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*CRITICAL REVIEW*

# MONOAMINERGIC REGULATION OF GROWTH HORMONE SECRETION IN RATS

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In recent years evidence has been accumulated which suggests an important role of brain biogemic amine in regulating the secretion of growth hormone (GH) in man and animals. However, the exact mechanism by which brain monoamines participate in regulating GH secretion remains unclear. To study further these problems, proper animal models are required, although species differences must be always considered. In this article, I want to describe the effect of various drugs which may affect brain monoamines on plasma GH levels in rats with hypothalamic surgery and to discuss possible roles of monoamines in the regulation of GH secretion.

*The Rat as an Animal Model for Studying the Regulation of GH Release.*

Although primates are the most preferable animal model for the study of the regulatory mechanism of pituitary hormone secretion, they are expensive and usually difficult to be handled. Rats have been used in this field due to several advantages, especially availability of radioimmunoassay of GH and easiness of handling. One of the difficulties in studying the regulation of GH secretion in rats is the remarkable variability from animal to animal in plasma GH levels, when they are decapitated while awake.[34,37] Kato et al.[26] have demonstrated that plasma rat GH showed the lowest basal values with least variability under urethane anesthesia. We confirmed this observation and, therefore, all experiments in the present study were performed under urethane anesthesia according to the experimental procedure shown in Table 1.

Table 1 Experimental protocol.

| Time | Event |
|---|---|
| −30 min | Intraperitoneal injection of urethane (150 mg/100 g, body wt.) |
| −15 min | Preparation of the jugular vein |
| − 1 min | Withdrawal of pretreatment blood sample from the right jugular vein |
| 0 min | Injection of test material into the left jugular vein |
| 10 min | Withdrawal of the second blood sample from the right jugular vein |
| 20 min | Withdrawal of the third blood sample |
| 40 min | Withdrawal of the fourth blood sample |

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Plasma rat GH was measured by specific radioimmunoassay using talcum powder (Table 2) which is detectable as little as 1.0 ng/ml of rat GH (Fig. 1).

Table 2 Radioimmunoassay procedure of rat GH.

Using 1.5×10.5 cm test tubes, the following solution are added in order and mixed by gentle shaking.

0.2 ml 2% BSA in Phosphosaline (pH 7.6)
0.1 ml Hypophysectomized Rat Plasma (or Sample)
0.1 ml Rat GH Reference Preparation (or Buffer only)
0.1 ml Anti-Rat GH Serum

Incubation at 4° C for 24 hrs.

0.1 ml $^{125}$I-Rat GH

Incubation at 4° C for 72 hrs.

0.2 ml Human Pooled Serum
1.7 ml Talc Solution (200 mg in 0.07 M Barbital Buffer, pH 8.6)

Mixture of the content.
Centrifugation at 2500 rpm for 30 minutes.
Decantation into the second set of numbered tubes.
Count of both supernatants and precipitates in the auto gamma-counter.

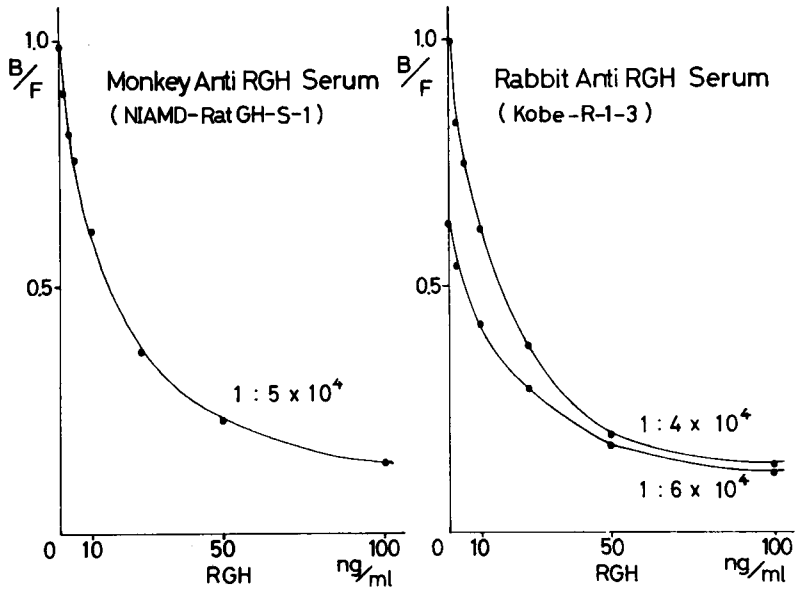


Fig. 1 Typical standard curves of radioimmunoassay for rat GH using two different antisera. Anti-rat GH serum (Kobe-R-1-3) was produced in a rabbit by weekly injections of rat GH (NIAMD-RatGH-B-1) with complete Freund's adjuvant. NIAMD-RatGH-I-1 and NIAMD-RatGH-RP-1 were used for iodination with $^{125}$I and as reference preparation, respectively.

