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Feedback inhibition of insulin secretion and insulin resistance in polycystic ovarian syndrome with and without obesity

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Abstract. – Hyperinsulinemia/insulin resistance is a well-known feature of polycystic ovarian (PCO) syndrome. In this study, the comparative roles of the peripheral tissues and the pancreatic beta-cells in its pathogenesis were evaluated.

We determined basal serum C-peptide values (index of insulin secretion) and in vivo insulin action on peripheral glucose utilization (by the euglycemic hyperinsulinemic clamp technique) in obese (n=5) and nonobese (n=5) PCO women compared to obese (n=5) and nonobese (n=5) normal ovulatory women. During the clamp, feedback inhibition of insulin on insulin secretion was studied by C-peptide percentage suppression. Serum C-peptide basal values did not differ significantly between the four groups. Insulin stimulated glucose utilization, expressed as M-value, was significantly decreased in both PCO groups compared to normal ovulatory women ($p<0.005$). The metabolic clearance rate of glucose (MCR) and insulin (M/I) had the same behaviour. No differences were found between M, MCR and M/I values and the two groups of PCO subjects (obese/nonobese). The C-peptide percentage suppression was similar in all the groups.

We conclude that PCO women have a significant insulin resistance that is indipendent of obesity, while basal and insulin-inhibited insulin secretion do not differ from normal-cycle subjects.

Key Words:

Polycystic ovarian syndrome, Insulin secretion, Insulin/insulin feed-back, Insulin resistance.

Introduction

Polycystic ovarian (PCO) syndrome is a complex disorder of unknown etiology, clinically and endocrinologically characterized by menstrual disfunctions, hirsutism, infertility, obesity, ovarian hyperandrogenism, and preferential hypersecretion of LH, together with the presence of bylateral polycystic ovaries[1,2].

Hyperinsulinemia[3] and decreased insulin-mediated glucose uptake[4,5], as expressions of insulin resistance, have in recent years become established as features of PCO, consistently found among obese women[6] but varyingly in nonobese subjects[7].

The circulating insulin levels are the result of the rate of insulin secretion and of its metabolic clearance rate. Secretion is in turn influenced by a complex of stimulatory and inhibitory influences on the beta cell. Among the inhibitory influences is the possibility of a direct or indirect negative feedback of circulating insulin on beta-cell secretion[8].

A more reliable assessment of insulin sensitivity and resistance can be made by euglycemic hyperinsulinemic clamp[9]. Using this technique, it is possible also to evaluate the insulin/insulin negative short-loop feed-back (by C-peptide percentage suppression), as further index of the beta-cell function[10].

The aim of the present study was to evaluate separately insulin secretion and peripheral insulin sensitivity in PCO obese and nonobese women compared to normal-cycle (NC) obese and nonobese control subjects.

Subject and Material

PCO subjects: Ten women between the ages of 20 and 29 yr (24 ± 3.48 yr) were studied. All were characterized by amenorrhea or

Table I. Endocrine pattern in PCO and NC subjects.

	PCOS	NC
FSH (mU/ml)	9.5 ± 2.4	7.2 ± 3.1
LH (mU/ml)	34 ± 7.5*	10.2 ± 2.3
PRL (ng/ml)	17.5 ± 4.0	7.5 ± 2.5
E1 (pg/ml)	104 ± 20.2*	50.5 ± 12
E2 (pg/ml)	57.4 ± 17.5	10.3 ± 10.4
PROG (ng/ml)	0.3 ± 0.7	0.3 ± 0.2
T (ng/ml)	1.5 ± 0.8	0.7 ± 0.2
A (ng/ml)	3.8 ± 1.5*	1.8 ± 1.1
DHEA (ng/ml)	13.2 ± 2.8*	7.2 ± 2.5
SHBG (μg%ml)	1.5 ± 0.3*	2.3 ± 0.4

M ± DS
*p <0.05 vs. NC

persistent oligomenorrhea of perimenarchial onset, and clinical or biochemical evidence of hyperandrogenism, high LH/FSH ratio (> 2.5) (Table I) and polycystic ovaries documented by ultrasonography.

