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THE UPTAKE OF TRYPTAMINE BY BRAIN *IN VIVO* AND ITS ALTERATION BY DRUGS

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Abstract—In rats pretreated with iproniazid, the penetration of injected tryptamine (s.c.) into the brain as well as into the heart has been measured under various conditions. The following results were obtained: The time course of the tryptamine concentration was similar in heart and blood showing a rapid decline ¼ hr after injection of the amine. In the brain maximal tryptamine levels persisted for at least 1 hr. Chlorpromazine, chlorprothixene and chlorisondamine counteracted the tryptamine-induced increase of the amine in the brain, but not in the heart. The inhibiting effect of chlorpromazine on the tryptamine-increase in the brain showed a similar time course as the hypothermic action of the neuroleptic. Prevention of hypothermia by elevation of the environmental temperature abolished the interference of chlorpromazine with the tryptamine-increase. The tryptamine uptake in brain is probably an active process. Its counteraction by chlorpromazine and other drugs seems at least partly to be due to their hypothermic effect.

CHLORPROMAZINE counteracts the increase of 5-hydroxytryptamine (5HT) and norepinephrine (NE) induced by monoamine oxidase (MAO) inhibitors as well as the reserpine-induced decrease of the amines in the brain.[1–5] These and other observations suggested that chlorpromazine might interfere with the penetration of monoamines through biological membranes, e.g. at the sites of amine storage.[3, 5] Further experiments have shown that the effects of chloropromazine mentioned are probably related to hypothermia.[2, 6] Therefore, the question arises whether hypothermia induced by chlorpromazine primarily attenuates the activity of reserpine and MAO inhibitors rather than inhibiting the penetration of monoamines *per se*. Measurements of the passage of monoamines from the blood into the brain might provide more direct information on the effect of chlorpromazine on monoamine pentration. 5HT and NE, however, cannot be used for this purpose, because except in a few areas they cross the blood/brain barrier only to a small extent.[7–9] Therefore, the present study deals with tryptamine. This naturally occurring amine seems to be an appropriate model since it enters the brain[10] and since its main metabolic pathway, i.e. oxidative desamination, can easily be blocked by inhibitors of MAO.[11]

EXPERIMENTAL PROCEDURE

White Wistar rats of 60–90 g, fasted for 16 hr, were injected with 15 mg/kg tryptamine i.p. 1–2 hr after pretreatment (s.c.) with chlorpromazine, chlorprothixene,* or chlorisondamine.† Spectrophotofluorimetric determinations of tryptamine[12] in

* α-2-chloro-9-(3-dimethylamino-propylidene)-thioxanthene (Taractan®).

† 4,5,6,7-tetrachloro-2-(2-dimethylaminoethyl)-2-methylisoindolinium chloride methochloride (Ecolid®).

brain, heart and blood of decapitated animals were carried out ½ hr, in some experiments also 1–4 hr after injection of the amine. Rats treated with tryptamine only served as controls. Rectal temperature was measured by a thermocouple immediately before tryptamine administration.

All the animals were administered 155 mg/kg iproniazid phosphate i.p. 12–16 hr prior to tryptamine in order to inhibit monoamine oxidase. Preliminary investigations have shown that iproniazid exerts maximal inhibition of tryptamine degradation in brain when injected 8–20 hr before the amine.

In order to determine a possible interference of the drugs or their metabolites with the fluorescence of tryptamine, known amounts of this amine were added to organ homogenates of untreated rats as well as of rats pretreated with chlorpromazine (10–20 mg/kg s.c.), chlorprothixene (10 mg/kg s.c.), or chlorisondamine (25 mg/kg s.c.). The following percentage of the amine added to the homogenates could be recovered as compared to untreated controls:

Organ	Pretreatment (1 hr before tryptamine)	Tryptamine recovered (%)
Brain	Chlorpromazine	78 ± 6
	Chlorprothixene	93 ± 14
	Chlorisondamine	92 ± 3
Heart	Chlorpromazine	93 ± 2
Blood	Chlorpromazine	109 ± 13

The tryptamine values are presented without correction if not otherwise stated.

RESULTS

1. In untreated rats, as well as in rats injected with 155 mg/kg iproniazid phosphate only, no tryptamine could be detected in the brain, heart and blood with the method applied. After combined treatment with iproniazid + tryptamine, the level of the amine rose markedly in these organs (Fig. 1).
2. In the *blood* of iproniazid-pretreated animals the tryptamine content was maximal ¼ hr after injection of the amine, thereafter rapidly declining to control levels within 3–4 hr (Fig. 1).
3. The tryptamine content of the *heart* also reached maximal values ¼ hr after injection and thereafter rapidly decreased to control values within about 2 hr. The maximal increase of tryptamine in the heart was about 3 times that in blood (Fig. 1).
4. The *brain* behaved differently from blood and heart showing a longer lasting maximal tryptamine concentration (up to at least 1 hr) and a relatively slow subsequent decline. After 1 hr, the tryptamine level in brain was more than twice as high as that in blood (Fig. 1).
5. Chlorpromazine and chlorprothixene diminished the tryptamine-induced increase of the amine in the brain, but not in the heart or blood. The action of chlorpromazine was dose-dependent. After 10 mg/kg chlorpromazine, for instance, the tryptamine content in brain increased only to about ⅓ of that in animals not pretreated with chlorpromazine (Fig. 2, Table 1). The inhibition of the tryptamine increase by

