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p-CHLOROAMPHETAMINE

TEMPORAL RELATIONSHIP BETWEEN PSYCHOMOTOR STIMULATION AND METABOLISM OF BRAIN NOREPINEPHRINE*

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Abstract—Unlike amphetamine, *p*-chloroamphetamine causes a decrease in cerebral serotonin (5HT) in rats. This effect on 5HT metabolism persists after the psychomotor stimulation has subsided. Like amphetamine, however, *p*-chloroamphetamine exerts a marked effect on the metabolism of intraventricularly administered ^{3}H-norepinephrine during the period of psychomotor stimulation. Thus, it markedly increases the level of ^{3}H-normetanephrine and decreases that of the tritiated deaminated catechol and the deaminated-*O*-methylated metabolites. Desipramine, which blocks the metabolism of amphetamine, prolongs both the pharmacological and biochemical effects caused by amphetamine. It is concluded that the psychomotor stimulation elicited by *p*-chloroamphetamine, like that of amphetamine, is associated with changes in the metabolism of brain norepinephrine and not of brain serotonin.

PARA-CHLORINATED amphetamine derivatives exert pharmacological effects which are qualitatively similar to those of their parent compounds.[1,2] Unlike amphetamine, however, *p*-chloroamphetamine and *p*-chloromethamphetamine cause a simultaneous and long-lasting decrease in the levels of cerebral 5-hydroxytryptamine (5HT) and 5-hydroxyindole-acetic acid (5HIAA) in rats and guinea pigs without appreciably altering the concentration of either norepinephrine or dopamine in brain.[3–6] It has been reported that a temporal relationship does not exist between the marked change in the level of cerebral 5HT and the behavioral stimulation elicited by these drugs.[5,6] Concerning amphetamine, recent studies have provided evidence that this drug both releases physiologically active norepinephrine from adrenergic neurons and prevents its re-uptake into the cell.[8–11] Moreover, studies with tyrosine hydroxylase inhibitors have suggested that amphetamine is an indirectly acting sympathomimetic amine whose central action requires an uninterrupted synthesis of norepinephrine.[12–14]

The present experiments were undertaken to determine whether the psychomotor stimulation elicited by *p*-chloroamphetamine is, like that of amphetamine, temporally related to its effect on the metabolism of norepinephrine in brain.

MATERIALS AND METHODS

Male Sprague–Dawley rats (190–220 g) were used in these studies. The drugs were

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injected intraperitoneally, *d*-amphetamine (3 mg/kg) as the sulfate; *dl-p*-chloroamphetamine (5 mg/kg) and desipramine (10 mg/kg) as the hydrochloride salts. *dl*-7-^{3}H-norepinephrine (6·6 c/m-mole) was obtained from the New England Nuclear Corp., Boston, Mass.

Psychomotor stimulation. Psychomotor activity was measured in Williamson activity cages over a period of 18 hr. The animals were allowed a 1-hr acclimation period in the cages followed by a 2-hr control recording period prior to the injection of drugs.

Intraventricular injections. During pentobarbital anesthesia, a small polyethylene cannula was implanted in the right-lateral ventricle according to the method of Noble *et al.*,[15] as modified by Robinson *et al.*[16] Within 1 to 3 days after cannula placement, the rats were gently restrained and 5 μc of *dl*-7-^{3}H-norepinephrine was injected into the ventricle in a total volume of 10 μl.

Assay of endogenous levels of 5HT. Animals were killed by decapitation. The brains were rapidly removed and homogenized in 0·1 N HCl. 5HT was determined by the spectrophotofluorometric method of Bogdanski *et al.*[17]

Assay of radioactive amines and metabolites. The brains were homogenized in 10 ml of 0·4 N chilled perchloric acid. The homogenate was centrifuged at 10,000 *g* (av.) for 20 min at 0° and the supernatant adjusted to pH 8·4 with 1 N NaOH. A 1-ml aliquot of the supernatant was added to 15 ml of dioxane containing 1·88 g of naphthalene, 33 mg of 2,5-diphenyloxazole (PPO) and 0·94 mg of 1,4-bis[2-(5-phenyloxazolyl)] benzene (POPOP) and assayed for total radioactivity in a liquid scintillation spectrometer.

