Increased Somatostatinergic Activity Induced by Acute Hyperglycemia is Not Mediated by Stimulation of the Beta-adrenergic System

Seungjae Hong, M.D., **Inmyung Yang**, M.D., **Gyuchoon Lee**, M.D., **Jeongtaek Woo**, M.D., **Sungwoon Kim**, M.D., **Jinwoo Kim**, M.D., **Youngseol Kim**, M.D., and **Youngkil Choi**, M.D.

Division of Endocrinology, Department of Internal Medicine, Kyunghee University School of Medicine, Seoul, Korea

급성 고혈당에 의해 유도된 시상하부성 소마토스타틴의 증가와 베타 아드레날린계의 상호작용에 관한 연구

경희대학교 의과대학 내과학교실 내분비연구소

홍승재 · 양인명 · 이규춘 · 우정택 · 김성운 · 김진우 · 김영설 · 최영길

국 문 초 록

연구배경: 급성 고혈당은 시상하부에서 소마토스타틴의 분비를 증가시키고, 소마토스타틴은 뇌하수체 전엽에 작용해서 성장호르몬의 분비를 억제시키는 것으로 알려져 있다. 하지만 고혈당이 시상하부에서 분비되는 소마토스타틴의 분비를 증가시키는 기전은 아직까지 알려져있지 않다. 한편, 베타-아드레날린계는 시상하부에서 소마토스타틴의 분비를 자극하는 것으로 알려져 있다. 이에 저자들은 고혈당에 의해 유발된 시상하부성 소마토스타틴의 분비 증가가 베타-아드레날린계의 자극에 의해 매개된다는 가정하에 베타차단제를 사용하여 고혈당에 의한 시상하부성 소마토스타틴의 분비를 억제시킬 수 있는지 알아보았다.

방법: 대상군은 10명의 건강한 성인 남자를 대상으로 하였으며 비만이나 당뇨병이 있는 경우는 없었다.

방법은 각각 4가지 검사를 시행하였는데, 검사 1은 검사시작시 100 μg의 성장호르몬 분비자극 호르몬의 투여하고 3시간에 걸쳐서 매 10분간격으로 혈액검사를 하여 혈중 포도당과 성장호르몬을 측정하였고, 검사 2는 검사시작 30분전에 포도당 75g을 먹인후 검사 1과 동일하게 하였고, 검사 3은 베타차단제인 propranolol(0.2 mg/kg)을 검사시작 60분전부터 120분 까지 3시간에 걸쳐서 점적주사 하면서 검사 1을 시행하였고, 검사 4는 propranolol과 포도당을 검사 2와 3처럼 투여후 혈중 포도당과 성장호르몬의 변화를 측정하였다.

결과: 포도당 경구투여한 검사 2에서는 검사 1과 비교하였을 때 유의성있게 성장호르몬분비가 억제되어 있었고, porpranolol을 점적주사한 검사 3에서는 성장호르몬이 유의성있게 증가되어, 각각 시

각 시상하부성 소마토스타틴의 분비가 증가되거나 억제되었음을 알수 있었다.

두 약제를 같이 투여한 검사 4에서는 성장호르몬의 분비가 검사 2와 별차이가 없어 propranolol의 전처치가 급성 고혈당에 의한 성장호르몬 분비억제를 회복시키지 못하는 것으로 밝혀졌다.

결론: 급성 고혈당에 의해 유발된 시상하부성 소마토스타틴의 분비증가는 베타-아드레날린계를 통하지 않는 것으로 사료된다. (대한내분비학회지 11:383-390, 1996)

Key Words: 급성고혈당, 뇌하수체분비성 소마토스타틴, 베타차단제

INTRODUCTION

Acute hyperglycemia suppresses basal growth hormone(GH) secretion[1~3] and GH response to growth hormone-releasing hormone(GHRH)[4~6] in normal subjects. The latter effect is reverted by the administration of pyridostigmine[7], a cholinesterase inhibitor, which is known to suppress the hypothalamic somatostatin(SRIH) release[8~13]. Those studies suggest that acute hyperglycemia stimulates the SRIH release from the hypothalamus, and the SRIH release may be mediated by cholinergic pathway. However, the SRIH-containing nerve fibers, which are located mainly in the anterior hypothalamic periventricular system, receives a variety of neural inputs from the principal ascending monoaminergic systems[14,15]. Thus, the possibility remains to be excluded that the other monoaminergic pathways are involved in the glucose-induced SRIH release

