NOTE

Effect of Neurotensin on Pituitary Gonadotropin Release in Vivo

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Synopsis

To investigate the effect of a newly purified hypothalamic tridecapeptide, neurotensin on LH and FSH release from the anterior pituitary gland in intact male rats, two different doses of neurotensin (0.2 nmole/animal: high dose, 0.02 nmole/animal: low dose) were injected intravenously into male mature Sprague-Dawley strain rats and blood was collected before and 30 min after the administration. Both doses of neurotensin increased serum LH and FSH levels but the alteration was slight and the values were not statistically significant and less potent to stimulate the anterior pituitary as compared to LH-RF. Neurotensin was suggested to be "kinin" rather than the releasing factor and its biological potency was discussed.

Previously we have reported that neurotensin, a newly purified hypothalamic hypotensive tridecapeptide (Carraway and Leeman, 1973), induced an elevation of plasma luteinizing hormon (LH) and follicle stimulating hormone (FSH) levels in ovariectomized estrogen-progesterone-treated rats (Makino et al., 1973). However, few studies since then have been reported on the effect of neurotensin concerning LH and FSH secretions in intact animals. This report describes the effect of intravenous administration of neurotensin on serum LH and FSH levels in intact mature male rats.

Materials and Methods

Animals and treatment

Male rats of the Sprague-Dawley strain weighing 280-350 gm were used in this study. They were caged in groups of 3-4, fed with rat chow and water ad libitum, and maintained on an artificial light regimen of 14 hr light and 10 hr darkness at least for 2 weeks before the experiment. Neurotensin, a hypotensive tridecapeptide isolated from acid-acetone extracts of bovine hypothalami, was the gift from Dr. S. E. Leeman of Harvard Medical School. This peptide was diluted with 0.15 M saline to a final concentration of 0.2 nmole/100 µl before use. All animals were injected with a high dose of neurotensin (0.2 nmole) or low dose (0.02 nmole) intravenously under light ether anesthesia. As the control 100 µl of normal saline or 100 ng of synthetic LH-releasing factor (LH-RF) was administered into other groups. Bloods were collected from tail arteries before and after the treatments, and the separated sera were kept frozen until assayed.

Rat LH and FSH assays

Serum LH and FSH concentrations were measured by the double antibody radioimmunoassay technique utilizing NIAMDD-rat LH and FSH assay kits. The values were expressed as nanograms of reference preparations of NIAMDD-rat LH-RP-1 and FSH-RP-1. Student's t test was used to determine significance of difference between the control and treated groups.

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Results

Table 1 shows the effect of high and low doses of neurotensin on male rat pituitary for LH and FSH release. Serum levels of LH were slightly increased by these doses after intravenous administration. However, the values were not statistically significant. Similarly, serum FSH concentrations were increased 30 min after the injection of neurotensin but the data were also not statistically different as compared with the initial control (0'). Contrarily, synthetic LH-RF increased serum levels of LH and FSH significantly in intact male rats as shown in Table 2.

Discussion

A newly purified hypothalamic tridecapeptide, neurotensin, is classified as a "kinin" and this chemical composition distinguishes neurotensin from the primary structure of porcine and bovine LH-RF. Furthermore, neurotensin possesses more varied biological properties than the decapeptide does; the hypotensive effect and induction of tachyphylaxis, the increases of vascular permeability, the stimulation of the contraction of guinea pig ileum and rat uterus and the relaxation of rat duodenum (Carraway and Leeman, 1973). The present data demonstrate that both high and low doses of this tridecapeptide slightly enhanced the pituitary release of LH and FSH in intact male rats, though the values were not statistically significant. It is of interest to observe the effect of neurotensin on the pituitary in another experimental animal model. As previously reported (Makino et al., 1973) the effect of neurotensin on gonadotropin release is more evident in ovariectomized, estrogen-progesterone-treated rats than in intact male rats. It is well known that LH release from the anterior pituitary is increased by ovariectomy due to the removal of gonadal negative feedback action and that both LH synthesis and release in the pituitary gland are depressed by gonadal steroids in ovariectomized animals. Thus, the ovariectomized, estrogen-progesterone-treated rat model has well controlled hormonal milieu and might be more appropriate to observe the alteration of pituitary gonadotropins by exogenous stimulation. Since neurotensin has no direct effect on the anterior pituitary to release LH and FSH (Makino et al., submitted to Biology of

Table 1. Effect of different doses of neurotensin on serum LH and FSH

<table>
<thead>
<tr>
<th>Dose of neurotensin</th>
<th>No of animals</th>
<th>serum LH (ng/ml)</th>
<th>serum FSH (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0' 30'</td>
<td>0' 30'</td>
</tr>
<tr>
<td>Control (100 µl of 0.15 M saline)</td>
<td>5</td>
<td>64.0±3.5</td>
<td>1233.0±50.6</td>
</tr>
<tr>
<td>Group I (0.2 nmole neurotensin)</td>
<td>6</td>
<td>64.3±0.6</td>
<td>1210.0±71.2</td>
</tr>
<tr>
<td>Group II (0.02 nmole neurotensin)</td>
<td>6</td>
<td>65.4±6.3</td>
<td>1350.2±130.2</td>
</tr>
</tbody>
</table>

Table 2. Effect of LH-RF on pituitary release of LH and FSH

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of animal</th>
<th>serum LH (ng/ml)</th>
<th>serum FSH (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0' 30'</td>
<td>0' 30'</td>
</tr>
<tr>
<td>Control (100 µl of 0.15 M saline)</td>
<td>5</td>
<td>64.0±3.5</td>
<td>1233.0±50.6</td>
</tr>
<tr>
<td>LH-RF 100 ng</td>
<td>6</td>
<td>74.1±16.0</td>
<td>1120.3±25.1</td>
</tr>
</tbody>
</table>

* p <0.01, ** p <0.05 vs values at 0'.

Reproduction) and LH-RF is more potent to synthesize and release LH and FSH, it is apparent that neurotensin does not act on the pituitary as a releasing factor of gonadotropin. As Carraway and Leeman reported (Carraway and Leeman, 1973 and 1974), the minimum effective dose to cause hypotension is 100 pmole/kg, 1 pmole/kg for cyanosis and 200 pmole/kg for hyperglycemia. They have also measured the physiological amount of immunoreactive neurotensin in the hypothalamus of mature rats and demonstrated that the average amount of neurotensin in the rat hypothalamus was $4.3 \pm 0.5$ pmole/hypothalamus (Carraway and Leeman, 1976). These data indicate that the dose used in the present study was pharmacological rather than physiological. Using specific radioimmunoassay for neurotensin, they have reported that thirty-five per cent of the total neurotensin in the brain was localized in the hypothalamus. These data suggest that this tridecapeptide might be one of the local regulators of the hypothalamic function as well as vaso-intestinal stimulant.

References


