ROLE OF BRAIN AMINES IN THE FATAL HYPERPYREXIA CAUSED BY TRANYLCYPROMINE IN LiCl-PRETREATED RATS

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Abstract—Tranylcypromine (TCP), a monoamine oxidase inhibitor, caused a fatal hyperpyrexia in rats pretreated with LiCl once a day for 4 days. Pretreatment with LiCl alone did not alter the level of serotonin (5-HT), dopamine (DA) and norepinephrine (NE) in the brain. In the fatal hyperpyrexia caused by LiCl plus TCP, the brain 5-HT and DA levels were increased, whereas the brain NE level was decreased. Reserpine and α-methyl-p-tyrosine completely prevented the hyperpyrexia, but FLA-63 did not show any effect. The hyperpyrexia was completely prevented by p-chlorophenylalanine (PCPA) given 72 hours before TCP but not by PCPA given 24 hours before TCP. Haloperidol and chlorpromazine, DA receptor blockers, inhibited the fatal hyperpyrexia, while cyproheptadine and methysergide, 5-HT receptor blockers, did not. These results suggest that DA plays an essential role in the hyperpyrexia induced by the combination of TCP and LiCl in rats, but the involvement of 5-HT is inconclusive.

The use of lithium salts for the treatment of manic disorders and prophylaxis of affective disorders is well established. However, the mechanism of action of lithium salts has not been clarified. There are a number of reports concerning the effect of lithium on the behaviour of laboratory animals. Lithium decreased the spontaneous locomotor activity (1, 2, 3) and the drug-induced hyperactivity in animals (4, 5, 6, 7). On the contrary, lithium, when combined with a monoamine oxidase inhibitor (MAOI), caused hyperactivity in rats (8, 9, 10), and this hyperactivity syndrome was assumed to be due to an effect of lithium on brain serotonergic and dopaminergic mechanisms.

In studies on the pharmacological properties of lithium, we found that the administration of tranylcypromine (TCP), a monoamine oxidase inhibitor, to rats pretreated with LiCl produced a marked and fatal hyperpyrexia in a large proportion of animals. Therefore, we attempted to clarify the possible relationship between the LiCl-TCP induced hyperpyrexia and brain amines in rats.

MATERIALS AND METHODS

Male Sprague-Dawley rats, weighing 220–280 g, were used throughout the experiments.

Drugs used: LiCl (Nakarai Chemicals), TCP (Sigma), reserpine (Serpasil®, Takeda), p-chlorophenylalanine (PCPA) (Sigma), DL-α-methyl-p-tyrosine methylester hydrochloride (α-MT) (Sigma), FLA-63 (Bis-(4-methyl-1-homopiperazinyl-thiocarbonyl) disulfide, Ishizu Seiyaku), Chlorpromazine hydrochloride (synthesized in our own Research Laboratories),
haloperidol (Janssen), cyproheptadine hydrochloride (Nihon Merck Banyu) and methysergide bimaleate (Sandoz). TCP, PCPA and FLA-63 were suspended in 0.5% methylcellulose aqueous solution (0.5% MC), haloperidol was dissolved in 20% acetic acid and diluted with distilled water, and other substances were dissolved in distilled water. All substances, being weighed as free bases, were given intraperitoneally.

**Measurement of rectal temperature:** A thermister probe (Thermo Finer ME-EPP5, Thermo Japan) was inserted about 4.5 cm deep into the rectum. The rectal temperature was measured by means of a thermometer (Thermo Finer Type N2, Thermo Japan). Rats were housed in individual cages during measurement of rectal temperature. All experiments were performed at an ambient temperature of 22.0-24.0°C.

**Chemical determination of biogenic amines:** Rats were injected with LiCl or saline once a day between 10:00 and 11:00 a.m. for 4 days. On day 4, these animals were given TCP or the vehicle 4 hr after the last injection of LiCl or saline. The animals were decapitated 2 hr after TCP or its vehicle, and the whole brain was rapidly removed for chemical determinations of norepinephrine (NE), dopamine (DA) and serotonin (5-HT). NE was determined by the method of Bertler et al. (11), DA by the method of Attack (12), and 5-HT by the method of Snyder et al. (13).

