Age-Related Differences in the Secretion of Calcitonin in Male Rats

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The mechanism of hypercalcitoninemia associated with aging was investigated in male rats. To mimic some of the hormonal changes with aging, orchidectomized (Orch) and hyperprolactinemic rats were used to mimic the physiological status of aging. Orch and haloperidol-induced hyperprolactinemic rats aged 3, 8, and 17 months were infused with $CaCl_2$ and then bled from a jugular catheter following the $CaCl_2$ challenge. Rat thyroid gland was incubated with Locke's medium at 37°C for 30 minutes. Compared with 8- and 3-month-old rats, 17-month-old rats exhibited the lowest levels of plasma testosterone and the highest levels of plasma prolactin (PRL) and calcitonin (CT). The release of CT in the thyroid glands in vitro was highest in 17-month-old rats. Orchidectomy decreased rat plasma CT and thyroid CT release in vitro. Hyperprolactinemic rats had higher levels of plasma PRL and CT compared with control animals. The release of thyroid CT in vitro was greater in hyperprolactinemic rats. These results suggest that the hypersecretion of CT in 17-month-old rats may be due in part to hyperprolactinemia.

AGE-ASSOCIATED or age-specific physiological changes in hormone secretion have been investigated in rats. For example, the plasma level of prolactin (PRL) is higher in aged rats[1] than in young rats. However, plasma testosterone in the rat declines with age.[2] Serum immunoreactive parathyroid hormone (PTH) is elevated with age in rats.[3-5]

There are also age-related changes in calcitonin (CT) levels in rats.[3-8] Hypercalcitoninemia occurs in aged rats,[3-8] and the increased secretion of CT is attributed to β-adrenergic agonist,[4] an aging-related decline in estrogen secretion,[8] or regulation of secretion by calcium.[5] While serum calcium itself does not change with age, hormones that regulate calcium metabolism change markedly with age.[3,5] However, the mechanisms of hypercalcitoninemia regulated by aging are still not clear.

CT is a powerful inhibitor of osteoclastic bone resorption. It has been found to be effective in reducing bone loss in women with established postmenopausal osteoporosis.[9] This hormone may produce small increases in bone mass, particularly during the first few years after menopause, when bone turnover is high.[9] Therefore, examining the changes of CT secretion in aging rats would be helpful for understanding the mechanism for the control of CT secretion in rats. These mechanisms may be helpful in the study of osteoporosis prevention.

Considering the age-related changes in hormone secretion, this study was designed to investigate CT secretion regulated by hormones that change with aging. It is well known that the plasma level of CT is influenced by gonadal steroid hormones.[8,10-12] Both estradiol and progesterone have been shown to cause an increase of in vitro CT release from the thyroid C cells of 8-day-old rats.[11] Administration of progesterone in ovariectomized rats results in an increase of basal and calcium-induced secretion of plasma CT.[12] Thus, gonadal steroids may be an age-related physiological regulator for CT secretion.

In addition to the changes of gonadal steroid hormones, PRL is an age-associated factor in regulating CT secretion in experimental animals.[13] Serum levels of CT have also been shown to decrease in Buffalo rats bearing the MMQ tumor with hyperprolactinemic syndrome.[13] The hyperprolactinemia with MMQ tumor does not increase plasma levels of CT, so it does not explain the hypercalcitoninemia in aged rats. Recently, we found that the hypersecretion of CT in old female rats was due in part to hyperprolactinemia.[7] Furthermore, hyperprolactinemia produced in rats by grafts of the anterior pituitary gland resulted in increased CT release in vitro by thyroid C cells through a cyclic adenosine monophosphate–dependent pathway.[14] Because the major neuroregulator of PRL is dopamine and because normal aging has been reported to be associated with reductions in hypothalamic dopamine content and effect,[15] a model of hyperprolactinemia induced by haloperidol (a dopamine receptor antagonist) was used to study the effects of aging on CT secretion.

The present study investigated the mechanism of aging effects on the secretion of CT both in vivo and in vitro in male rats. The models of hyperprolactinemia and hypogonadism were used to mimic the hormone changes that occur during aging. The role of PRL and testosterone in regulating CT secretion both in vivo and in vitro in rats was studied.

We found that the increase of CT release in vitro and the basal and calcium-stimulated increase of plasma CT were correlated with age. Basal and calcium-stimulated levels of plasma calcium were age-independent. Hypogonadism induced by orchidectomy resulted in a decrease of CT release. However, haloperidol-induced hyperprolactinemia resulted in an increase of CT release both in vivo and in vitro. These results suggest that the calcium-independent hypercalcitoninemia in male rats during aging is due, at least in part, to a hypersecretion of PRL.

