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Pituitary Response to TRH and LHRH in Spontaneously Hypertensive Rats (40356)

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The isolation from Wistar rats of a strain with spontaneous hypertension has provided investigators with an excellent experimental model for studying essential hypertension in man (1). Like man in the early stages of essential hypertension (2), the young, spontaneously hypertensive rat (SHR) responds to stress with exaggerated blood pressure and heart rate rises (3). It has been proposed that the cardiovascular system of the SHR is exposed to increased neurohormonal stimulation due to exaggerated hypothalamic defense area activity (4). The SHR has been noted to have larger pituitary, thyroid and adrenal glands and to have intensified activity of the sympathicoadrenal and ACTH-corticoid axis in comparison to Wistar controls (1, 5). In this study we have examined the luteinizing hormone (LH) response to luteinizing hormone releasing hormone (LHRH) and the thyrotropin (TSH) and prolactin (PRL) response to thyrotropin releasing hormone (TRH) in SHR and normotensive control Wistar rats in an attempt to determine if the pituitary response to these releasing hormones is altered in the SHR.

Materials and methods. Fourteen male SHR and 14 normotensive Wistar Kyoto rats weighing 180–225 g were individually caged and maintained at (27 ± 2°) on a 14:10 light–dark cycle. The animals were fed and watered *ad libitum.* A 20-cm polyethylene catheter (PE 50) was inserted into the right common carotid artery under Nembutal anesthesia as previously described (6). The catheters were passed subcutaneously, exteriorized, and coiled immediately posterior to the shoulders. Catheters were filled with heparinized saline (200 USP units/ml) and sealed with heat. Patency was maintained by daily flushing with 200 USP units of heparin. Blood was drawn through a 23-gauge needle inserted into the opened catheter 48 hr after the surgery. Mean arterial blood pressure was monitored from the same cannula with a physiograph pressure transducer and recorder.

Experimental protocol. A baseline sample of 400 μl of blood for measurement of thyroxine, LH, TSH and PRL was withdrawn from 14 SHR and 14 control rats 60 min after the animals' cannulas were opened. During the sampling, they were allowed to move about fully in their cages and appeared calm. In all experiments the intravascular volume was maintained by replacement with normal saline. Six of the SHR and 6 controls received TRH (10 μg/kg) injected and flushed through the catheter. Blood samples (400 μl) for TSH and PRL determination were withdrawn from the catheter at 10, 15, 30, and 45 min after TRH injection.

Assays of T_4, TSH, PRL and LH. Measurement of T_4 was performed by a radioimmunoassay technique employing dextran-charcoal to separate bound from free T_4, as previously described (7). Serum TSH was measured by a double antibody method using reagents provided by the NIAMDD. NIH Rat TSH-RP-1 was the reference preparation. Serum PRL was measured by a double antibody radioimmunoassay using reagents provided by the RIAMDD. NIH γ PRL-RP-1 served as the reference preparation. Serum LH was measured by a double antibody radioimmunoassay using reagents provided by the NIAMDD, with NIH Rat LH-RP-1 serving as the reference preparation. All measurements of each hormone were performed in duplicate in the same assay to avoid inter-assay variation.

Statistical differences between the responses of SHR and controls were evaluated with Student's *t* test for unpaired data.

Results. The mean baseline serum T_4 of the SHR group (3.1 ± 0.2 μg/dl) was similar to that of the controls (3.0 ± 0.2 μg/dl). Figure 1 shows that the mean baseline serum TSH levels were higher ($P < 0.05$) for the SHR group (1700 ± 325 ng/ml) than for the control

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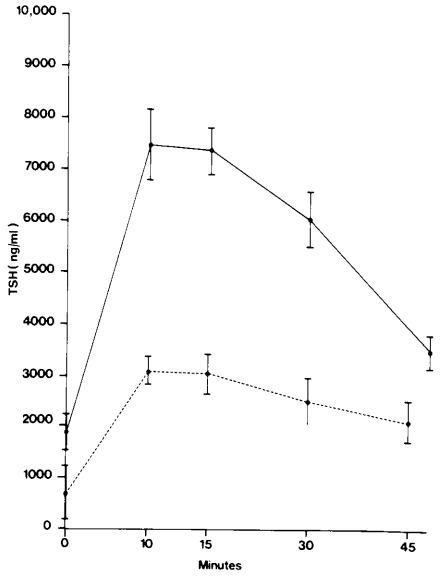

FIG. 1. Mean serum TSH responses to TRH (given at 0 time) in six spontaneously hypertensive rats (solid line) and in 6 normotensive Wistar-Kyoto rats (broken line); vertical bars show SEM.

group (718 ± 3.4 ng/ml). The maximal ΔTSH (difference between peak responses and baseline levels) in response to TRH was greater ($P < 0.01$) for the SHR (6362 ± 549 ng/ml) than for the controls (2760 ± 549 ng/ml).