*Effects of Various Catecholaminergic Agents on Rat GH Release.*

Stimulating and inhibiting effects of various adrenergic agents on plasma GH suggest the participation of the catecholaminergic mechanism in the regulation of GH secretion in the rat,[27] although adrenergic receptor mechanisms were reciprocal between the rat and man.[3, 4, 9]

We observed that the intravenous injection of isoproterenol, a beta-adrenergic stimulating agent, raised plasma GH, which was inhibited by propranolol, a beta-adrenergic blocking agent, in the rat (Fig. 2). These findings are in agreement with the previous report.[27] In contrast, propranolol stimulates GH secretion in man.[9, 20]

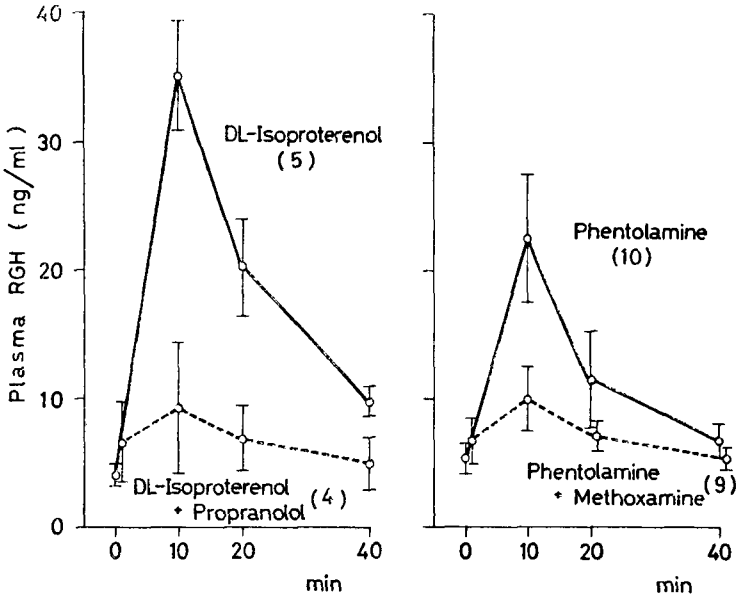


Fig. 2 The left panel shows effect of isoproterenol (50 μg/100 g, iv) alone or with propranolol (200 μg/100 g, iv) on plasma rat GH. The right panel shows effect of phentolamine (500 μg/100 g, iv) alone or with methoxamine (500 μg/100 g, iv) on plasma rat GH. Means±SE are shown. The number of animals in each group is indicated in parentheses.

The intravenous injection of phentolamine, an alpha-adrenergic blocking agent, caused a significant increase in plasma GH in the rat, which was suppressed by methoxamine (Fig. 2) and phenylephrine,[27] alpha-adrenergic stimulants, whereas phentolamine inhibited GH release in man.[9]

Chlorpromazine (CPZ) administration depresses GH secretion in man.[30, 35] We[23] confirmed, however, that intravenous injection of CPZ in the rat caused a significant and dose-related increase in plasma GH,[27] as shown in Fig. 3. CPZ is

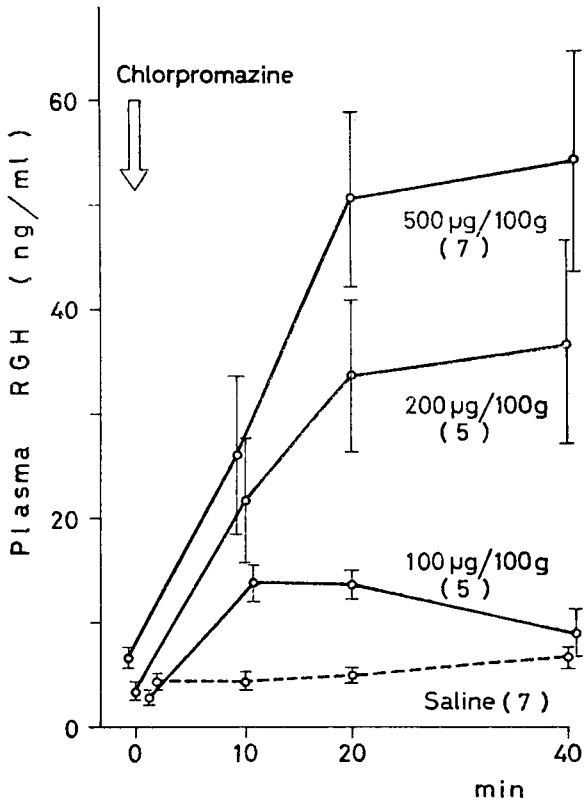


Fig. 3 Plasma rat GH responses to intravenous injections of varying doses of chlorpromazine (CPZ). Means±SE are shown. The number of animals in each group is indicated in parentheses.