MATERIALS AND METHODS

Animals

Male Sprague-Dawley rats aged 3, 8, and 17 months were housed in a temperature-controlled (22° ± 1°C) environment with 14 hours of artificial illumination daily (6 AM to 8 PM) and food and water ad libitum.[7,16-18]

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To study the above-mentioned age-related effects, 3-month-old rats were orchidectomized (Orch) or administered haloperidol to mimick the low testosterone and high PRL in aging rats. Orchidectomy was performed under ether anesthesia. Two weeks after the procedure, the Orch and sham control rats were studied. Haloperidol (2.5 mg/kg) was injected subcutaneously at 42 and 18 hours before the experiments. The 3-month-old rats that were injected with vehicle (0.2% acetic acid and 30% ethanol 1 mL/kg) were used as a control.[19]

In Vivo Experiments

The rats were catheterized via the right jugular vein and left femoral vein[8,12,20] prior to a challenge of $CaCl_2$ (30 mg/kg body weight) at a rate of 1 mL/30 min.[6,12] The infusion was performed with the femoral catheter connected to a peristaltic pump. Blood samples (0.6 mL each) were collected from the right jugular vein at 0, 30, 60, and 120 minutes following the challenge.[8,12,16] Plasma was separated by centrifugation at 10,000 × *g* for 1 minute and stored at −20°C for radioimmunoassay (RIA) of CT. The plasma calcium concentration was determined by an automatic calcium analyzer (Calcette; Precision Systems, Natick, MA).

In Vitro Experiments

After decapitation of the rats, blood samples were collected and CT, PRL, and testosterone plasma levels were measured by RIA. Rat thyroparathyroid glands were excised, bisected, and preincubated with Locke's solution containing 10 mmol/L glucose, 0.003% bacitracin, and 0.05% HEPES at 37°C for 90 minutes. The thyroparathyroid glands were then incubated with Locke's medium containing calcium chloride (1.25, 2.5, or 5 mmol/L) for 30 minutes. At the end of the incubation, the tissue was weighed and the medium was collected and analyzed for CT by RIA.

RIAs

CT. The CT concentration in plasma and medium samples was measured by the human CT RIA kit purchased from Nichols Institute Diagnostics (San Juan Capistrano, CA). The inhibition curves of rat thyroid medium and plasma or human plasma were plotted and shown parallel to the standard curve of human CT.[8,12] The antisera for CT showed virtually no cross-reactivity against bovine PTH-(1-84), human PTH-(1-34), insulin, PRL, human growth hormone, thyrotropin, and corticotropin. Salmon CT up to 40 ng/mL did not cross-react with the antisera. The sensitivity was 4 pg/mL. The recovery of human CT from human serum pools was 86% to 94%. The intraassay and interassay coefficients of variation were 6.7% (n = 10) and 8.3% (n = 10), respectively.

PRL. The concentration of PRL in the plasma samples was determined by RIA as described previously.[20] The rat PRL kit was provided by the National Institute of Diabetes and Digestive and Kidney Diseases (Bethesda, MD). Rat PRL-I-6 was used for radioiodination and rat PRL-RP-3 was the standard. The sensitivity of the rat PRL RIA was 3 pg per assay tube. The intraassay and interassay coefficient of variation was 3.8% and 3.2%, respectively, for the PRL RIA.

Testosterone. The testosterone concentration in plasma samples was determined by RIA as described previously with antitestosterone serum W8.[16] The sensitivity of the testosterone RIA was 2 pg per assay tube. The intraassay and interassay coefficient of variation was 4.1% (n = 6) and 4.7% (n = 10), respectively, for the testosterone RIA.

Statistical Analysis

All values are presented as the mean ± SEM. The treatment means were tested for homogeneity using an ANOVA, and the difference between specific means was tested for significance using Duncan's multiple-range test.[21] A difference between 2 means was considered statistically significant at a *P* level less than .05.

RESULTS

Plasma Testosterone and PRL in Male Rats of Different Ages

The plasma concentration of testosterone was lower in 17-month-old rats (272 ± 53 pg/mL) versus 3-month-old rats (512 ± 73 pg/mL ($P < .01$). Plasma PRL was higher in 17-month-old rats (91.3 ± 21.8 ng/mL) versus 3-month-old (31.2 ± 2.8 ng/mL, $P < .01$) and 8-month-old rats (22.5 ± 5.2 ng/mL, $P < .05$) (Fig 1).

Effects of Aging on Plasma Calcium and CT in Male Rats

There was no difference in the basal plasma calcium level among 17-month-old (10.0 ± 0.2 mg/dL), 3-month-old (10.2 ± 0.4 mg/dL), and 8-month-old rats (10.4 ± 0.2 mg/dL). Basal plasma CT levels were higher ($P < .01$) in 17-month-old (49.4 ± 7.8 pg/mL) and 8-month-old (29.8 ± 2.2 pg/mL) rats compared with 3-month-old rats (18.1 ± 1.3 pg/mL). Basal plasma CT gradually increased during aging (correlation coefficient = .72, $P < .01$) (Fig 2).

