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Acute Elevation of Endogenous Prolactin Does Not Influence Glucose Homeostasis in Healthy Men

M. VIGAŠ, I. KLIMEŠ, J. JURČOVIČOVÁ, D. JEŽOVÁ

Institute of Experimental Endocrinology, Slovak Academy of Sciences, Bratislava, Slovak Republic

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Summary

The diabetogenic effect of prolactin observed in patients with pathological hyperprolactinaemia was verified in healthy subjects. Plasma prolactin elevation was induced by administration of a dopamine antagonist drug domperidone (Motilium 10 mg orally, 9 subjects) and 2 h later the oral glucose tolerance test was performed. The influence of dopamine receptor stimulation on glucose homeostasis was tested by dopamine infusion (0.3 mg in saline or 20 % glucose, 1 g/min for 60 min, 11 subjects). After the blockade of dopamine receptors, a significant and prolonged increase of prolactin concentration was found. However, the levels of glucose, insulin, and C-peptide either before or after the glucose load were not different from control ones. The decreased number of insulin receptors (1.97 ± 0.41 vs 0.51 ± 0.14 pmol per 2.10^9 red blood cells) was compensated by increased affinity (0.51 ± 0.17 vs 1.00 ± 0.22 K_e 10^8 $mol.^{-1}$ per l]) of insulin receptors. The stimulation of dopamine receptors showed a negligible effect on glucose regulation. It may be suggested that an endogenous increase of prolactin concentration in the physiological range does not participate in the regulation of glucose homeostasis in healthy subjects.

Key words

Plasma prolactin – Glucose – C-peptide – Insulin – Insulin receptors

Introduction

The suggestion that prolactin has a diabetogenic effect arose from clinical investigations in hyperprolactinaemic patients (Landgraf *et al.* 1977, Johnston *et al.* 1980, Schernthaner *et al.* 1985) as well as *in vitro* (Sorenson *et al.* 1987, Cabrera *et al.* 1988) and *in vivo* (Brelje and Sorenson 1988, Brelje *et al.* 1989) animal studies using pharmacological doses of prolactin. The observed impairment of glucose tolerance seems to depend on a complex of factors, such as the degree of hyperprolactinaemia and the form of circulating prolactin (Sinha 1992). Thus the diabetogenic effect of prolactin was not confirmed in some other studies (Katz *et al.* 1981). Prolactin is a gestational hormone and its participation in decreased sensitivity to insulin during pregnancy in both humans (Cousins 1991) and animals (Ryan and Enns 1988) was postulated. Moreover, prolactin is released during hypoglycaemia in healthy as well as in diabetic subjects and is considered to be a contraregulatory hormone.

Even less clear is the effect of short, acute hyperprolactinaemia in healthy subjects. To our knowledge, the only pertinent information available is that cimetidine- (Eversmann *et al.* 1979) and sulpiride-induced (Hagen *et al.* 1979) increase in prolactin release failed to influence blood glucose, insulin release and glucose utilization. In spite of its potential physiological importance, the issue of prolactin and glucose homeostasis has not been studied recently.

The aim of our investigations was to follow the mutual relationship between prolactin release and glucose homeostasis in healthy men. Attention has been paid to some metabolic consequences of hyperprolactinaemia in the physiological range induced by dopamine receptor blockade, the role of dopamine receptors themselves for insulin release and glucose tolerance.

Material and Methods

Subjects

Healthy non-obese male volunteers aged 22–34 years gave informed written consent for participation in the study. The investigations started at 0730 h after an overnight fast. An indwelling catheter was inserted into the cubital vein for blood sampling. Infusions were given into the contralateral vein. The first blood sample for basal values was taken at least 30 min after inserting the catheter.

Insulin release and binding to receptors and glucose tolerance after hyperprolactinaemia induced by blockade of dopamine receptors

Domperidone (Motilium, JANSSEN) was given orally (10 mg) to 9 subjects immediately after the first blood sample had been withdrawn. Two hours after domperidone (or placebo) administration, the oral glucose tolerance test was performed (75 g of glucose in 400 ml water). Each subject participated in the study twice (placebo or domperidone) within a one-week interval, the order of the treatments being randomized.