Among the monoaminergic pathways, beta-adrenergic pathway deserves to be considered as a candidate. Propranonol, a beta-adrenergic receptor antagonist, exaggerates GH release induced by hypoglycemic stress[16], exercise[17], glucagon[18], and GHRH[19, 20] in humans. It inhibits the SRIH release from the hypothalamus in conscious rabbits[21] and in the dispersed rat hypothalamic cells[22]. These studies suggest that beta-adrenergic pathway stimulates the hypothalamic SRIH release. Therefore, we investigated whether the glucose-induced SRIH release is mediated by the stimulation of central beta-adrenergic system.

MATERIALS AND METHODS

1. Subjects

Ten healthy young men, aged 20 to 24 years, were enrolled after getting informed consents from the subjects and an approval from an ethical committee at Kyung Hee University Hospital. All the subjects had not been on any medication at least two weeks prior ot the study and were not obese. Their mean body weight was 65.5±3.5 kg and their mean body mass index was 21.3±0.5 kg/m^2. None of them had a family history of diabetes mellitus or obesity.

2. Endocrine tests

Four tests were carried out as below in random order on four separate occasions at least one week apart. The subjects were fasted from midnight until completion of each test. The tests commenced at 0900 h. An indwelling venous cannula was placed into a forearm vein an hour prior to the first collection of blood sample at - 90 min and kept open with a slow infusion of 0.9% NaCl for sampling. Each subject remained sitting in a chair comfortably throughout the tests. They were allowed to read news papers or magazines during the tests. No one was allowed to sleep during the tests. Blood was collected every 10 min during each test(Test 1). GHRH (Bachem, CA, U.S.A.), 100 μg bolus, was given

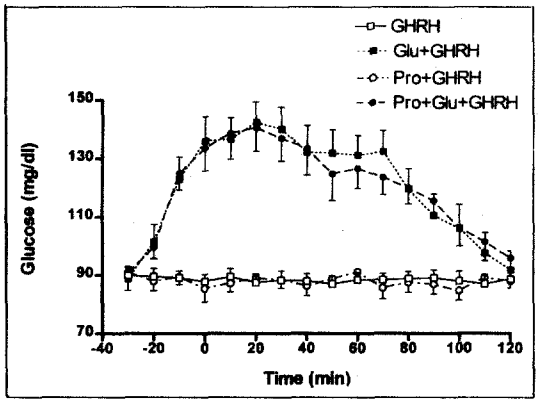

Fig. 1. Changes of the plasma glucose concentration. The open and closed squares denote the plasma glucose concentrations in Test 1 and Test 2, respectively. The open and closed circles depict those in Test 3 and Test 4, respectively. The data represent mean±S.E.

intravenously at 0 min(Test 2). Glucose, 75 gm dissolved in cold water, was given orally at -30 min and GHRH was administered as Test 1(Test 3). Propranonol(Inderal, ICI, U.K.), 0.2 mg/kg, was continuously infused between -60 min and 120 min, and GHRH was administered as Test 1(Test 4). Propranolol(inderal), 0.2 mg/kg, was continuously infused between -60 min and 120 min, and glucose and GHRH were administered as Test 2.

