

Depletion of brain noradrenaline and dopamine by 6-hydroxydopamine

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Summary

1. After intracisternal administration, 6-hydroxydopamine had a greater effect on brain noradrenaline than on dopamine.
2. Administration of two doses of 6-hydroxydopamine increased the depletion of noradrenaline but not of dopamine.
3. Small doses of 6-hydroxydopamine decreased the concentration of noradrenaline with little or no effect on dopamine. Tyrosine hydroxylase activity was not reduced with these treatments.
4. While pargyline pretreatment offered no advantage in the depletion of brain noradrenaline after 6-hydroxydopamine, depletion of brain dopamine was greatly potentiated by this treatment. The reduction of striatal tyrosine hydroxylase activity observed after 6-hydroxydopamine was also potentiated by pargyline pretreatment.
5. The amounts of labelled noradrenaline and dopamine formed from ^3H -tyrosine were greatly reduced by 6-hydroxydopamine treatment. After ^3H -DOPA, formation of noradrenaline was greatly reduced while formation of labelled dopamine was only moderately reduced suggesting that decarboxylation of DOPA can occur in other than catecholamine containing neurones.
6. Desmethylinipramine and imipramine inhibited depletion of noradrenaline produced by 6-hydroxydopamine but did not alter depletion of dopamine. Reserpine did not inhibit depletion of catecholamines produced by 6-hydroxydopamine.
7. Administration of 6-hydroxydopamine to developing rats lowered both noradrenaline and dopamine concentrations as well as the tyrosine hydroxylase activity in the brains of these animals.

Introduction

Depletion of the catecholamine content of sympathetically innervated tissues by 6-hydroxydopamine was reported several years ago (Porter, Totaro & Stone, 1963; Laverty, Sharman & Vogt, 1965). From the observation that 6-hydroxydopamine caused an enduring depletion of tissue noradrenaline, Porter *et al.* (1963) suggested that this compound might destroy noradrenaline binding sites. Recently, several workers have extended these observations and found that 6-hydroxydopamine actually causes degeneration of peripheral adrenergic nerves (Tranzer & Thoenen, 1968; Thoenen & Tranzer, 1968; Malmfors & Sachs, 1968).

These reports indicating that 6-hydroxydopamine produces a chemical sympathectomy peripherally soon led to investigations of the possibility that this compound might also produce destruction of brain catecholamine neurones after being injected into brain (Ungerstedt, 1968 ; Bloom, Algeri, Groppetti, Revuetta & Costa, 1969 ; Uretsky & Iversen, 1970 ; Breese & Traylor, 1970). Examination of areas rich in adrenergic neurones with electron microscopy has indicated that 6-hydroxydopamine can indeed produce degeneration of central noradrenergic fibres (Bloom *et al.*, 1969). Support for this view was extended in reports that indicated that tyrosine hydroxylase activity was reduced in the caudate nucleus and other parts of brain after 6-hydroxydopamine administration (Breese & Traylor, 1970 ; Uretsky & Iversen, 1970).

The purpose of our experiments was to examine further the effects of 6-hydroxydopamine in depleting catecholamines from brain, to define the effects of multiple injections of 6-hydroxydopamine at several doses, and to determine the effect of various psychoactive drugs known to alter uptake, storage and metabolism of catecholamines on brain amine depletion produced by 6-hydroxydopamine.

Methods

Male Sprague-Dawley rats (140–200 g) received 25–200 μ g of 6-hydroxydopamine intracisternally in 25 μ l of saline solution as described previously (Schanberg, Schildkraut, Breese & Kopin, 1968 ; Breese, Kopin & Weise, 1970). The saline solution contained 0.4 mg/ml of ascorbic acid to prevent oxidation of the 6-hydroxydopamine ; animals which did not receive 6-hydroxydopamine received the saline solution containing ascorbic acid.

After killing the animals by cervical fracture, brains were removed, homogenized in 0.4 N perchloric acid and the homogenates kept frozen until they were analysed. After thawing and centrifugation of the homogenate, brain noradrenaline and dopamine were isolated according to the procedure of Anton & Sayre (1962). Noradrenaline was assayed according to the method of Häggendal (1963) ; dopamine according to the method of Anton & Sayre (1964).

