IN Volvement of Central Noradrenergic System in Thyrotropin-Releasing Hormone-Induced BehavioralExcitement in 6-OHDOPA-Treated, Infant Rats

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A subcutaneous (s.c.) injection of thyrotropin-releasing hormone (TRH) 20 mg/kg, produced body shake and struggle, consequently induced an increase of count in ANIMEX activity meter in 7-day-old rats pretreated with 6-hydroxydopa (6-OHDOPA), 75 mg/kg, on days 0, 2 and 4. TRH-induced behavioral excitement was markedly attenuated in the infant animals which were injected desmethylinpiramine, 5 mg/kg, 30 min before 6-OHDOPA on days 0, 2 and 4. It is suggested that central catecholaminergic, in particular, noradrenergic system is involved in TRH-induced body shake and struggle in 6-OHDOPA-treated, infant rats.

Keywords—TRH; 6-OHDOPA; desmethylinpiramine; behavioral excitement; central noradrenergic system; infant rats

INTRODUCTION

Several papers have reported that thyrotropin releasing hormone (TRH) produces behavioral excitement by activating central catecholaminergic system.1-6) In 7-day-old rats, a TRH-induced increase of count in ANIMEX activity meter was markedly enhanced by pretreatment with 6-hydroxydopa (6-OHDOPA) but not in both 14-day-old and adult animals following 6-OHDOPA.6) Difference in TRH-responses in developing rats prompted us to investigate the action of TRH in 7-day-old rats. Furthermore, TRH-induced behavioral excitement in 7-day-old animals was significantly inhibited by α-flupenthixol and phenoxybenzamine, suggesting that the central dopaminergic and noradrenergic systems are involved in the TRH-induced behavioral excitement. Since desmethylinpiramine (DMI), a tricyclic antidepressant drug, has been known to selectively inhibit the noradrenaline (NA) uptake into NA nerve terminals,7,8) pretreatment with DMI could protect NA terminals from lesion by 6-OHDOPA. In fact, biochemically the lesion causes a large depletion of DA with relatively little loss of NA in the frontal cortex of the DMI plus 6-hydroxydopamine (6-OHDA)-treated rats.9)

The present study was designed to get an information regarding the involvement of the NA and dopamine (DA) system in TRH-induced behavioral excitement in 7-day-old rats.

MATERIALS AND METHODS

Wistar rats of both sexes were used. Neonatal rats from the same litter were divided into two groups: one was 6-OHDOPA-treated group and the other was DMI plus 6-OHDOPA (DMI/6-OHDOPA)-treated group. The treatment with 6-OHDOPA was carried out by the method of Nomura et al.10) A dose of 75 mg/kg (0.1 ml/10 g of body weight) of the drug dissolved in saline containing 0.001 N HCl, was first injected s.c.

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into the neonatal animals within several hours after birth and followed by the second and third injection on days 2 and 4. DMI, 5 mg/kg, dissolved in saline or saline was injected s.c. 30 min before every dose of 6-OHDOPA.

TRH-induced behavioral excitement was estimated in 6-OHDOPA- and DMI 6-OHDOPA-treated rats. All behavioral studies were carried out between 10:00 and 17:00 in a quiet room maintained at 23±1°C. Behavioral observation began immediately after an s.c. injection of TRH, 20 mg/kg, and continued for 180 min. Each rat was placed into a plastic cage (24×18 cm). Head and body shake, struggle and falling, eating-like movement of forepaws, preening, chewing and Straub tail response were assessed by means of the following rating scale: –, not observed; +, slight; ++, moderate; ++++, marked. The “marked” was defined as the behavior without intermission during observation period. Behavioral excitement was also measured with an ANIMEX activity meter (Type S, LKB Instrument, sensitivity, 40 μA). Recording was made for 5 min at every 10 min from 60 to 180 min after s.c. injection of TRH, since a preliminary experimentation showed that behavioral stimulant action of TRH appeared at this period.