Figure 2 shows that the mean baseline serum PRL levels were higher ($P < 0.05$) for the SHR (26.1 ± 2.1 ng/ml) than for the controls (16.3 ± 2.8 ng/ml). The ΔPRL response to TRH was greater ($P < 0.025$) for the SHR (12.0 ± 0.8 ng/ml) than for the controls (6.2 ± 1.9 ng/ml).

Figure 3 shows that the mean baseline serum LH for the SHR (45.6 ± 12.5 ng/ml) was not significantly different from that of the controls (41.5 ± 12.4 ng/ml). The ΔLH in response to LHRH was less ($P < 0.001$) for the SHR (126 ± 12.8 ng/ml) than for the controls (252 ± 24.8).

The mean arterial blood pressure for the SHR group (159 ± 8.6 mm Hg) was greater ($P < 0.05$) than for the Wistar control group (110 ± 6.1 mm Hg).

Discussion. The results of this study suggest that spontaneously hypertensive rats (SHR) display elevated basal serum levels of TSH and PRL exaggerated TSH and PRL resplases to TRH. These data cannot be explained by differences in thyroid status since the serum T_4 levels were similar to the SHR and control group, a finding in contrast with previous studies which reported significantly lower T_4 levels in the SHR (8, 9).

Although the baseline serum LH levels were not significantly different in SHR, the LH response to LHRH was significantly less

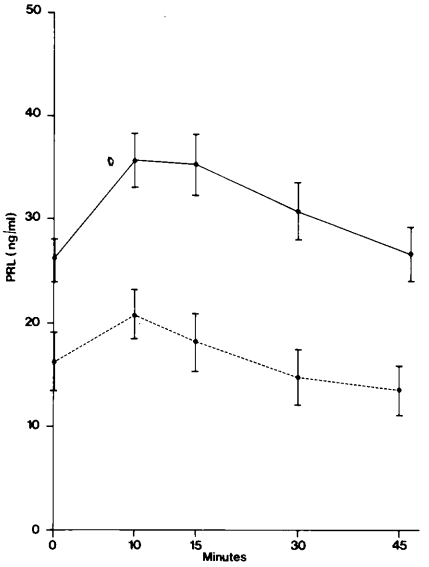

FIG. 2. Mean serum PRL responses to TRH (given at 0 time) in six spontaneously hypertensive rats (solid line) and in six normotensive Wistar-Kyoto rats (broken line); vertical bars show SEM.

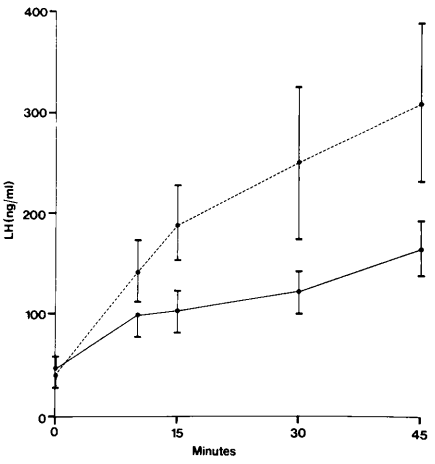

FIG. 3. Mean serum LH responses to LHRH (given at 0 time) in eight spontaneously hypertensive rats (solid line) and in 8 normotensive Wistar-Kyoto rats (broken line); vertical bars show SEM.

in the SHR than the controls. The composite findings of greater pituitary basal and stimulated TSH and PRL release and suppressed LH response to LHRH is consistent with altered central dopamine metabolism. Dopamine inhibits PRL and TSH release from the pituitary and has been reported to both stimulate and inhibit LH release under different experimental conditions (10–13). Thus, altered synthesis or turnover of dopamine in the hypothalamus of SHR could account for these observations. Although decreased levels of noradrenaline have been found in the hypothalamus of young SHR (14), there are no reports of hypothalamic dopamine levels nor dopamine turnover studies in the SHR.

Results of previous studies suggest that central dopaminergic activity may be involved in blood pressure regulation (15, 16). That the central dopaminergic system plays a direct role in blood pressure regulation is suggested by animal studies showing that the antihypertensive effect of L-dopa is associated with an accumulation of catecholamines in the cerebral parenchyma (15) and a decrease in central sympathetic outflow (16). It is thus possible that altered central dopaminergic activity in the SHR could contribute to the development of hypertension as well as the alterations in pituitary release of TSH, PRL and LH observed in this study.

Summary. The LH response to LHRH and the TSH and PRL response to TRH were examined in spontaneously hypertensive rats and normotensive control Wistar rats to determine if the pituitary response to these releasing hormones is altered in the hypertensive rats. Although basal levels of LH were similar in the two groups of rats, the LH response to LHRH was significantly less in the hypertensive rats than in the normotensive controls. The spontaneously hypertensive rats had higher basal levels of TSH and PRL and significantly greater TSH and PRL responses to TRH. The results of this study suggest that the hypothalamo-pituitary axis is altered in the spontaneously hypertensive rat.

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