Aliquots of the supernatant were also analyzed for ^{3}H-norepinephrine (^{3}H-NE) by the alumina-absorption method of Whitby *et al.*[18] and ^{3}H-normetanephrine (^{3}H-NMN) by a modification of the procedure of Iversen *et al.*,[19] as previously described.[20] The deaminated catechol metabolites were separated from norepinephrine by extraction of the former into ethyl acetate at acid pH according to the method of Kopin *et al.*[21] Radioactive deaminated catechols were determined by measuring the radioactivity of an aliquot of the ethylacetate extract which had previously been evaporated to dryness and redissolved in alcohol. Tritiated-*O*-methylated deaminated metabolites were estimated by calculating the difference between the total radioactivity and the sum of norepinephrine, normetanephrine and deaminated catechols. Although it is possible that tritium exchange with water could affect the estimation by difference of the tritiated-*O*-methylated deaminated metabolites, no quantitative data on this exchange in brain are available. The average recoveries of ^{3}H-NE and ^{3}H-NMN, added to 0·01 N HCl and carried through this procedure, were 95 and 60 per cent respectively. The data on the deaminated catechols were corrected according to Kopin *et al.*[21] Moreover, all data were corrected for counting efficiency using external standardization and for the appropriate recoveries.

RESULTS

Effect of p-*chloroamphetamine on psychomotor stimulation and on the level of 5HT in brain.* In rats, *p*-chloroamphetamine (5 mg/kg) elicited a marked psychomotor stimulation which persisted for 6 to 8 hr, with the maximum activity occurring 1 hr after its administration (Fig. 1). The level of 5HT in brain declined slowly; the minimum concentration of the amine occurred 4 hr after the administration of the

drug and persisted for many hours. It is noteworthy that 16 hr after the administration of *p*-chloroamphetamine, the level of 5HT was only about 50 per cent of that of untreated control animals. Accordingly, there exists no temporal relationship between the psychomotor stimulation elicited by *p*-chloroamphetamine and its effect on the level of 5HT in brain.

Effect of p-*chloroamphetamine and amphetamine on the initial content and metabolism of intraventricularly administered* ^{3}*H-norepinephrine.* ^{3}H-NE (5 μc) was given intraventricularly to unanesthetized rats which had been treated 1 hr previously with

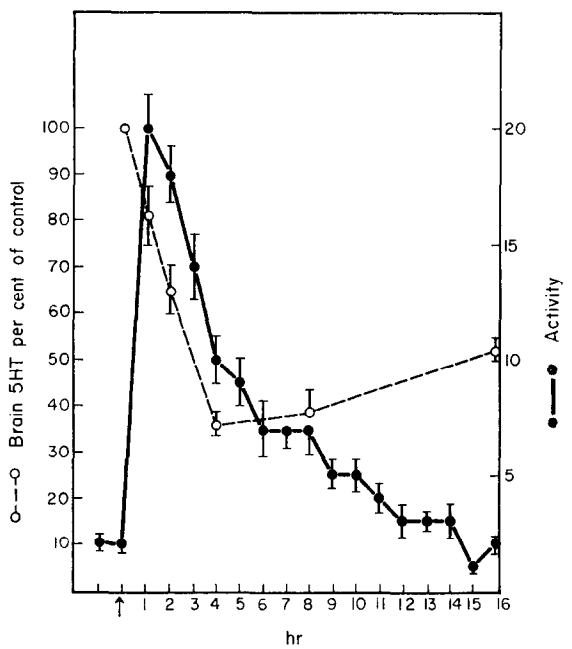

FIG. 1. The effect of *p*-chloroamphetamine on psychomotor activity and on the level of serotonin (5HT) in brain. *p*-Chloroamphetamine (5 mg/kg, i.p.) was given after a 2-hr control period (designated by the arrow). Activity is expressed as integrated counts per hour. Each value represents the mean activity of 20 animals. The 5HT values represent the mean of 4 animals and are expressed as a percentage of control. Brain 5HT levels in control rats: 0·45 $\pm$ 0·01 μg/g. Vertical bars indicate the standard error of the mean.

p-chloroamphetamine (5 mg/kg) or amphetamine (3 mg/kg). The animals were sacrificed 6 min after the intraventricular injection and the brains were analyzed for ^{3}H-HE and its metabolites as described in Methods. *p*-Chloroamphetamine and amphetamine caused similar metabolic alterations. Both drugs significantly increased the amount of ^{3}H-NMN and reduced the amount of the tritiated deaminated catechols (Table 1). Moreover, pretreatment with amphetamine slightly reduced the amount of ^{3}H-NE found in the brain 6 min after its intraventricular administration.