Response of CT to $CaCl_2$ Challenge in Male Rats of Different Ages

The percent change of plasma calcium and CT levels in response to intravenous infusion of $CaCl_2$ are illustrated in Fig 3. Post-$CaCl_2$ plasma calcium levels at 60 and 120 minutes were lower in 3-month-old rats versus 8- and 17-month-old rats (Fig 3). At 3.5 hours after termination of the $CaCl_2$ infusion, rat plasma calcium levels exhibited no difference among the 3 groups.

Infusion of $CaCl_2$ for 30 minutes increased the plasma

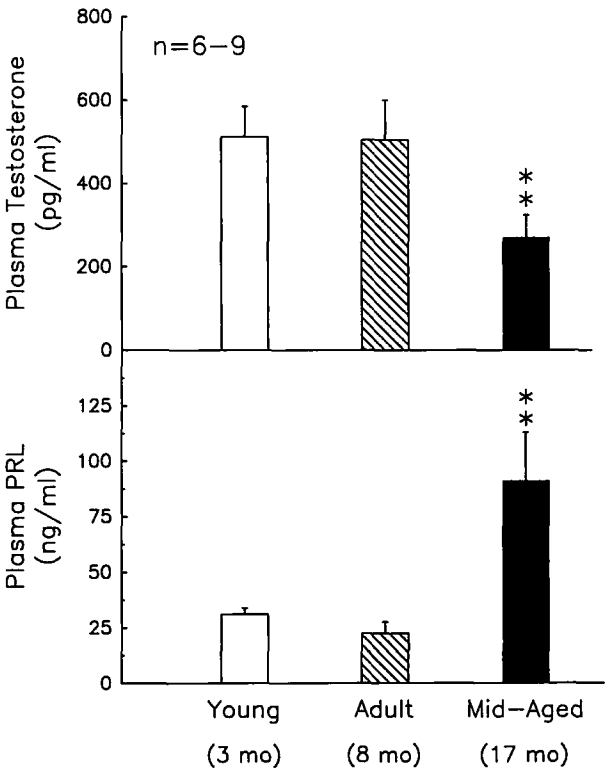

Fig 1. Plasma testosterone and PRL levels in male rats of different ages. **$P < .01$ *v* young rats.

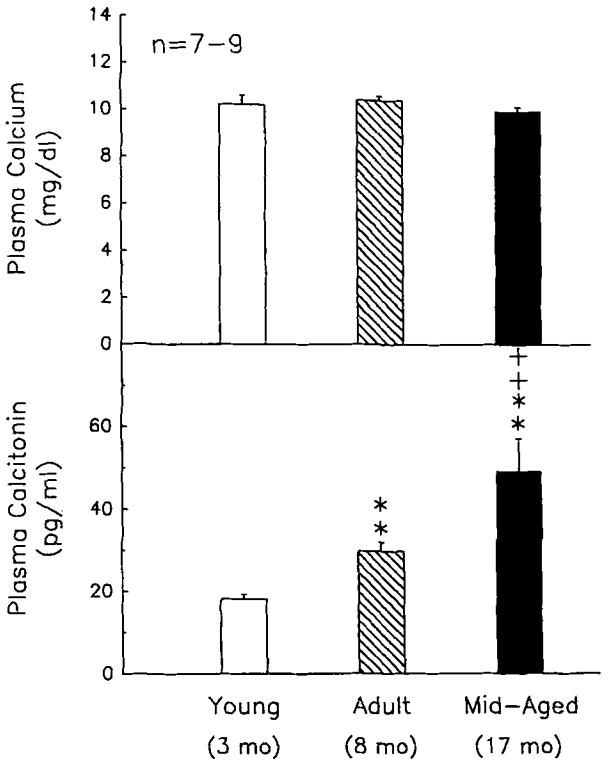

Fig 2. Basal plasma calcium and CT levels in male rats of different ages. **$P < .01$ *v* young rats, $^{++}P < .01$ *v* adult rats.