On the basis of clinical examination there was no evidence of acanthosis nigricans. The average body mass index (BMI) of the group was 28.41 ± 8.07 kg/m^2 (range 18-46). Five of the subjects were nonobese (BMI < 27) (NO-PCO), the remainder (n= 5) could be classified as obese (BMI > 27) (O-PCO).

Normal subjects: Ten normal cycling (NC) women matched for age (range 19-30 yr; 24.5 ± 2.8 yr, p= ns) and BMI (28.14 ± 7.94 kg/m^2, p= ns, range 18.7-43.1) served as controls. The distribution between nonobese (n=5) (NO-NC) and obese (n=5) (O-NC) was the same as the PCO group. They were in general good health, with no clinical and biochemical evidence of hyperandrogenism (Table I). All had 27-32 day cycles, and were

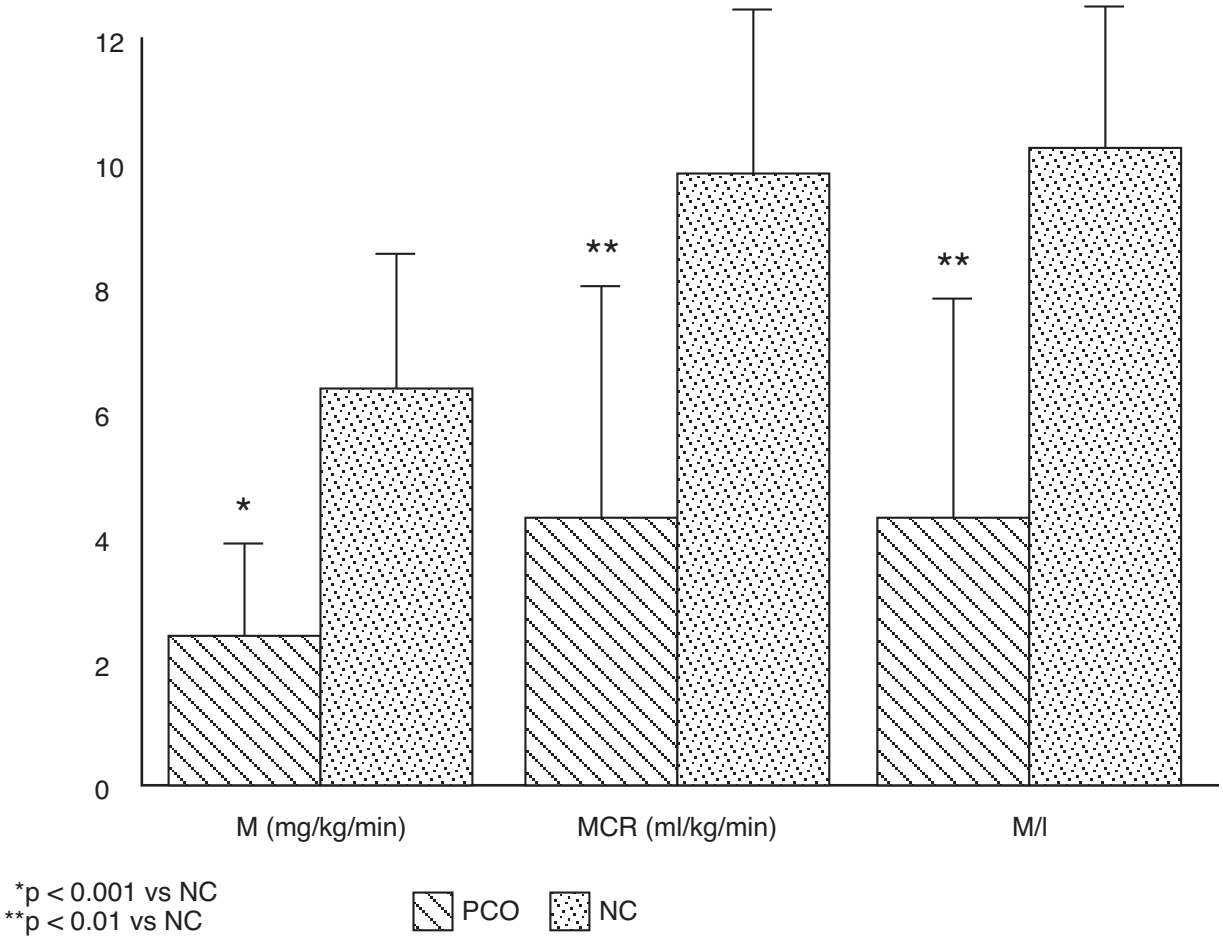

Figure 1. M, MCR and M/I values in PCO and NC subjects.

studied during the early follicular phase (days 2-11) of the menstrual cycle.

Neither PCO nor NC subjects had used any hormonal preparation during the 3 months preceeding the study.

Informed written consent was obtained from each subject.

Methods

This study was performed in the follicular phase of the cycle on days 2-11 in the normal women and during a period of amenorrhea in the PCO women.

After an overnight fast, subjects were admitted to the University Hospital at 8.00 h. Indwelling catheters were placed in both antecubital areas and kept open with a slow saline infusion for blood sampling.