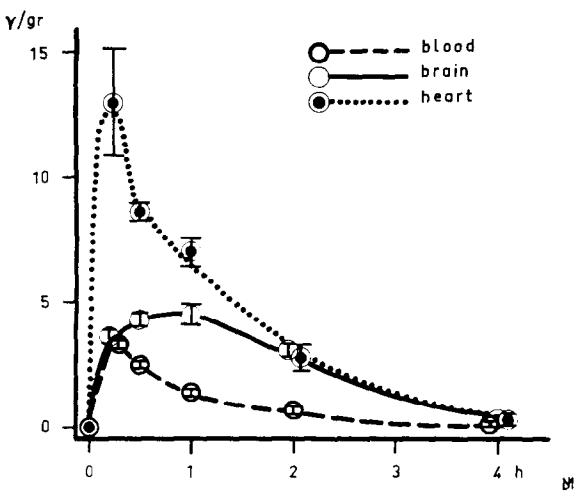

FIG. 1. Time course of the tryptamine level in brain, heart, and blood after i.p. injection of 18·5 mg/kg tryptamine HCl (15 mg/kg tryptamine base)

Ordinate: Tryptamine (base) concentration in γ per g tissue

Abscissa: Time in hours after tryptamine injection

The animals were pretreated with 155 mg/kg iproniazid phosphate (100 mg/kg iproniazid base) i.p. 16 hr before decapitation.

The points represent average values of 5–8 experiments with standard error.

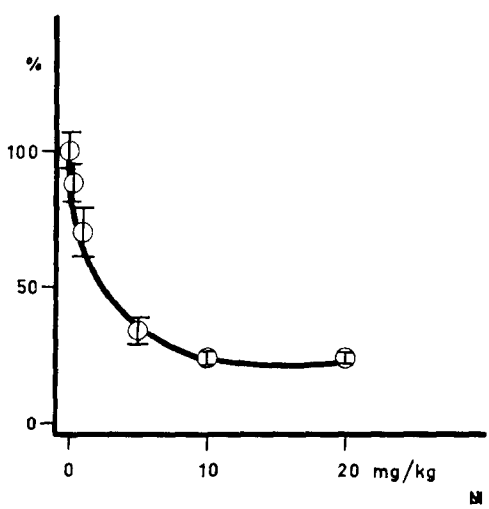

FIG. 2. Influence of various doses of chlorpromazine on the uptake of tryptamine by brain of intact rats

Ordinate: Increase of the tryptamine content of brain in per cent of controls receiving tryptamine alone (controls: 4·26 $\pm$ 0·32 γ/g tryptamine = 100 $\pm$ 7 per cent).

Abscissa: Dose of chlorpromazine in mg/kg.

18·5 mg/kg tryptamine HCl were administered s.c. 1 hr after chlorpromazine and $\frac{1}{2}$ hr before decapitation. Pretreatment with 155 mg/kg iproniazid phosphate i.p. 16 hr before chlorpromazine.

Each point represents an average of 6 experiments with standard error.

TABLE 1. EFFECT OF VARIOUS DRUGS ON TRYPTAMINE-CONTENT OF BRAIN, HEART, AND BLOOD AS WELL AS BODY TEMPERATURE IN RATS

Drug	Body temperature	Tryptamine content in % of controls		
	in °C	Brain	Heart	Blood
Controls	37·0 ± 0·2	100 ± 10	100 ± 6	100 ± 7
Chlorpromazine 10 mg/kg s.c.	30·7 ± 0·3	25 ± 2*	95 ± 6	100 ± 8
Chloprothixene 10 mg/kg s.c.	32·5 ± 0·8	58 ± 7	90 ± 9	88 ± 9
Chlorisondamine 25 mg/kg s.c.	32·2 ± 0·2	58 ± 5	100 ± 7	105 ± 8

18·5 mg/kg tryptamine HCl were administered i.p. 1½ hr after the drugs and ½ hr before decapitation. All the animals were pretreated with 155 mg/kg iproniazid phosphate 16–18 hr before decapitation. The figures represent mean values of 4–12 experiments with standard error.

* Corrected values (see page 1066).

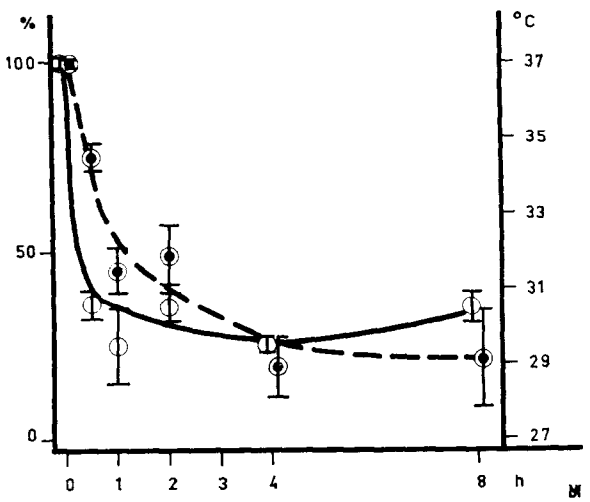

FIG. 3. Time course of the effect of chlorpromazine on the tryptamine-increase in brain and on body temperature of rats

Ordinate: left: Tryptamine-increase in brain in per cent of controls treated with tryptamine alone (controls = 100 ± 2 per cent)

right: Rectal temperature in °C.