known to block dopamine receptors[28, 31] and alpha-adrenergic receptors in the central nervous system.[8] As shown in Fig. 4, we observed that stimulation of GH release by CPZ was significantly inhibited by the concomitant injection of either phenylephrine, alpha-adrenergic stimulant, or L-dihydroxyphenyl alanine(L-dopa), a precursor of dopamine. The suppressive effect of L-dopa on CPZ-induced GH release is in agreement with the previous report[27] and also support the observation that the intraventricular injection of dopamine depressed plasma GH levels in rats.[13] It is possible, therefore, that stimulation of GH secretion by CPZ in the rat is caused through the blockade of dopaminergic or alpha-adrenergic receptors.

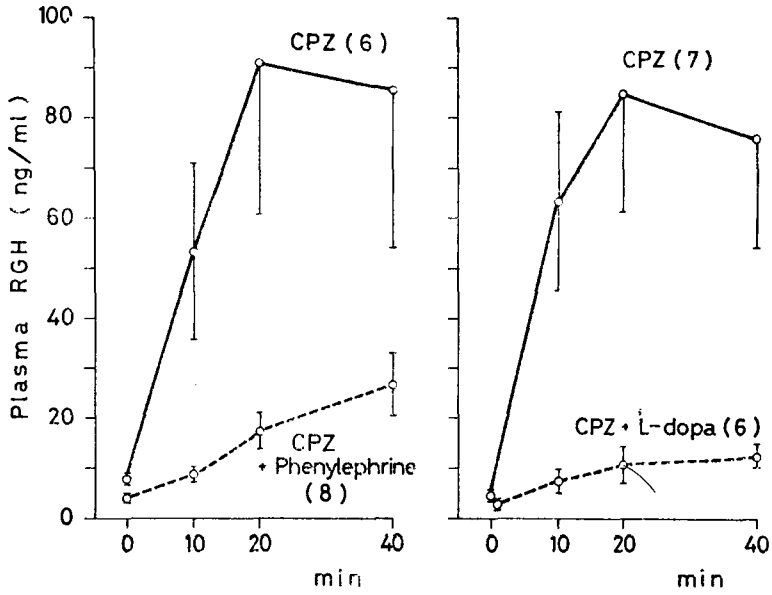


Fig. 4 Effect of phenylephrine (30 $\mu$g/100 g, iv) (left panel) and L-dihydroxyphenylalanine (L-dopa, 1 mg/100 g, iv) (right panel) on plasma rat GH rises induced by CPZ (200 $\mu$g/100 g, iv), respectively. Means±SE are shown. The number of animals in each group is indicated in parentheses.

*Effects of Central Catecholamine and Serotonin Depletors on Plasma Rat GH Response to CPZ.*

Plasma rat GH response to CPZ was significantly blunted after the pretreatment with reserpine or alpha-methyl-p-tyrosin ($\alpha$-MT) in our studies (Fig. 5). Reserpine depletes both catecholamines and serotonin in the brain.[16] $\alpha$-MT inhibits the action of tyrosine hydroxylase, the rate-limiting enzyme in the biosynthesis of brain catecholamines, thus depleting dopamine and norepinephrine in the central nervous system.[36]

In contrast, we observed that CPZ-induced increases of plasma rat GH were not suppressed either by the simultaneous injection of 5-hydroxytryptophan (5-HTP), a precursor of serotonin, nor by pretreatment with para-chlorphenylalanine (PCPA), an inhibitor of tryptophan hydroxylase, which caused a decrease of brain serotonin levels[29] (Fig. 6).

