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Effect of depletion of cerebral monoamines on the concentration of glycogen and on amphetamine-induced glycogenolysis in the brain

D. A. HUTCHINS* AND K. J. ROGERS

Department of Pharmacology and Therapeutics, University of Sheffield

Summary

1. An increase in the concentration of glycogen occurs in the mouse brain after depletion of cerebral catecholamines by alpha methyl-*p*-tyrosine methyl-ester (H44/68), diethyldithiocarbamate, or reserpine.

2. Depletion of cerebral 5-hydroxytryptamine with parachlorophenylalanine (PCPA) does not result in a change in the concentration of brain glycogen.

3. When H44/68 is administered together with reserpine to inhibit the synthesis and storage of cerebral catecholamines, and thus bring about their total depletion from the brain, the cerebral glycogenolytic effect of amphetamine is abolished.

4. Amphetamine-inducing glycogenolysis is only partially antagonized if only one of the catecholamine-depleting agents H44/68, diethyldithiocarbamate, or reserpine is injected prior to the amphetamine. The persistence of this glycogenolytic effect of amphetamine is possibly due to the presence of residual stores of catecholamines available for release by the stimulant drug.

5. Depletion of cerebral 5-hydroxytryptamine by PCPA does not result in any antagonism of amphetamine-induced glycogenolysis.

6. The results suggest that amphetamine depletes brain glycogen by the release of central catecholamines rather than by a direct action at receptors.

Introduction

It has been established that the catecholamines stimulate the metabolism of glycogen in peripheral tissues by activation of the adenyl cyclase system (Sutherland & Rall, 1960). Although the concentration of cyclic adenosine monophosphate in cerebral tissue is increased *in vitro* by noradrenaline (Kakiuchi & Rall, 1968a, b), the relation of the catecholamines to the adenyl cyclase system and glycogen metabolism in the brain has yet to be determined. Hutchins & Rogers (1970) have found that only those drugs that are believed to release intraneuronal catecholamines onto extracellular receptor sites within the central nervous system, also deplete brain glycogen *in vivo*.

Amphetamine, which is known to cause the release of cerebral catecholamines, is one of the most potent glycogenolytic agents tested in this laboratory (Rogers &

* Present address: Agricultural Research Council Institute of Animal Physiology, Babraham, Cambridge.

Hutchins, 1972). If the hypothesis is correct that amphetamine-induced glycogenolysis is mediated by the release of endogenous catecholamines (Hutchins & Rogers, 1970) then it should be possible to antagonize this glycogenolytic effect of amphetamine with drugs having either a selective blocking action at adrenoceptors or an action which prevents the initial release of the catecholamines. It has been shown that amphetamine-induced cerebral glycogenolysis can be selectively antagonized by propranolol and pronethalol, drugs that block β-adrenoceptors (Hutchins & Rogers, 1971). This antagonism occurs without modification of the increased locomotor activity and excitation caused by the amphetamine. Other receptor blocking drugs do not antagonize amphetamine-induced glycogenolysis when administered at doses that do not antagonize the stimulant action of amphetamine.

This paper describes experiments in which the release of cerebral monoamines is modified by the administration of drugs that inhibit the synthesis or storage of monoamines within the brain. These drugs were examined for their ability to antagonize the glycogenolytic effect of amphetamine in mouse brain.

Methods

The experiments were performed on male albino mice weighing between 20 and 30 g. The animals were kept in a laboratory with a 12 h light–12 h dark cycle (06.00–18.00 h, light) and were allowed free access to food and water before and during the experiments. Unless otherwise stated the environmental temperature was maintained at 20–22° C. Mice in groups of 5 were injected intraperitoneally with the monoamine depleting agent at a suitable time interval before the intraperitoneal administration of (+)-amphetamine sulphate, 5 mg/kg.

In order to minimize the effect of circadian fluctuations in the concentration of brain glycogen (Hutchins & Rogers, 1970) the injections were given at a time such that the experimental mice were killed within 1 h of the control animals during the late evening.