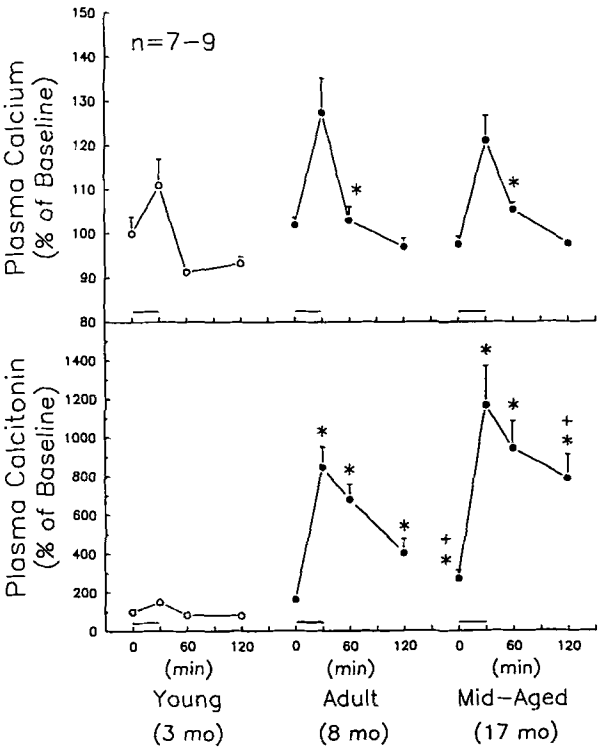

Fig 3. Effects of intravenous infusion of $CaCl_2$ on plasma calcium and CT in male rats of different ages. Rats were infused intravenously with $CaCl_2$ (30 mg/kg) from 0 to 30 minutes (as shown by horizontal line) via a peristaltic pump (1 mL/30 min). Values are expressed as the percentile increase of basal plasma calcium or CT in young rats. *$P < .05$ *v* young rats, $^{+}P < .05$ *v* adult rats.

concentration of CT in all rats. After $CaCl_2$ infusion, plasma CT was higher ($P < .05$) in 17- and 8-month-old rats than in 3-month-old rats. The post-$CaCl_2$ plasma CT levels remained higher ($P < .05$) in 17- and 8-month-old rats versus 3-month-old rats. $CaCl_2$-stimulated plasma CT returned to pre-$CaCl_2$ levels 30 minutes after termination of $CaCl_2$ infusion in 3-month-old rats, but required at least 4 hours in 8- and 17-month-old rats.

Effects of Age on the Release of Thyroid CT In Vitro

The in vitro release of CT from the thyroid was higher in 17-month-old versus 3- and 8-month-old rats (Fig 4).

Plasma Calcium and CT in Orch Rats

There was no difference in the basal plasma calcium level between Orch rats (10.5 ± 0.1 mg/dL), and intact rats (10.0 ± 0.2 mg/dL). Post-$CaCl_2$ plasma calcium levels at 30, 60, and 120 minutes exhibited no difference between the 2 groups. Basal plasma CT levels were lower ($P < .01$) in Orch rats (5.5 ± 0.3 pg/mL) compared with intact rats (13.3 ± 1.1 pg/mL). Infusion of $CaCl_2$ for 30 minutes increased the plasma concentration of CT in all rats. Post-$CaCl_2$ plasma CT levels remained higher ($P < .01$) in intact versus Orch rats. $CaCl_2$-stimulated plasma CT levels had returned to pre-$CaCl_2$ values at 120 minutes following termination of $CaCl_2$ infusion in all rats (Fig 5).

Effects of Orchidectomy on the Release of Thyroid CT In Vitro

In both intact and Orch rats, the in vitro release of CT from the thyroid exhibited a dose-dependent response to different concentrations of $CaCl_2$. The in vitro release of thyroid CT in response to 1.25 and 2.5 mmol/L $CaCl_2$ was higher in intact versus Orch rats (Fig 6).

Effects of Haloperidol on Plasma PRL, Calcium, and CT

Plasma PRL was higher ($P < .01$) in male rats treated with haloperidol (86.90 ± 9.89 ng/mL) versus those treated with

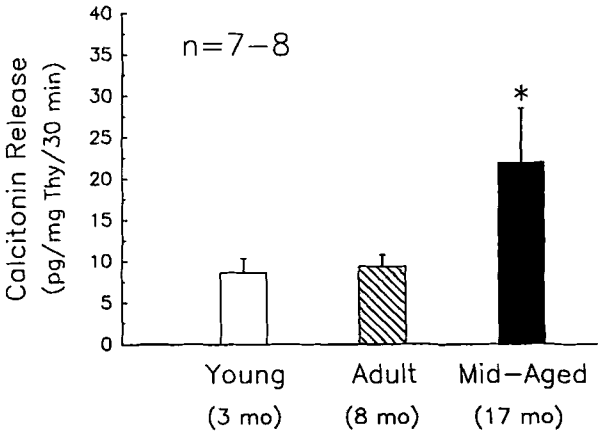

Fig 4. In vitro release of CT from the thyroid of male rats of different ages. Rat thyroid tissue was excised, bisected, and preincubated with Locke's solution containing 10 mmol/L glucose, 0.003% bacitracin, and 0.05% HEPES at 37°C for 90 minutes. Thyroparathyroid glands were then incubated with Locke's medium for 30 minutes. At the end of incubation, the tissue was weighed, and the medium was collected and measured for CT by a RIA. *$P < .05$ *v* young rats.