3. Assays and Statistics

Plasma was separated immediately and frozen at -20℃ until assays. Plasma glucose was measured by a glucose autoanalyzer using glucose oxidase method. The plasma GH concentration was determined by a commercial immunoradiometric assay kit(Nichols Institute Diagnostics, California, U.S.A.). The sensitivity was 0.02 μg/L, the intraassay variation 3.3% and the interassay variation 5.1%. Data were expressed as mean ± SE. Statistical comparisons were made by one-way repeated measures analysis of variance. All statistical analyses were performed by using a statistical software(GraphPad Prism,

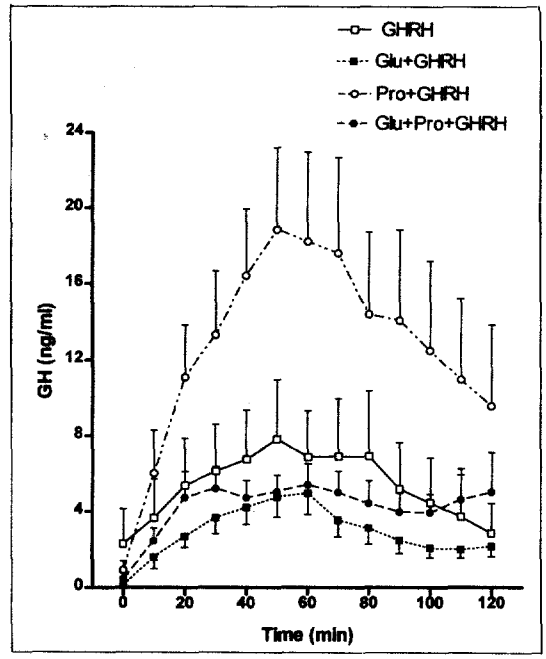

Fig. 2. Changes of the plasma GH concentration. The open and closed squares denote the plasma GH concentrations in Test 1 and Test 2, respectively. The open and closed circles depict those in Test 3 and Test 4, respectively. The data represent mean±S.E.

GraphPad Software, Inc, CA, USA). Significance was defined as $p<0.05$.

RESULTS

No significant change in the plasma glucose concentration was noted after GHRH administration(Fig. 1). Administration of GHRH induced a significant increment in the GH level with a peak of 7.83±2.97 μg/L at 50 min in Test 1(Fig. 2).

In Test 2, the oral glucose administration induced a peak plasma glucose concentration of 142±7 mg/dl at 20 min, which was significantly higher than that (87 ±3 mg/dL) in Test 1(Fig. 1). The acute hyperglycemia significantly suppressed the peak of GHRH-induced GH secretion(4.98±1.07 μg/L vs. 7.83±2.97

μg/L, $p<0.05$)(Fig. 2).

In Test 3, the propranolol pretreatment did not affect the plasma glucose concentration(Fig. 1). In contrast, it significantly increased the GHRH-induced GH levels between 30 and 120 min($p<0.05$), with a peak of 18.87 ± 4.13 μg/L at 50 min, compared to those in Test 1(Fig. 2).

However, the propranolol pretreatment did not revert the suppression of GHRH-induced GH secretion by glucose in Test 4. The mean of GH peak did not differ significantly from that in Test 1(5.41 ± 1.05 μg/L vs. 4.98 ± 1.07 μg/L)(Fig. 2).

DISCUSSION

Although it is well known that acute hyperglycemia not only suppresses basal GH secretion but suppresses the GHRH-stimulated GH release, the mechanism how acute hyperglycemia suppresses the GH secretion is not clear. Penalva et al.[7] demonstrated that pyridostigmine, a cholinesterase inhibitor, reverts the suppression by glucose of GHRH-induced GH secretion and hyperglycemia is unable to reduce the potentiating effect of pyridostigmine on the GHRH-induced GH release. The study suggests that acute hyperglycemia suppresses the GH release from the anterior pituitary gland by inducing the hypothalamic SRIH release.

Since the hypothalamic SRIH release is under the controls of various inputs from other parts of the central nervous system, other monoaminergic pathways may involve in the regulation of SRIH release. In fact, Richardson and Twente[22] demonstrated that propranolol, a beta-adrenergic antagonist, augments GH response by inhibiting the hypothalamic SRIH release from the dispersed hypothalamic cells of rats. Although the study suggests that the beta-adrenergic pathway can stimulate the hypothalamic SRIH release, it has not yet been investigated whether the glucose-induced SRIH release is mediated by the the beta-adrenergic pathway.