Estimation of brain glycogen

The mice were killed by complete immersion in liquid nitrogen and the brains were chiselled out of the skull whilst in the deeply frozen state. Each brain was weighed rapidly before crushing on a stainless steel anvil cooled with liquid nitrogen. One mouse brain was used for each determination. Cerebral glycogen was determined using a modification (Hutchins & Rogers, 1970) of the method of Le Baron (1955).

Estimation of monoamines in the brain

Mice were killed by decapitation and the brains from 2 animals were pooled and frozen in liquid nitrogen until used for assay. The monoamines were extracted simultaneously using the method of Shore & Olin (1958). Aliquots of the final acid extract were used for the assay of noradrenaline (Anton & Sayre, 1962), dopamine (Carlsson & Waldeck, 1958) and 5-hydroxytryptamine (Bogdanski, Pletscher, Brodie & Udenfriend, 1956).

Locomotor activity

Spontaneous locomotor activity was recorded using activity cages (Ugo Basile, Milan) in which movement of the mice was measured by completion of electronic circuits as the animals moved across the bars on the floor of the cages. Recordings of locomotor activity were made simultaneously from 3 cages connected in parallel. Each cage contained 3 mice and at least 6 recordings were made.

Body temperature

Body temperature was measured by means of an electric thermometer and oesophageal probe (Brittain & Spencer, 1964).

Drugs

The drugs used were (+)-amphetamine sulphate, *p*-chlorophenylalanine, diethyldithiocarbamate sodium, α-methyl-*p*-tyrosine methylester (H44/68) and reserpine. The drugs were dissolved in distilled water except for *p*-chlorophenylalanine (dissolved in M sodium hydroxide solution and adjusted to pH 8–9 with M hydro-

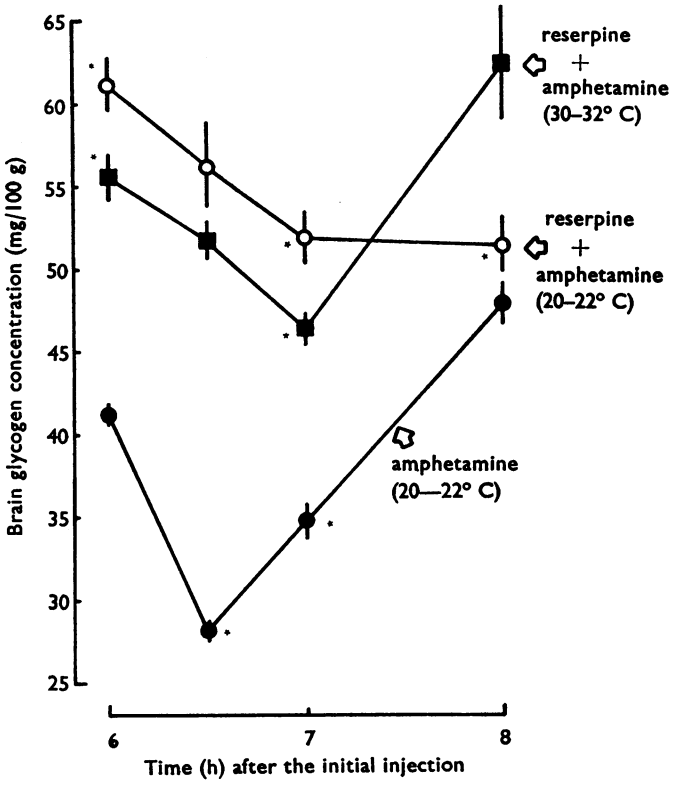

FIG. 1. Effect of amphetamine on the concentration of cerebral glycogen of mice treated with reserpine. Amphetamine sulphate, 5 mg/kg, was injected 6 h after the administration of reserpine, 10 mg/kg, to mice maintained at an environmental temperature of 20–22° C (○——○) or 30–32° C (■——■). Mice from other groups maintained at an environmental temperature of 20–22° C were injected with amphetamine 6 h after an injection of the vehicle for reserpine (●——●). Each point is the mean of 5 estimations. The S.E.M. is indicated by vertical lines. Difference from the respective control value $*P<0{\cdot}05$, Student's *t* test.

chloric acid) and reserpine (dissolved according to Leyden, Pomerantz & Bouchard, 1956). Each drug was administered in a volume of 1·0 ml/100 g body weight and injected by the intraperitoneal route unless otherwise stated.