Some animals received 50 μ Ci of 3 H-tyrosine (34.7 Ci/mmol) or 100 μ Ci of 3 H-DOPA (3.0 Ci/mmol) intravenously. Animals were killed 1 h after injecting the labelled compounds and the radioactive noradrenaline and dopamine was isolated according to the method of Sedvall, Weise & Kopin (1968). All radioactivity was measured using scintillation spectrometry ; an internal standard of 3 H-toluene was used to correct for counting efficiency.

The 'striatum' was dissected from brain on a chilled glass plate and refers to that area of brain adjacent to the lateral ventricle and bounded by the radiation of the corpus callosum. Access to this mass was obtained through the lateral ventricle after hemisection of the whole brain. Tyrosine hydroxylase was isolated from these tissues according to the method of Musacchio, Julou, Kety & Glowinski (1969). Enzyme activity was determined by the method of Nagatsu, Levitt & Udenfriend (1964). For the measurement of enzyme activity in the striatum half quantities of each reagent were used with the final volume measuring 0.5 ml.

At 13 days of age, rat pups were injected intracisternally with 100 μ g of 6-hydroxydopamine ; 26 days later the animals were killed. Brains were divided sagittally

along the midline; one-half of the brain from each animal was analysed for noradrenaline and dopamine and the other half for tyrosine hydroxylase.

Several drugs were used in combination with intracisternally administered 6-hydroxydopamine (100 μg). These included pargyline (50 mg/kg), desmethyl-imipramine (25 mg/kg), imipramine (25 mg/kg), chlorpromazine (25 mg/kg), and D-amphetamine (10 mg/kg). All of the compounds were administered intraperitoneally 30 min before 6-hydroxydopamine. Metaraminol (100 μg) was adminis-

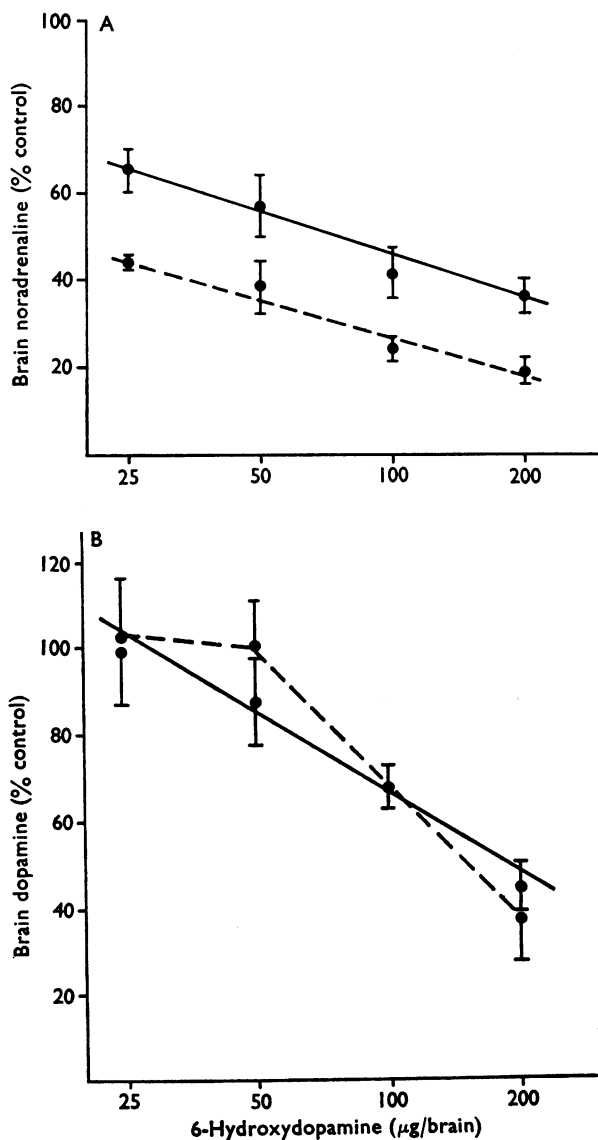


FIG. 1. Comparison of the effect of one dose (●—●) with that of two doses (●---●) of 6-hydroxydopamine on brain noradrenaline (A) and dopamine (B). Animals received 6-hydroxydopamine intracisternally. The rats given one dose were killed 2 weeks later. When two doses were administered, they were separated by 1 week, the first dose being given 2 weeks before the animals were killed. The animals which received only one dose received a saline injection 1 week after the first injection. Control values for brain noradrenaline were 330 ± 32 ng/g and 592 ± 42 ng/g for dopamine. Vertical bars indicate the S.E.M. Each point represents six to eight determinations.