The remarkable increase of GH level after propranolol pretreatment indicated that propranolol successfully blocked beta-adrenergic receptors of the hypothalamus, which in turn inhibited the somatostatin release. The present study demonstrates that the pretreatment with propranolol can not revert the suppressive effect of glucose on the GHRH-induced GH secretion. It suggests that the glucose-induced SRIH release is not mediated by the beta-adrenergic pathway. This conclusion needs to be proved further by demonstrating that a beta-adrenergic agonist has an additive effect on the suppressive effect of glucose on the GHRH-induced GH secretion.

If it is the case, the combined treatment with propranolol and glucose can be used as a potent stimulation test for the evaluation of the hypothalamic somatostatin release. This study also suggests that the pathway that mediates the glucose-induced somatostatin release palys more important role in the regulation of the hypothalamic somatostatin release than beta-adrenergic pathway. It remains to be determined which pathway mediates the glucose-induced hypothalamic SRIH release. Pulsatile GH secretion is regulated by the interaction between GHRH and SRIH. Both of them are under the controls of a variety of neurotransmitters.

The alpha-adrenergic system is known to stimulate GH secretion by enhancing the release of GHRH [23,24]. No evidence is reported that the alpha-adrenergic pathway stimulates the hypothalamic SRIH release. On the contrary, it has been demonstrated that central alpha 2-adrenergic blockade causes suppression of the release of hypothalamic GHRH and enhanced release of endogenous somatostatin, and hypothalamic GHRH neurons may show a more sensitive response to alpha 2-adrenergic blockade than somatostatin neurons[25]. Other studies reported

that an alpha 2-adrenergic agonist enhances the GH response to GHRH through an inhibition of hypothalamic somatostatin release in men[26,27]. Therefore, alpha 2-adrenergic pathway is less likely to mediate the glucose-induced somatostatin release.

Dopamine is known to stimulate the SRIH release in vitro from the rat hypothalamus[28,29], dispersed hypothalamic cells[30], median eminence[31], or mediobasal hypothalamus[32,33]. Intraventricular administration of dopamine also enhances somatostatin release into the rat hypophyseal portal blood[34]. Although there is no evidence that glucose induces the hypothalamic dopamine release, the possibility can not be excluded by this study.

A large body of both direct and circumstantial evidence has established that acetylcholine regulates the GH secretion by tonically inhibiting the hypothalamic SRIH release in vitro[35] and in vivo[36~38].

Earlier studies[7,39] demonstrated that pyridostigmine completely counteracted the inhibitory action of glucose on GH release and hyperglycemia was unable to reduce GH secretion elicited by pyridostigmine. Those studies suggest that the glucose-induced hypothalamic SRIH release may be mediated by cholinergic pathway. One might speculate that acute hyperglycemia suppresses cholinergic inhibition of the hypothalamic SRIH release. The hypothesis needs to be tested in future.

The link between the hypothalamic glucose sensor and the SRIH containing neurons is unknown, as is the precise location of the cholinergic interneuron with respect to these two structures. Investigation also need to be done in future to clarify the neuronal connection between the cholinergic regulatory system and the somatostatin neuron.

CONCLUSION

The present study demonstrates that the pretreatment with propranolol can not revert the suppressive effect of glucose on the GHRH-induced GH secretion. It suggests that the glucose-induced SRIH release is not mediated by the beta-adrenergic pathway. This conclusion needs to be proved further by demonstrating that a beta-adrenergic agonist has a synergistic effect on the suppression by glucose of GHRH-induced GH secretion.

CONDENSATION

Background and Objectives: Acute hyperglycemia stimulates somatostatin(SRIH) release from the hypothalamus, and which in turn suppresses growth hormone(GH) secretion from the anterior pituitary gland. However, the mechanism by which glucose increases the hypothalamic SRIH secretion is unknown. Beta-adrenergic pathway is known to stimulate the hypothalamic SRIH release. We, therefore, hypothesized that the glucose-induced SRIH release may be mediated by the stimulation of central beta-adrenergic system, and investigated to determine whether the beta-adrenergic antagonist, propranolol, can revert the suppressive effect of glucose on the GHRH-induced GH secretion.