Results

Reserpine

Mice in groups of 5 were injected with reserpine, 10 mg/kg, and then maintained at an environmental temperature of either 20–22° C or 30–32° C; the higher ambient temperature prevented reserpine-induced hypothermia. Six hours after the administration of reserpine, the mice were given an injection of amphetamine, 5 mg/kg, and killed at intervals for up to 2 h after amphetamine.

The concentration of brain glycogen was increased significantly after treatment with reserpine at either of the environmental temperatures, and the increase was sustained for at least 8 hours. Treatment with reserpine did not antagonize the ability of amphetamine to reduce the concentration of glycogen, although the loss of glycogen was not significant until 1 h after injection of amphetamine (Fig. 1). However, mice treated with reserpine and amphetamine and kept at room temperature (20–22° C) did not show a secondary increase in glycogen content subsequent to the initial decrease. A secondary increase did occur after the administration of these drugs to animals maintained at an environmental temperature of 30–32° C. This rapid secondary increase in concentration is a characteristic effect of amphetamine on brain glycogen (Hutchins & Rogers, 1970; Rogers & Hutchins, 1972). The mice treated with both drugs and kept at room temperature were not hypothermic since body temperature increased to near normal values after the injection of amphetamine. The excitation and increase in locomotor activity observed when amphetamine was injected into mice previously treated with reserpine was similar for mice kept at 20–22° C or 30–32° C.

Diethyldithiocarbamate sodium

Initially mice in groups of 5 were injected with diethyldithiocarbamate, 500 mg/kg i.p., a second dose of 500 mg/kg being administered subcutaneously at 2 hours. This treatment with diethyldithiocarbamate resulted in hypothermia which lasted for approximately 5 hours. Six hours after the initial dose of diethyldithiocarbamate when body temperature had returned to normal, amphetamine (5 mg/kg) was injected and the mice were killed at intervals for up to 2 h after amphetamine.

After the injections of diethyldithiocarbamate, an inhibitor of dopamine β-hydroxylase, the concentration of noradrenaline in the mouse brain was reduced by 46% at 6 h and by 30% at 8 hours (Table 1). The dopamine content of the

TABLE 1. *Effect of diethyldithiocarbamate sodium (DDC) on the concentration of noradrenaline (NA), dopamine (DA) and 5-hydroxytryptamine (5-HT) in the mouse brain*

Treatment	Dose (mg/kg)	Duration of treatment (h)	Brain amine concentration (μg/g $\pm$ S.E.M.) NA	DA	5-HT
Control	—	–	0·50±0·02	0·60±0·01	0·62±0·05
DDC	2×500	6	0·27±0·01†	0·74±0·03*	0·67±0·02
DDC	2×500	8	0·35±0·04*	0·78±0·05*	0·70±0·04

Mice in groups of 5 were injected with DDC (i.p.) initially and DDC (s.c.) at 2 h. Difference from control values: * $P<0·01$; † $P<0·001$; Student's t test.

