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EVIDENCE FOR INVOLVEMENT OF 5-HYDROXYTRYPTAMINE IN THE ACTIONS OF AMPHETAMINE

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1 Pargyline treatment, 1 h before (+)-amphetamine (1 mg/kg), reduced amphetamine-stimulated motor activity. This inhibition was reversed in animals pretreated with *p*-chlorophenylalanine (PCPA).

2 Following treatment with PCPA or 5,6-dihydroxytryptamine (5,6-DHT), amphetamine-induced locomotor activity was significantly potentiated. The increased response to amphetamine in PCPA-treated rats was reversed in animals pretreated with 5-hydroxytryptophan.

3 The inhibition of amphetamine-stimulated locomotor activity by treatment with 6-hydroxydopamine was not reversed by PCPA treatment.

4 Stereotypies produced by amphetamine were not found to be altered by depletion of 5-hydroxytryptamine.

5 Induction of adrenal tyrosine hydroxylase activity produced by chronic amphetamine administration was significantly potentiated by PCPA, emphasizing the involvement of a 5-hydroxytryptamine inhibitory system in more than one action of amphetamine.

Introduction

Extensive efforts have been made during the past few years to correlate central pharmacological actions of amphetamine with neurochemical alterations in brain. Agents which interfere with synthesis of catecholamines or destroy central catecholamine-containing fibres have been found to antagonize the actions of amphetamine (Weissman, Koe & Tenen, 1966; Hanson, 1966, 1967; Fibiger, Fibiger & Zis, 1973; Creese & Iversen, 1973; Hollister, Breese & Cooper, 1974). These findings suggest that the central actions of this drug are mediated through the indirect release of catecholamines.

Failure of amphetamine to deplete brain 5-hydroxytryptamine (5-HT) has generally discouraged speculation that serotoninergic neurones are involved in the actions of amphetamine (Paasonen & Vogt, 1956; Pletscher, Bartholini, Bruderer, Burkard & Gey, 1964). However, Reid (1970) has reported that amphetamine increased turnover rate of brain 5-HT, but attributed this change to the hyperthermia produced by this drug. In support of these biochemical changes, Fuxe & Ungerstedt (1970) suggested that amphetamine released 'extragranular' stores of 5-HT. In spite of this work, few studies have indicated a role for 5-HT in the behavioural actions of amphetamine. This paper describes experiments which suggest that brain 5-HT may have an inhibitory role in the modulation of the locomotor stimulant effects and the induction of adrenal tyrosine hydroxylase activity produced by amphetamine.

Methods

Male Sprague-Dawley rats (275-350 g), housed in rooms with controlled lighting (10 h light, 14 h dark), were used in this study. Motor activity was recorded (starting at 8 h 00 min-9 h 00 min) in 'doughnut' shaped activity cages housed in a dark, soundproof room away from recording equipment. Counts from six photocell sensors mounted on the outer wall of the runway were automatically recorded at 15 min intervals over a 4 h period. Animals were habituated to the chamber for 1 h before receiving (+)-amphetamine sulphate intraperitoneally.

Stereotyped behaviour produced by amphetamine was studied in rats with and without

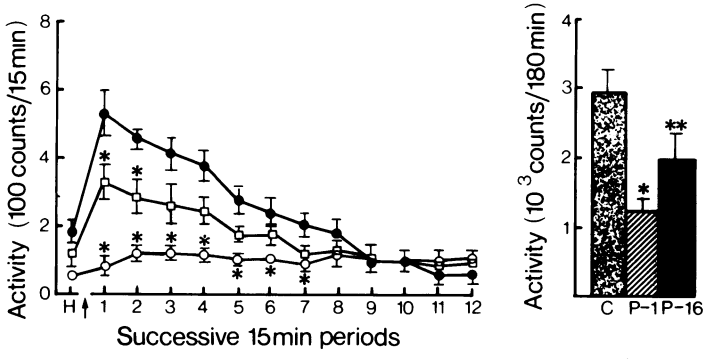

Fig. 1 Effect of pargyline on (+)-amphetamine-stimulated motor activity. Rats were treated with (+)-amphetamine sulphate (1 mg/kg; at arrow) 1 h (○, P-1) or 16 h (□, P-16) after pargyline (50 mg/kg i.p.). (●) Animals that received only (+)-amphetamine. H refers to the activity counts accumulated during the last 15 min period of a 1 h habituation period. $*P < 0.01$ when compared with control; $**P < 0.05$ when compared with control.

iproniazid (150 mg/kg i.p.) pretreatment. Following (+)-amphetamine, compulsive gnawing behaviour was rated as described by Taylor & Snyder (1971). Presence or absence of this behaviour was examined every 30 min for 3 hours.