**Treatment with drugs:** When the effects of various drugs on LiCl-TCP induced hyperpyrexia were examined, the drugs were administered before TCP by respective schedules as follows: reserpine (1 mg/kg) 24 hr, PCPA (300 mg/kg) 24 or 72 hr, α-MT (64 or 125 mg/kg) 3 hr, FLA-63 (16 mg/kg) 3 hr, chlorpromazine (1 or 4 mg/kg) 0.5 hr, haloperidol (1 mg/kg) 0.5 hr, cyproheptadine (16 or 32 mg/kg) 0.5 hr and methysergide (16 mg/kg) just before TCP.

**Statistical analysis:** Calculations of p values according to Student’s t-test or Cochran-Cox test were performed using a computer program.

**RESULTS**

**Effects of LiCl and TCP on the rectal temperature of normal rats**

Saline or 0.5% MC given i.p. to rats produced no significant change in the rectal temperature measured 0.5, 1, 2, 4, 6 and 24 hr after the injection. Injection of LiCl 125 (2.9 mEq/kg) or 250 (5.9 mEq/kg) mg/kg, however, produced a rapid decrease in the rectal temperature, the effect being dose dependent in both potency and duration. When LiCl 125 mg/kg was given, the rectal temperature decreased by about 2°C at 0.5 hr and then recovered in 4 hr. When LiCl 250 mg/kg was given, the maximum decrease in the rectal temperature was of 3°C at 2 hr after dosing and recovery was attained in 6 hr (Fig. 1A). On the other hand, TCP 8 or 16 mg/kg given i.p. produced a slow decrease in the rectal temperature which lasted at least for 4 hr. The rectal temperature recovered to a normal level after 24 hr (Fig. 1B).

**Effects of combined treatment with LiCl and TCP on the rectal temperature**

LiCl 125 or 250 mg/kg or saline was given to rats daily for 4 days. On day 4, the animals were given TCP 4 hr after the last injection of LiCl or saline. At this time the rectal temperature of rats pretreated with LiCl 250 mg/kg was below the normal level as
illustrated in Fig. 1A. As seen in Fig. 2, TCP 16 mg/kg caused a significant fall of the rectal temperature in rats pretreated with saline or LiCl 125 mg/kg. On the contrary, in rats pretreated with LiCl 250 mg/kg, the rectal temperature rapidly and progressively rose with injection of TCP 16 mg/kg, and the rats showed symptoms of hyperexcitement, motor restlessness, tremor and increased reactivity. A high proportion of rats died between 3 to 4 hr after the injection of TCP, when the rectal temperature had reached about 41–42°C. When the vehicle (0.5% MC) instead of TCP was given to the LiCl-pretreated rats, the rectal temperature returned slowly to normal levels.

The incidence of hyperpyrexia is summarized in Fig. 3. In the present study it was defined that the hyperpyrexia was present when the rectal temperature of rats dosed with TCP rose 3°C or over, or the death of rats was noted and there were marked rises in the rectal temperature. A low incidence of the hyperpyrexia was noted after the injection of LiCl 250 mg/kg \( \times 4 \) and TCP 8 mg/kg. The combination of LiCl 250 mg/kg \( \times 4 \) and TCP 16 mg/kg produced hyperpyrexia at a higher rate. When animals were dosed with TCP 16 mg/kg 4 hr after a single injection of LiCl 250 mg/kg, a very low incidence of the hyperpyrexia was observed. In the following experiments, LiCl 250 mg/kg \( \times 4 \) plus TCP 16 mg/kg was used to produce the hyperpyrexia, unless stated otherwise.
FIG. 2. Effects of tranylcypromine (TCP) on the rectal temperature of rats pretreated with LiCl or saline once a day for 4 days. TCP 16 mg/kg or vehicle (0.5% MC) was injected 4 hr after the last injection of LiCl or saline on the 4th day. Rectal temperatures were measured at 1 hr intervals for 4 hr after TCP or vehicle. Each group included 5 animals. The vertical lines indicate the standard errors. (●): LiCl 250 mg/kg × 4 plus TCP, (○): LiCl 250 mg/kg × 4 plus vehicle, (▲): LiCl 125 mg/kg × 4 plus TCP, (△): saline × 4 plus TCP. *P<0.05, **P<0.01: significantly different from rectal temperature at zero time. **P<0.01: significantly different from LiCl 250 mg/kg × 4 plus vehicle group.

