Effects of cytidine 5'-diphosphocholine administration on basal and growth hormone-releasing hormone-induced growth hormone secretion in elderly subjects

Gian Paolo Ceda, Graziano Ceresini, Licia Denti, Dario Magnani, Lorenzo Marchini, Giorgio Valenti and Andrew R. Hoffman

Chair of Gerontology and Geriatrics, University of Parma, Parma, Italy, and Medical Service 1, VA Medical Center, Palo Alto, and Department of Medicine, Stanford University, Stanford, California, USA

Abstract. The basal and GH-releasing hormone-stimulated secretion of GH declines in the elderly. We tested the ability of cytidine 5'-diphosphocholine, a drug used in the treatment of stroke and Parkinson's disease, to alter GH secretion in 11 healthy elderly volunteers, aged 69-84. Each subject received an iv infusion of 2 g of cytidine 5'-diphosphocholine or normal saline. GHRH and TRH were also administered during cytidine 5'-diphosphocholine infusions. The infusion of cytidine 5'-diphosphocholine induced a 4-fold (p<0.05) increase in serum GH levels over basal values. A small increase in GH was seen after GHRH administration. However, the addition of GHRH to the cytidine 5'-diphosphocholine infusion resulted in a GH response which was significantly greater than that seen after GHRH alone; the integrated concentration of GH was more than 2-fold greater in the cytidine 5'-diphosphocholine treated group (706.85 ± 185.1 vs 248.9 ± 61.4 μg · l⁻¹ · (120 min)⁻¹; p=0.01). The PRL and TSH responses to TRH were not significantly affected by cytidine 5'-diphosphocholine infusion, indicating that dopaminergic mechanisms are not involved. These studies demonstrate that cytidine 5'-diphosphocholine can enhance basal and GHRH-stimulated GH release in the elderly, but the mechanism of action of the drug remains unclear.

Numerous studies have documented significant changes in GH secretion in aging experimental animals and in human subjects. Decreased pulsatile secretion of GH (1), a reduced ability of GHRH to release GH both in vivo and in vitro from pituitary cells in primary cultures (2), and a reduced pituitary content of GH and GH mRNA (3,4) have been reported in aged rats. Most, but not all (5), studies have confirmed that GH secretion is impaired in elderly humans. The number of sleep-related GH secretory pulses decreases in most people over 50 years of age (6,7), and there is an age-related decline in GHRH-induced GH secretion (8). The serum GH-binding protein also declines in the elderly (9).

The etiology of impaired GH secretion in aging remains unclear. Alterations in the synthesis or release of GHRH or somatostatin have been implicated, but remain unproven. Cholinergic agonists can inhibit hypothalamic somatostatin release (10) and thereby modulate GH secretion (11-13). Activation of cholinergic receptors by the anticholinesterase pyridostigmine has been shown to restore GH responsiveness to GHRH in obese individuals (14-15) and in normal subjects (16,17). Brain acetylcholine synthesis may decline with aging (18), and it is possible that hypothalamic somatostatin tone is increased, leading to the relative hyposomatropinemia of old age. Since dopamine stimulates GH release (19), it is also possible that decreased hypothalamic dopaminergic tone could lead to decreased GH release.

Cytidine 5'-diphosphocholine (CDP-choline) is a parenteral medication which has been used as a cerebral vasodilator in elderly patients (20). It has also been used in patients with stroke and Parkin-
sons' disease (21). Although its mechanism of action is not proven, most studies have suggested that CDP-choline is a precursor for phosphatidylcholine (lecithin) synthesis. While it has been suggested that CDP-choline can serve as precursor for acetylcholine and thereby interact with cholinergic receptors (22), other studies indicate that CDP-choline does not in fact function as a cholinergic agent (23). Finally, Martinet et al. (24) have demonstrated that CDP-choline enhances central nervous system dopamine tone by increasing dopamine turnover.

In this report, we have studied the effect of an infusion of CDP-choline on pituitary secretion in healthy elderly subjects in order to learn how this medication affects adenohypophyseal function.

Subjects and Methods
Eleven subjects, 5 men and 6 women, aged 69-84 were studied on three separate days at >1 week intervals according to the following protocols. Each subject received in a randomized order: 1. an iv infusion over 15 min of 2 g CDP-choline (Nicholin, Cyanamid, Italia) dissolved in 100 ml normal saline, or 100 ml of normal saline alone; blood samples were obtained at -15, 0, 15, 30, 45, 60, 90 and 120 min from the start of the infusion; 2. a bolus injection of GHRH (Sanofi, Midy) at a dose of 1 μg/kg; blood samples were taken at -15 and 0 min and at 15, 30, 45, 60, 90 and 120 min after the bolus injection; and 3. a 15 min infusion of CDP-choline followed by a bolus injection of GHRH at the same doses. Finally, in an additional group of 5 subjects of comparable age, TSH and PRL responses to TRH (200 μg iv) were evaluated at baseline and during the infusion of CDP-choline, as described above. These procedures were in accordance with the ethical standards of the Helsinki Declaration of 1975.