The effect of (+)-amphetamine treatment on adrenal tyrosine hydroxylase was determined in animals that were housed singly at least 2 days prior to treatment. Rats were injected twice daily with (+)-amphetamine or saline (0.9% w/v NaCl solution) at 8 h 30 min and 17 h 00 minutes.

Drug treatment

(+)-Amphetamine was administered intraperitoneally to rats that had received *p*-chlorophenylalanine (PCPA), 5,6-dihydroxytryptamine (5,6-DHT) or 6-hydroxydopamine (6-OHDA). The PCPA (150 mg/kg), suspended in a 0.5% methylcellulose solution, was administered orally for 1 day or 2 successive days to reduce 5-HT (Koe & Weissman, 1966). (+)-Amphetamine was administered 24 h after PCPA. Some rats that received PCPA were given 5-hydroxytryptophan (75 mg/kg) 1 h before (+)-amphetamine to replace brain 5-HT. The 5,6-DHT (75 μg) was administered intracisternally in 25 μl of saline to destroy serotoninergic fibres (Baumgarten, Bjorklund, Lachenmayer, Nobin & Stenevi, 1971; Breese, Cooper, Grant & Smith, 1974a). Effects of (+)-amphetamine were examined 10 days after treatment. Other rats received 6-OHDA treatment to destroy dopaminergic fibres preferentially (Breese & Traylor, 1971; Cooper, Breese, Grant & Howard, 1973) or to destroy both catecholamine fibre systems (Breese & Traylor, 1970, 1971). At least 30 days were allowed for recovery from acute effects of these 6-OHDA treatments. For activity studies, animals were pretreated with pargyline (50 mg/kg i.p.) 1 h or 16 h before receiving (+)-amphetamine sulphate.

Drugs

(+)-Amphetamine sulphate was obtained from Sigma Chemical Company (St. Louis, Mo.), 6-hydroxydopamine and 5,6-dihydroxytryptamine were from Regis Chemical Company (Chicago, Ill.), *p*-chlorophenylalanine was a gift from Pfizer, Inc. (Groton, Conn.); the desipramine hydrochloride was from USV Pharmaceutical Corp., (Tuckahoe, N.Y.). Doses of (+)-amphetamine sulphate and desipramine hydrochloride are given as their salt, and other drugs as the free base.

Biochemical measures,

Determinations of brain noradrenaline, dopamine, and 5-HT were carried out as previously described (Breese & Traylor, 1970). The adrenal glands were homogenized in 2 ml 0.25 M sucrose and the homogenate centrifuged at 22,000 *g* for 10 minutes. Tyrosine hydroxylase was determined on the supernatant by the procedure described by Mueller, Thoenen & Axelrod (1969) using purified L-[3,5-^{3}H]-tyrosine (24.7 Ci/mmol).

Statistics

Statistical comparisons between groups were made either with Student's or Dunnett's *t* test, except for the comparison of groups examined for stereotyped behaviour when the Fisher exact probability test was used.

Results

Effects of pargyline on amphetamine-induced motor activity

In initial experiments, administration of pargyline (50 mg/kg) 1 h before injection of (+)-amphetamine sulphate (1 mg/kg) significantly reduced the locomotor response to amphetamine. This reduced response included a decrease in peak activity as well as in total activity during the 3 h period following drug administration (Figure 1). Intermediate hyperactivity was produced in rats treated 16 h earlier with pargyline. When higher doses of amphetamine (2 and 3 mg/kg) were given in combination with this monoamine oxidase (MAO) inhibitor there was no significant reduction of the locomotor response to amphetamine (Table 1). Effects of pargyline treatment on brain amines are shown in Table 2.

Effects of p-chlorophenylalanine on amphetamine-induced hyperactivity following pargyline

Since 5-HT in brain rises rapidly following inhibition of MAO (Spector, Shore & Brodie, 1960), the possibility that the antagonism of amphetamine-induced hyperactivity by pargyline might be mediated by 5-HT (See Table 1) was examined by pretreating rats with PCPA. PCPA alone reduced 5-HT by about 48% and it antagonized the rise due to pargyline by about 50% (Table 2). Figure 2 shows the PCPA treatment also antagonized the inhibition by pargyline of amphetamine-induced hyperactivity.