FIG. 3. The hyperpyrexia (a rise of rectal temperature of 3°C or over, or death due to the hyperthermia) caused by tranylcypromine (TCP) in rats pretreated with a single or repeated doses of LiCl. TCP 8 or 16 mg/kg or vehicle (0.5%, MC) was injected 4 hr after the last injection of LiCl. Repeat: LiCl 250 mg/kg was given to rats once a day for 4 days. Single: a single dose of LiCl 250 mg/kg was given to rats. The ordinate indicates the percentages of animals showing the hyperpyrexia. Rectal temperatures were measured at 1 hr intervals for 4 hr. Number of animals is given in parentheses.
The results are shown in Table 1. There were no differences in the 5-HT, DA and NE levels between saline- and LiCl-pretreated rats after injection of the vehicle. After TCP at a dose of 8 mg/kg, the contents of the three amines in the LiCl-pretreated rats were not significantly different from those in the saline-pretreated rats though the 5-HT level was somewhat higher in the LiCl-pretreated rats. After TCP at a dose of 16 mg/kg, the rectal temperature of LiCl-pretreated rats showed a rise up to 40.4°C. In these rats, the 5-HT and DA levels were significantly higher than those in the saline-pretreated rats, whereas the NE level in the LiCl-pretreated rats was significantly lower than that in the saline-pretreated rats.

**Effects of amine depletors on the hyperpyrexia**

As the results described in the preceding section suggested that brain amines were related to the hyperpyrexia, effects of amine depletors on the hyperpyrexia and brain amine

### Table 1. Effects of LiCl and tranylcypromine (TCP), alone or in combination, on rectal temperature (°C), and brain 5-HT, DA and NE levels (μg/g wet weight)

| Pretreatment | challenge | No. | Rectal temp. (°C) | 5-HT | DA | NE |
|--------------|-----------|-----|------------------|------|----|----|
| Saline       | vehicle   | 5   | 37.4±0.2         | 0.35±0.02 | 0.54±0.01 | 0.34±0.01 |
| LiCl         | vehicle   | 5   | 37.1±0.5         | 0.36±0.01 | 0.55±0.01 | 0.33±0.01 |
| Saline       | TCP 8 mg/kg | 5   | 36.2±0.4         | 0.74±0.04 | 0.73±0.02 | 0.38±0.02 |
| LiCl         | TCP 8 mg/kg | 5   | 37.4±0.4         | 0.84±0.02 | 0.74±0.02 | 0.35±0.03 |
| Saline       | TCP 16 mg/kg | 5   | 35.9±0.2         | 0.72±0.02 | 0.72±0.02 | 0.30±0.01 |
| LiCl         | TCP 16 mg/kg | 10  | 40.4±0.7**       | 0.86±0.03* | 0.85±0.04* | 0.24±0.02** |

Measurements were performed 2 hr after administration of the vehicle or TCP. Results are expressed as mean±S.E.M. *P<0.05, **P<0.01: significantly different from the corresponding saline-pretreated group.

**Chemical determination of brain amines in the state of hyperpyrexia**

The results are shown in Table 1. There were no differences in the 5-HT, DA and NE levels between saline- and LiCl-pretreated rats after injection of the vehicle. After TCP at a dose of 8 mg/kg, the contents of the three amines in the LiCl-pretreated rats were not significantly different from those in the saline-pretreated rats though the 5-HT level was somewhat higher in the LiCl-pretreated rats. After TCP at a dose of 16 mg/kg, the rectal temperature of LiCl-pretreated rats showed a rise up to 40.4°C. In these rats, the 5-HT and DA levels were significantly higher than those in the saline-pretreated rats, whereas the NE level in the LiCl-pretreated rats was significantly lower than that in the saline-pretreated rats.