Plasma concentrations of glucose, insulin, C-peptide and prolactin were determined during the investigation at the time intervals indicated in Fig. 1. Insulin binding to red blood cell receptors was assessed before domperidone administration and 2 h later (before glucose administration).

Insulin release and glucose tolerance after stimulation of dopamine receptors

Dopamine (Dopamine, GIULINI) was administered by intravenous infusion to 11 volunteers at the rate of 0.3 mg/min for 60 min. Dopamine was either diluted in 0.9 % NaCl (saline) or in 20 % glucose solution (1 g per minute). All subjects underwent both treatments. Six volunteers were also treated with saline and with glucose infusion without dopamine (control experiments). The time interval between different treatments in each subject was 5–8 days and the order of the treatments was randomized. Blood for glucose and insulin determination was collected as indicated in Table 1.

Hormone measurements

Plasma hormonal concentrations were measured by radioimmunoassays using commercial kits (PRL and C-peptide – UVVR, Czechoslovakia, IRI – OPIDI, Poland). Plasma glucose was determined by the glucose oxidase method (Oxochrom, LACHEMA). All samples of one trial were run in one assay in duplicates. For measurement of insulin binding to receptors on erythrocytes the method of Gambhir *et al.* (1978) was used as modified in our laboratory (Klimeš *et al.* 1986).

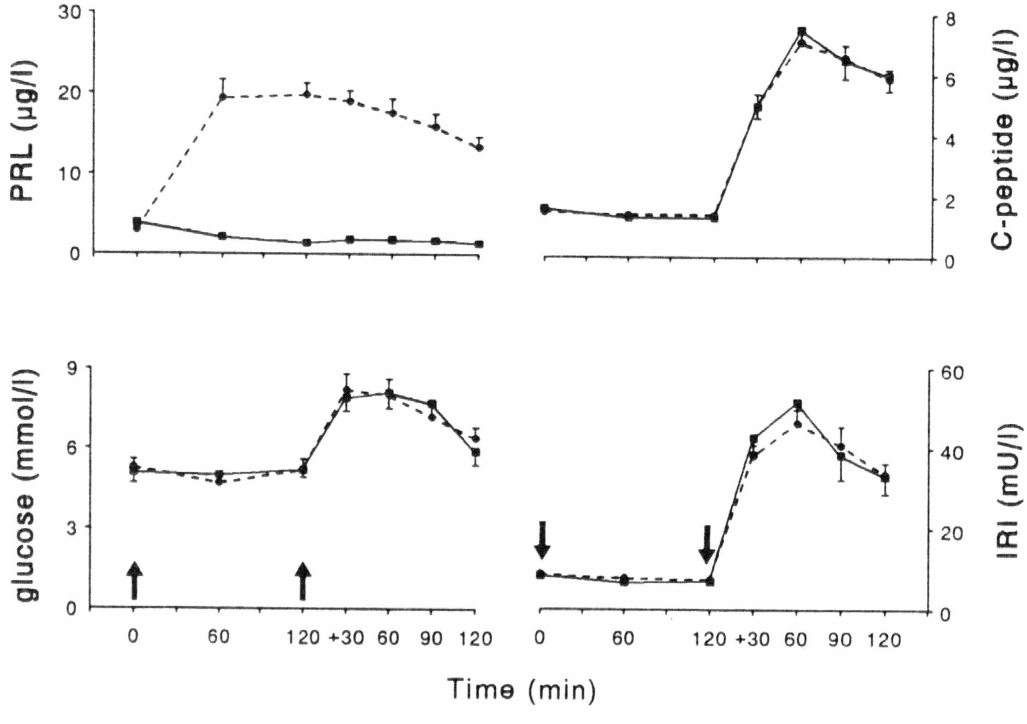

Fig. 1
Effect of domperidone-induced hyperprolactinaemia (black circles) on basal concentrations and glucose-induced increases of plasma glucose, C-peptide and insulin. Domperidone (10 mg, orally) was given at 0 min, glucose load (75 g) at 120 min. The difference in glucose, C-peptide and insulin concentrations between hyperprolactinaemic and control groups (black squares) are not significant. Mean of 9 subjects ± S.E.M.

The data were statistically evaluated by analysis of variance (ANOVA) followed by pair-wise comparisons according to Dunn and Dunnett.