Effects of p-chlorophenylalanine and 5,6-dihydroxytryptamine on amphetamine-induced motor activity

If serotoninergic fibres were exerting an inhibitory

Table 1 Effect of pargyline on amphetamine-induced motor activity

	Activity response to amphetamine	
Amphetamine (mg/kg)	*Control (ct/180 min)*	*Pargyline (ct/180 min)*
1.0	2970 ± 306	1275 ± 138*
2.0	3938 ± 306	2930 ± 950
3.0	6014 ± 579	6787 ± 1660

Animals were treated with pargyline (50 mg/kg) 1 h before receiving various doses of amphetamine. Values represent the mean counts with s.e. mean that occurred during the 3 h period after amphetamine of at least 8 animals. (ct/180 min) = activity counts obtained during a 180 min period following amphetamine sulphate.
* $P < 0.001$ when compared with control.

Table 2 Effects of pargyline and *p*-chlorophenylalanine (PCPA) in combination with pargyline on brain monoamine concentrations

	Whole brain monoamines		
Treatments	*Noradrenaline (ng/g)*	*dopamine (ng/g)*	*5-HT (ng/g)*
Experiment I			
Control	329 ± 25	688 ± 22	371 ± 15
Pargyline—1 h	418 ± 9	706 ± 52	600 ± 25*
Pargyline—16 h	479 ± 27*	774 ± 59	803 ± 36*
Experiment II			
Control	388 ± 20	756 ± 52	347 ± 21
PCPA	317 ± 12	613 ± 20	182 ± 15*
Control + Pargyline—1 h	457 ± 29*	779 ± 51	558 ± 40*
PCPA + Pargyline—1 h	423 ± 18*	740 ± 20	235 ± 10*

In experiment I, animals ($n = 6$) were treated with pargyline (50 mg/kg) either 1 or 16 h before they were killed. In experiment II, the group designated PCPA received *p*-chlorophenylalanine (150 mg/kg) orally 23 h before any drug treatments. Control and PCPA-treated groups received pargyline (50 mg/kg) 1 h before they were killed.
* $P < 0.001$ when compared with control.

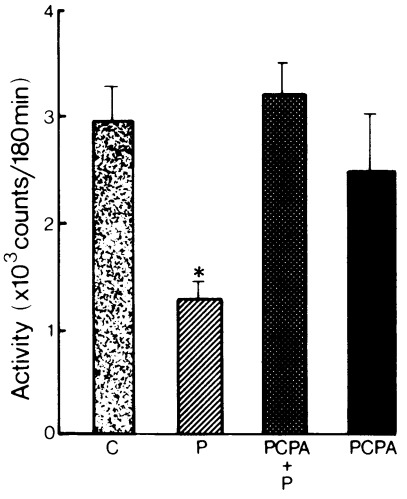

Fig. 2 Effect of *p*-chlorophenylalanine (PCPA) on the locomotor response to (+)-amphetamine (1 mg/kg) in pargyline-treated rats. P indicates animals that received pargyline (50 mg/kg). PCPA (150 mg/kg, orally) was administered 23 h before pargyline and 24 h before (+)-amphetamine injection. C refers to animals that received saline before (+)-amphetamine administration. *$P < 0.001$ when compared with control.