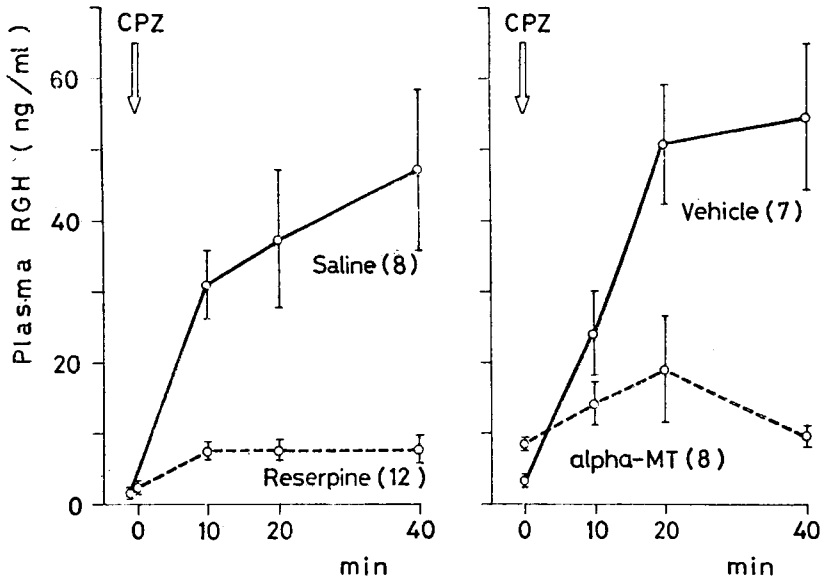


Fig. 5 Effect of reserpine (0.3 mg/100 g, ip, 17 h before CPZ injection) (left panel) and $\alpha$-methyl-p-tyrosine ($\alpha$-MT, 10 mg/100 g, ip, 16, 12 and 6 h before CPZ injection) (right panel) on plasma rat GH rises induced by CPZ (500 $\mu$g/100 g, iv), respectively. Means±SE are shown. The number of animals in each group is indicated in parentheses.

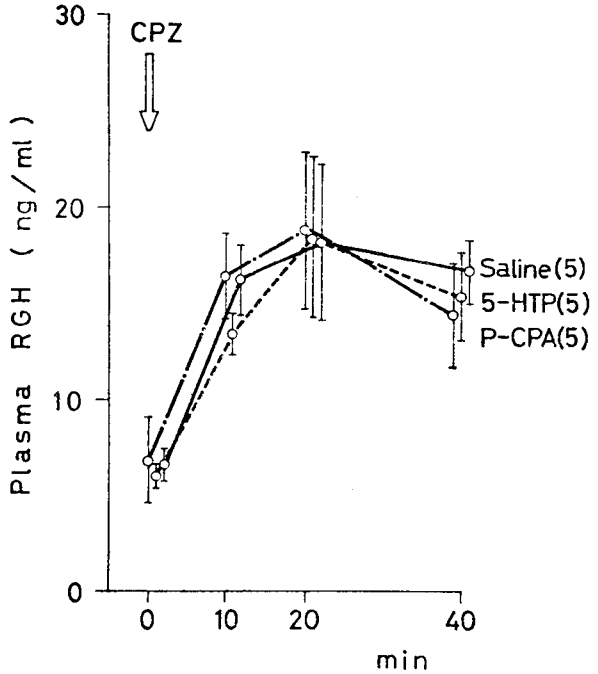


Fig. 6 Effect of para-chlorphenylalanine (PCPA, 15 mg/100 g, ip, 40 and 16 h before CPZ injection) and 5-hydroxytryptophan (5-HTP, 5 mg/100 g, ip, 16 and 3 h before CPZ injection) on CPZ (200 $\mu$g/100 g, iv)-induced rat GH release. Means±SE are shown. The number of animals in each group is indicated in parentheses.

These findings suggest that catecholamines, but not serotonin, in the brain are involved in CPZ-induced rat GH secretion.

*Effects of Hypothalamic Surgeries on Plasma GH Responses to CPZ.*

In order to study further the site of action of CPZ, the medical basal hypothalamus (MBH) was stereotaxically deafferentated or ablated and then plasma GH responses to CPZ was studied.

Deafferentation of the MBH was performed with a modification of the Halàsz's knife[17] (1.5 mm lateral×1.5 mm vertical), as described previously.[9, 23] Complete ablation of the MBH was performed by a modification[10, 23] of the method described by Arimura et al.,[2] using a stirrup-shaped knife (3.0 mm diameter×2.0 mm vertical) to interrupt the vascular supply from the ventral surface of the brain.

We observed that rats with hypothalamic deafferentations (complete, anterior and antero-lateral cuts) showed higher basal levels and greater responses of plasma GH to CPZ compared with results in sham-operated control rats[9, 23] (Fig. 7).