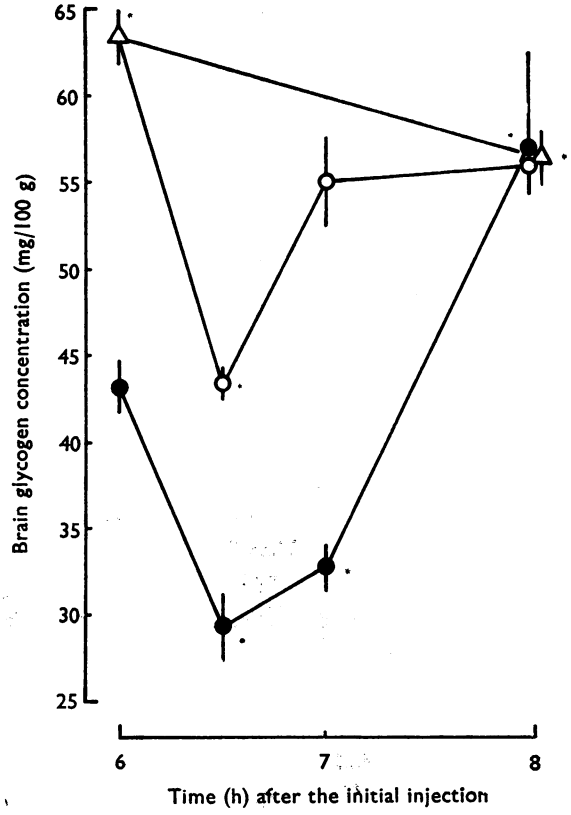

FIG. 2. Effect of amphetamine on the concentration of cerebral glycogen of mice treated with diethyldithiocarbamate sodium. Mice in groups of 5 were injected with diethyldithiocarbamate (500 mg/kg) at times 0 and 2 hours. Six hours after the initial injection the mice were treated with amphetamine sulphate (5 mg/kg) (○——○) or distilled water (△——△) and killed at intervals for up to 2 h later. Mice from other groups were injected twice with distilled water before the administration of amphetamine at 6 h (●——●). Each point is the mean of 5 estimations. Vertical lines indicate the S.E.M. Difference from the respective control value. $*P<0.05$, Student's t test.

brain was increased significantly at both times, whereas the concentration of 5-hydroxytryptamine was unchanged. The concentration of cerebral glycogen was increased by 63% at 6 h and 56% at 8 hours (Fig. 2). However, diethyldithiocarbamate did not antagonize the effect of amphetamine on brain glycogen and failed to modify the excitation evoked by amphetamine.

Alpha methyl-p-tyrosine methylester (H44/68)

Cerebral noradrenaline and dopamine concentrations were reduced rapidly by H44/68 (250 mg/kg) with minimum concentrations occurring at 4 hours (Fig. 3). Although the concentration of dopamine increased continuously after the initial reduction the noradrenaline content remained constant at a low level for up to 16 hours. A small but significant increase in the concentration of 5-hydroxytryptamine occurred over the 24 h period of the experiment. The concentration of cerebral glycogen was increased significantly at 2 h ($P<0.02$) and continued to increase for 12 hours (Fig. 4). During the first 2 h after treatment with H44/68 there was a slight depression of locomotor activity but at 12 h the behaviour of the

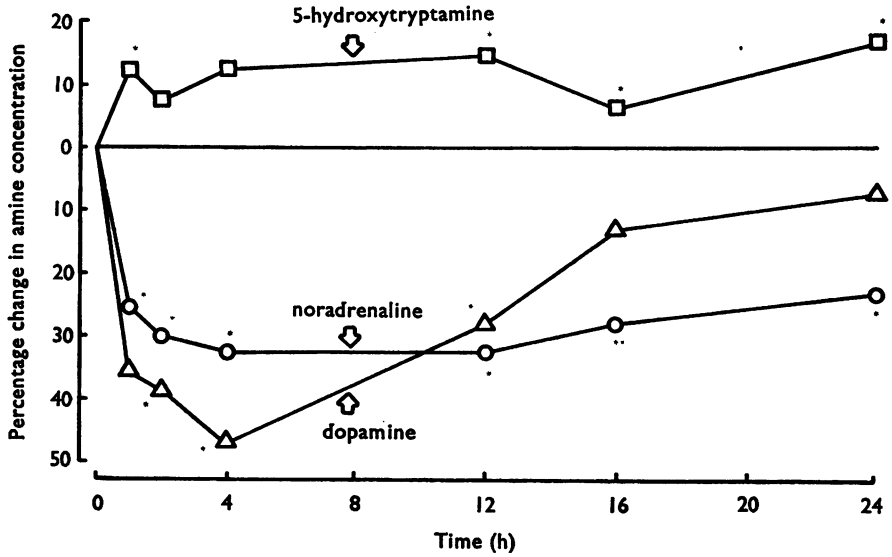

FIG. 3. The effect of alpha methyl-*p*-tyrosine methylester, 250 mg/kg, on the concentration of noradrenaline (○——○), dopamine (△——△) and 5-hydroxytryptamine (□——□) in the brains of mice. Each point is the mean of 5 estimations. An asterisk indicates a difference from the control value ($P<0.05$), Student's *t* test.