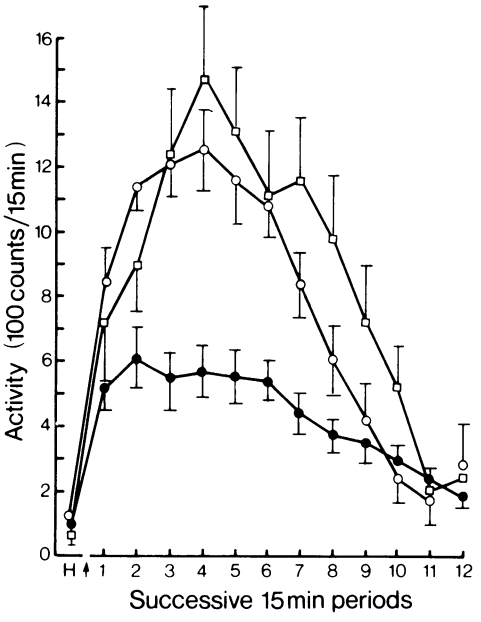

Fig. 3 Effect of *p*-chlorophenylalanine (PCPA) and 5,6-dihydroxytryptamine (5,6-DHT) on (+)-amphetamine-stimulated motor activity. (●) Animals which received only (+)-amphetamine (3 mg/kg; at arrow); (○) animals treated with PCPA before receiving (+)-amphetamine; (□) animals treated with 5,6-DHT before receiving (+)-amphetamine. Animals were treated with two oral doses of PCPA (150 mg/kg) or with 5,6-DHT (75 μg) intracisternally before receiving (+)-amphetamine sulphate (3 mg/kg). The (+)-amphetamine was administered 24 h after the last dose of PCPA and 10 days after treatment with 5,6-DHT.

influence on amphetamine stimulation, it was reasoned that reduction of 5-HT should have the opposite effect. While a single dose of PCPA did not alter amphetamine-induced hyperactivity (Fig. 2), two doses of PCPA, which reduced 5-HT to 14 ± 2% of control, potentiated the locomotor response to (+)-amphetamine (3 mg/kg) ($P < 0.001$; Figure 3). The locomotor response to (+)-amphetamine (1 mg/kg) was also increased after two doses of PCPA (not shown), but the degree of potentiation was only of marginal significance ($P < 0.05$). In addition, the response to (+)-amphetamine was enhanced (Fig. 3) following intracisternal administration of 5,6-DHT, an agent which causes destruction of serotoninergic fibres (Baumgarten *et al.*, 1971; Breese *et al.*, 1974a). However, a whole brain concentration of 5-HT was reduced to only 55 ± 4% of control after this latter treatment.

In an additional group of experiments, animals treated with PCPA were given 5-hydroxytryptophan (75 mg/kg) 1 h before receiving (+)-amphetamine to replete brain 5-HT content. This treatment eliminated the potentiation of amphetamine-induced motor activity observed after PCPA treatment (Table 3). The effect of 5-hydroxytryptophan on brain 5-HT in control and PCPA-treated rats is shown in Table 3.

Effects of p-chlorophenylalanine on amphetamine-stimulated motor activity in 6-hydroxydopamine-treated rats

As previously reported (Breese, Cooper & Hollister, 1974b; Hollister *et al.*, 1974), treatment with 6-OHDA blocked amphetamine-stimulated motor activity (Figure 4). Since increased activity of 5-HT fibres can inhibit amphetamine hyperactivity, the possibility existed that the antagonism of amphetamine in 6-OHDA-treated rats was due to an inhibition caused by activation of 5-HT containing fibres. If this were the case, depletion of 5-HT might be expected to restore the stimulant effects of amphetamine in 6-OHDA-treated rats. However, PCPA treatment did not significantly alter the responses to (+)-amphetamine in 6-OHDA-treated rats (Figure 4).

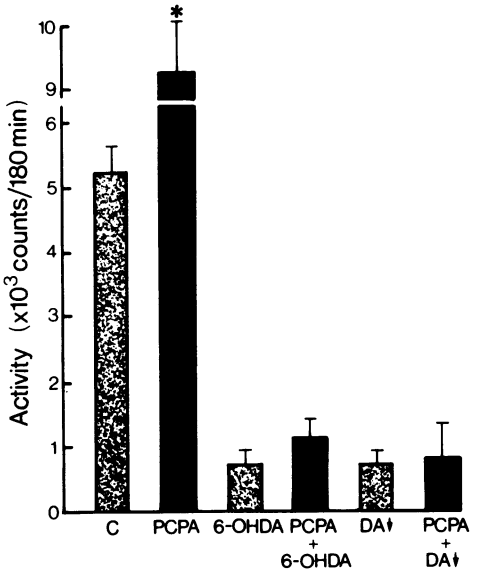

Fig. 4 Effect of *p*-chlorophenylalanine (PCPA) on inhibition of (+)-amphetamine-stimulated motor activity produced by 6-hydroxydopamine (6-OHDA) treatment. All animals received (+)-amphetamine sulphate (3 mg/kg). PCPA (2 x 150 mg/kg) was given as described in Fig. 3 and in the methods section. 6-OHDA refers to animals that received two doses of 6-OHDA (200 μg) intracisternally, one with and the second without pargyline pretreatment, as described in the methods section. This treatment reduced noradrenaline to 12.2 ± 1% of control and dopamine to 9.2 ± 1% of control. DA ↓ refers to animals that received 6-OHDA (240 μg) intracisternally 1 h after desipramine (30 mg/kg, i.p.) on two occasions to reduce brain dopamine. This treatment reduced noradrenaline to 85 ± 5% of control and dopamine to 11 ± 2% of control. PCPA reduced 5-HT to 12 ± 3% of control in animals that did not receive 6-OHDA. *$P < 0.001$ when compared with the response in control rats.