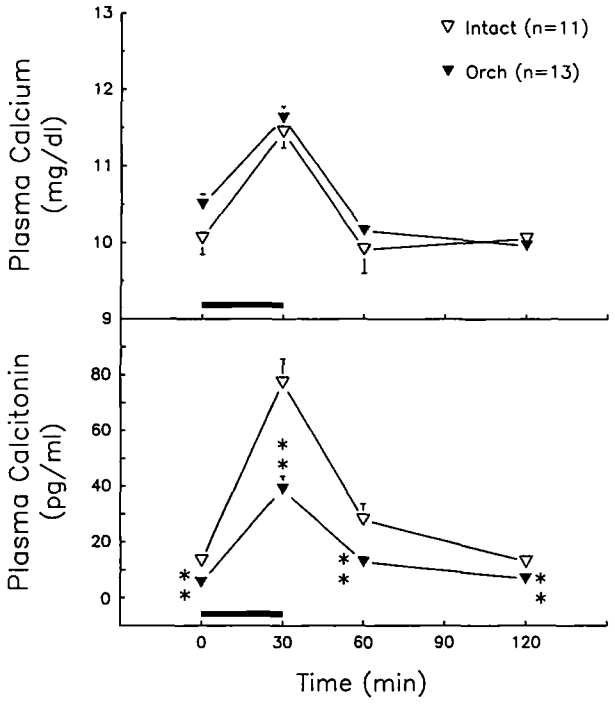

Fig 5. Effect of intravenous infusion of $CaCl_2$ on plasma calcium and CT in intact and Orch rats. Rats were intravenously infused with $CaCl_2$ (30 mg/kg) from 0 to 30 minutes via a peristaltic pump at a rate of 1 mL/30 min. **$P < .01$ v intact rats. Horizontal bar represents the duration of $CaCl_2$ infusion.

vehicle (31.96 ± 3.79 ng/mL; Fig 7). Basal, $CaCl_2$-stimulated, and post-$CaCl_2$ plasma calcium levels were not different in haloperidol-treated rats compared with vehicle-treated rats. Compared with vehicle-injected animals, haloperidol increased

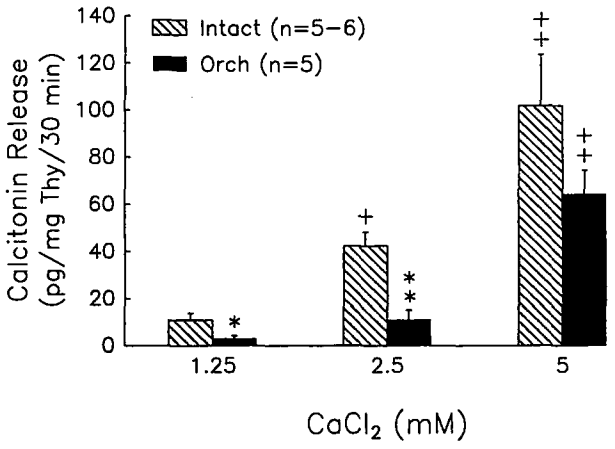

Fig 6. In vitro release of CT from the thyroid of intact and Orch rats. Rat thyroid tissue was excised, bisected, and preincubated with Locke's solution containing 10 mmol/L glucose, 0.003% bacitracin, and 0.05% HEPES at 37°C for 90 minutes. Thyroparathyroid glands were then incubated with Locke's medium containing 1.25, 2.5, or 5 mmol/L $CaCl_2$ for 30 minutes. At the end of incubation, the tissue was weighed and the medium was collected and measured for CT by a RIA. *$P < .05$, **$P < .01$ v intact rats, +$P < .05$, ++$P < .01$ v corresponding 1.25-mmol/L $CaCl_2$ group.

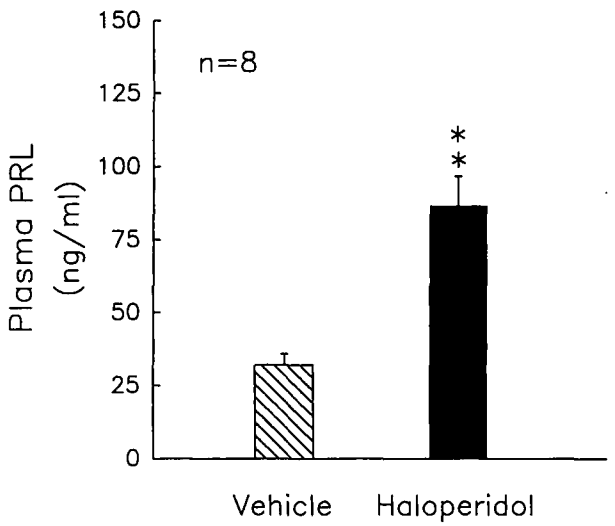

Fig 7. Plasma PRL in male rats injected subcutaneously with haloperidol (2.5 mg/kg 42 and 18 hours before the experiment) or vehicle (0.2% acetic acid and 30% ethanol, 1 mL/kg). **$P < .01$ v vehicle-treated group.

basal plasma CT by 58% and $CaCl_2$-stimulated plasma CT by 2.9-fold. Thirty minutes after $CaCl_2$ infusion, the elevated plasma CT was higher ($P < .01$) in haloperidol-treated versus vehicle-treated rats (Fig 8).