tered intracisternally 15 min before the 6-hydroxydopamine. Reserpine (5 mg/kg) was administered 18 h before a second dose of 2.5 mg/kg. The 6-hydroxydopamine was administered 3 h after the last dose of reserpine.

The 6-hydroxydopamine HBr was purchased from Regis Chemical Company. Pargyline was kindly supplied by Abbott Laboratories. The D-amphetamine and chlorpromazine were gifts of Smith, Kline & French Laboratories. The desmethyl-imipramine and imipramine were kindly furnished by Geigy Laboratories. The reserpine was a gift from Ciba Laboratories. ^3H -Tyrosine and ^3H -DOPA were purchased from Amersham-Searle Corporation.

Results

Catecholamine content in rat brain after 6-hydroxydopamine treatment

Noradrenaline and dopamine contents were determined in rat brain 14 days after the intracisternal administration of various doses of 6-hydroxydopamine. In confirmation of earlier studies (Uretsky & Iversen, 1970; Breese & Traylor, 1970), 6-hydroxydopamine had a greater effect on noradrenaline than dopamine (Fig. 1). The dose of 25 μg reduced noradrenaline approximately 35% and 200 μg approximately 63%. Dopamine was not significantly altered at the smaller doses of 6-hydroxydopamine but was reduced 49% at the higher dose. A linear dose-response relation was noted for the depletion of both amines (Fig. 1).

The effect of multiple dose administration was also determined. A comparison of one dose with two doses is also shown in Fig. 1. Two injections significantly enhanced the depletion of brain noradrenaline. Dopamine depletion, on the other hand, was not increased by the second dose of 6-hydroxydopamine (Fig. 1). At a dose of 25 μg of 6-hydroxydopamine, noradrenaline depletion increased with an additional dose while dopamine concentrations remained unaltered by this procedure (Figs. 1 & 2). To determine if this depletion of noradrenaline might be increased

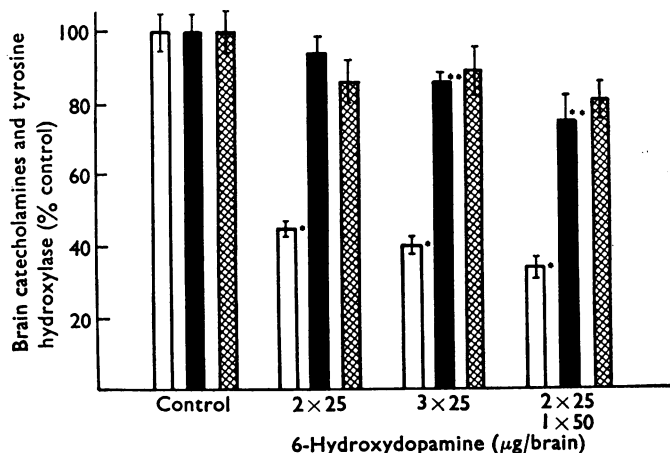


FIG. 2. Effect of multiple doses of 6-hydroxydopamine on brain concentrations of noradrenaline \square , dopamine \blacksquare and on tyrosine hydroxylase \boxtimes activity. Animals were given doses of 6-hydroxydopamine intracisternally 1 week apart and killed 1 week after the last dose. Control values for noradrenaline and dopamine were 352 ± 18.1 and 658 ± 35.8 ng/g respectively. Tyrosine hydroxylase activity was $(4.40 \text{ pmol/mg})/\text{h}$ in the control animals. Values represent the mean from six to ten animals. Significance when compared with controls * $P < 0.001$; ** $P < 0.05$.

further if additional small doses were administered, other multiple dose sequences were studied (Fig. 2). As previously observed 2 times 25 μg reduced the concentration of noradrenaline by 55% without having an effect on dopamine. Three injections of 25 μg caused a further small decrease in noradrenaline concentration, but dopamine was now significantly reduced by 14%. Two doses of 25 μg with an additional dose of 50 μg of 6-hydroxydopamine lowered the noradrenaline concentration by 66% and the dopamine concentration was reduced by 25%. None of the treatments significantly altered tyrosine hydroxylase activity.