Effect of depletion of brain 5-hydroxytryptamine on amphetamine-induced stereotypies and induction of tyrosine hydroxylase activity

In view of the results suggesting that 5-HT fibres might be involved in amphetamine-induced motor activity, other actions of amphetamine were also examined. The ability of amphetamine to induce stereotyped behaviour (Taylor & Snyder, 1971) and to increase adrenal tyrosine hydroxylase activity (Mandell & Morgan, 1970) were the responses chosen for study. Rats were treated with PCPA (2 x 150 mg/kg) prior to receiving (+)-amphetamine (2 or 3 mg/kg) 16 h after iproniazid (Taylor & Snyder, 1971); they showed no significant alterations in the frequency of stereotypies ($P < 0.1$). Similar results were obtained in PCPA-treated rats that received only (+)-amphetamine (8 mg/kg). However, animals treated with PCPA seemed to show greater rearing activity than control animals, suggesting that subtle qualitative differences may exist. Nevertheless, no quantitative evidence could be obtained that depletion of 5-HT changed amphetamine-induced stereotyped behaviour.

In accordance with previous reports (Mandell & Morgan, 1970; Koda & Gibb, 1973), chronic administration of (+)-amphetamine (5 mg/kg) enhanced tyrosine hydroxylase activity in the adrenals while administration of (+)-amphetamine 2.5 mg/kg did not (Table 4). When amphetamine (2.5 mg/kg) was administered to PCPA-treated rats, the increase in adrenal tyrosine hydroxylase activity was not only greater than in untreated rats but was also greater than could be expected if these two treatments had additive effects. PCPA-treatment alone produced a slight but significant increase in adrenal tyrosine hydroxylase activity. Induction of tyrosine hydroxylase

Table 3 Effects of 5-hydroxytryptophan (5-HTP) on amphetamine-induced motor activity in *p*-chlorophenylalanine (PCPA)-treated rats

Treatment	*Amphetamine-induced motor activity (ct/180 min)*	*Brain 5-HT (ng/g)*
Control	5670 ± 371	396 + 24
Control + 5-HTP	4192 ± 778	1750 + 125*
PCPA	10,006 ± 1070*	77 + 7*
PCPA + 5-HTP	3776 ± 429*	922 + 69*

Animals were treated with *p*-chlorophenylalanine (150 mg/kg, orally) on 2 successive days. Twenty three hours after the last dose some of these animals received 5-hydroxytryptophan (5-HTP, 75 mg/kg, i.p.). Control animals received vehicle orally; some of these animals also received 5-HTP. 5-Hydroxytryptamine (5-HT) concentration was determined in brain 1 h after 5-HTP injection. All animals received amphetamine sulphate (3 mg/kg) after a 1 h period of habituation and the dose of 5-HTP. Values represent the mean with s.e. mean from at least six rats. * $P < 0.001$ when compared with control.

Table 4 Effect of *p*-chlorophenylalanine (PCPA) on the induction of adrenal tyrosine hydroxylase produced by amphetamine

Treatments	*Adrenal tyrosine hydroxylase activity* (nmol/h)	*% Control*
Control	7.85 ± 0.50	–
Control + Amphetamine (2.5 mg/kg)	8.80 ± 0.39	112
Control + Amphetamine (5.0 mg/kg)	14.60 ± 1.06*	186
PCPA	9.27 ± 0.27**	118
PCPA + Amphetamine (2.5 mg/kg)	16.67 ± 1.85*	212
PCPA + Amphetamine (5.0 mg/kg)	15.86 ± 1.84*	202

Animals were given PCPA (150 mg/kg) on 2 successive days. Twenty-four hours after the last dose of PCPA, amphetamine (2.5 or 5 mg/kg) was administered twice daily for 3 days as described in the methods section. Adrenal tyrosine hydroxylase activity is given as nmol/h for both glands combined. Each value represents the mean with s.e. mean of at least 6 determinations.
** $P < 0.05$ when compared with control.
* $P < 0.001$ when compared with control.

activity caused by amphetamine (5.0 mg/kg) was not increased by PCPA, suggesting that this dose elicits a near maximal response.