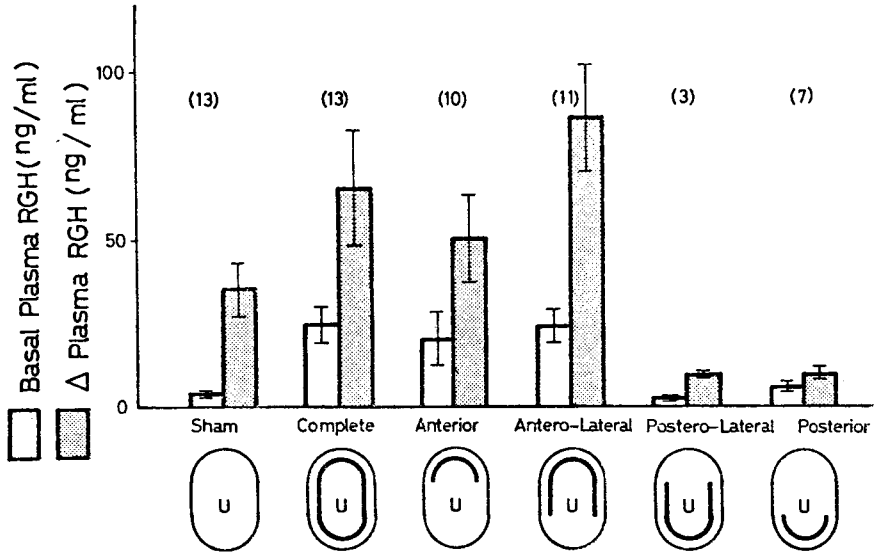


Fig. 7 Effects of various hypothalamic cuts on basal levels of plasma rat GH and the maximum increments of plasma rat GH (△RGH) after injection of CPZ (200 μg/100 g, iv). Means±SE are shown. The number of animals in each group is indicated in parentheses.

In contrast, plasma GH responses to CPZ were smaller in rats with posterior and postero-lateral cuts than in control rats. These results suggested the existence of the extrahypothalamic influences on the regulation of rat GH secretion: the inhibitory influence on GH secretion reaches the MBH through anterior neural pathways, whereas the stimulating influence possibly reaches from the posterior.

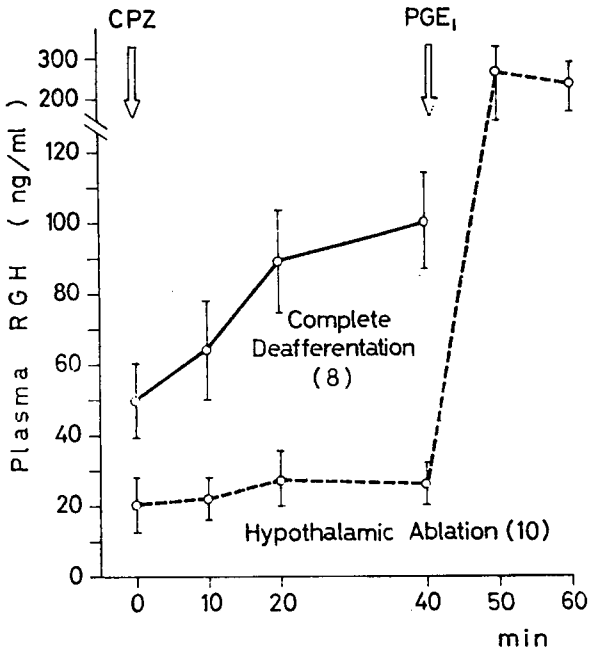


Fig. 8 Plasma GH responses to CPZ (200 $\mu$g/100 g, iv) in rats with complete deafferentation and ablation of the hypothalamus. In rats with hypothalamic ablation, prostaglandin $E_1$ ($PGE_1$, 5 $\mu$g/100 g, iv) was given at 40 min after CPZ injection. Means±SE are shown. The number of animals in each group is indicated in parentheses.

Our findings that CPZ injection caused GH release even in rats with the MBH neurally isolated from the surrounding hypothalamus suggest that CPZ acts either on the isolated island of MBH or on the pituitary or both. However, plasma GH responses to CPZ were significantly blunted in rats with extensive hypothalamic ablation[9, 23] (Fig. 8). The pituitary gland is considered to be functionally intact in these animals since prostaglandin $E_1$ raised plasma GH in rats with hypothalamic ablation, probably by acting directly on the pituitary gland. These results strongly suggest that CPZ acts at the level of the MBH in regulating rat GH release.

*Effects of Drugs Influencing Brain Catecholamine Levels on Rat GH Release.*

In order to examine further the relationship between hypothalamic catecholamines and rat GH release, $\alpha$-MT, a central depletor of catecholamines, was administered into rats with complete deafferentation or ablation of the hypothalamus and in control rats with sham operation.

In our studies,[10] pretreatment with $\alpha$-MT caused significant increases of plasma GH in rats with complete deafferentation as well as sham operation (Fig. 9),