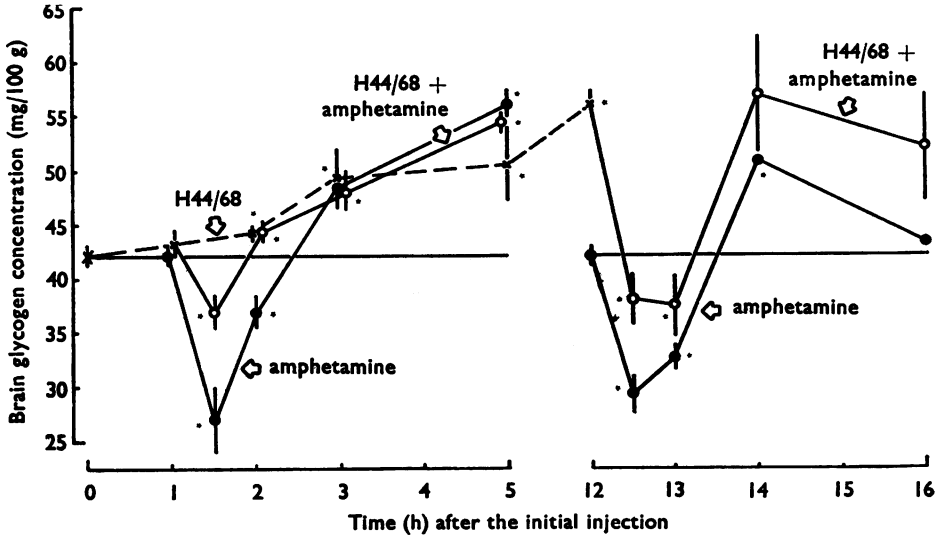

FIG. 4. Effect of amphetamine on the concentration of cerebral glycogen of mice treated with alpha methyl-*p*-tyrosine methylester (H44/68). Mice were injected with amphetamine sulphate (5 mg/kg) (●——●), H44/68 (250 mg/kg) (×----×), or amphetamine administered 1 or 12 h after H44/68 (○——○). Vertical lines indicate the S.E.M. Difference from the control value, $*P<0.05$, Student's *t* test.

mice treated with H44/68 was indistinguishable from that of the control animals. There was little change in the body temperature of mice treated with H44/68.

Amphetamine, 5 mg/kg, was injected either 1 h or 12 h after the injection of H44/68, 250 mg/kg, and the mice were killed at appropriate intervals up to 4 h later (Fig. 4). Control groups of animals were treated with either H44/68 or amphetamine. When the mice were pretreated with H44/68 for 1 h amphetamine-