An euglycemic hyperinsulinemic clamp[9] (insulin infusion rate for 120 min: 1 mU/Kg /min) was performed in order to evaluate the insulin-induced glucose utilization in the last 40 min of steady-state. Plasma glucose was measured every 5 min. (Beckman Glucose Analyzer) and 20% glucose was infused to maintain the plasma glucose at the target level of approximately 5 mmol/l using an infusion pump. Blood samples for free-insulin and C-peptide determinations (radioimmunoassay) were drawn at 0', 30', 60', 90' and 120' during clamp. The glucose disposal (M) during the glucose clamp was calculated on the basis of the amount of glucose infused and is expressed per kilogram body weight (mg/kg/min). Metabolic clearance rate of glucose (MCR) is calculated dividing the M-value by the mean plasma glucose concentration (ml/kg/min). The M/I ratio (the amount of glucose metabolized per unit of plasma insulin) as a measure of the tissue sensivity to the attained insulin concentration was calculated by dividing M by the mean insulin concentration during the last 60 min of the clamp. For conve-

Table II. Basal C-peptide values in the four subgroups of subjects.

Groups	Basal CPR (ng/ml)
NO-PCO	1.97 ± 0.97
O-PCO	4.02 ± 3.14
NO-NC	1.69 ± 0.48
O-NC	1.37 ± 1.07