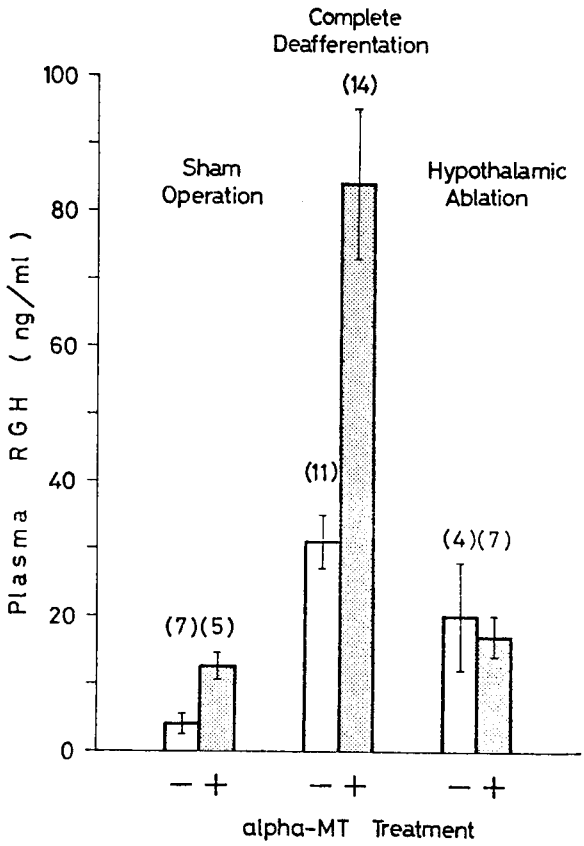


Fig. 9 Effects of pretreatment with $\alpha$-MT (10 mg/100 g, ip, 16, 12 and 6 h before blood sampling) on plasma rat GH in rats with sham operation, complete deafferentation and hypothalamic ablation. Means±SE are shown. The number of animals in each group is indicated in parentheses.

supporting the hypothesis that catecholamines in the MBH are involved in the secretion of GH in rats. Since norepinephrine, but not dopamine, is known to decrease considerably in the MBH isolated by deafferentation,[21, 38] the stimulating effect of $\alpha$-MT on plasma GH may be explained by the depletion of dopamine which is assumed to inhibit GH secretion. The important role of depamine of the MBH in regulating GH release was further endorsed by our findings[10] that markedly elevated levels of plasma GH in $\alpha$-MT pretreated rats with complete deafferentation were decreased following the injection of L-dopa, but not by DL-erythro-dihydroxyphenylserine (DL-dops) (Fig. 10). Since L-dopa restores dopamine and norepinephrine levels[14] and

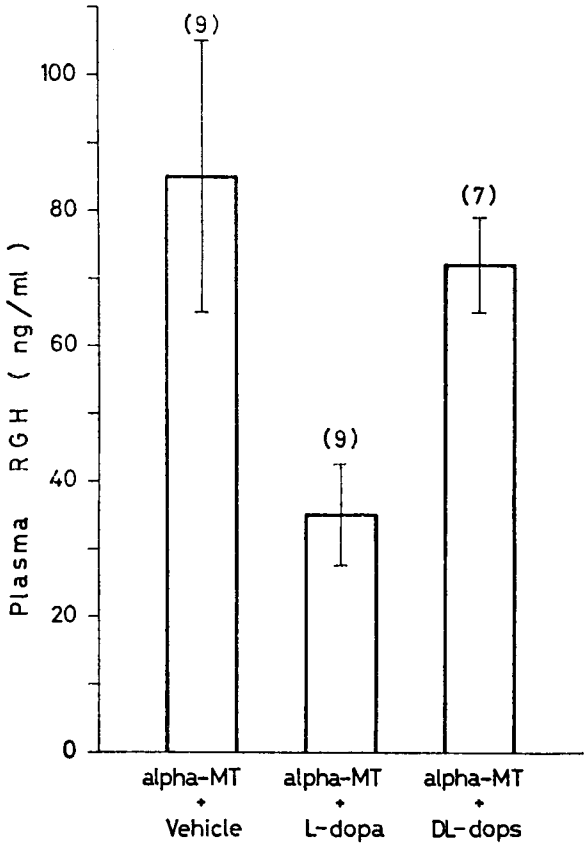


Fig. 10 Effects of L-dopa (20 mg/100 g, ip, 2 h before blood sampling) and DL-erythro-dihydroxyphenylserine (DL-dops, 10 mg/100 g, ip, 2 h before blood sampling) on plasma GH levels in completely deafferentated rats with $\alpha$-MT pretreatment. Mean±SE are shown. The number of animals in each group is indicated in parentheses.

DL-dops is postulated to restore only the norepinephrine content,[15] we can assume that dopamine has a tonic inhibitory influence on GH secretion in rats and that CPZ stimulates GH release by antagonizing the action of dopamine.

*Effects of Somatostatin (GIF) and Thyrotropin-Releasing Hormone (TRH) on Rat GH Release Induced by CPZ.*

GH secretion from the pituitary has been believed to be regulated by dual mechanisms, namely GH releasing factor (GRF) and GH inhibiting factor (GIF), somatostatin. The structure of GRF and its localization in the brain have not been clarified yet, whereas somatostatin has been isolated from the hypothalamus of the sheep and identified as a tetradecapeptide.[5]

As shown in Fig. 11, we observed that somatostatin inhibited plasma GH responses to both CPZ and isoproterenol.[23, 24] Since somatostatin was reported to be localized in nerve endings mainly in the median eminence and the ventromedial nucleus, and in nerve cell bodies of the supraoptic area of the hypothalamus,[1,18,32] stimulation of GH release induced by CPZ and isoproterenol may be caused by a decrease of somatostatin release from the hypothalamus. However, the possibility that GRF is the mediator of the hypothalamus in GH release induced by these agents can not be ruled out completely.

