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Hypercalcaemia and Calcitonin Inhibit Prolactin Secretion

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With 1 Figure

Summary. The authors investigated the effect of acute hypercalcaemia induced by a 2-hour intravenous infusion of calcium gluconate (8.9 mg Ca^{2+}/kg b. w.) on the lactotrophic secretory reserve assessed by the test with insulin hypoglycaemia (Δ PRL) and the effect of an intravenous bolus of 50 IU synthetic salmon calcitonin on the lactotrophic secretory reserve assessed by means of the TRH test (Δ PRL). Acute hypercalcaemia inhibits PRL levels stimulated by insulin hypoglycaemia ($p < 0.01$) as well as Δ PRL ($p < 0.01$). Calcitonin reduces PRL levels at rest and TRH stimulated levels ($p < 0.05$ and $p < 0.01$, respectively) as well as Δ PRL ($p < 0.01$). The prolactin inhibiting effect of calcitonin resembles markedly the effect of hypercalcaemia. The exact mechanism of these changes and the physiological impact of calcitonin on the regulation of PRL secretion is not known.

Key words: Hypercalcaemia, calcitonin, prolactin

Introduction

Previous studies in vitro provided evidence of the importance of calcium in the control of prolactin (PRL) secretion (MacDonald and McKeown, 1983; Gautvik et al., 1980; Moriarty and Leuschen, 1981). It is known that some secretagogues stimulate secretion of lactotrophic cells only when calcium ions are present in the secretory medium (Gautvik et al., 1980; Moriarty and Leuschen, 1981). However, calcium ions exert a positive effect on PRL secretion in vitro only within the range of physiological concentrations, while higher and lower concentrations exert an inhibitory effect (MacDonald and McKeown, 1983). The inhibitory action of higher calcium concentrations is explained by the direct stabilizing action of calcium on secretory granules and altered electric properties of the cell membrane of the lactotrophs (Maruyama et al., 1981). Acutely induced hypercalcaemia in vivo moreover activates a number of humoral reactions which modify the action proper exerted by calcium. This explains the frequently encountered controversial results of investigation in vivo and in vitro. We proved already previously the inhibitory action of acute hypercalcaemia and calcitonin on thyrotropin secretion (Žofková et al., 1981; Žofková and Bednář, 1984). We were therefore interested to know whether the inhibitory effect of hypercalcaemia and calcitonin in vivo is specific, i.e. whether it affects a certain secretory system or whether it is of a more general character.

Material and Methods

The lactotrophic secretory reserve was assessed always in a standard way on fasting in the morning using the test of insulin induced hypoglycaemia with assessement of PRL plasma levels at rest and 60 min after the intravenous administration of 0.1 U insulin/kg b.w., or using the TRH test with assessment of PRL levels at rest and 30 min after the intravenous administration of 200 μg TRH (Relefact Hoechst). In experiment 1, the secretory reserve of PRL was examined in eight healthy women with a mean age of 31. 5 years (16—50 years) using the test with insulin induced hypoglycaemia at the end of a 2-hour intravenous infusion of 400 ml saline. One week later, the test was repeated in the same subjects at the end of a 2-hour infusion of 400 ml saline containing 8.9 mg Ca^{2+}/kg body weight added to the infusion as calcium gluconate. In experiment 2, the secretory reserve of PRL was assessed by the TRH test in 13 healthy volunteers (10 women and 3 men) with a mean age of 34.3 years (20—52 years) 120 min after administration of 20 ml saline by the i.v. route. After one week, the test was repeated in the same subjects during the 120th minute following an intravenous bolus of 50 IU of synthetic salmon calcitonin (Calcitonin Woelm-Pharma) diluted with 20 ml saline. Closely before administration of insulin or TRH, the plasma calcium level was assessed complexometrically. PRL was estimated by the RIA method using a PROLK-PR CEA Sorin kit. The results were evaluated by the paired t-test.

Results

Fig. 1 indicates that in acute hypercalcaemia the PRL values at rest were only insignificantly lower while PRL levels stimulated by insulin-induced hypoglycaemia were significantly reduced as compared with stimulated values recorded during normocalcaemia ($p < 0.01$). The secretory PRL response assessed from the difference between values at rest and stimulated values (Δ PRL) was during hypercalcaemia significantly

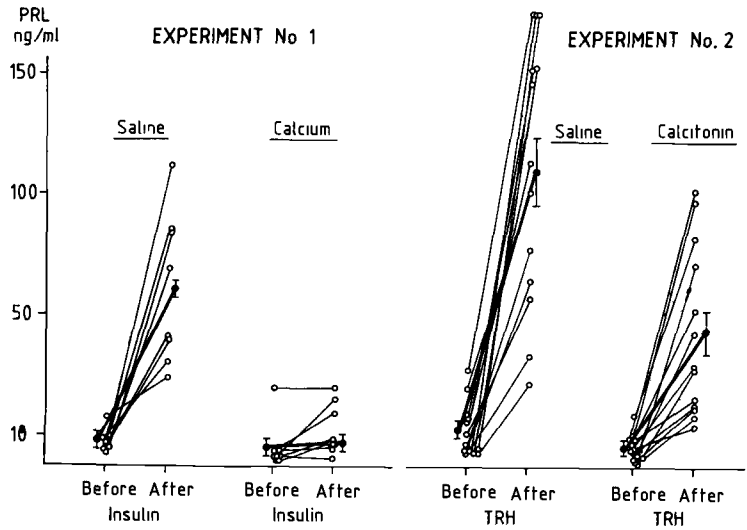

Fig. 1 The effect of acute hypercalcaemia (experiment 1) and intravenous bolus of 50 IU salmon calcitonin (experiment 2) on plasma levels of PRL at rest and insulin or TRH stimulated PRL levels in comparison with the effect of adequate bulk of saline administered intravenously. Each experiment evaluated by paired t-test: Experiment 1: stimulated PRL levels during normocalcaemia vs. stimulated PRL levels during hypercalcaemia, $p < 0.01$. Experiment 2: control PRL levels at rest vs. PRL levels at rest after calcitonin, $p < 0.05$; control stimulated PRL values vs. stimulated values after calcitonin, $p < 0.01$. Expressive bars represent means ± SEM

inhibited as compared with the control examination under normocalcaemia ($p < 0.01$) (Table 1).