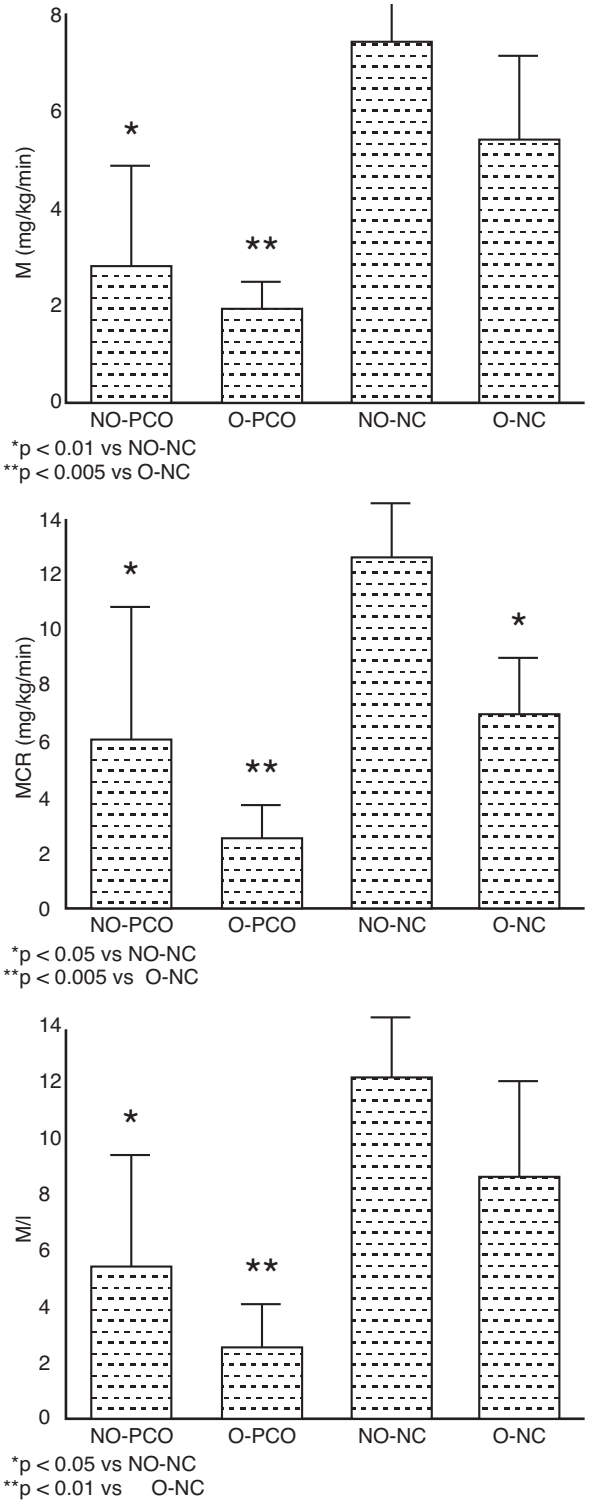

Figure 2. M, MCR and M/I values in the four subgroups of subjects.