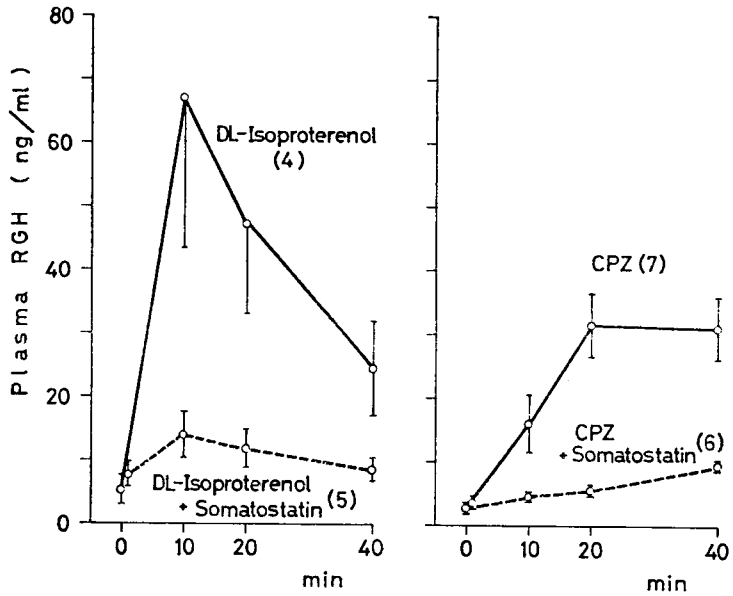


Fig. 11 Effects of somatostain (5 $\mu$g/100 g, iv) on plasma rat GH responses to isoproterenol (100 $\mu$g/100 g, iv) or CPZ (100 $\mu$g/100 g, iv). Means±SE are shown. The number of animals in each group is indicated in parentheses.

Very recently, the role of thyrotropin-releasing hormone (TRH) in regulating GH release in rats was proposed.[11, 12, 22] We observed that the intravenous injection of TRH caused a dose-related increase in plasma GH in a range from 0.04 to 3 $\mu$g /100 g body wt in rats.[22] TRH stimulates GH release in the rat by possible direct action on the pituitary gland, since enhancement of GH release by TRH was observed even in rats with extensive hypothalamic ablation in our studies.[11] We also found that plasma GH responses to the intravenous injection of CPZ (200 $\mu$g/100 g body wt) were significantly augmented by the concomitant intravenous injection of TRH in a dose of 3 $\mu$g/100 g body wt (Fig. 12). However, a larger dose of TRH (25 $\mu$g/100 g

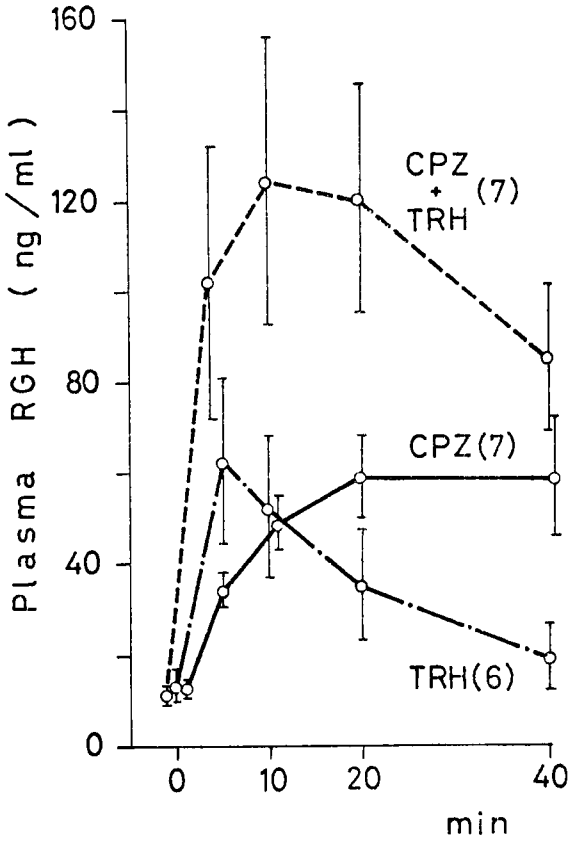


Fig. 12 Plasma GH responses to TRH (3 μg/100 g, iv), TRH with chlorpromazine (200 μg/100 g, iv) and chlorpromazine alone in rats. Means±SE are shown. The number of animals in each group is indicated in parentheses.

body wt) injected intravenously with CPZ caused a significantly smaller increase in plasma GH than did smaller doses of TRH (0.2 and 3 μg/100 g body wt) with CPZ[11] (Fig. 13). Furthermore, we demonstrated that TRH in relatively smaller doses (0.02 and 0.2 μg/100 g body wt) injected into the lateral ventricle significantly inhibited CPZ-induced GH release[11] (Fig. 14). Brown and Vale[7] have also reported that plasma GH rise induced by morphine and pentobarbital was inhibited by TRH *in vivo*, although TRH failed to inhibit prostaglandin $E_1$ induced GH release from enzymatically dispersed anterior pituitary cells *in vitro*. These results suggest that TRH exerts its inhibitory action on GH release through the central nervous system.

