of PCPA the inhibitory effects of pargyline on activity stimulated by 5 mg/kg methylphenidate were antagonized. In this case, PCPA pretreatment reduced brain serotonin content by approximately 40% and antagonized the rise in serotonin due to pargyline by the same degree.

Effect of Various MAO Inhibitors on Methylphenidate-induced Motor Activity

In order to determine whether the inhibition of methylphenidate by pargyline might be shared by other MAO inhibitors, several compounds in this class were examined for their effect on methylphenidate-induced motor activity. As shown in Table 3, lower doses of tranylcypromine, nialamide, and clorgyline, in addition to pargyline, were found that would significantly inhibit the locomotion induced by methylphenidate. Lower doses of pheniprazine showed a tendency for reduction of methylphenidate-induced motor activity, but the reduction was not great enough to be significant. In most cases, higher doses of the MAO inhibitors produced no change or enhanced the increase in locomotor activity caused by methylphenidate. All doses of iproniazid examined seemed to enhance the effects of methylphenidate. The effect of these MAO inhibitors on brain monoamines at the time methylphenidate was injected is also shown in Table 3. Based on changes in brain monoamines, these latter results did not provide an obvious predictor of how these MAO inhibitors would interact with methylphenidate-induced motor activity. (Correlation coefficients: activity with norepinephrine, $r = -0.0159$; activity with dopamine, $r = 0.217$; activity with serotonin, $r = -0.0878$). However, in those groups of animals which exhibited a significant inhibition of methylphenidate-induced activity, a negative correlation between activity and brain serotonin content was found which approached the 0.05 level of significance ($r = -0.865$, $n = 5$, $0.1 > P > 0.05$).

Discussion

In accord with the view that methylphenidate acts by releasing catecholamines (Costall and Naylor, 1974), the locomotor stimulatory actions of this compound were found to be reduced by pretreating reserpinized animals with α -methyltyrosine. Since blockade of norepinephrine synthesis with U-14,624 in the reserpinized rats did not decrease methylphenidate-induced motor activity, it would appear that the locomotor stimulation induced by methylphenidate is dependent upon an intact dopaminergic mechanism. Although a similar conclusion has been reached concerning *d*-amphetamine-induced locomotor activity (Thornburg and Moore, 1973; Hollister *et al.*, 1974), the mechanism of action of methylphenidate would appear to differ from that of *d*-amphetamine in that methylphenidate stimulation is not antagonized by α -methyltyrosine unless reserpine is present (see Thornburg and Moore, 1973; Franklin and Herberg, 1974).

This study also provides evidence for an involvement of serotonergic fibers in the action of methylphenidate. Similar to reports that reduction of serotonin in brain will enhance locomotor activity induced by *d*-amphetamine (Neill *et al.*, 1972; Mabry and Campbell, 1973; Breese *et al.*, 1974a, b), methylphenidate hyperactivity was found to be potentiated following reduction of brain serotonin with PCPA or 5,7-DHT. Although it is possible to argue that PCPA may interfere with methylphenidate metabolism or alter its uptake into brain, this would not explain why the activity response to methylphenidate is enhanced 10 days after treatment with 5,7-DHT or why 5-hydroxytryptophan would antagonize the effect of PCPA. In addition, 50 mg/

kg of pargyline administered 1 hr before methylphenidate was found to reduce locomotor activity. Since this action of pargyline was antagonized by PCPA, serotonin fibers were implicated in the inhibition produced by pargyline. However, it was found that one MAO inhibitor, iproniazid, enhanced rather than reduced methylphenidate locomotor activity. Whether this could be related to changes in drug metabolism or to other interactions between these compounds will require additional investigation.