Effects of Haloperidol on the Release of Thyroid CT In Vitro in Male Rats

In vivo administration of haloperidol increased the in vitro release of CT from the thyroid in male rats by 2-fold ($P < .05$; Fig 9). The in vitro release of CT from the thyroid was not changed by in vitro administration of haloperidol at a concentration of 1 to 100 μmol/L (data not shown).

DISCUSSION

In the present study, we found that (1) 17-month-old rats had the lowest plasma testosterone and the highest plasma PRL and CT compared with 8- and 3-month-old rats; (2) $CaCl_2$-stimulated plasma CT levels rendered the plasma calcium less able to return to normal levels after stimulation with $CaCl_2$ in 17-month-old versus 3-month-old rats; (3) the release of CT in the thyroid was greatest in 17-month-old rats; (4) orchidectomy decreased basal and $CaCl_2$-stimulated plasma CT and CT release from the thyroid in vitro as compared with intact rats; and (5) the hyperprolactinemia induced by haloperidol resulted in an increase of CT secretion both in vivo and in vitro.

Age-associated morphological and physiological changes of the thyroid have been described. In elderly humans, thyroid weight has been shown to decrease, remain substantially unchanged, or increase; the last condition is unrelated to physiological aging, and is instead the consequence of an increased prevalence of nodular goiter in the elderly.[22,23] An age-dependent increase in thyroid weight occurs in rats.[4,24] This finding is similar to our result (3-month-old rats, 18.70 ± 0.95 mg/thyroid; 8-month-old rats, 28.03 ± 2.36 mg/thyroid; and 17-month-old rats, 28.35 ± 1.63 mg/thyroid; sample size, 7 to 8). The correlation coefficient for age and thyroid weight in rats

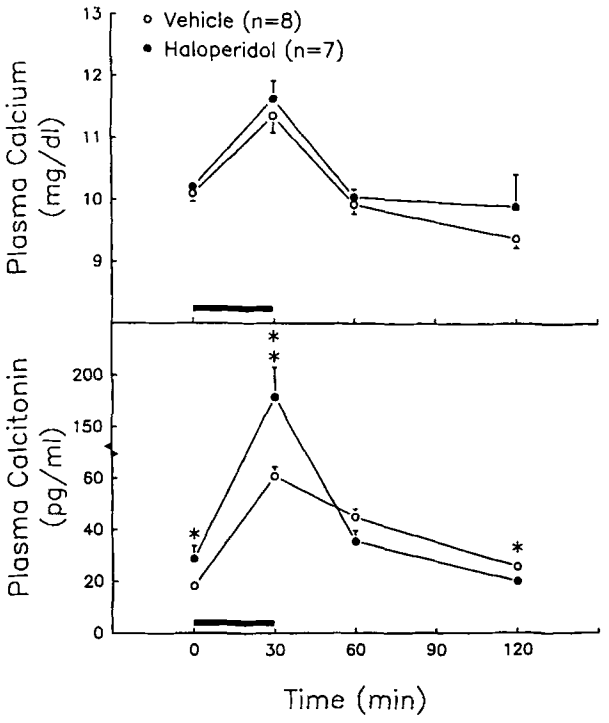

Fig 8. Effect of intravenous infusion of $CaCl_2$ on plasma calcium and CT in male rats injected subcutaneously with haloperidol or vehicle. Rats were intravenously infused with $CaCl_2$ (30 mg/kg) from 0 to 30 minutes via a peristaltic pump at a rate of 1 mL/30 min. *$P < .05$, **$P < .01$ *v* vehicle-treated group. Horizontal bar represents the duration of $CaCl_2$ infusion.

is .59 ($P < .01$). The number of C cells has been shown to increase from birth to 120 days of age in rats.[25] However, in humans, the number of C cells appears to decrease with age.[26,27] This may be one of the reasons that plasma CT is decreased in elderly humans but increased in aged rats.

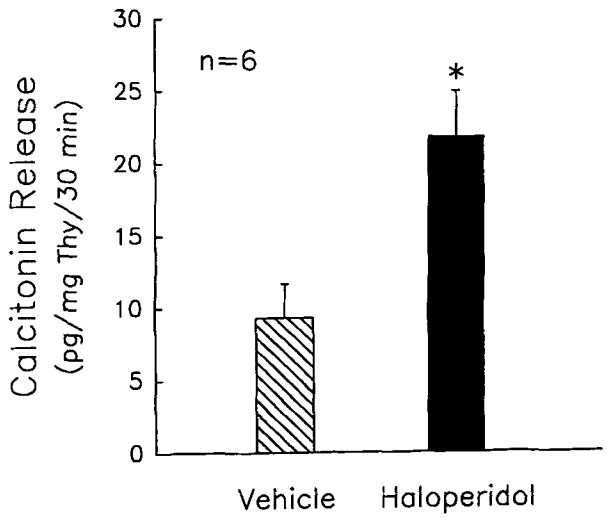

Fig 9. In vitro release of CT by the thyroid of male rats injected subcutaneously with haloperidol or vehicle. Rat hemithyroid glands were incubated with Locke's medium at 37°C for 30 minutes. *$P < .05$ *v* vehicle-treated group.