Effect of pargyline on the dose-response relation of the reduction of brain noradrenaline and dopamine by 6-hydroxydopamine

Previous studies have demonstrated that pargyline offered no advantage in the reduction of brain noradrenaline by 6-hydroxydopamine but potentiated the reduction of cerebral dopamine by 6-hydroxydopamine at higher doses (Traylor & Breese, 1970). These results are reaffirmed in this study (Tables 3 & 4). Since it is well established that a large portion of the cerebral dopamine is contained in the striatum (Carlsson, 1959), the relation of the dose of 6-hydroxydopamine to the effect on dopamine as well as on tyrosine hydroxylase activity was examined in this brain area (Fig. 3). As might have been expected, both dopamine and tyrosine hydroxy-

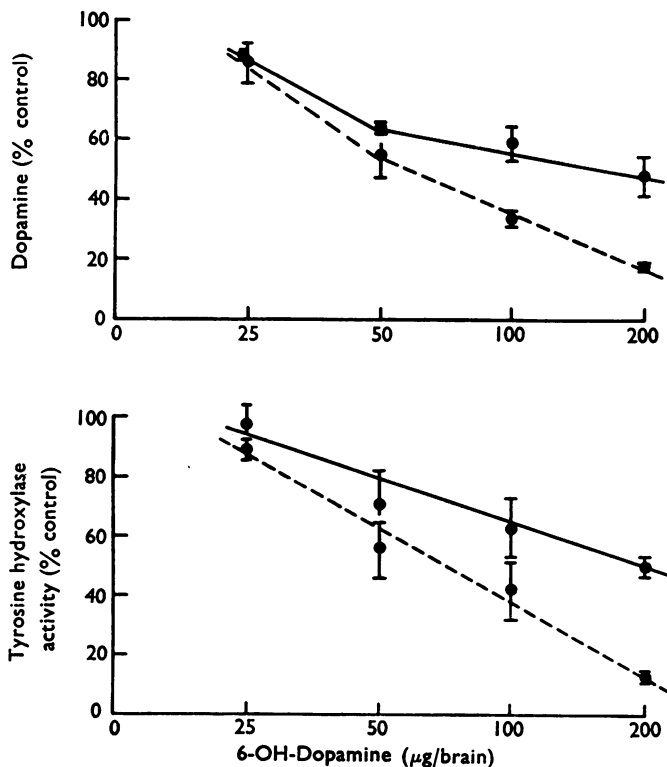


FIG. 3. Effect of 6-hydroxydopamine on the concentration of dopamine and tyrosine hydroxylase activity in the striatum. Various doses of 6-hydroxydopamine were administered intracisternally to animals with (●—●) and without (●---●) pargyline pretreatment. Animals were killed 14 days later. Control value for striatal dopamine was $6.04 \pm 0.2 \mu\text{g/g}$; control tyrosine hydroxylase activity was $(21.6 \pm 2.1 \text{ pmol/mg})/\text{hour}$. Mean values were determined from groups of seven animals.

lase were reduced in proportion to the dose of 6-hydroxydopamine. The reduction of both was enhanced by pargyline treatment (Fig. 3) as already observed in whole brain (Breese & Traylor, 1970).

A comparison of the effect of one dose with that of two doses of 6-hydroxydopamine was also made in pargyline treated animals. In contrast to the effect on cerebral noradrenaline without pargyline pretreatment (Fig. 1), two doses did not