The mechanism for the paradoxical quieting effects of *d*-amphetamine and methylphenidate in hyper-kinetic children has yet to be resolved. By studying the basic mechanisms responsible for the actions of such drugs, we have attempted to define new therapeutic approaches to alleviate the symptoms of this disease. Since the present data suggest that both *d*-amphetamine and methylphenidate activate a serotonergic neural system which inhibits locomotor activity, it would not seem unreasonable to believe that this action may have relevance to the mechanism by which these drugs act in hyperkinetic children. Such a proposal need not be contradictory with the view that brain dopamine is involved in the effects of such drugs upon the symptoms of MBD (Snyder and Meyerhoff, 1973), if an intact dopaminergic function is necessary for activation of this inhibitory serotonergic system (Breese *et al.*, 1974b). Obviously, further work will be necessary to define interactions between these monoamine systems. Nevertheless, the observation that serotonergic systems play an inhibitory role in the actions of methylphenidate suggests the possibility that administration of serotonin precursors, such as tryptophan or 5-hydroxytryptophan, may be of value in the symptomatic control of hyperkinesia. Such therapy would be expected to enhance the "tone" of the serotonergic system, allowing its inhibitory function on locomotor activity to predominate. If this approach should be successful, it would not only support the proposal concerning the mechanism of action of *d*-amphetamine and methylphenidate, but also may provide additional information concerning the neurochemical basis of MBD.

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References

- Baumgarten HA, Bjorklund A, Lachenmayer L, Nobin A. Evaluation of the effects of 5,7-dihydroxytryptamine on serotonin and catecholamine neurons in the rat CNS. *Acta physiol. scand. Suppl* 1973;391:1–9. [PubMed: 4521070]
- Breese GR, Cooper BR. Interactions of 5,7-dihydroxytryptamine with various drugs when administered intracisternally to adult and developing rats. *Brain Res.* 1975 in Press.
- Breese GR, Cooper BR, Hollister AS. Relationship of biogenic amines to behavior. In: *Catecholamines and their enzymes in the neuropathology of schizophrenia*. J. psychiat. Res. Suppl 1974a;11:125–134.
- Breese GR, Cooper BR, Mueller RA. Evidence for an involvement of 5-hydroxytryptamine in the actions of amphetamine. *Brit. J. Pharmacol* 1974b;52:307–319. [PubMed: 4155993]
- Breese GR, Traylor TD. Effect of 6-hydroxydopamine on brain norepinephrine and dopamine: evidence for selective degeneration of catecholamine neurons. *J. Pharmacol. exp. Ther* 1970;174:413–420. [PubMed: 5456173]
- Costall B, Naylor RJ. The involvement of dopaminergic systems with the stereotyped behavior patterns induced by methylphenidate. *J. Pharm. Pharmacol* 1974;26:30–33. [PubMed: 4150931]
- Creese I, Iversen SD. Blockade of amphetamine induced motor stimulation and stereotypy in the adult rat following neonatal treatment with 6-hydroxydopamine. *Brain Res* 1973;55:369–382. [PubMed: 4145950]

- Fibiger HC, Fibiger HP, Zis AP. Attenuation of amphetamine-induced motor stimulation and stereotypy by 6-hydroxydopamine in the rat. *Brit. J. Pharmacol* 1973;47:683–692. [PubMed: 4146741]
- Franklin KBJ, Herberg LJ. Self-stimulation and catecholamines: Drug-induced mobilization of the “reserve”-pool re-establishes responding in catecholamine-depleted rats. *Brain Res* 1974;67:429–437. [PubMed: 4470433]
- Green TK, Harvey JA. Enhancement of amphetamine action after interruption of ascending serotonergic pathways. *J. Pharmacol. exp. Ther* 1974;190:109–117. [PubMed: 4136228]
- Hanson LCF. Evidence that the central action of amphetamine is mediated via catecholamines. *Psychopharmacologia (Berl.)* 1966;9:78–80.
- Hollister AS, Breese GR, Cooper BR. Comparison of tyrosine hydroxylase and dopamine- β -hydroxylase inhibition with effects of various 6-hydroxydopamine treatments on d-amphetamine-induced motor activity. *Psychopharmacologia (Berl.)* 1974;36:1–16.
- Koe BK, Weissman A. p-Chlorophenylalanine: A specific depletor of brain serotonin. *J. Pharmacol. exp. Ther* 1966;154:499–516. [PubMed: 5297133]
- Mabry PD, Campbell BA. Serotonergic inhibition of catecholamine-induced behavioral arousal. *Brain Res* 1973;49:381–391. [PubMed: 4269051]
- Millichap JG. Drugs in management of hyperkinetic and perceptually handicapped children. *J. Amer. med. Ass* 1968;206:1527–1530.
- Neill DB, Grant LD, Grossman SP. Selective potentiation of locomotor effects of amphetamine by midbrain raphe’ lesions. *Physiol. Behav* 1972;9:655–657. [PubMed: 4670860]
- Scheel-Krüger J, Hasselager E. Studies of the various amphetamines, apomorphine, and clonidine on body temperature and brain 5-hydroxytryptamine metabolism in rats. *Psychopharmacologia (Berl.)* 1974;36:189–202.
- Seger EY, Hallum G. Methylphenidate in children with minimal brain dysfunction: Effects on attention span, visual-motor skills, and behavior. *Current. ther. Res* 1974;16:635–641.
- Snyder SH, Meyerhoff JL. How amphetamine acts in minimal brain dysfunction. *Ann. N.Y. Acad. Sci* 1973;205:310–320. [PubMed: 4570236]
- Thornburg JE, Moore KE. The relative importance of dopaminergic neural systems for the stimulation of locomotor activity induced by amphetamine and other drugs. *Neuropharmacology* 1973;12:853–866. [PubMed: 4147726]
- Von Voigtlander PF, Moore KE. Involvement of nigrostriatal neurons in the *in vivo* release of dopamine by amphetamine, amantadine, and tyramine. *J. Pharmacol. exp. Ther* 1973;184:542–552. [PubMed: 4687219]
- Weissman A, Koe BK, Tenen SS. Antiamphetamine effects following inhibition of tyrosine hydroxylase. *J. Pharmacol. exp. Ther* 1966;151:339–352. [PubMed: 5938473]