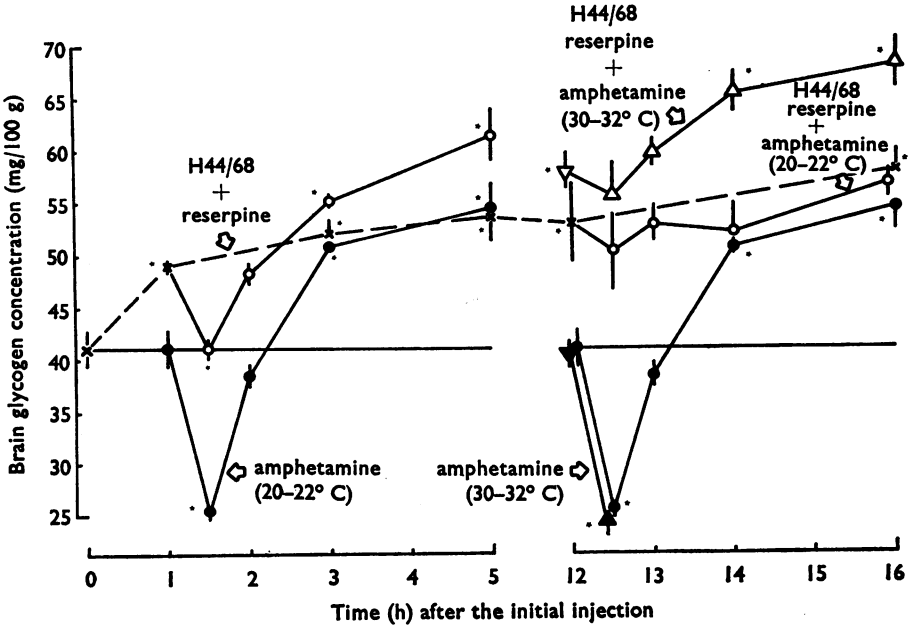

FIG. 5. Effect of amphetamine on the concentration of cerebral glycogen of mice treated with alpha methyl-*p*-tyrosine methylester (H44/68) and reserpine. Mice maintained at an environmental temperature of 20–22° C were injected with amphetamine sulphate (5 mg/kg) (●——●), H44/68 (250 mg/kg) together with reserpine (5 mg/kg) (×----×), or amphetamine administered 1 or 12 h after the administration of H44/68 and reserpine (○——○). Mice maintained at an environmental temperature of 30–32° C were injected with distilled water (▼) 12 h before the administration of amphetamine (▼——▲), or injected with H44/68 and reserpine (▽) 12 h before the administration of amphetamine (△——△). Vertical lines indicate the S.E.M. Difference from the control value, $*P<0.05$, Student's *t* test.

induced glycogenolysis was partially antagonized. No antagonism of the effect of amphetamine on brain glycogen was evident 12 h after H44/68. The excitation and increase in locomotor activity caused by amphetamine was only slightly attenuated 1 h after treatment with H44/68 and was not affected at 12 hours.

Administration of H44/68 with reserpine

The previous experiment was repeated but H44/68, 250 mg/kg, was injected together with reserpine, 5 mg/kg. The hypothermia caused by the reserpine necessitated the inclusion of additional groups of mice incubated at an environmental temperature of 30–32° C to minimize the possibility of lowered body temperature influencing the results. Drug treated mice incubated at 30–32° C were compared with control groups of animals incubated over the same period.

The increase in the concentration of cerebral glycogen of the mice treated with both of the amine-depleting agents was very similar to that observed after H44/68 alone. A significant increase in concentration occurred at 1 h ($P<0.01$) and the concentration continued to increase to a level of 58 mg/100 g at 16 h when the experiment was concluded (Fig. 5). The body temperatures of animals that were maintained at an environmental temperature of 30–32° C after the injection of H44/68 and reserpine remained approximately normal, and the increase in the concentration of glycogen after 12 h incubation was not significantly different from that of drug-treated hypothermic mice.

The administration of amphetamine to mice 1 h after they had been injected with the amine depleting agents resulted in a significant loss of cerebral glycogen although this decrease was less than that seen in control animals treated with amphetamine alone. However, when amphetamine was administered to animals that had been injected with H44/68 and reserpine 12 h previously, the glycogenolytic effect of the sympathomimetic drug was completely antagonized in mice left at room temperature or incubated at 30–32° C.

An injection of amphetamine 1 h after the administration of H44/68 and reserpine resulted in an alerting effect which was probably an attenuated form of the central excitation normally observed in the behaviour of the mice; the increase in locomotor activity was abolished. When the mice were treated with amphetamine 10–12 h after the amine depleting agents there was a small increase in locomotor activity and a greater tendency for the mice to become excited.

Parachlorophenylalanine (PCPA)

p-Chlorophenylalanine (150 mg/kg) was administered to groups of 4–5 mice twice daily at 12 h intervals for 3 days. Amphetamine was injected 12 h after the last dose of PCPA.