Abscissa: Time in hours between 10 mg/kg chlorpromazine s.c. and 18·5 mg/kg tryptamine HCl i.p.

——— tryptamine increase

– – – – rectal temperature

Decapitation ½ hr after tryptamine. Pretreatment with 155 mg/kg iproniazid phosphate 16½ hr before decapitation. The points represent average values of 6–10 experiments with standard error.

10 mg/kg chlorpromazine lasted for more than 8 hr and paralleled the degree of hypothermia (Fig. 3).

6. If hypothermia was prevented (by keeping the rats at environmental temperatures of 32–33°), chlorpromazine no longer counteracted the tryptamine-increase in brain (Table 2).

7. Chlorisondamine, a hypothermia-producing ganglion blocking agent[13] which (owing to its quarternary nitrogen) hardly crosses the blood/brain barrier, also counteracted the tryptamine-induced nicrease of the amine in brain, but not that in heart and blood (Table 1).

TABLE 2. EFFECT OF CHLORPROMAZINE ON THE TRYPTAMINE CONTENT OF BRAIN IN HYPO- AND NORMOTHERMIC RATS

Drug	Environmental temperature °C	Body temperature °C	Tryptamine content %	p
I Controls	18–20	37·2 ± 0·2	100 ± 9	
II Controls	30–31	37·7 ± 0·1	107 ± 3	I/II >0·05
III Chlorpromazine	18–20	30·7 ± 0·4	25 ± 2*	I/III, IV/III <0·01
IV Chlorpromazine	30–31	37·9 ± 0·1	113 ± 5*	I/IV >0·05 III/IV <0·01

10 mg/kg chlorpromazine were administered s.c. 2 hr before 18·5 mg/kg tryptamine HCl i.p. Decaptitation 1½ hr after tryptamine. Pretreatment with 155 mg/kg iproniazid phosphate i.p. 14 hr prior to tryptamine. Each figure represents an average of 9–12 experiments with standard error.

* Corrected values (see page)1066.

DISCUSSION

The above results show that chlorpromazine inhibits the penetration of tryptamine from blood into brain. The following findings suggest that this effect is at least in part due to hypothermia:

1. The chlorpromazine-induced diminution of the tryptamine-increase in brain shows a similar time course as hypothermia (Fig. 3).
2. Prevention of hypothermia (by elevation of the environmental temperature) abolishes the effect of chlorpromazine on amine penetration (Table 2).
3. The ganglion blocking agent chlorisondamine which hardly enters the brain, but causes hypothermia, markedly counteracts the tryptamine-increase in the brain, similarly to chlorpromazine (Table 1).
4. Chlorprothixene, a neuroleptic related to chlorpromazine which causes hypothermia, also antagonizes the tryptamine-increase in the brain (Table 1).

On the basis of the present findings it can, however, not be exlcuded that chlorpromazine and related drugs in addition to their effect via hypothermia act also by other mechanisms. Thus, chlorpromazine has been shown to interfere with monoamine penetration *in vitro*.[14–16] Experiments with ^{14}C-dopa[17] also indicate that the neuroleptic alters the cerebral metabolism of this amino acid *in vivo* not only via hypothermia, but also by a mechanism not releated to body temperature.

The present study further demonstrates that the brain, in contrast to the heart, takes up tryptamine by an active mechanism. This may be concluded from the following results:

1. In the *brain* the maximum tryptamine level shows no significant change ¼–1 hr after injection of the amine, although in the blood the tryptamine content decreases considerably during this time period (Fig. 1). Thus, the brain is able to maintain high concentrations of the amine despite decreasing blood levels.

2. In the *heart* the time course of the amine concentration parallels that in the blood: maximal values are reached $\frac{1}{4}$ hr after injection of tryptamine; thereafter a rapid decrease of the amine occurs (Fig. 1). This indicates that in- and efflux of tryptamine are due to passive diffusion. The fact that the absolute concentration of tryptamine in heart is higher than in brain might be explained by different properties of the two tissues, e.g. in protein binding, lipid composition, etc.
3. Chlorpromazine, chlorprothixene and chlorisondamine markedly counteract the tryptamine increase in the brain, but not in the heart (Table 1). This suggests an active transfer into the brain, since active processes are likely to be more sensitive to hypothermia-producing drugs than passive diffusion.

The findings with tryptamine support the assumption that chlorpromazine and related drugs interfere also with the transport of endogenous monoamines which are actively stored in the brain, e.g. 5HT and NE.

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