Fig. 1.

Effects of α -methyltyrosine (α -MPT) and U-14,624 on methylphenidate-induced locomotor activity in reserpinized rats. All animals received 2.5 mg/kg of reserpine (s.c.) 24 hrs before the administration of methylphenidate HCl (5 mg/kg). α -MPT (25 mg/kg) or U-14,624 (75 mg/kg) were administered at the beginning of the habituation period, 1 hr before methylphenidate. H refers to the activity counts accumulated during the last 15 min period of habituation.

The average activity for control animals that received 5 mg/kg methylphenidate is shown in Figs. 3 and 4. Each value represents the mean $\pm$ S.E.M. of at least 8 animals. C = control; R = reserpine.

* $P < 0.001$ when compared with responses in rats that received only reserpine

Fig. 2. Effect of p-chlorophenylalanine (PCPA) and 5,7-dihydroxytryptamine (5,7-DHT) on methylphenidate-stimulated motor activity. Animals received two oral doses of PCPA (150 mg/kg) or a single intracisternal injection of 200 μ g of 5,7-DHT as described in Methods before receiving methylphenidate (10 mg/kg). Each value represents the mean $\pm$ S.E.M. of at least 8 rats. C = control.

* $P < 0.01$ when compared with control

Fig. 3.

Effect of pargyline on methylphenidate-stimulated motor activity. Rats were treated with methylphenidate (5.0 mg/kg) 1 hr after pargyline (50 mg/kg). Each value represents the mean $\pm$ S.E.M. of at least 10 rats

* $P < 0.001$ when compared with control

Fig. 4.

Effect of p-chlorophenylalanine (PCPA) on the locomotor response to methylphenidate (5 mg/kg) in pargyline-treated rats.

Pargyline (50 mg/kg) was administered 1 hr before methylphenidate. PCPA (200 mg/kg orally) was administered 23 hrs before the pargyline was injected. Control animals received the appropriate vehicle before receiving methylphenidate. Each value represents the mean $\pm$ S.E.M. of at least 7 rats

* $P < 0.001$ when compared with control

Table 1

Effect of 5-hydroxytryptophan (5-HTP) on PCPA enhancement of methylphenidate-induced locomotor activity

Treatment	Methylphenidate-induced motor activity (CTS/180 min)	Brain Monoamine content(ng/g)		
		5HT	NE	DA
Control	2685 ± 340	418 ± 12	308 ± 23	549 ± 15
Control + 5HTP	2496 ± 292	2874 ± 323 *	176 ± 24 *	581 ± 70
PCPA	5396 ± 672 *	74 ± 2 *	242 ± 12 *	562 ± 25
PCPA + 5HTP	3448 ± 379	2049 ± 855 *	164 ± 14 *	458 ± 33 *