Effect of p-*chloroamphetamine and amphetamine on the metabolism of intraventricularly administered* ^{3}*H-norepinephrine.* Rats were pretreated with *p*-chloroamphetamine (5 mg/kg) or amphetamine (3 mg/kg) 1, 4 or 16 hr prior to the intraventricular injection

of 5 μc of ^{3}H-NE. The animals were sacrificed 60 min after injection of the labeled amine and the brains analyzed for ^{3}H-NE and its metabolites as described in Methods.

Two hr after the administration of amphetamine and *p*-chloroamphetamine, both drugs caused qualitatively similar effects on the metabolism of ^{3}H-NE, that is, a significant increase in the level of ^{3}H-NMN and a concomitant decrease in that of both the tritiated deaminated catechols and the deaminated-*O*-methylated metabolites. The effect of *p*-chloroamphetamine on the level of ^{3}H-NMN is, however, more

TABLE 1. EFFECT OF *p*-CHLOROAMPHETAMINE AND AMPHETAMINE ON THE INITIAL CONTENT AND METABOLISM OF ^{3}H-NOREPINEPHRINE IN THE RAT BRAIN*

	Control	*p*-Chloro-amphetamine	Amphetamine
Total radioactivity (TR)	100 ± 3	94 ± 3	89 ± 4†
^{3}H-norepinephrine (NE)	100 ± 5	90 ± 4	81 ± 7†
^{3}H-normetanephrine (NMN)	100 ± 5	138 ± 11‡	136 ± 5‡
^{3}H-deaminated catechols (DCM)	100 ± 4	58 ± 3§	63 ± 6§
^{3}H-deaminated-*O*-methylated metabolites (DOM)	100 ± 11	81 ± 7	95 ± 15

* *p*-Chloroamphetamine (5 mg/kg) or amphetamine (3 mg/kg) was given 1 hr before the intraventricular injection of 5 μc of ^{3}H-norepinephrine. Animals were sacrificed 6 min after the administration of the labeled amine. The results are expressed as a percentage of the control values ± S.E.M. Control mean values: TR = 2633 mμc; NE = 1871 mμc; NMN = 314 mμc; DCM = 35 mμc; DOM = 413 mμc. N = 7.
† $P < 0.05$.
‡ $P < 0.01$.
§ $P < 0.001$.

TABLE 2. EFFECT OF *p*-CHLOROAMPHETAMINE AND AMPHETAMINE ON THE METABOLISM OF ^{3}H-NOREPINEPHRINE IN THE RAT BRAIN*

	Control	*p*-Chloro-amphetamine	Amphetamine
Total radioactivity (TR)	100 ± 9	92 ± 4	80 ± 4†
^{3}H-norepinephrine (NE)	100 ± 8	92 ± 5	86 ± 5†
^{3}H-normetanephrine (NMN)	100 ± 16	335 ± 36‡	148 ± 15†
^{3}H-deaminated catechols (DCM)	100 ± 7	36 ± 6‡	46 ± 5‡
^{3}H-deaminated-*O*-methylated metabolites (DOM)	100 ± 10	72 ± 7†	71 ± 4†

* *p*-Chloroamphetamine (5 mg/kg) or amphetamine (3 mg/kg) was given 1 hr before the intraventricular injection of 5 μc of ^{3}H-norepinephrine. Animals were sacrificed 60 min after the administration of the labeled amine. The results are expressed as a percentage of the control values ± S.E.M. Control mean values: TR = 2447 mμc; NE = 978 mμc; NMN = 137 mμc; DCM = 80 mμc; DOM = 1255 mμc. N = 7.
† $P < 0.05$.
‡ $P < 0.001$.

pronounced than that of amphetamine (Table 2). Amphetamine caused a slight reduction in both the amount of ^{3}H-NE and the total radioactivity found in the brain. Two hr after their administration, both drugs still elicited marked psychomotor stimulation (Fig. 2).