**Effects of amine depletors on the hyperpyrexia**

As the results described in the preceding section suggested that brain amines were related to the hyperpyrexia, effects of amine depletors on the hyperpyrexia and brain amine

**Fig. 4.** Effect of pretreatment with (A) reserpine or (B) p-chlorophenylalanine (PCPA) on the hyperpyrexia caused by tranylcypromine (TCP) in rats pretreated with LiCl for 4 days. Reserpine was injected 24 hr before TCP, and PCPA was injected 24 hr or 72 hr before TCP. The control group was given the vehicle only. The ordinate indicates the percentages of animals showing the hyperpyrexia. Rectal temperatures were measured at 1 hr intervals for 4 hr. n=number of animals in parentheses.
contents were studied. Reserpine 1 mg/kg completely prevented the hyperpyrexia (Fig. 4A). PCPA 300 mg/kg, a tryptophan hydroxylase inhibitor, also completely blocked the hyperpyrexia when given 72 hr before TCP, but was not so effective when given 24 hr before TCP (Fig. 4B). In the PCPA-treated rats, the 5-HT content was only 20-34% of control, while slight but significant reduction in DA and NE levels was also evident (Table 2). It is noteworthy that a greater reduction of the 5-HT level was observed at 74 hr than at 26 hr after PCPA. When α-MT, a tyrosine hydroxylase inhibitor, was given in a dose of 64 or 125 mg/kg, the hyperpyrexia was prevented (Fig. 5A). Brain NE and DA contents, but not 5-HT, were decreased markedly (Table 2). FLA-63, a dopamine-β-hydroxylase inhibitor, injected in a dose of 16 mg/kg failed to prevent the hyperpyrexia (Fig. 5B). In this case, NE level was decreased but there were no changes in 5-HT and DA contents (Table 2).

**Effects of DA- and 5-HT-receptor blockers on the hyperpyrexia**

Effects of DA receptor blockers, chlorpromazine and haloperidol, and 5-HT receptor

### TABLE 2. Brain 5-HT, DA and NE levels in rats given identical treatments as in Figs. 4 and 5

| Treatment       | before TCP (hr) | No. | 5-HT % of control | DA % of control | NE % of control |
|-----------------|-----------------|-----|-------------------|----------------|----------------|
| Control         |                 | 6   | 0.71 ± 0.04       | 0.93 ± 0.06    | 0.21 ± 0.03    |
| PCPA 300 mg/kg  | 24              | 5   | 0.24 ± 0.02**     | 0.61 ± 0.04**  | 0.13 ± 0.01*   |
| PCPA 300 mg/kg  | 72              | 5   | 0.14 ± 0.02**     | 0.67 ± 0.02**  | 0.13 ± 0.02*   |
| Control         |                 | 5   | 0.80 ± 0.04       | 1.08 ± 0.05    | 0.21 ± 0.03    |
| α-MT 64 mg/kg   | 3               | 5   | 0.85 ± 0.07       | 0.35 ± 0.04**  | 0.07 ± 0.01**  |
| α-MT 125 mg/kg  | 3               | 5   | 0.96 ± 0.10       | 0.23 ± 0.02**  | 0.06 ± 0.01**  |
| FLA-63 16 mg/kg | 3               | 5   | 0.92 ± 0.09       | 1.01 ± 0.08    | 0.06 ± 0.01**  |

Measurements were performed 2 hr after tranylcypromine (TCP). Results are expressed as mean±S.E.M. *P<0.05, **P<0.01; significantly different from control.
a) P<0.01: significantly different from PCPA 300 mg/kg 72 hr group.

![Fig. 5. Effect of pretreatment with (A) α-methyl-p-tyrosine (α-MT) or (B) FLA-63 on the hyperpyrexia caused by tranylcypromine (TCP) in rats pretreated with LiCl. α-MT or FLA-63 was injected 3 hr before TCP. The control group was given the vehicle only. The ordinate indicates the percentages of animals showing the hyperpyrexia. Rectal temperatures were measured at 1 hr intervals for 4 hr. Number of animals is given in parentheses.](image-url)
blockers, cyproheptadine and methysergide, on hyperpyrexia were studied. The injection of chlorpromazine in a dose of 1 or 4 mg/kg, or haloperidol in a dose of 1 mg/kg prevented the hyperpyrexia (Fig. 6A). On the other hand, cyproheptadine in a dose of 16 or 32 mg/kg, and methysergide in a dose of 16 mg/kg were without effects (Fig. 6B).