Animals were treated with PCPA (200 mg/kg, orally) on 2 successive days, 23 hrs after the last dose of PCPA some of the animals received 5-HTP (75 mg/kg, i.p.) and were habituated to the activity chamber for 1 hr. Control rats received vehicle orally and some rats received 5-HTP. All animals received methylphenidate (5 mg/kg) after the 1 hr habituation period. Monoamine content was determined in brain 1 hr after 5-HTP injection. Values represent the mean ± S.E.M. of counts generated during the 180 min period (CTS/180 min) by at least 6 rats. NE = norepinephrine; DA = dopamine; 5HT = serotonin.

* $P < 0.001$ when compared with control.

Table 2

Effect of pargyline on the locomotor response to various doses of methylphenidate

Methylphenidate (mg/kg)	Control (CTS/180 min)	Pargyline (CTS/180 min)
2.5	1163 ± 507	781 ± 179
5.0	2905 ± 525	1480 ± 241 *
10.0	3700 ± 421	5461 ± 1152

Rats were treated with pargyline (50 mg/kg) or saline 1 hr before receiving various doses of methylphenidate. Values represent the mean ± S.E.M. of counts generated during the 180 min period (CTS/180 min) after methylphenidate. $N = 8-14$ rats per group.

* $P < 0.001$ when compared with control response.

Table 3

Effect of various monoamine oxidase inhibitors on methylphenidate-induced motor activity and brain monoamine content

Treatment	Dose (mg/kg)	Methylphenidate response (CTS/180 min)	Brain monoamines (ng/g $\pm$ S.E.M.)		
			NE	DA	5HT
Saline	–	3530 $\pm$ 558	396 $\pm$ 25	602 $\pm$ 20	412 $\pm$ 11
Pargyline	25	2235 $\pm$ 565	451 $\pm$ 22	704 $\pm$ 46	546 $\pm$ 49 *
Pargyline	50	1400 $\pm$ 290 ***	465 $\pm$ 37	737 $\pm$ 28 ***	661 $\pm$ 25 ***
Pargyline	100	4829 $\pm$ 1394	468 $\pm$ 13	699 $\pm$ 36	651 $\pm$ 19 ***
Tranylcypromine	2	1642 $\pm$ 321 *	565 $\pm$ 38 ***	702 $\pm$ 57	629 $\pm$ 38 ***
Tranylcypromine	10	5969 $\pm$ 922 *	364 $\pm$ 32	796 $\pm$ 27 ***	614 $\pm$ 63 ***
Nialamide	2	2175 $\pm$ 390 *	431 $\pm$ 10	586 $\pm$ 45	465 $\pm$ 30 *
Nialamide	10	4073 $\pm$ 838	419 $\pm$ 27	543 $\pm$ 38	493 $\pm$ 20 ***
Iproniazid	50	4163 $\pm$ 825	–	–	–
Iproniazid	150	8509 $\pm$ 907 **	465 $\pm$ 21	695 $\pm$ 47	507 $\pm$ 9 ***
Pheniprazine	1	2116 $\pm$ 537	609 $\pm$ 26 *	591 $\pm$ 21	632 $\pm$ 15 ***
Pheniprazine	10	5669 $\pm$ 1324	405 $\pm$ 19	632 $\pm$ 25	607 $\pm$ 39 ***
Clorgyline	1	2068 $\pm$ 350 *	393 $\pm$ 30	635 $\pm$ 39	488 $\pm$ 31 *
Clorgyline	10	2826 $\pm$ 523	477 $\pm$ 31	632 $\pm$ 25	607 $\pm$ 39 ***

Various doses of the MAO inhibitors were administered 1 hr before methylphenidate (5 mg/kg). Activity was accumulated over a 3 hrs period (CTS/180 min). Brain monoamine content was determined 1 hr after the MAO inhibitors. Each value represents the mean $\pm$ S.E.M. of 7–20 determinations.

* $P < 0.05$ when compared with control.

** $P < 0.01$ when compared with control.

*** $P < 0.001$ when compared with control.