Results

Insulin release, its binding to receptors and glucose tolerance after hyperprolactinaemia induced by blockade of dopamine receptors

The blockade of dopamine receptors by domperidone significantly elevate circulating prolactin levels. Plasma prolactin concentrations increased to a similar extent as after most physiological stimuli of lactotropic function. However, the rise in prolactin levels was found to be longlasting and the hormone concentrations did not decline to their initial values even at the end of the investigation.

Concentrations of plasma glucose, insulin and C-peptide were not influenced by increased prolactin levels during the first two hours of investigation. There was no difference in glucose, insulin and C-peptide responses to an oral glucose load during hyperprolactinaemia as compared to those in the control setting (Fig. 1).

The number of insulin receptors on red blood cells was significantly decreased after domperidone-induced hyperprolactinemia compared to that in the placebo study. Concurrently, however, the affinity of receptors to insulin was significantly increased (Fig. 2).

Insulin release and glucose tolerance after stimulation of dopamine receptors

Stimulation of dopamine receptors by dopamine infusion failed to influence plasma glucose concentrations. Dopamine infusion resulted in a statistically significant increase of insulin concentration, however, the hormone values were still within the normal range of basal insulin levels (Table 1).

Administration of glucose and dopamine was followed by similar plasma concentrations of glucose and insulin as recorded after administration of glucose alone (Table 1).

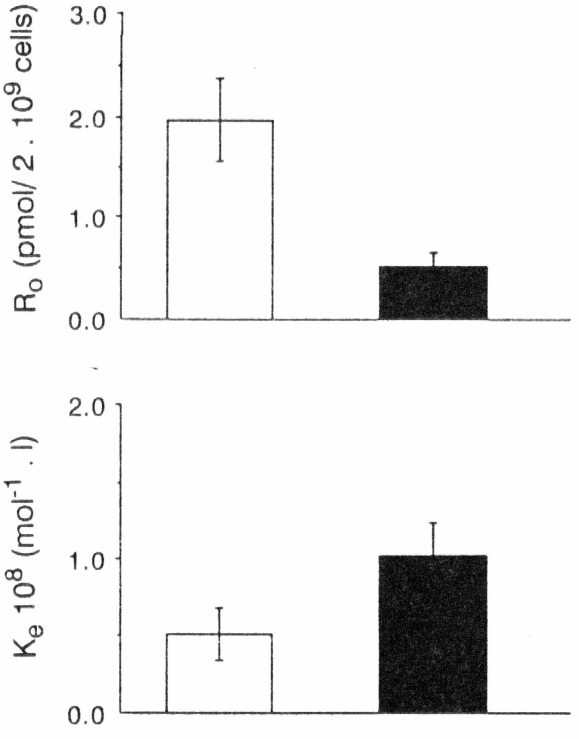

Fig. 2
Number of insulin receptors (upper panel) during domperidone-induced hyperprolactinaemia (black bar, $p<0.05$) vs control group (white bar). However, apparent affinity constant of insulin receptors on erythrocytes (lower panel) is increased ($p<0.05$). Samples were taken 2 h after domperidone (10 mg) or placebo administration. Mean of 9 subjects ± S.E.M.

Discussion

Several physiological and particularly stress stimuli triggering prolactin release are accompanied by changes in glucose tolerance. Obviously, such observations do not demonstrate a diabetogenic effect of prolactin as several other pituitary and peripheral hormones are released simultaneously. For a proper investigation, pharmacological stimulation of prolactin secretion with a negligible influence on other endocrine functions was required.

Such an approach was used in the present study in which the release of prolactin was induced by the domperidone blockade of dopamine receptors.. This blockade protects the pituitary lactotrophs from the inhibitory effect of central dopaminergic control (Martinez de la Escalera and Weiner 1992), which increases circulating prolactin levels similar to that usually observed after physiological stimulation such as exercise or hypoglycaemia. The data obtained show that selective acute hyperprolactinaemia induced by domperidone does not evoke pronounced changes in glucose homeostasis. After domperidone treatment, plasma glucose and insulin concentrations as well as glucose, insulin and C-peptide responses during the oral glucose tolerance test were the same as in the control setting. After acute hyperprolactinaemia, the number of insulin receptors on red blood cells was significantly decreased, yet the affinity of receptors to insulin was enhanced. Thus, though significant differences in individual insulin binding parameters were observed, the net effect seems to be balanced and no appreciable consequences for the biological action of insulin are to be expected.