**DISCUSSION**

In the present study, we found that TCP 16 mg/kg i.p. produced a fatal hyperpyrexia in rats given LiCl 250 mg/kg i.p. once a day for 4 days. The hyperpyrexia was specifically attributed to the combination of LiCl and TCP. LiCl could not be replaced by NaCl, KCl, RbCl or CsCl, and TCP could not be replaced by pargyline, iproniazide or nialamide (in preparation). LiCl plus TCP produced a hyperexcitement as well as hyperpyrexia. It has been reported that an increased motor activity with hyperthermia occurred in rats exposed to a high ambient temperature. However, a causal effect relationship between the increased motor activity and the hyperthermia was not well elucidated in this literature (14). In the present study also, the hyperexcitement and hyperpyrexia might be interrelated, however, no attempt was made to clarify the nature of the interrelationship.

In a state of fatal hyperpyrexia, the brain 5-HT and DA levels were increased, whereas
the NE level was decreased, these results suggesting the involvement of these amines in hyperpyrexia. The depletion of all of these amines by reserpine and the depletion of DA and NE by α-MT completely prevented the fatal hyperpyrexia. FLA-63, which significantly decreased the NE level alone, failed to prevent the hyperpyrexia. Furthermore, DA receptor blockers, chlorpromazine and haloperidol, prevented the hyperpyrexia. Thus, DA but not NE appears to be involved in the hyperpyrexia. The role of DA in thermoregulation in rats is still open for discussion. There is a report that an intraventricular administration of DA, amphetamine, and apomorphine produced hypothermia in rats (15). In contrast, it has been reported that a low dose of DA given intraventricularly to rats produced a rise in rectal temperature (16). Furthermore, Matsumoto and Griffin have reported that pimozide, a DA receptor blocker, effectively antagonized the amphetamine-induced hyperthermia in rats (17). These results emphasized the hyperthermic property of DA in the central nervous system of rats. LiCl has been reported to cause an increased turnover rate of NE (1, 18, 19, 20, 21) and 5-HT (22, 23, 24), but not that of DA (20, 25, 26). However, there is the possibility that LiCl, when combined with TCP, could promote the synthesis and release of DA which in turn excites the central pathway for the heat gain. Further study is needed to elucidate the precise mechanism involved.

A marked reduction in the 5-HT content, and less but significant reductions of the DA and NE levels were noted at both 26 and 74 hr after the injection of PCPA. The decreased DA levels should result in a decreased incidence of LiCl-TCP induced hyperpyrexia. However, no reduction in the incidence of the hyperpyrexia was noted when PCPA was injected 24 hr before TCP. On the other hand, when PCPA was injected 72 hr before TCP, the hyperpyrexia was completely prevented, despite no further reduction in DA content. The difference in the effects of PCPA on the hyperpyrexia between 24 and 72 hr after the pretreatment might be attributed to the difference in 5-HT levels. At 26 and 74 hr after PCPA, the 5-HT contents in the brain were 34 and 20% of the control, respectively, being significantly lower in the latter case than in the former. This more striking depletion in 5-HT pool might have been responsible for the prevention of hyperpyrexia. In this respect, brain 5-HT as well as DA may play a key role in production of the hyperpyrexia. Grahame-Smith has reported that hyperactivity and hyperpyrexia were developed in rats given MAOI and L-tryptophan, and the syndromes were ascribed to the increased synthesis and accumulation of brain 5-HT (27). However, this author did not examine effects of 5-HT receptor blockers. In our study, high doses of cyproheptadine and methysergide, 5-HT receptor blockers, failed to prevent the LiCl-TCP induced hyperpyrexia. This finding is incompatible with the idea that 5-HT would be essential for the hyperpyrexia. Therefore, the involvement of 5-HT in the LiCl-TCP induced hyperpyrexia is inconclusive in the present experiment.

In summary, the combination of repeated doses of LiCl 250 mg/kg and a single dose of TCP 16 mg/kg produced a fatal hyperpyrexia in rats. DA seems to play an important role here, although contribution of 5-HT cannot be ruled out.
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