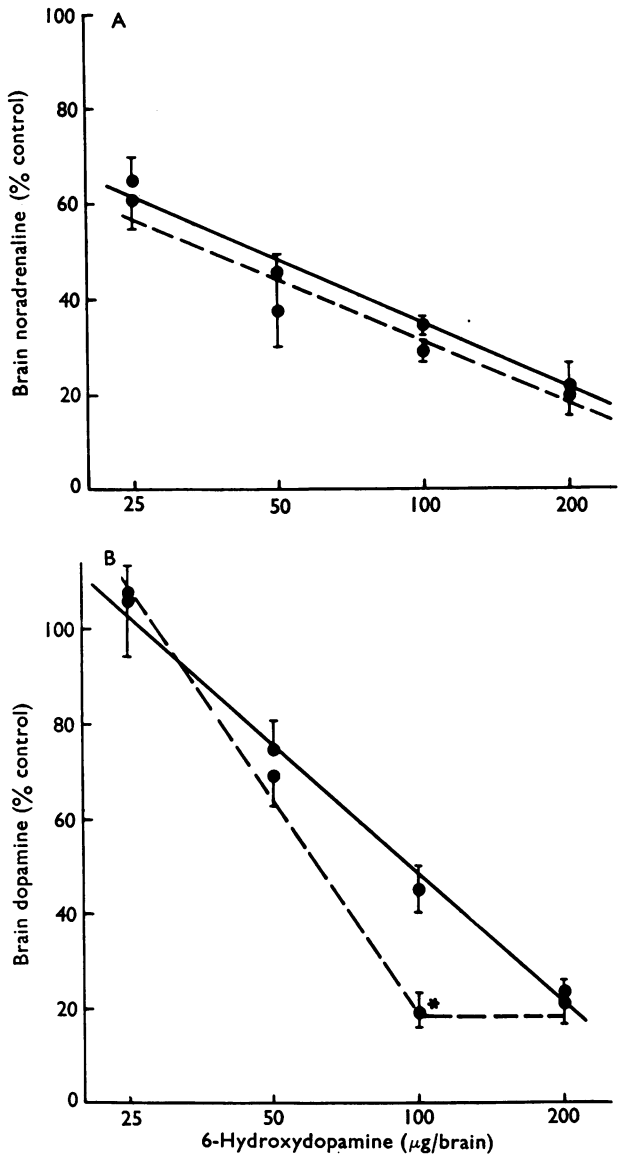


FIG. 4. Comparison of the effect of one dose (●—●) with that of two doses (●---●) of 6-hydroxydopamine in pargyline treated animals on brain noradrenaline (A) and dopamine (B). Animals received various doses of 6-hydroxydopamine 30 min after being given pargyline; 1 week later one half of the group received saline and the other half 6-hydroxydopamine in combination with pargyline. Brain noradrenaline and brain dopamine values for saline treated controls were 360 ± 40 and 582 ± 39 ng/g respectively. Values represent the mean from six animals. * $P < 0.001$ when compared with the result from animals receiving a single dose of 6-hydroxydopamine.

significantly enhance the reduction of the concentration of noradrenaline over a single dose (Fig. 4). The reduction of dopamine after two injections was significantly greater than after a single injection at the 100 µg dose level (Fig. 4). At a dose of 200 µg, the reduction of dopamine with a single dose was not significantly different from that observed after two doses.

In our experience, two injections of 200 µg 6-hydroxydopamine, one with pargyline and the other without pargyline, produced the most consistent depletion of brain catecholamines of any of the sequences tested. The effect on brain noradrenaline, dopamine, and tyrosine hydroxylase was examined after treatment with this sequence (Table 1). The concentration of brain noradrenaline was reduced by 88%, dopamine concentration by 87%, and tyrosine hydroxylase activity comparably by 93%. This sequence is most routinely used in our laboratory to treat animals for pharmacological experimentation.

Effect of 6-hydroxydopamine on the synthesis of catecholamines from radioactively labelled DOPA and tyrosine

Synthesis of catecholamines from ³H-tyrosine and ³H-DOPA was determined 14 days after the intracisternal administration of 6-hydroxydopamine (Table 2). The amount of radioactively labelled noradrenaline and dopamine isolated from the brains of animals treated with 6-hydroxydopamine after ³H-tyrosine was reduced by 83 and 76% respectively, when compared with normal animals. The amount of labelled noradrenaline in the brain of 6-hydroxydopamine treated rats after ³H-DOPA was as low as that seen in the animals that received ³H-tyrosine. In contrast to these results, the amount of radioactive dopamine isolated from the brains of rats treated with 6-hydroxydopamine and which received ³H-DOPA was only 33% lower than in normal animals, considerably less than the reduction for dopamine observed after ³H-tyrosine administration (Table 2).