Gh, TSH and PRL levels were measured using commercial kits obtained from Ares-Serono (Milan, Italy). Serum GH was measured by a specific double-antibody radioimmunoassay with a sensitivity of 0.25 µg/l and intra- and inter-assay coefficients of variation of 4 and 8%, respectively. Serum TSH and PRL levels were measured by enzyme-linked immunoassays. The reference standard for TSH was calibrated against the Second International Reference Preparation (2nd IRP-TSH 80/558). The sensitivity of the assay was 0.03 mU/l and the intra-assay coefficients of variation were 2.4, 1.4 and 2.7% at TSH levels of 0.41, 2.1 and 8.3 mU/l, respectively. The sensitivity of the PRL assay was 13.52 pmol/l and the intra-assay coefficients of variation were 4.5 and 2.3% at PRL concentrations of 244.2 and 1438.5 pmol/l, respectively; the inter-assay coefficient of variation was <10% for both TSH and PRL.

Statistical evaluation was performed using analysis of variance according to a randomized block factorial design and Wilcoxon's test (due to the relatively low numbers of subjects). The area under the curve (AUC) of GH after GHRH, with or without CDP-choline, was calculated by the trapezoidal method.

Results
The infusion of CDP-choline induced a 4-fold (p<0.05) increase in serum GH levels over basal values by 60 min from the start of the infusion (Fig. 1). Analysis of the individual responses revealed that 8 of the subjects demonstrated a significant increase in serum GH levels (>2 sd of basal values). When GHRH was given during the administration of CDP-choline, the GH responses were significantly greater than those seen after GHRH alone (p<0.02 by ANOVA; Fig. 2). The integrated concentration (AUC) of GH was more than 2-fold greater in the GHRH plus CDP-choline treated group than in the group treated with GHRH alone: 706.8±185.1 vs 248.9±61.4 μg·l⁻¹·(2h)⁻¹ (p=0.009, by Wilcoxon's test). CDP-choline administration (Fig. 1) resulted in an increase in GH release similar to that seen after a GHRH infusion: 215.6±60.4 vs 248.9±61.4 μg·l⁻¹·(2h)⁻¹.

Since CDP-choline has also been shown to enhance central dopaminergic neurotransmission (25,26), the PRL and TSH responses to TRH were also investigated after the infusion of the drug. The lactotrope and thyrotrope responses to TRH were...
Serum GH (mean ± SEM; N=11) responses to GHRH (open bars) and GHRH plus cytidine 5'-diphosphocholine (striped black bars). p<0.02 by analysis of variance.

not significantly affected by CDP-choline infusion (Fig. 3).

No adverse effects were noted by any of the subjects.

Discussion

In order to assess the effect of CDP-choline on pituitary secretion in the elderly, we infused the drug into 11 aged subjects and determined the response to GHRH and TRH. CDP-choline administration resulted in an increase in basal GH secretion as well as greatly enhanced somatotrope responsiveness to GHRH. These data extend previous reports which documented a stimulatory effect of CDP-choline on basal GH secretion in young normal subjects (27).

The precise mechanism by which CDP-choline increased GHRH-stimulated GH responses is still unclear, since CDP-choline mediates several other biologic functions. CDP-choline is a precursor essential for the synthesis of phosphatidylcholine, a major structural component of the cell membrane (28,29). It is possible, therefore, that CDP-choline loading could alter membrane fluidity and amplify GHRH signal transduction at the pituitary level. In addition, CDP-choline administration has been shown to increase dopaminergic tone (26), and dopamine can stimulate GH secretion. If changes in dopamine neurotransmission did occur, however, PRL and TSH secretion should be blunted in subjects receiving CDP-choline. However, when TSH and PRL responses to TRH were tested after the infusion of CDP-choline, no significant change was observed. These results argue against an important role for dopamine in the increase of GH secretion after CDP-choline administration.

Although CDP-choline is devoid of cholinergic side-effects unless given at doses greatly exceeding those given in this study, it has been suggested that
CDP-choline could function as a precursor for central acetylcholine synthesis. Acetylcholine plays a major role in the control of GH secretion in humans. Anticholinergic drugs can blunt the GH response to a variety of stimuli (12), while agents which enhance acetylcholine action, like the cholinesterase inhibitor pyridostigmine, induce GH release, potentiate the stimulatory effect of GHRH (13) and restore the GH response after pituitary desensitization induced by intermittent GHRH administration (30).

In conclusion, these data demonstrate that CDP-choline increased basal and stimulated GH secretion in the elderly. The mechanism by which CDP-choline exerts this action remains unknown. Studies using anticholinesterases or antimuscarinic agents will be needed to define further the role of decreased acetylcholine transmission in the diminished secretion of GH in aging humans.

References


Received August 15th, 1990.
Accepted November 26th, 1990.

Dr Gian Paolo Ceda,
c/o Division of Endocrinology,
Stanford University Medical Center,
Stanford, California 94305-5103,
USA.