Subjects: Ten healthy young men, aged 20 to 24 years, were studied. None of them was obese.

Design: Test 1: GHRH, 100 μg bolus, was administered intravenously at 0 min. Test 2: Glucose, 75 g, was given orally at -30 min and GHRH was administered as Test 1. Test 3: Propranolol(Inderal), 0.2 mg/kg, was continuously infused between -60 min and 120 min, and GHRH was administered as Test 1. Test 4: Propranolol(Inderal), 0.2 mg/kg, was continuously infused as test 3, and glucose and GHRH were administered as Test 2.

Measurement: Blood was collected every 10 min for the determination of plasma glucose and GH concentration. Plasma GH level was measured by

radioimmunometric assay using monoclonal antibody, and plasma glucose level was measured by glucose oxidase method.

Results: Oral glucose ingestion significantly suppressed the GHRH-induced GH secretion. The pretreatment with propranolol significantly increased the GH levels between 20 and 100 min compared to those in Test 1. The pretreatment with propranolol could not revert the glucose-induced GH suppression in Test 4.

Conclusion: These data suggest that the increased hypothalamic somatostatinergic activity induced by oral glucose administration is not mediated the beta-adrenergic pathway in normal men.

Key Words: Hyperglycemia, SRIH, Beta-antagonist, Glucose-induced SRIH release

ACKNOWLEDGEMENT

I am very grateful to professor Inmyung Yang for his supervision, to the students at Kyunghee Medical School for their voluntary participation, and to Mr. Hokhang Jhang and Mr. Jeongrhyung Paeng for the technical assistance for GH radioimmunometric assay and measurement of plasma glucose.

REFERENCES

1. Jansz A, Doorenbos H, Reitsma WD: *Effect of food intake on growth-hormone level. Lancet 1: 250-251, 1963*
2. Yalow RS, Goldsmith SJ, Berson SA: *Influence of physiologic fluctuations in plasma growth-hormone on glucose tolerance. Diabetes 18:402-408, 1966*
3. Shibasaki T, Masuda A, Hotta M, Yamauchi N, Hizuka N, Takano K, Demura H, Shizume K: *Effects of ingestion of glucose on GH and TSH secretion: Evidence for stimulation of somatostatin release from the hypothalamus by acute hyperglycemia in normal man and its impairment in acromegalic patients. Life Sci 44:431-438, 1989*
4. Sharp PS, Foley K, Chahal P, Kohnor EM: *The effect of plasma glucose on the growth hormone response to human pancreatic growth hormone releasing factor in normal subjects. Clin Endocr 20:497-501, 1984*
5. Davies RR, Turner S, Johnsston DG: *Oral glucose inhibits growth hormone secretion induced by human pancreatic growth hormone releasing factor 1-44 in normal man. Clin Endocr 21:477-481, 1984*
6. Masuda A, Shibasaki T, Nakahara M, Imaki T, Kiyosawa Y, Jibiki K, Demura H, Ling N: *The effect of glucose on growth-hormone(GH)-releasing hormone-mediated GH secretion in man. J Clin Endocrinol Metab 60:523-526, 1985*
7. Penalva A, Burguera B, Casabiell X, Tresguerres J.A.F, Dieguez C, Casanueva F.F: *Activation of cholinergic neurotransmission by pyridostigmine reverses the inhibitory effect of hyperglycemia on growth hormone releasing hormone induced growth hormone seccretion in man: suggesting that glucose acts through hypothalamic release of somatostatin. Neuroendocrinol 49:551-554, 1984*
8. Ghigo E, Mazza E, Imperiale E, Rizzi G, Benso L, Muller E.E, Massara F: *Enhancement of cholinergic tone by pyridostigmine promotes both basal and growth hormone(GH)-releasing hormone-induced GH secretion in children of short stature. J Clin Endocrinol Metab 65:452-456, 1987*
9. Ross RJM, Tsagarakis S, Grossman A, Nhagafoong L, Touzel RJ, Rees LH, Besser GM: *GH feedback occurs through modulation of hypothalamic somatostatin under cholinergic*