Drugs used were TRH tartrate monohydrate (Takeda Chemical Industries, Ltd.), 6-OHDOPOA hydrochloride (Nippon-Roche Research Center) and desmethylimipramine hydrochloride (Daiichi Pharmaceutical Co. Ltd.).

RESULTS AND DISCUSSION

Table I shows the effect of TRH on general behavior in 6-OHDOPA- or DMI/6-OHDOPA-treated, 7-day-old rats. A s.c. injection of TRH, 20 mg/kg, produced head and body shake, struggle and falling down, eating-like movement of forepaws, preening, chewing and Straub tail response. However, body shake and struggle (falling down) markedly reduced, and eating-like movement of forepaws and preening slightly reduced in DMI/6-OHDOPA group as compared with those in 6-OHDOPA group. In contrast, neither chewing nor tail erection differed in the two groups. As shown in Fig. 1, TRH, 20 mg/kg, caused an increase of ANIMEX counts in 6-OHDOPA group. Interestingly, however, TRH, 20 mg/kg, did not cause any increase in ANIMEX counts in DMI/6-OHDOPA group at all. TRH-induced body shake and an increase in

<p>| TABLE I. TRH-induced Behavioral Arousal in 6-OHDOPA- and DMI/6-OHDOPA- treated, 7-day-old Rats |</p>
<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>Treatment (mg/kg)</th>
<th>Head and body Shake</th>
<th>Struggle and Falling</th>
<th>Eat-like movement of forepaws</th>
<th>Preening</th>
<th>Chewing</th>
<th>Straub tail</th>
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</thead>
<tbody>
<tr>
<td>Saline plus 6-OHDOPA</td>
<td>Saline</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>±</td>
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<tr>
<td>TRH 20</td>
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<td>+++</td>
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<td>+++</td>
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<tr>
<td>DMI plus 6-OHDOPA</td>
<td>Saline</td>
<td>–</td>
<td>–</td>
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<tr>
<td>TRH 20</td>
<td>+</td>
<td>+</td>
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6-OHDOPA- and DMI/6-OHDOPA-treated, 7-day-old rats were s.c. injected with TRH 20 mg/kg. Behavioral observation was begun immediately after an i.p. injection of TRH 20 mg/kg and continued for 180 min. Each behavior was assessed as follows: –, not observed; +, slight; ++, moderate; ++++, marked. n = 6 – 10 for each group.
ANIMEX count in 6-OHDOPA group almost disappeared in DMI/6-OHDOPA group, indicating that an increase in ANIMEX count by TRH is due to head and body shake and struggle and falling. It is well known that DMI inhibits the uptake of 6-OHDA, a decarboxylated product of 6-OHDOPA, into NA nerve terminals and protects NA neurons from lesion by 6-OHDA.8) If this is the case in the present study, TRH-induced body shake as well as TRH-induced increase in ANIMEX count is perhaps related to NAergic activation by TRH. A result that a preceding injection of DMI did not affect chewing and tail erection, suggests that these behaviors may be due to activation by TRH of neurons other than NA neurons. α-Flupenthixol, a specific DA receptor antagonist, effectively inhibits TRH-receptor increase in ANIMEX counts in 6-OHDOPA-treated, 7-day-old rats.8) Thus, it is presumable that NAergic activation by TRH could produce body shake and DAergic activation by the peptide may induce chewing and tail erection. Detail of the neurochemical mechanism of TRH-induced behavioral excitement remains to be clarified in 6-OHDOPA-treated, infant rats, although it is speculated that 6-OHDOPA induces postsynaptic hypersensitivity to NA and DA in catecholaminergic synapses and that TRH directly and/or indirectly act these receptors. TRH at high concentration, 100 μM, has been shown to stimulate release of DA and NA from slices of nucleus accumbens and hypothalamus, respectively.11,12)

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TRH and Newborn Rats

(1980).