Age-associated or age-specific physiological changes in CT secretion have been extensively investigated in both humans and experimental animals. Deftos et al[28] found that irrespective of age, the increase in CT in response to calcium infusion was greater in men versus women, but basal levels of CT and the response to calcium waned with age in both sexes. Queener et al[4] found that hypercalcitoninemia occurs in aged Buffalo rats, as does hyperparathyroidism, and have suggested that CT concentrations in blood are modulated by β-adrenergic agonist. In this study, we found that the pre- and post-$CaCl_2$ plasma CT and the in vitro release of CT reach the highest levels in 17-month-old rats compared with 3- and 8-month-old rats. After $CaCl_2$ stimulation, the plasma level of calcium was higher in 8- and 17-month-old versus 3-month-old rats at 60 and 120 minutes. Thus, 8- and 17-month-old rats had a low ability to recover plasma calcium after $CaCl_2$ stimulation. The increased in vitro release of CT in aged rats has also been observed by Wongsurawat and Armbrecht.[5] Tsai et al[8] have reported that the basal CT secretion and maximal CT level in female rats during calcium infusion are increased with age. The link between estrogen and the hypocalcemic effect of CT observed in rats is actually an age-related phenomenon instead of a physiological regulation at all ages.[8] Thus, hypercalcitoninemia occurs in aged rats,[4,5,8] and the increased secretion of CT is probably attributable to β-adrenergic agonist,[4] an aging-related decline in estrogen secretion,[8] or regulation of secretion by calcium.[5]

Previous studies have demonstrated that the circulating PRL concentration in rats[1] and humans[29] increases during aging. The plasma testosterone level markedly decreased in aged animals.[1,2,30] In humans, it has been shown that androgen deficiency may decrease plasma CT,[9] and basal plasma CT levels are slightly reduced in hyperprolactinemic women.[31] These phenomena may explain why aged humans have low testosterone, high PRL, and low basal plasma CT.

In the present study, we have confirmed that plasma PRL is higher and plasma testosterone is lower in rats during aging. Orchidectomy decreased the release of thyroid CT both in vivo and in vitro. The plasma calcium level in basal, $CaCl_2$-stimulated, and post-$CaCl_2$ conditions was not different between Orch and intact rats. The production of CT, changes in serum calcium, or changes in response to $CaCl_2$ were not in agreement with values in aged rats. Thus, the hypersecretion of CT in male rats during aging is not due to the decline of testosterone production.

Previous studies have demonstrated that hyperprolactinemia is associated with decreased bone mineral density and plasma CT levels are slightly reduced in hyperprolactinemic women,[31] similar to CT levels in older humans. Recently, we also demonstrated that the hypersecretion of CT in old female rats is, at least in part, due to hyperprolactinemia.[7] Hyperprolactinemia increases the release of CT by thyroid C cells in rats.[13] In the present study, hyperprolactinemia induced by haloperidol in rats was used to mimic the hormone changes of an aged animal. We found that both basal and calcium-stimulated plasma CT levels are markedly higher in haloperidol-induced hyperprolactinemic rats independently of plasma calcium. These phenomena were similar in aged rats. Furthermore, the in vitro release of CT was also higher in hyperprolactinemic rats versus control

rats. These data imply that hyperprolactinemia is involved in the mechanism regulating the hypersecretion of CT in rats during aging.

In summary, the present results demonstrate that the hypersecretion of CT both in vivo and in vitro in male rats during aging is, at least in part, due to an increase of plasma PRL arising from hyperprolactinemia.

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REFERENCES

1. Bolzan AD, Brown OA, Goya RG, et al: Hormonal modulation of antioxidant enzyme activities in young and old rats. Exp Gerontol 30:169-175, 1995

2. Mendis-Handagama SM, Gelber SJ: Signs of aging are apparent in the testis interstitium of Sprague-Dawley rats at 6 months of age. Tissue Cell 27:689-699, 1995

3. Kalu DN, Masoro EJ, Yu BP, et al: Modulation of age-related hyperparathyroidism and senile bone loss in Fischer rats by soy protein and food restriction. Endocrinology 122:1845-1847, 1988

4. Queener SF, Bell NH, Larson SM, et al: Comparison of the regulation of calcitonin in serum of old and young Buffalo rats. J Endocrinol 87:73-80, 1979

5. Wongsurawat N, Armbrecht HJ: Comparison of calcium effect on in vitro calcitonin and parathyroid hormone release by young and aged thyroparathyroid glands. Exp Gerontol 22:263-269, 1987

6. Flynn JJ, Margules DL, Peng TC, et al: Serum calcitonin, calcium and thyroxine in young and old Zucker fatty rats (fa/fa). Physiol Behav 31:79-84, 1983