Effect of various agents on the depletion of brain catecholamines by 6-hydroxydopamine

To obtain some insight into the mechanism by which 6-hydroxydopamine may cause neuronal degeneration, various pharmacological agents known to influence

TABLE 1. *Effect of two doses of 6-hydroxydopamine, one dose with and one without pargyline pretreatment, on the concentrations of catecholamines and on tyrosine hydroxylase activity in the rat brain*

Treatment	Noradrenaline ng/g	Dopamine ng/g	Tyrosine hydroxylase (pmol/mg)/h
Control	433 ± 20.6	658 ± 35.8	5.35 ± 0.32
6-Hydroxydopamine	45 ± 6.8*	85 ± 11.8*	0.36 ± 0.08*

Animals received two doses of 200 µg of 6-hydroxydopamine intracisternally 1 week apart; the first dose was in combination with pargyline (50 mg/kg) and the second dose without pargyline. Animals were killed 2 weeks after the last dose. Values represent the mean ± S.E.M. from nine animals. **P* < 0.001 when compared with controls.

TABLE 2. *Effect of 6-hydroxydopamine on the synthesis of ³H-catecholamines from ³H-tyrosine and ³H-dopa*

Isotope	Treatment	³ H-Noradrenaline	³ H-Dopamine
³ H-Tyrosine	Saline	750 ± 60	570 ± 36
	6-Hydroxydopamine	128 ± 25*	135 ± 25*
³ H-DOPA	Saline	577 ± 66	330 ± 17
	6-Hydroxydopamine	87 ± 7.3*	219 ± 10*

Animals were given either ³H-tyrosine (40 µCi) or ³H-DOPA (80 µCi) intravenously 14 days after 6-hydroxydopamine (2 × 200 µg). Values expressed as c.p.m./brain ± S.E.M. **P* < 0.001 when compared with controls.

different aspects of the mechanisms that control neuronal function were administered before the intracisternal administration of 6-hydroxydopamine (Table 3). Compounds previously shown to inhibit uptake of noradrenaline into brain (Schanberg, Schildkraut & Kopin, 1967), desmethyl imipramine and imipramine, inhibited the depletion of noradrenaline produced by 6-hydroxydopamine. Metaraminol and amphetamine, phenylethylamine derivatives, likewise inhibited the reduction of the concentration of noradrenaline produced by 6-hydroxydopamine. Chlorpromazine inhibited the effect of 6-hydroxydopamine but less so than the other compounds. In contrast, neither pargyline nor reserpine altered the noradrenaline depletion produced by this dose schedule of 6-hydroxydopamine.

Dopamine was also determined after several treatments (Table 4). In contrast to their effect on noradrenaline depletion, desipramine, imipramine and chlorpromazine had no effect on the dopamine depletion induced by 6-hydroxydopamine. As noted in an earlier study (Breese & Traylor, 1970), pargyline significantly enhanced the depletion of brain dopamine. Reserpine produced a similar effect to that of pargyline enhancing the reduction of brain dopamine by 6-hydroxydopamine.

TABLE 3. *Effect of various agents on the depletion of brain noradrenaline by 6-hydroxydopamine*

Treatment	Dose	Noradrenaline	
		ng/brain	Percent control
Saline	—	245 ± 10.7	34.2 ± 1.5
Pargyline	50	252 ± 19.3	35.2 ± 2.7
Desipramine	25	529 ± 35.8	74.0 ± 5.0*
Imipramine	25	496 ± 32.9	69.4 ± 4.6*
Chlorpromazine	25	391 ± 32.2	54.7 ± 4.5*
Metaraminol	100†	543 ± 35.0	75.9 ± 4.9*
Amphetamine	10	590 ± 29.3	82.5 ± 4.1*
Reserpine	7.5	234 ± 24.3	32.7 ± 3.4

All animals received 100 µg of 6-hydroxydopamine intracisternally and were killed 21 days later. †Drug doses are expressed as mg/kg for all compounds except metaraminol which was given intracisternally and is expressed as µg/brain. The values represent the mean ± s.e.m. from eight–twelve animals. The mean control value for animals which did not receive 6-hydroxydopamine was 715 ± 35 ng/brain. **P* < 0.001 when compared with saline treatment.