From Fig. 1 it is furthermore apparent that calcitonin reduced significantly the PRL levels at rest ($p < 0.05$) as well as TRH stimulated values ($p < 0.01$). The secretory PRL response measured as the difference between values at rest and TRH stimulated values (Δ PRL) was after calcitonin significantly lower as compared with the control Δ PRL ($p < 0.01$) (Table 1).

Table 1 Secretory reserve of PRL assessed from the difference between values at rest and insulin or TRH stimulated PRL levels and calcaemia following intravenous administration of saline and intravenous administration of 8.9 mg Ca^{2+}/kg b.w. or 50 IU synthetic salmon calcitonin. Each experiment evaluated by paired t-test; mean values ± SEM. Blood sugar level 1 = before insulin, blood sugar level 2 = 60 min after insulin administration

	Δ PRL ng/ml	Calcaemia mmol/l	Blood sugar level mmol/l 1	2
Experiment 1 (test with insulin)				
Saline	49.9 ± 9.1	2.4 ± 0.02	3.8 ± 0.2	1.1 ± 0.2
p	< 0.01	< 0.01	N.S.	N.S.
Calcium n = 8	6.0 ± 2.4	3.1 ± 0.07	3.8 ± 0.2	1.3 ± 0.2
Experiment 2 (TRH test)				
Saline	86.6 ± 11.7	2.4 ± 0.03	—	—
p	< 0.01	< 0.05		
Calcitonin n = 13	36.3 ± 7.1	2.3 ± 0.02	—	—

Discussion

From the results it is apparent that a similar inhibition of the secretory response of PRL is found after calcitonin administration as during hypercalcaemia. Quantitative differences of effects induced by hypercalcaemia (almost complete inhibition) and calcitonin (partial reduction of the secretory PRL response) can be explained by the relatively small dose of calcitonin and by different stimuli applied in the two experiments.

The finding of an inhibitory effect of calcium on PRL secretion is consistent with data reported in the literature (Ajlouni and El Khateeb, 1981; Kruse and Kracht, 1981). The ratio of a direct inhibitory action of extracellular calcium and action mediated by other humoral factors, such as e.g. calcitonin the blood level of which rises promptly after acute induction of hypercalcaemia (Vora et al., 1978; Heynen et al., 1981) is not known. Evidence of an inhibitory action of calcitonin on PRL secretion was proved also by other authors (Ziliotto et al., 1981; Isaak et al., 1980). The phenomenon cannot be explained by changes of the extracellular calcium concentration. While the maximum of hormonal changes occurs between the 30th and 60th minute following i.v. calcitonin administration (Isaak et al., 1980), a significant decline of the blood calcium level in

healthy subjects was not recorded at all by some authors (Ziliotto et al., 1981) and we observed it only during the 90th minute after calcitonin administration (Žofková and Bednář, 1984).

Pecile et al. (1981) locate the site of calcitonin action in the hypothalamus, where it probably acts directly on the dopaminergic system. However, a direct effect on lactotrophic cells cannot be ruled out. The idea of a direct effect of calcitonin is supported by the bond of isotope-labelled calcitonin with hypothalamic and pituitary cell membranes (Flynn et al., 1981; Maurer et al., 1983). Hormonal effect could be attributed to a change in cytosolic calcium of the secreting cells. Although the exact mechanism of action of hypercalcaemia and calcitonin on PRL secretion remains open, the assessed analogy of the hormonal response to hypercalcaemia and calcitonin permits to assume possible mutual causal relations between hypercalcitoninaemia and inhibited PRL secretion which develop in acute hypercalcaemia. Raymond et al. (1983) proved experimentally during acute hypercalcaemia and hypocalcaemia the parallelism of changes in PRL levels and calcitonin or parathormone (PTH) levels, respectively. He considers therefore an inhibition or stimulation of PRL secretion during impaired calcium homeostasis as the consequence of an imbalance between calcitonin and PTH and not the direct action of extracellular calcium. However, from the work of other authors ensues that in hypercalcaemia changes of the PRL secretion do not depend on calcitonin levels (Kruse and Kracht, 1981). Calcitonin is, however, not the only possible mediator of secretory changes in the course of hypercalcaemia. PRL secretion may be modified by other humoral factors, the level of which rises during hypercalcaemia, e.g. by somatostatin (Cooper and Shin, 1981; Kanatsuka et al., 1981).

As acute hypercalcaemia and calcitonin inhibit also the secretion of thyrotrophic cells (Žofková et al., 1981; Žofková and Bednář, 1984), obviously no specific lactotroph inhibiting effect is involved but a more general molecular biological mechanism which influences the secretion of at least two adenopituitary hormones.

Finally, acute hypercalcaemia and intravenously administered salmon calcitonin inhibit the lactotrophic secretory reserve. This effect must be taken into account in all conditions associated with hypercalcaemia and hypercalcitoninaemia and during the therapeutic administration of calcitonin. The question of hormonal changes in the course of long-term calcitonin administration still remains open. The precise mechanism of the inhibitory action of hypercalcaemia on secretory activity of some adeno-pituitary trophic cells and the physiological impact of calcitonin in the regulation of PRL secretion remain to be elucidated.

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