control: Studies with pyridostigmine and GHRH. Clin Endocrinol 27:727-733, 1987

10. Freeman E, Trouzel R, Grossman A, Besser M, Ross R: *Pyridostigmine, an acetylcholinesterase inhibitor, stimulates growth hormone release, but has no effect on basal thyrotropin-releasing hormone. Neuroendocrinol 2:429-432, 1990*
11. Ghigo E, Bellone J, Mazza E, Imperiale E, Procopio M, Valente F, Lala R, DeSanctis C, Camanni F: *Arginine potentiates the GHRH-but not the pyridostigmine-induced GH secretion in normal short children: Further evidence for a somatostatin suppressing effect of arginine. Clin Endocrinol 32:763-767, 1990*
12. Kelijman M, Frohman L.A: *The role of the cholinergic pathway in growth hormone feedback. J Clin Endocrinol Metab 72:1081-1087, 1991*
13. Yang I, Woo J, Kim S, Kim J, Kim Y, Choi Y: *The combined pyridostigmine-TRH test for the evaluation of the hypothalamic somatostatinergic activity in healthy normal men. Eur J Endocrinol 133:457-462, 1995*
14. Reichlin S, Mothon S: *Carbamazepine and phenytoin inhibit somatostatin release from dispersed cerebral cells in culture. Ann Neurol 29:413-417, 1992*
15. Kakucska I, Makara GB: *Various putative neurotransmitters affect growth hormone(GH) release in rats with anterolateral hypothalamic deafferentation of the medial basal hypothalamus: evidence for mediation by a GH-releasing factor. Endocrinology 113:318-323, 1983*
16. Blackard WG, Heidingsfelder SA: *Adrenergic receptor control mechanism for growth hormone secretion. J Clin Invest 47:1407-1409, 1968*
17. Hansen AP: *The effect of adrenergic receptor blockade on the exercise-induced serum growth hormone rise in normals and juvenile diabetes. J Clin Endocrinol Metab 33:807-810, 1971*
18. Mitchell ML, Suvunrungsi P, Sawin CT: *Effect of the propranolol on the response of serum growth hormone to glucagon. J Clin Endocrinol Metab 32:470-475, 1971*
19. Chihara K, Kodama H, Kaji H, Kita T, Kashio Y, Okimura Y, Abe H, Fujzita T: *Augmentation by propranolol of growth hormone-releasing hormone-(1-44)-NH2-induced growth hormone release in normal short and normal children. J Clin Endocrinol Metab 61:229-233, 1985*
20. Kelijman M, Frohman LA: *Beta-adrenergic modulation of growth hormone(GH) autofeedback on sleep-associated and pharmacologically induced GH secretion. J Clin Endocrinol Metab 69:1187-1194, 1989*
21. Chihara K, Minamitani N, Kaji H, Kodama H, Kita H, Fujita T: *Noradrenergic modulation of human pancreatic growth hormone-releasing factor(hpGHRF1-44)-induced growth hormone release in conscious male rabbits: involvement of endogenous somatostatin. Endocrinology 114: 1402-1406, 1984*
22. Richardson SB, Twente S: *Inhibition of hypothalamic somatostatin release by β-adrenergic antagonists. Endocrinology 126:1043-1046, 1990*
23. Eden S, Eriksson E, Martin JB, Modigh K: *Evidence for a growth hormone releasing factor mediating alpha-adrenergic influence on growth hormone secretion in the rat. Neuroendocrinol 33:24-27, 1981*
24. Yasuhiro K, Yuzuru K, Yoshio M, Hiromitsu T, Hiroo I: *Stimulation by alpha-adrenergic mechanisms of the secretion of growth hormone releasing factor(GRF) from perifused rat hypothalamus. Endocrinology 119:432-434, 1986*
25. Minamitani N, Chihara K, Kaji H, Kodama H, Kita T, Fujita T: *Alpha 2-adrenergic control of growth hormone(GH) secretion in conscious male rabbits: Involvement of endogenous GH-releasing*