TABLE 4. *Effect of various agents on the depletion of brain dopamine by 6-hydroxydopamine*

Treatment	Dose	Dopamine	
		ng/brain	Percent control
Saline	—	526 ± 50	57.6 ± 4.8
Pargyline	50	333 ± 42	36.4 ± 4.6*
Desipramine	25	530 ± 45	57.9 ± 4.9
Imipramine	25	537 ± 35	58.7 ± 3.8
Chlorpromazine	25	491 ± 38	53.7 ± 4.1
Metaraminol	100†	815 ± 37	89.1 ± 4.0*
Reserpine	7.5	340 ± 24	37.2 ± 3.4*

All animals received 100 µg of 6-hydroxydopamine intracisternally and were killed 21 days later. †Drug doses are expressed as mg/kg for all compounds except metaraminol which was given intracisternally and is expressed as µg/brain. Values represent the mean ± s.e.m. from eight–twelve animals. The control value for dopamine was 915 ± 41 ng/brain. **P* < 0.001 when compared to saline treatment.

TABLE 5. *Brain dopamine, noradrenaline and tyrosine hydroxylase after 6-hydroxydopamine administration to developing rats*

Treatment	Noradrenaline ng/g	Dopamine ng/g	Tyrosine hydroxylase (pmol/mg)/h
Saline (control)	346 ± 15.7	654 ± 41.6	7.15 ± 0.51
6-Hydroxydopamine	119 ± 7.5*	207 ± 59*	1.62 ± 0.52*

6-Hydroxydopamine (100 µg) was injected intracisternally to rats 13 days after birth. Animals were killed 26 days later. All values are the mean ± s.e.m. from five–six animals. **P* < 0.001 when compared with corresponding control.

Administration of 6-hydroxydopamine to developing rats

Animals, 13 days old, were given 100 μ g of 6-hydroxydopamine intracisternally. The brains were analysed and the results compared with those obtained with saline treated controls after the animals were maintained for 26 days. At this time, the concentrations of noradrenaline and dopamine, and tyrosine hydroxylase activity were determined (Table 5). The concentration of brain noradrenaline was lowered by 66% and the dopamine concentration was 32% of control. Tyrosine hydroxylase activity was significantly reduced to 23% of control.

Discussion

Several laboratories have clearly indicated that 6-hydroxydopamine produces a profound and long lasting depletion of brain catecholamines after being administered into the brain (Uretsky & Iversen, 1970; Breese & Traylor, 1970). This depletion has been accompanied by a fall in brain tyrosine hydroxylase activity (Uretsky & Iversen, 1970; Breese & Traylor, 1970) as well as by observable ultrastructural changes in central adrenergic neurones indicative of degenerating fibres (Bloom *et al.*, 1969; Bartholini, Richards & Pletscher, 1970). Inhibition of synthesis of catecholamines from labelled tyrosine has also been observed (Anagnoste, Backstrom & Goldstein, 1969; Breese & Traylor, 1970). Such observations are similar to results obtained in the periphery after 6-hydroxydopamine treatment (Tranzer & Thoenen, 1968; Mueller, Thoenen & Axelrod, 1969) and in the caudate nucleus after making a lesion in the substantia nigra (Hököfelt & Ungerstedt, 1969). This information is consistent with the viewpoint that 6-hydroxydopamine can indeed produce destruction of catecholamine containing neurones after being administered into brain.

A previous report (Breese & Traylor, 1970) indicated that pargyline enhanced the depletion of brain dopamine by 6-hydroxydopamine while offering no advantage to the depletion of brain noradrenaline. This observation was confirmed in our study (Tables 3 & 4). As might have been expected, the reduction in the concentration of dopamine and tyrosine hydroxylase activity in the striatum by 6-hydroxydopamine was also enhanced by pargyline pretreatment (Fig. 3). The original viewpoint associated with combining 6-hydroxydopamine and pargyline was to prevent deamination of 6-hydroxydopamine since several reports have indicated that pargyline will spare the metabolism of a variety of amines (Schanberg *et al.*, 1968; Breese, Chase & Kopin, 1969). However, the lack of further depletion of noradrenaline in animals given 6-hydroxydopamine and pargyline might not support this reasoning. Thus, it is not yet clear whether the increased depletion of dopamine by 6-hydroxydopamine in pargyline treated animals is directly related to inhibition of monoamine oxidase or to some other pharmacological action of pargyline (Breese, Chase & Kopin, 1970).

