CHARACTERISTIC HYPERPYREXIA INDUCED BY LiCl
AND TRANYLCYPROMINE IN RATS

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In previous studies (1, 2), we showed that tranylcypromine (TCP), a monoamine oxidase inhibitor (MAOI), caused a fatal hyperpyrexia in rats which had been given repeated doses of LiCl. This phenomenon is one of the most conspicuous responses concerned with lithium. The present work was an attempt to test whether or not the hyperpyrexia is induced specifically by the combination of LiCl and TCP.

Male Sprague-Dawley rats weighing 220–280 g, supplied by CLEA Japan Inc., were used. Five to 17 animals were used per group. In one series of experiments, rats were given a drug or an alkali metal once daily for 4 days. Control animals were given LiCl at a dose of 250 mg/kg which was used in our previous experiments (1, 2). The alkali metals other than LiCl were given in two doses which were equivalent to that of LiCl either on the weight or molar basis. On day 4, these rats were given TCP 4 hr after the last injection of an alkali metal or a drug. In another series of experiments, rats were given LiCl at a dose of 250 mg/kg once daily for 4 days. On day 4, a MAOI was given to rats 4 hr after the last injection of LiCl. In both series of experiments, the rectal temperatures were measured with a thermister probe (Thermo Japan) inserted about 4.5 cm into the rectum 1, 2, 3 and 4 hr after the injection of a MAOI. Rats were housed in individual cages during the measurement of rectal temperature. All experiments were performed at an ambient temperature of 22.0–24.0°C. Drugs used were haloperidol (Janssen), fluphenazine dihydrochloride, chlordiazepoxide hydrochloride, chlorpromazine hydrochloride (synthesized in our Research Laboratories), sulpiride and imipramine hydrochloride (Fujisawa), diazepam (Cercine-Takeda), cyproheptadine hydrochloride (Nihon Merck Banyu), phenolamine mesylate (Regitine, CIBA-Geigy), tranylcypromine, DL-propranolol hydrochloride and nialamide (Sigma), tolazoline hydrochloride and iproniazid phosphate (Aldrich), methamphetamine hydrochloride (Hiropon, Dainippon), LiCl, NaCl, KCl, RbCl, CsCl and pargyline hydrochloride (Nakarai Chemicals). TCP and nialamide were suspended in 0.5% methylcellulose aqueous solution (0.5% MC). Haloperidol and sulpiride were dissolved in mini-
mum amounts of 20% acetic acid and 1N H₂SO₄, respectively, and diluted with distilled water. All other substances were dissolved in or diluted with distilled water. All substances, being expressed as free bases, were given i.p.

Results with alkali metals are shown in Table 1. As described in the previous study (1), the hyperpyrexia was defined as follows: the rectal temperature of rat rose 3 °C or over, or death of the animals occurred and there was a marked rise in the rectal temperature after the injection of TCP. LiCl-pretreated rats showed the hyperpyrexia at a high rate after dosing of TCP 16 mg/kg. There was no incidence of hyperpyrexia after dosing of TCP in rats pretreated with NaCl, KCl, RbCl or CsCl, each at a dose of 250 mg/kg, but a low incidence of hyperpyrexia was observed in the rat pretreated with RbCl 654 mg/kg. CsCl at a dose of 990 mg/kg resulted in death in 5 of 7 rats during the pretreatment period, and the remaining two rats showed the hyperpyrexia after dosing of TCP. On the other hand, TCP did not induce a hyperpyrexia in any rat pretreated with one of psychotropic drugs (chlorpromazine 10 mg/kg, haloperidol 1 and 10 mg/kg, fluphenazine 10 mg/kg, sulpiride 32 mg/kg, chlor Diazepoxide 32 mg/kg, diazepam 10 mg/kg, imipramine 32 mg/kg, methamphetamine 10 mg/kg), α- and β-adrenergic blockers (tolazoline 10 mg/kg, phenotolamine 32 mg/kg or DL-propranolol 10 mg/kg) or serotonin blocker (cyproheptadine 10 mg/kg). Only in the rats pretreated with desipramine 32 mg/kg, was there a low incidence of hyperpyrexia (10%).

In the following experiments pargyline, iproniazid or nialamide, instead of TCP, was injected into rats which had been given LiCl 250 mg/kg daily for 4 days. Fig. 1 shows that pargyline, iproniazid, and nialamide, up to a dose of 250 mg/kg, produced a fall in rectal temperature of rats given LiCl. On the contrary, TCP 16 mg/kg produced a marked rise in the rectal temperature of the rats.

### Table 1. Hyperpyrexia induced by dosing of tranylcypromine in the alkali metal-pretreated rats

| Drug | dose (mg/kg, i.p.) | N | 1 | 2 | 3 | 4 hr |
|------|--------------------|---|---|---|---|-----|
| LiCl | 250                | 17| 47| 71| 82| 88  |
| NaCl | 250                | 5 | 0 | 0 | 0 | 0   |
|      | 314                | 5 | 0 | 0 | 0 | 0   |
| KCl  | 250                | 5 | 0 | 0 | 0 | 0   |
|      | 440                | 5 | 0 | 0 | 0 | 0   |
| RbCl | 250                | 5 | 0 | 0 | 0 | 0   |
|      | 654                | 5 | 0 | 0 | 14| 14  |
| CsCl | 250                | 5 | 0 | 0 | 0 | 0   |
|      | 990                | 7 | (100) | (100) | (100) | (100) |

Rats were injected with an alkali metal once daily for 4 days. On day 4, tranylcypromine 16 mg/kg was given to rats 4 hr after the last injection of an alkali metal. The rectal temperatures were measured 1, 2, 3 and 4 hr after the injection of tranylcypromine.

( ) the incidences of hyperpyrexia in the remaining two rats; 5 of 7 rats died during the pretreatment period.
The results show that the hyperpyrexia is a specific phenomenon for the combination of LiCl and TCP. It has been reported that lithium can replace sodium as a depolarizing substance during the upward phase of the action potential (3). Although how this property is related to the mechanism of action of lithium has not been defined, this property may render lithium a character that cannot be seen with other alkali metals.

Our previous studies have shown that the dopamine (DA) in the caudate nucleus plays an important role in hyperpyrexia (1, 2), as the occurrence of the hyperpyrexia was dependent on an increase in the brain DA and was suppressed by DA blockers. TCP increased the DA in the caudate nucleus, while pargyline was without effect (4). TCP is also known to have a potent central stimulant activity (5). Thus, there is the possibility that these properties of TCP contribute to the production of the hyperpyrexia. However, it is not certain how these properties of LiCl and TCP contribute to the specificity of the combination of LiCl and TCP.

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