Significant effects on the metabolism of norepinephrine were observed 5 hr after

treatment with *p*-chloroamphetamine. Under these conditions, amphetamine did not appreciably alter the metabolism of the labeled amine (Tables 3 and 4). It is noteworthy that the psychomotor stimulation elicited by *p*-chloroamphetamine persisted for almost 10 hr, whereas that evoked by amphetamine had subsided after 4 hr (Fig. 2). Moreover, pretreatment with *p*-chloroamphetamine for 16 hr did not cause, with the exception of a slight decrease in the deaminated catechols, a significant alteration in the metabolism of intraventricularly administered ^{3}H-NE (Table 5). At this time, the

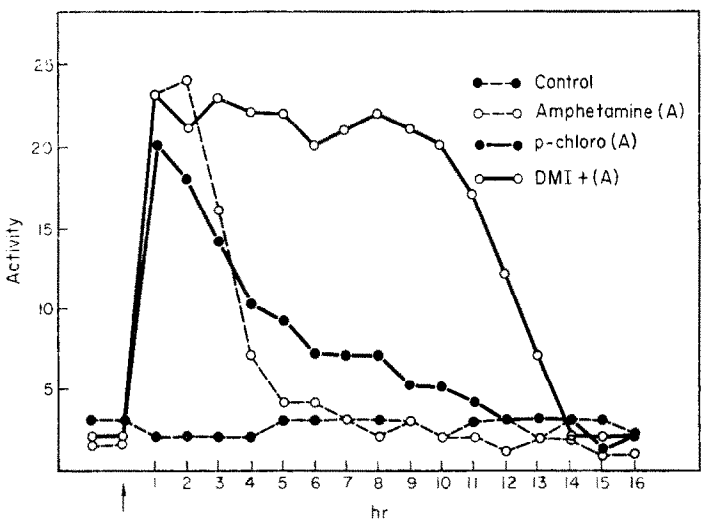

FIG. 2. Effect of various drugs on psychomotor activity. Amphetamine (3 mg/kg) or *p*-chloroamphetamine (5 mg/kg) was given intraperitoneally after a 2-hr control period (designated by arrow). DMI (10 mg/kg) was injected 1 hr before the administration of amphetamine. Activity is expressed as integrated counts per hour. Each value represents the mean activity of 20 animals.

TABLE 3. EFFECT OF *p*-CHLOROAMPHETAMINE ON THE METABOLISM OF ^{3}H-NOREPINEPHRINE IN THE RAT BRAIN*

	Control	*p*-Chloro-amphetamine
Total radioactivity (TR)	100 ± 3	95 ± 8
^{3}H-norepinephrine (NE)	100 ± 5	94 ± 7
^{3}H-normetanephrine (NMN)	100 ± 7	304 ± 45†
^{3}H-deaminated catechols (DCM)	100 ± 6	71 ± 6‡
^{3}H-deaminated-*O*-methylated metabolites (DOM)	100 ± 5	65 ± 5‡

* *p*-Chloroamphetamine (5 mg/kg) was administered 4 hr before the intraventricular injection of 5 μc of ^{3}H-norepinephrine. Animals were sacrificed 60 min after administration of the labeled amine. The results are expressed as a percentage of the control values ± S.E.M. Control mean values: TR = 2030 mμc; NE = 823 mμc; NMN = 142 mμc; DCM = 90 mμc; DOM = 975 mμc. N = 7.

† $P < 0.001$.

‡ $P < 0.005$.