TABLE 2. *Effect of amphetamine on the concentration of cerebral monoamines in mice treated with parachlorophenylalanine (PCPA)*

Treatment	Duration of treatment	Concentration of cerebral monoamines (μg/g$\pm$S.E.M.) NA	DA	5-HT
PCPA vehicle (control)	3 days	0·42±0·01	0·56±0·01	0·53±0·01
PCPA	3 days	0·34±0·02†	0·40±0·01‡	0·09±0·004‡
Amphetamine	0·5 h	0·37±0·01†	0·57±0·02	0·56±0·01*
	2 h	0·36±0·01†	0·66±0·02†	0·59±0·01†
PCPA+amphetamine	3 days 0·5 h	0·34±0·01	0·51±0·02†	0·10±0·01
PCPA+amphetamine	3 days 2 h	0·30±0·02	0·46±0·02†	0·09±0·01

Mice in groups of 5 were injected with PCPA (150 mg/kg) or its vehicle (see **Methods**), twice daily for 3 days. Amphetamine sulphate (5 mg/kg) was injected 12 h after the final injection of PCPA or the vehicle. Each value is the mean of 5 estimations. Asterisks indicate a difference from the control value (* $P<0·05$, † $P<0·01$, ‡ $P<0·001$), Student's t test.

The 5-hydroxytryptamine content of the brain was diminished by 83% following treatment with PCPA (Table 2). Significant, but much smaller decreases also occurred in the concentrations of the catecholamines. When amphetamine was administered to control mice the concentration of noradrenaline was decreased and the concentrations of 5-hydroxytryptamine and dopamine were increased. After the administration of amphetamine to PCPA treated mice there was no increase in the concentration of 5-hydroxytryptamine although the effect of amphetamine on the catecholamines was the same as for the control mice.

The concentration of cerebral glycogen was not altered significantly by treatment for 3 days with PCPA or the vehicle (Fig. 6). The administration of amphetamine to animals pretreated with PCPA resulted in a depletion of brain glycogen to a concentration that did not differ from that found in mice treated with amphetamine alone. However, the subsequent increase in glycogen to a concentration above the control value was not found to occur in mice pretreated with PCPA.

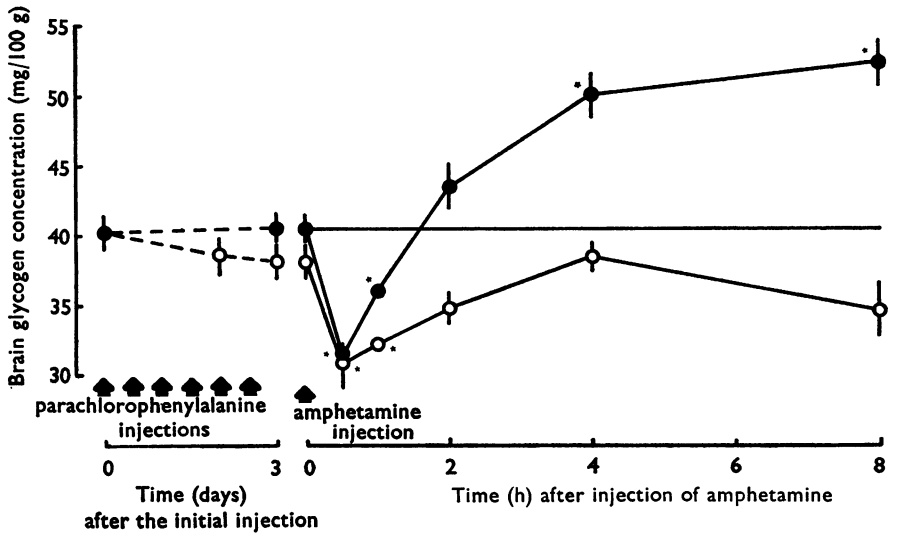

FIG. 6. Effect of amphetamine on the concentration of cerebral glycogen in mice treated with parachlorophenylalanine (PCPA). Mice in groups of 5 were injected with PCPA (150 mg/kg, twice daily for 3 days) (○- - -○) and then injected with amphetamine sulphate (5 mg/kg) (○——○). Mice from other groups were injected with PCPA vehicle (see **Methods**) twice daily for 3 days (●- - -●) before the administration of amphetamine (●——●). Vertical lines indicate the S.E.M. Difference from the respective control value $*P<0.05$, Student's *t* test.