Table 1
Plasma glucose and immunoreactive insulin after stimulation of dopamine receptors by dopamine infusion

Time (min)	Plasma glucose (mmol/l) 0	15	30	45	60	90
Saline	4.9±0.3	4.8±0.3	4.7±0.3	4.6±0.1	4.7±0.1	4.9±0.3
Saline + Dopamine	5.0±0.3	5.4±0.1	5.3±0.3	5.3±0.1	5.1±0.1	4.8±0.1
Glucose	4.9±0.3	8.6±0.6	11.1±0.9	11.8±2.2	13.2±1.3	8.8±0.5
Glucose + Dopamine	4.6±0.2	8.7±0.4	10.4±0.5	11.2±0.6	11.0±0.7	7.1±1.1
Time (min)	**Plasma insulin (mU/l) 0**	**15**	**30**	**45**	**60**	**90**
Saline	7.8±1.3	6.3±1.5	6.0±1.3	4.8±1.3	8.0±3.3	8.5±2.5
Saline + Dopamine	6.7±1.3	13.3±2.5[a]	12.5±2.1[a]	10.9±2.1[a]	8.4±1.6	4.6±1.1
Glucose	13.2±2.8	64.4±17.4	67.0±18.0	58.4±19.2	88.0±20.7	78.8±23.1
Glucose + Dopamine	6.3±2.1	43.8±10.1	48.0±10.6	58.4±11.5	67.5±18.0	22.1±3.3

Effect of dopamine infusion (0.3 mg per min) for 60 min in 0.9 % saline or glucose solution (20 %, 1 g per min) in 11 subjects and saline or glucose infusion (1 g per min) in 6 subjects on plasma concentrations of glucose and insulin. Sample "0 min" was taken immediately before drug administration. Means ± SEM. [a]$p<0.05$ vs basal value (0 min) and vs appropriate intervals in the saline group.

Despite the evidence presented, the possibility had to be excluded that the dopaminergic blockade for stimulation of prolactin release could itself interfere directly with glucose homeostasis and mask the effects of prolactin. To clarify this point, we evaluated the role of dopamine for glucose tolerance. The effect of dopamine on glucose regulation was studied less thoroughly than the effects of epinephrine or norepinephrine (Havel and Taborsky 1989). In our previous investigations in male subjects, the administration of the dopamine precursor L-dihydroxyphenylalanine resulted in a mild increase of glucagon levels without changes in insulin and glucose concentrations (Klimeš *et al.* 1978). Leblanc *et al.* (1977) found a small increase in glucagon, insulin and glucose concentrations in response to a large dose of dopamine. Stimulation of dopamine receptors by apomorphine was without any effect (Huupponen *et al.* 1985). In agreement with the data of Leblanc *et al.* (1977), dopamine infusion in the present study induced a mild increase in insulin concentration. The hormone levels remained in the range of normal basal values and the plasma glucose concentration was not changed. Furthermore, plasma insulin and glucose levels measured after glucose ingestion failed to be modified by simultaneous administration of dopamine. These results show that the role of dopamine receptors in glucose regulation is negligible and make it possible to suggest that our results during acute hyperprolactinaemia were not affected by the direct action of the dopamine blockade on glucose homeostasis.

In accord with our observations, the importance of prolactin in pregnancy complicated by gestational diabetes mellitus has not been convincingly established (Cousins 1991). The postbinding effect of insulin action during pregnancy is related to placental lactogen concentrations rather than to circulating prolactin (Schmitz *et al.* 1985). Therefore, it may be concluded that, under physiological conditions, prolactin does not play an important role in the regulation of glucose homeostasis in man.

It may be concluded that the diabetogenic effect of prolactin occurs only after pathological concentrations of the hormone, as found in some patients with prolactinoma. Under physiological conditions, at least in male subjects, prolactin fails to exert any important influence on glucose homeostasis and can thus hardly play the role of a contraregulatory hormone during hypoglycaemia.

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Reprint Requests

M. Vigaš, M.D., D.Sc., Institute of Experimental Endocrinology, Slovak Academy of Sciences, 83306 Bratislava, Vlárska 3, Slovak Republic.