TABLE 4. MODIFICATION BY DESIPRAMINE (DMI) OF THE EFFECT OF AMPHETAMINE ON THE METABOLISM OF ^{3}H-NOREPINEPHRINE IN THE RAT BRAIN*

	Control	DMI	Amphetamine	DMI + amphetamine
Total radioactivity (TR)	100 ± 5	108 ± 5	81 ± 3†	76 ± 5†
^{3}H-norepinephrine (NE)	100 ± 6	103 ± 3	86 ± 3	74 ± 5†
^{3}H-normetanephrine (NMN)	100 ± 8	100 ± 9	111 ± 8	246 ± 34‡
^{3}H-deaminated catechols (DCM)	100 ± 9	84 ± 10	73 ± 3†	38 ± 6§
^{3}H-deaminated-*O*-methylated metabolites (DOM)	100 ± 6	117 ± 12	73 ± 5†	51 ± 5§

* Desipramine (10 mg/kg) was given 5 hr and amphetamine (3 mg/kg) 4 hr prior to intraventricular injection of 5 μc of ^{3}H-norepinephrine. Animals were sacrificed 60 min after the administration of the labeled amine. The results are expressed as a percentage of the control values ± S.E.M. Control mean values: TR = 2247 mμc; NE = 943 mμc; NMN = 161 mμc; DCM = 75 mμc; DOM = 1068 mμc. N = 6.
† $P < 0.05$.
‡ $P < 0.005$.
§ $P < 0.001$.

TABLE 5. EFFECT OF *p*-CHLOROAMPHETAMINE ON THE METABOLISM OF ^{3}H-NOREPINEPHRINE IN THE RAT BRAIN*

	Control	*p*-Chloro-amphetamine
Total radioactivity (TR)	100 ± 5	94 ± 6
^{3}H-norepinephrine (NE)	100 ± 5	93 ± 6
^{3}H-normetanephrine (NMN)	100 ± 13	158 ± 28
^{3}H-deaminated catechols (DCM)	100 ± 12	68 ± 7†
^{3}H-deaminated-*O*-methylated catechols (DOM)	100 ± 7	86 ± 6

* *p*-Chloroamphetamine (5 mg/kg, i.p.) was given 16 hr before the intraventricular injection of 5 μc of ^{3}H-norepinephrine. Animals were sacrificed 60 min after the administration of the labeled amine. The results are expressed as a percentage of the control values ± S.E.M. Control mean values: TR = 1676 mμc; NE = 825 mμc; NMN = 114 mμc; DCM = 54 mμc; DOM = 684 mμc. N = 7.
† $P < 0.05$.

level of cerebral 5HT in treated animals is still only about 50 per cent of that in control animals (Fig. 1).

Modification by desipramine (DMI) of the effect of amphetamine on the metabolism of ^{3}H-norepinephrine. The relatively short-lasting effect of amphetamine on the metabolism of ^{3}H-NE might be the consequence of a rapid metabolism of this drug. Therefore, rats were pretreated with 10 mg/kg of DMI, a compound which prolongs the psychomotor stimulation of amphetamine by inhibiting its hepatic metabolism and thereby sustaining elevated levels of amphetamine in brain.[22–25]

Amphetamine (3 mg/kg) given 4 hr prior to the intraventricular injection of ^{3}H-NE did not alter the metabolism of the catecholamine appreciably. However, when DMI was given 1 hr prior to amphetamine, the effects of amphetamine on psychomotor stimulation (Fig. 2) and on the metabolism of norepinephrine were still marked 5 hr after its administration (Table 4). In fact, the increase in ^{3}H-NMN and the

reduction in the levels of the deaminated catechols and of the deaminated-*O*-methylated metabolites 5 hr after the combined administration of DMI and amphetamine are more pronounced than the changes observed 2 hr after the injection of amphetamine alone. It is pertinent that pretreatment with DMI (10 mg/kg) for 6 hr did not significantly alter the metabolism of the tritiated catecholamine (Table 4).