factor and somatostatin. Endocrinology 125: 2839-2845, 1989

26. Devesa J, Arce V, Lois N, Tresguerres JA, Lima L: *Alpha 2-adrenergic agonism enhanced the growth hormone(GH) response to GH-releasing hormone through an inhibition of hypothalamic somatostatin release in normal men. J Clin Endocrinol Metab 71:1581-1588, 1990*
27. Devesa J, Diaz MJ, Tresguerres JA, Arce V, Lima L: *Evidence that alpha 2-adrenergic pathways play a major role in growth hormone(GH) neuroregulation; alpha 2-adrenergic agonism counteracts the inhibitory effect of muscarinic cholinergic receptor blockade on the GH response to GH-releasing hormone, while alpha 2-adrenergic blockade diminishes the potentiating effect of increased cholinergic tone on such stimulation in normal men. J Clin Endocrinol Metab 73:251-256, 1991*
28. Bennett GW, Edwardson JA, Marcano De Cotte D, Berelowitz M, Pimstone B, Kronheim S: *Release of somatostatin from rat brain synaptosomes. J Neurochem 32:1127-1131, 1979*
29. Kitajima N, Chihara K, Abe H, Okimura Y, Fuji Y, Sato M: *Effects of dopamine on immunoreactive growth hormone-releasing factor and somatostatin secretion from rat hypothalamic slices perifused in vitro. Endocrinology 124:69-76, 1989*
30. Richardson SB, Greenleaf P, Hollander CS: *Somatostatin release from dispersed hypothalamic cells-effects of membrane depolarization, calcium and glucose deprivation. Brain Res 266: 75-81, 1983*
31. Negro-Vilar A, Ojeda SR, Arimura A, McCann SM: *Dopamine and norepineprine stimulate somatostatin release by median eminence fragments in vitro. Life Sci 23:1493-1496, 1978*
32. Maeda K, Frohman LA: *Release of somatostatin and thyrotropin -releasing hormone from rat hypothalamic fragments in vitro. Endocrinology 106:1837-1841, 1980*
33. Lewis BM, Dieguez C, Lewis M, Hall R, Scanlon MF: *Hypothalamic D2 receptors mediate the preferential release of somatostatin-28 in response to dopaminergic stimulation. Endocrinology 119:1712-1716, 1986*
34. Chihara K, Arimura A, Schally AV: *Effect of intraventricular injection of dopamine, norepinephrine, acetylcholine and 5-hydroxytryptamine on immunoreactive somatostatin release into rat hypophyseal portal blood. Endocrinology 104: 1656-1662, 1979*
35. Richardson SB, Hollander CS, D'Eletto R, Greenleaf PW, Thaw C: *Acetylcholine inhibits the release of somatostatin from rat hypothalamus in vitro. Endocrinology 107:122-129, 1980*
36. Locatelli V, Torsello A, Redaelli M, Ghigo E, Massara F, Muller EE: *Cholinergic agonist and antagonist drugs modulate the growth hormone response to growth hormone-releasing hormone in the rat: evidence for mediation by somatostatin. J Endocr 111:271-278, 1986*
37. Torsello A, Panzeri G, Cermentati P, Caroleo MC, Ghigo E, Camanni F, Muller EE, Locatelli V: *Involvement of the somatostatin and cholinergic systems in the mechanism of growth hormone autofeedback regulation in the rat. J Endocr 117: 273-281, 1988*
38. Wehrenberg WB, Wiviott SD, Voltz DM, Giustina A: *Pyridostigmine-mediated growth hormone release; evidence for somatostatin involvement. Endocrinology 130:1445-1450, 1992*
39. Yang I, Woo J, Kim S, Kim J, Kim Y, Choi Y: *Suppression of TRH- stimulated TSH secretion by glucose-induced hypothalamic somatostatin rele ase. Horm Metab Res, 28:555-557, 1996*