Discussion

In this investigation various drugs were administered to mice, to impair the storage or synthesis of cerebral monoamines, prior to the administration of amphetamine. Each of the drugs causing depletion of the catecholamines resulted in an increase in the concentration of brain glycogen, whereas PCPA which depleted 5-hydroxytryptamine to less than 20% of the control value did not alter the glycogen content. These results suggest that a change in the metabolic activity of the catecholamine-containing neurones of the central nervous system can influence cerebral glycogen metabolism. After treatment with H44/68 or diethyldithiocarbamate the increase in the concentration of glycogen showed a closer temporal correlation with the loss of noradrenaline than with the change in the concentration of dopamine (Figs. 2, 3, 4 and Table 1). Further studies are required, however, to elucidate the relative importance of the two catecholamines in the control of glycogen metabolism.

None of the monoamine depleting agents, when administered individually, was able to antagonize the glycogenolytic or central stimulant effect of amphetamine completely. Reserpine depletes cerebral monoamines by inhibiting the mechanisms responsible for their storage within the nerve, without impairing catecholamine synthesis in the brain (Glowinski, Iversen & Axelrod, 1966). It has been suggested that after treatment with reserpine a small ' reserpine-resistant pool ' of monoamines remains (Glowinski & Axelrod, 1965) which may be available for release by amphetamine. The storage of catecholamines, however, is not essential for the central stimulant action of amphetamine as long as catecholamine synthesis is maintained (Sulser, Owens, Norvich & Dingell, 1968). The rate limiting enzyme in the synthesis of the catecholamines, tyrosine hydroxylase, is inhibited maximally

1 h after an injection of H44/68 (Weissman, Koe & Tenen, 1966). Antagonism of the glycogenolytic and central stimulant effect of amphetamine was greatest at this time (Fig. 4), although maximum depletion of the catecholamines did not occur until 4 h after injection (Fig. 3). The glycogenolytic activity of amphetamine, after treatment with either reserpine or H44/68, may be due therefore to the presence of small amounts of the catecholamines available for displacement from the neurone by amphetamine. Glowinski *et al.* (1966), however, found that the small amount of radioactively labelled noradrenaline retained in the brains of 24 h reserpinized rats was resistant to release by amphetamine. Thus direct stimulation of receptors by amphetamine, after depletion of the monoamines by reserpine or H44/68, cannot be discounted.

Six hours after the administration of diethyldithiocarbamate, and 12 h after H44/68, the cerebral glycogenolytic and central stimulant effects of amphetamine were similar to those obtained in control animals (Figs. 2 & 4). At these times it is likely that the synthesis of the catecholamines was being re-established as indicated by the tendency of noradrenaline to re-accumulate after diethyldithiocarbamate (Table 1) and the concentration of noradrenaline and dopamine to increase towards the control value after treatment with H44/68 (Figure 3).

In a further experiment reserpine and H44/68 were given in combination, in an attempt to ensure total depletion of the catecholamines prior to the injection of amphetamine. The glycogenolytic activity of amphetamine was partially antagonized 1 h after treatment with reserpine and H44/68, and completely abolished 12 h after treatment (Fig. 5). Similar results were obtained in hypothermic mice and in mice whose body temperature had been maintained, and they are consistent with the hypothesis that amphetamine depletes brain glycogen by the release of central catecholamines rather than by a direct action at receptors.

The concentration of 5-hydroxytryptamine in the brain was depleted selectively by the repeated administration of PCPA, an inhibitor of tryptophan hydroxylase (Koe & Weissman, 1966), the rate limiting enzyme in the synthesis of the indoleamine (Table 2). The concentration of cerebral glycogen and the glycogenolytic effect of amphetamine were not altered by pretreatment with PCPA but the characteristic secondary increase in glycogen to a concentration greater than the control value did not occur (Fig. 6). A similar blockade of glycogen replenishment was observed in mice pretreated with reserpine. These results indicate that 5-hydroxytryptamine does not exert an obvious effect on glycogenolysis but this monoamine may have an important role to play in the biosynthesis of glycogen.

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