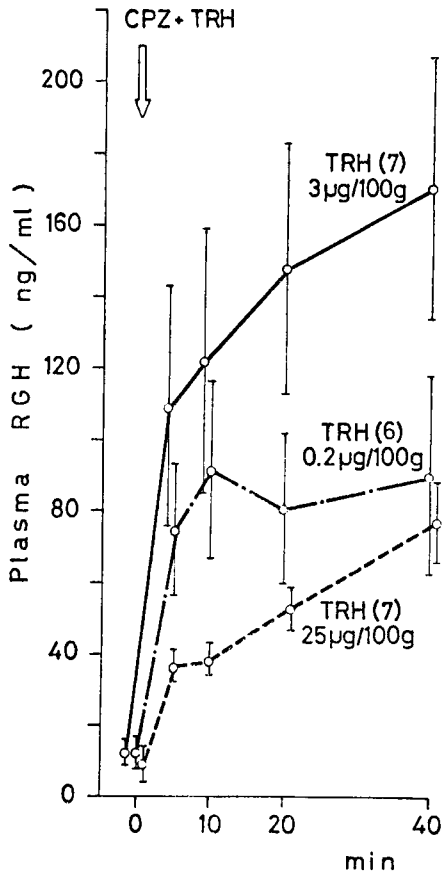


Fig. 13 Plasma rat GH responses to intravenous injections of different doses of TRH (3 and 25 $\mu$g/100 g) with CPZ (200 $\mu$g/100 g, iv). Means$\pm$SE are shown. The number of animals in each group is indicated in parentheses.

The exact mechanism by which TRH inhibits CPZ-induced GH secretion remains to be investigated. CPZ caused GH release, possibly by antagonizing the dopaminergic neurons or receptors in the MBH.[10, 17, 20] TRH enhanced the behavioral effects of L-dopa in pargyline treated mice[33] and stimulated the conversion of L-$^{14}$C-tyrosine to $^{14}$C-norepinephrine.[28] It is possible, therefore, that TRH stimulates catecholamine synthesis and/or enhances the action of catecholamines in the hypothalamus, thus leading to an inhibition of GH secretion in rats. An alternate explanation is that TRH may act through the cholinergic mechanisms. The inhibitory effect of TRH on pentobarbital induced sleep and hypothermia was known to be blocked by atropine.[6] Since nicotine, a cholinergic agent, showed an inhibitory effect on GH secretion in rats in our studies,[25] cholinergic mechanisms may participate in the inhibition of GH release by TRH.

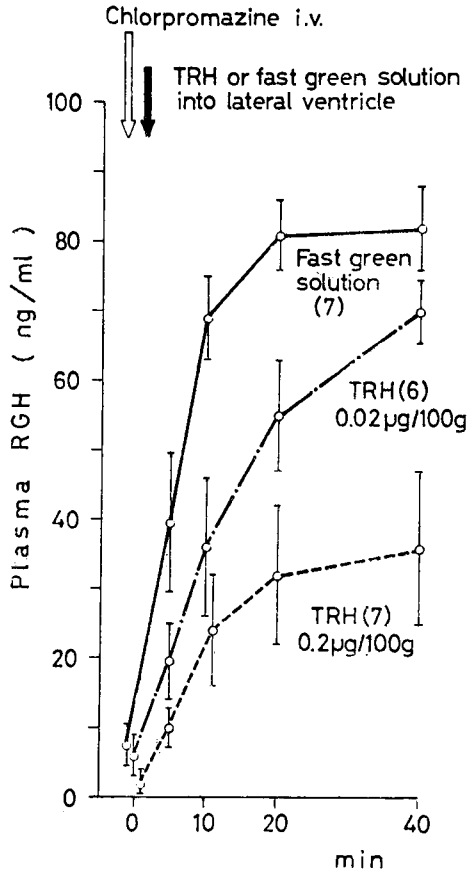


Fig. 14 Effect of intraventricular injection of TRH (0.02 and 0.2 $\mu$g/100 g) on plasma rat GH release induced by CPZ (200 $\mu$g/100 g, iv). Mean$\pm$SE are shown. The number of animals in each group is indicated in parentheses.

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