Bartholini *et al.* (1970) recently reported that a small dose of 6-hydroxydopamine injected into the cerebral ventricle lowered the concentrations of brain catecholamines without inducing any ultrastructural damage that could be observed with electron-microscopy. In our study, the administration of several small doses of 6-hydroxydopamine caused a significant depletion of catecholamines without a comparable reduction of tyrosine hydroxylase activity. Since denervation has been associated with a reduction in tyrosine hydroxylase activity (Mueller *et al.*,

1969), perhaps this lack of correlation in our study between amine depletion and enzyme reduction may also reflect a disruption of neuronal mechanisms thus permitting amine depletion without ultrastructural destruction (Bartholini *et al.*, 1970).

The effects of various drugs have been studied by several investigators to determine if the action of 6-hydroxydopamine on peripheral adrenergic fibres might be altered (Porter *et al.*, 1963; Bennett, Burnstock, Cobb & Malmfors, 1970). In our study, reserpine did not diminish the reduction of brain noradrenaline (Table 3). This is in agreement with the earlier work of Porter *et al.* (1963) on the heart. Since reserpine is believed to block the ATP-Mg⁺⁺ dependent uptake mechanism in storage granules (Carlsson & Waldeck, 1965), Bennett *et al.* (1970) have suggested that neuronal storage is not a prerequisite for axonal damage by 6-hydroxydopamine. The enhanced depletion of dopamine observed after 6-hydroxydopamine in reserpine treated animals may be similar to the increased effectiveness of 6-hydroxydopamine observed on noradrenergic stores in the periphery after reserpine administration (Bennett *et al.*, 1970). Both imipramine and desipramine inhibited noradrenaline depletion by 6-hydroxydopamine without altering the reduction of brain dopamine (Table 4). Recently, Evetts & Iversen (1970) have reported similar findings using protriptyline. These results probably reflect the ability of these compounds to inhibit amine uptake by noradrenaline-containing neurones (Carlsson & Waldeck, 1965; Schanberg *et al.*, 1967), but not by dopaminergic fibres (Fuxe & Ungerstedt, 1968). Since phenylethylamine derivatives like metaraminol have a differential effect on brain catecholamines after intracisternal injection (Breese *et al.*, 1970), it was puzzling to find that metaraminol had an inhibitory effect on 6-hydroxydopamine depletion of both dopamine and noradrenaline. Additional studies to determine the effects of other drugs on the depletion of catecholamines by 6-hydroxydopamine would seem worthwhile since a procedure which drastically reduces brain noradrenaline without affecting dopamine would seem desirable.

The development of monoamine systems in the rat has been studied by Agrawal, Glisson & Himwich (1966). Our interest in the administration of 6-hydroxydopamine to developing animals was to determine if neuronal damage to noradrenergic neurones would occur before they were totally developed. Strong support for the view that neuronal damage occurred was to be found in the reduction of tyrosine hydroxylase and catecholamines 26 days after administration of 6-hydroxydopamine (Table 5). This may be comparable to the results reported for destruction of the peripheral sympathetic system when administered postnatally to developing rats (Angeletti & Levi-Montalcini, 1970).

Several reports indicate that the gross appearance of rats treated with 6-hydroxydopamine is not greatly altered (Bloom *et al.*, 1969; Breese & T aylor, 1970; Uretsky & Iversen, 1970). Treated animals also appear to have normal activity (Burkard, Jalfre & Blum, 1969; Evetts, Uretsky, Iversen & Iversen, 1970) as well as the ability to control body temperature in the cold (Breese, Howard & Moore, unpublished observations). Furthermore, while chronic treatment with 6-hydroxydopamine has not altered operant behaviour performance, it has caused a significant decrease in response rate in self-stimulating animals (Leahy & Breese, unpublished observations). Studies are in progress to further evaluate the behaviour of animals treated with 6-hydroxydopamine.

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