7. Lu CC, Tsai SC, Wang SW, et al: Age-related differences in the secretion of calcitonin in female rats. Am J Physiol 275:E735-E739, 1998

8. Tsai CL, Pu HF, Lau CP, et al: Age-related differences in basal and calcium-stimulated plasma calcitonin levels in female rats. Am J Physiol 262:E557-E560, 1992

9. Deal CL: Osteoporosis: Prevention, diagnosis, and management. Am J Med 102:35S-39S, 1997 (Suppl)

10. Foresta C, Zanatta GP, Busnardo B, et al: Testosterone and calcitonin plasma levels in hypogonadal osteoporotic young men. J Endocrinol Invest 8:377-379, 1985

11. Greenberg C, Kukreja SC, Bowser EN, et al: Effects of estradiol and progesterone on calcitonin secretion. Endocrinology 118:2594-2598, 1986

12. Lu CC, Tsai SC, Wang SW, et al: Effects of ovarian steroid hormones and thyroxine on calcitonin secretion in pregnant rats. Am J Physiol 274:E246-E252, 1998

13. Adler RA, Farrell ME, Deiss WP, et al: Hypercalciuria in a new rat model of hyperprolactinemia. Metabolism 40:292-296, 1991

14. Lu CC, Tsai SC, Huang WJS, et al: Effects of hyperprolactinemia on calcitonin secretion in male rats. Metabolism 48:221-226, 1999

15. Greenspan SL, Klibanski A, Rowe JW, et al: Age alters pulsatile prolactin release: Influence of dopaminergic inhibition. Am J Physiol 258:E799-E804, 1990

16. Wang PS, Tsai SC, Hwang GS, et al: Calcitonin inhibits testosterone and luteinizing hormone secretion through a mechanism involving an increase in cAMP production in rats. J Bone Miner Res 9:1583-1590, 1994

17. Lu SS, Lau CP, Tung YF, et al: Lactate stimulates progesterone secretion via an increase in cAMP production in exercised female rats. Am J Physiol 271:E910-E915, 1996

18. Tsai SC, Lu CC, Lau CP, et al: Progesterone stimulates in vitro release of prolactin and thyrotropin involving cAMP production in rat pituitary. Chin J Physiol 39:245-251, 1996

19. Arita J, Kimura F: Characterization of in vitro dopamine synthesis in the median eminence of rats with haloperidol-induced hyperprolactinemia and bromocriptine-induced hypoprolactinemia. Endocrinology 119:1666-1672, 1986

20. Wang PS, Liu JY, Hwang CY, et al: Age-related differences in the spontaneous and thyrotropin-releasing hormone–stimulated release of prolactin and thyrotropin in ovariectomized rats. Neuroendocrinology 49:592-596, 1989

21. Steel RGD, Torrie JH: Principles and Procedures of Statistics. New York, NY, McGraw-Hill, 1960

22. Berghout A, Wiersinga WM, Smits NJ, et al: Interrelationships between age, thyroid volume, thyroid nodularity, and thyroid function in patients with sporadic nontoxic goiter. Am J Med 89:602-608, 1990

23. Mariotti S, Franceschi C, Cossarizza A, et al: The aging thyroid. Endocr Rev 16:686-715, 1995

24. Rao-Rupanagudi S, Heywood R, Gopinath C: Age-related changes in thyroid structure and function in Sprague-Dawley rats. Vet Pathol 29:278-287, 1992

25. Martín-Lacave I, Conde E, Montero C, et al: Quantitative changes in the frequency and distribution of the C-cell population in the rat thyroid gland with age. Cell Tissue Res 270:73-77, 1992

26. Wolfe HJ, DeLellis RA, Voelkel EF, et al: Distribution of calcitonin-containing cells in the normal neonatal human thyroid gland: A correlation of morphology with peptide content. J Clin Endocrinol Metab 41:1076-1081, 1975

27. Wolfe HJ, Voelkel EF, Tashjian AH: Distribution of calcitonin-containing cells in the normal adult human thyroid gland: A correlation of morphology with peptide content. J Clin Endocrinol Metab 38:688-694, 1974

28. Deftos LJ, Weisman MH, Williams GW, et al: Influence of age and sex on plasma calcitonin in human beings. N Engl J Med 302:1351-1353, 1980

29. Urban RJ: Neuroendocrinology of aging in the male and female. Endocrinol Metab Clin North Am 21:921-931, 1992

30. Jorgensen JO, Vahl N, Hansen TB, et al: Influence of growth hormone and androgens on body composition in adults. Horm Res 45:94-98, 1996

31. Torring O, Isberg B, Sjoberg HE, et al: Plasma calcitonin, IGF-I levels and vertebral bone mineral density in hyperprolactinemic women during bromocriptine treatment. Acta Endocrinol (Copenh) 128:423-427, 1993