DISCUSSION

Marked qualitative differences exist between the effects elicited by amphetamine and *p*-chloroamphetamine on brain monoamines while the differences in the pharmacological actions of the 2 drugs are only quantitative in nature.[1,2] The more recent experimental data on the mode of action of amphetamine favor the view that the psychomotor stimulation of amphetamine is mediated through the release of catecholamines in the brain[8-11] and that the size of the catecholamine store itself is not critical as long as synthesis is not impaired.[12-14] The marked lowering of 5HT and 5HIAA in brain by *p*-chloroamphetamine has recently been suggested to be the consequence of an inhibition of cerebral tryptophan hydroxylase.[26,27] The long-lasting depletion of 5HT may be associated with the prolonged insomnia caused by the drug.[28] Moreover, it has been suggested that the central stimulatory action of *p*-chloroamphetamine depends, at least in part, on an alteration in the levels of cerebral 5HT.[2]

In agreement with results of other investigations[5,6] the present studies demonstrate that a temporal relationship does not exist between the psychomotor stimulation elicited by *p*-chloroamphetamine and its effect on the level of brain serotonin. The initial excitatory action of *p*-chloroamphetamine, like that of amphetamine, is however temporally related to its effect on norepinephrine metabolism. The chlorinated amphetamine derivative exerts a much longer lasting effect than does amphetamine, which probably reflects the marked difference in the rate of metabolism and disappearance of the two drugs from brain.[4,29,30] In agreement with this view, pretreatment of rats with DMI, which leads to a striking and sustained increase in the level of amphetamine in brain,[22-24] prolonged both the pharmacological and the biochemical effects elicited by amphetamine.

The large increase in the concentration of normetanephrine and the marked reduction in the levels of the deaminated and to a lesser degree of the deaminated-*O*-methylated metabolites after *p*-chloroamphetamine are qualitatively similar to those elicited by amphetamine. Accordingly, similar mechanisms might be responsible for their effects: release of norepinephrine, blockade of its reuptake, and inhibition of monoamine oxidase.[8,9] Compounds such as amphetamine with an isopropylamine side-chain are not substrates for monoamine oxidase but can act as competitive inhibitors of the enzyme.[31] In fact, it has been demonstrated that both amphetamine and *p*-chloroamphetamine can inhibit monoamine oxidase *in vitro*.[7,9]

Though the effects of *p*-chloroamphetamine on the metabolism of norepinephrine are similar at 2 and 5 hr, the psychomotor activity has declined markedly in this period of time. Moreover, the maximum behavioral effects evoked by both *p*-chloroamphetamine and amphetamine were comparable. *p*-Chloroamphetamine, however, caused more pronounced changes in the metabolism of the tritiated norepinephrine. At first glance, these findings appear to preclude a quantitative relationship between the psychomotor stimulation evoked by the two drugs and their effect on norepinephrine metabolism in brain. However, the metabolic data in brain homogenates do

not accurately reflect the actual availability of physiologically active norepinephrine at adrenergic receptor sites, and many other factors besides catecholamine metabolism in brain will contribute to such a complex behavioral parameter as psychomotor stimulation. Since the tritiated norepinephrine represents stored and not newly synthesized norepinephrine, it is tempting to speculate that *p*-chloroamphetamine exerts its effect mainly through stored catecholamines, whereas storage of norepinephrine does not appear to be essential for the central stimulatory action of amphetamine, as long as catecholamine synthesis is maintained. Data obtained from drug interaction studies are consistent with this view. Thus, low doses of the tyrosine hydroxylase inhibitor, α-methyltyrosine, block the psychomotor stimulation elicited by amphetamine,[12-14] but very high doses of α-methyltyrosine are required to antagonize that caused by *p*-chloroamphetamine.[2] Moreover, reserpine, which impairs the storage but not the synthesis of catecholamines, blocks the central action of *p*-chloroamphetamine[32] but does not appreciably change that of amphetamine.[33,34] The apparent higher affinity of *p*-chloroamphetamine for the store could be the consequence of its more lipophilic character, its stronger binding to the particulate fraction in the CNS,[29] as well as its slower rate of metabolism.[4,29,30] Recent studies with a push–pull cannula have in fact demonstrated that *p*-chloroamphetamine, in contrast to amphetamine, causes a many-fold increase in the release of stored tritiated norepinephrine and of normetanephrine into the perfusate of the hypothalamus.[35]

Although complete dose–response curves with amphetamine and *p*-chloroamphetamine must be established before definite conclusions on the relative affinities of the 2 drugs for stored versus newly synthesized catecholamines can be drawn, the present studies indicate that the central stimulatory activity of both amphetamine and *p*-chloroamphetamine is associated with marked changes in the metabolism of brain norepinephrine.

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