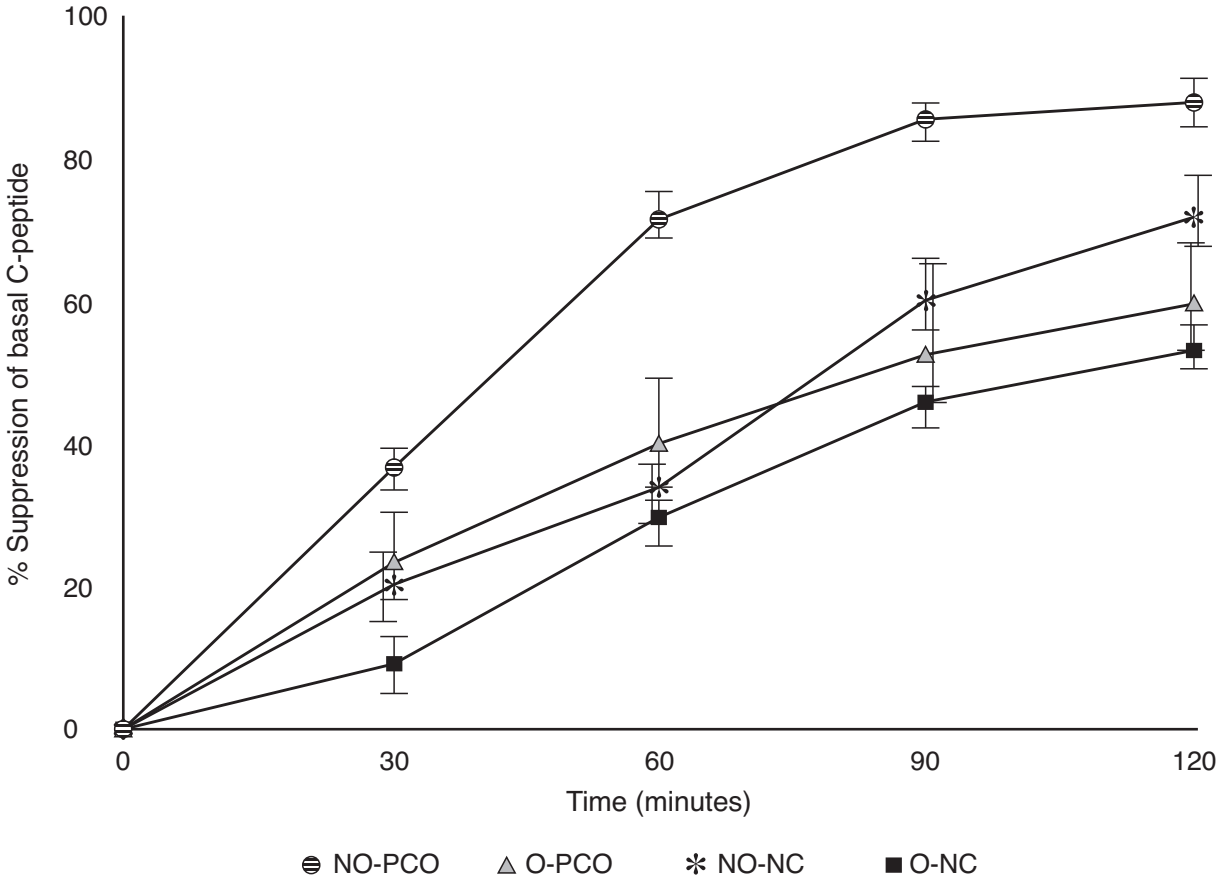

Figure 3. Percentage suppression of basal C-peptide during glucose clamp in the four subgroups of subjects.

nience M/I ratio was multiplied by 100. Data are expressed as mean ± SD. Statistical analysis was performed by Student t test for unpaired data; the percentage suppression of C-peptide levels during clamp vs. basal values was also calculated.

P< 0.05 was regarded as significant.

Results

C-peptide basal values are not different between the PCO and NC groups (respectively, 3 ± 2.4 and 1.53 ± 0.80 ng/ml, p n.s.). By dividing the groups according to body excess, no significant difference remains between the four subgroups in basal C-peptide (Table II).

On the contrary, M, MCR and M/I values are significantly lower in PCO vs. NC (p< 0.005) (Figure 1).

Neither difference is demonstrated in M, MCR and M/I values between O-PCO and NO-PCO subgroups, nor between NC ones, except for MCR. Significant differences are shown, on the contrary, in M, MCR and M/I considering separately the obese and nonobese subjects (PCO vs. NC) (Figure 2).

The insulin/insulin negative short-loop feed-back, evaluated as percentage suppression of C-peptide values during the glucose-clamp, is not different between the four subgroups of subjects (Figure 3).

Discussion

At first, our data show a severe peripheric insulin resistance in PCO women, either in nonobese as in obese subjects. In fact, the insulin-induced glucose utilization parameters (M, MCR, M/I values) are in PCO subjects sig-

nificantly lower than in NC ones, and in the PCO subgroups (obese and nonobese) the same parameters are not different by each one. So, our PCO patients show an insulin resistance state despite the obesity. Furthermore, in our young subjects the insulin resistance of the PCO is not additive to that one of obesity, because the obese patients with this syndrome are not more insulin resistant than their nonobese counterparts, as suggested otherwise[1].

The beta-cell function, considering the C-peptide basal values and the insulin/insulin negative short-loop feed-back, evaluated as percentage suppression of C-peptide levels during the glucose clamp, is normal in all the groups.

These results are in agreement with that ones of Dunaif et al[4], who demonstrated the profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome.

The cause of insulin resistance in these patients is still not fully understood. Dunaif et al[12] demostrated a defect of tyrosine-kinase activity in some patients with polycystic ovary syndrome. Ciaraldi et al[13] found tyrosine-kinase activity in polycystic ovary syndrome to be normal. However, they demonstrated an unique defect of glucose transport in adipocytes from patients with the syndrome.

Despite the normal insulin-receptor number and tyrosine kinase activity, the insulin resistance in PCO involves a novel postreceptor defect in the insulin signal transduction chain between the receptor kinase and glucose transport.

A hypersecretion of insulin, not demostrated in our PCO young patients but present in other reports[14], is probably produced by a perfectly functioning beta-cell, as a compensatory response to the peripheral insulin resistance.

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