Discussion

Although amphetamine does not alter brain 5-HT content, (Paasonen & Vogt, 1956; Pletscher *et al.*, 1964), several reports have proposed that amphetamine can activate serotoninergic fibres (Fuxe & Ungerstedt, 1970; Reid, 1970). The evidence from the present experiments suggests that release of brain 5-HT can influence certain behavioural actions of amphetamine. Confirming earlier reports (Neill, Grant & Grossman, 1972; Mabry & Campbell, 1973; Breese *et al.*, 1974b), amphetamine hyperactivity was found to be potentiated markedly following the reduction of 5-HT with PCPA or 5,6-DHT. These reports, along with the finding that 5-hydroxytryptophan reverses the potentiation of amphetamine-induced motor activity by PCPA, provide convincing evidence for an involvement of serotoninergic fibres.

Additional evidence for this was obtained when interactions between pargyline and amphetamine were examined. MAO inhibitors have generally been reported to enhance amphetamine-stimulated motor activity (Smith, 1963; Van Rossum & Hurkmans, 1964). However, Lew, Iversen & Iversen (1971) found that the MAO inhibitors, pheniprazine and iproniazid, which potentiated the stimulant effects of amphetamine, interfered with its metabolism. Pargyline, which was less effective in potentiating the locomotor actions of amphetamine, had no effect on the disappearance of amphetamine from brain. Nevertheless, the antagonism of amphetamine-induced motor activity 1 h after pargyline could not have been expected. The observation that PCPA antagonized this reduced response clearly implicated brain 5-HT in the inhibition. In contrast to the inhibition observed at the lower dose pargyline did not significantly change the response to amphetamine (3 mg/kg). This finding suggests that mediator system(s) responsible for increasing motor activity after amphetamine can overcome the inhibition produced by serotoninergic fibres in pargyline-treated rats. Since this procedure with pargyline reveals an inhibitory action of amphetamine, it may have relevance to the mechanism by which it acts in hyperkinetic children.

The ability of serotoninergic fibres to influence amphetamine-induced motor activity raised the possibility that inhibition by 6-OHDA of the locomotor response (Breese *et al.*, 1974b; Hollister *et al.*, 1974) depended upon an inhibitory input from serotoninergic fibres in the absence of normal catecholaminergic function. However, inhibition of amphetamine hyperactivity following the 6-OHDA treatments was not significantly altered by PCPA treatment. In addition, we have observed that pargyline will reduce further the response to amphetamine in rats treated with 6-OHDA. These observations suggest that the involvement of serotoninergic fibres in the actions of amphetamine are probably secondary to an indirect release of catecholamines.

Marsden & Guldberg (1973) indicated that amphetamine-induced rotation was not influenced by raphé lesions, in accordance with Randrup & Munkvad (1964) who suggested that 5-HT fibres

have no involvement in the stereotyped behaviour produced by amphetamine. Present results with amphetamine in PCPA-treated rats are not at variance with these earlier studies.

Chronic methamphetamine administration has been reported to induce tyrosine hydroxylase activity in the adrenal (Mandell & Morgan, 1970; Koda & Gibb, 1973). The present study indicates that this is also true of (+)-amphetamine and to some extent of PCPA alone. As well as producing potentiation of locomotor activity, reduction of brain 5-HT by PCPA also enhanced the induction of adrenal tyrosine hydroxylase by amphetamine and by brain stimulation (Mueller, Smith, Breese & Cooper, 1973). Ito & Schanberg (1972) found that chronic treatment with PCPA produces a hypertensive response which is prevented by central lesions. These findings could be explained if a serotoninergic system is proposed which is inhibitory to peripheral sympathetic outflow.

The idea that brain 5-HT and catecholamine fibres interact is not a new concept. On the basis of their experimental work with reserpine Brodie & Shore (1957) were the first to suggest that brain serotoninergic fibres were responsible for the trophotropic activity described by Hess (1954) and that catecholamine fibres in brain represented the opposing ergotropic system. In the present study, evidence is presented that serotoninergic fibres have an inhibitory action on catecholaminergic fibres responsible for amphetamine-induced motor activity. Serotoninergic fibres also appear to inhibit neural control to the adrenal. The possibility that this may also involve catecholamine input is being investigated.

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