Drug Development Research 2:95-99 (1982)

Effect of Cyproterone Acetate and Conjugated Estrogens on the Human Insulin Receptor

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ABSTRACT

De Pirro, R., F. Forte, M. Liberti, M. Gallucci, F. Monaco, and R. Lauro: Effect of cyproterone acetate and conjugated estrogens on the human insulin receptor. Drug Dev. Res. 2:095-099, 1982.

It has recently been reported that prednisone increases whereas dexamethasone and cortisone decrease insulin binding to monocytes, thus suggesting that different steroids may exert opposite effects on the insulin receptor, depending on their chemical structure. In order to gain further insight into the modulations of the insulin receptor by other steroids, the effect in male patients of short- and long-term oral treatment with cyproterone acetate (100-150 mg/day) or conjugated estrogens (20 mg/day) was evaluated. Cyproterone acetate did not produce any statistical, evident change in insulin binding to monocytes after either short-term (5 days) or long-term (1 year) treatment. Short-term (5 days) administration of conjugated estrogens did not affect insulin binding; however, long-term (1 year) treatment produced a highly significant decrease in insulin binding due mainly to changes in receptor concentration. Thus, cyproterone acetate does not affect the insulin receptor, whereas conjugated estrogens reduce insulin receptors after long-term treatment, as with dexamethasone and cortisone.

Estrogens probably play a role in the insulin binding impairment which occurs during the luteal phase of the menstrual cycle as well as in users of the "pill."

Key words: cyproterone acetate, conjugated estrogens, insulin receptor, steroids

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0272-4391/82/0201-0095$02.00

INTRODUCTION

Various physiological and pathological conditions are characterized by variations in the insulin receptor status [Bar et al., 1976; Beck-Nielsen, 1978; Bertoli et al., 1980a; De Pirro et al., 1978; De Pirro et al., 1979; De Pirro et al., 1980a; Olefsky 1976a, b]; in particular, insulin-resistant states are often associated with decreased receptor concentration and/or affinity [Bar et al., 1976; Beck-Nielsen 1978; De Pirro et al., 1980a; De Pirro et al., 1980c; Olefsky 1976a, b]. Insulin resistance following glucocorticoid administration is well documented and some early studies indicated that corticosteroids induce insulin receptor impairment [De Pirro et al., 1980b; Goldfine et al., 1973; Kahn et al., 1978; Krauth and Schillinger 1977; Olefsky et al., 1975]. More recently, however, it has been demonstrated that some glucocorticoids also have opposite effects on the receptor concentration; in fact, whereas dexamethasone and cortisone produce decreased receptor concentration and/or affinity [De Pirro et al., 1980b; Goldfine et al., 1973; Kahn et al., 1978; Olefsky et al., 1975], prednisone [Beck-Nielsen et al., 1980] and its active metabolite prednisolone [De Pirro et al., 1981b] induce an increase in receptor concentration.

In order to gain further insight into the modulations of the insulin receptor by other steroids, investigations were carried out to study the effect of two steroids widely used in clinical practice.

MATERIALS AND METHODS

Seventeen patients, aged 57–72 years, with cancer of the prostate and six patients aged 15–22 years, with hypospadia were investigated; all were nonobese [Documenta Geigy, 1978] and presented no overt modification in glucose metabolism. All patients were volunteers, informed about the study and all gave written consent.

In the group of patients with cancer of the prostrate six were studied both at the time of diagnosis and after five days of treatment with cyproterone acetate (Androcur, 100–150 mg/day per os), six were studied after 1 year of cyproterone acetate treatment at the same doses and five were studied after 1 year of treatment with conjugated estrogens (Premarin, 20 mg/day per os). The patients with hypospadia were studied upon admission and after 5 days of treatment with conjugated estrogens (20 mg/day per os) prior to surgery for hypospadia repair. Insulin binding studies were carried out as previously described [De Pirro et al., 1979] on monocytes obtained from 70 ml of blood drawn at 08:00 hr, after overnight fasting, from an antecubital vein. Labeled insulin (180–200 μCi/μg) was purchased from CEA-IRE SORIN, Saluggia, Italy. Analysis of variance was used for statistical analyses.

RESULTS

Studies performed before the beginning of treatment showed that no difference exists in insulin binding to monocytes between boys with hypospadia and patients with prostatic cancer (data not shown); furthermore, comparison of data obtained in these two groups and those previously described in healthy male subjects [Bertoli et al., 1980a; De Pirro et al., 1978; De Pirro et al., 1979] demonstrated that the disease states do not induce any variation in insulin receptor concentration and/or affinity (data not shown). Studies performed at time of diagnosis were thus used as controls.

Cyproterone acetate (CPA) did not induce any statistical change in insulin binding to monocytes after either 5 days or 1 year of treatment (Fig. 1); furthermore, this steroid did not produce any variation in receptor concentration or receptor affinity as suggested by overlapping of competition–inhibition curves obtained in controls and in treated patients (Fig. 2). Conversely, conjugated estrogen (CE) treatment induced a variation in insulin binding ($p < 0.05$; df 2,20; $F = 3.87$) due to decreased binding after 1 year of treatment ($p < 0.02$; df 1,16; $F = 7.54$) (Fig. 1); 5 days of treatment was without any effect (p = NS; df 1,17; $F = 0.16$) (Figs. 1, 3). On account of the well-known controversy regarding the presence of one or more insulin binding sites [De Meyts and Roth, 1975; Maturo and Hollenberg, 1978; Pollet et al., 1977], a

model able to give the precise number of receptors or the value of receptor affinity, is still lacking; thus it is difficult to decide whether insulin binding reduction is due to a change in receptor concentration or to a variation in receptor affinity. On the other hand 1 year of estrogen treatment does not appear to produce gross changes in the shape of the Scatchard plot (Fig. 4), thus suggesting that these compounds affect receptor concentration rather than receptor affinity.

DISCUSSION

Five days or 1 year of treatment with cyproterone acetate, at doses used in the management of prostatic cancer do not induce variations in insulin binding to monocytes or in receptor concentration and/or affinity, thus suggesting that progestational steroids with antiandrogen activity do not affect the insulin receptor. It has recently been reported that cyproterone acetate induces a decrease in the insulin receptor number of adipocytes from female, treated rats [Krauth and Schillinger, 1977]. The reason for the apparent discrepancy between our results and those reported by those authors is not clear; it might be due to the different model (human monocytes vs rat adipocytes) or to the different sex investigated. The latter might be of importance, since it would suggest that there may be different reactivity to some steroids between male and female insulin receptors or that steroids act through factors differently affected according to sex.

Estrogens, on the contrary, exert an effect even if after several days; in fact 5 days of treatment showed no effect, whereas 1 year of treatment produced insulin binding impairment due to decreased insulin receptor concentration.

In recent years some authors have demonstrated insulin binding impairment due to steroid treatment [Goldfine et al., 1973; Kahn et al., 1978; Krauth and Schillinger, 1977; Olefsky et al., 1975] in agreement with the well-known steroid-induced insulin resistance. The later demonstration that prednisone and prednisolone induce insulin binding improvement [Beck-

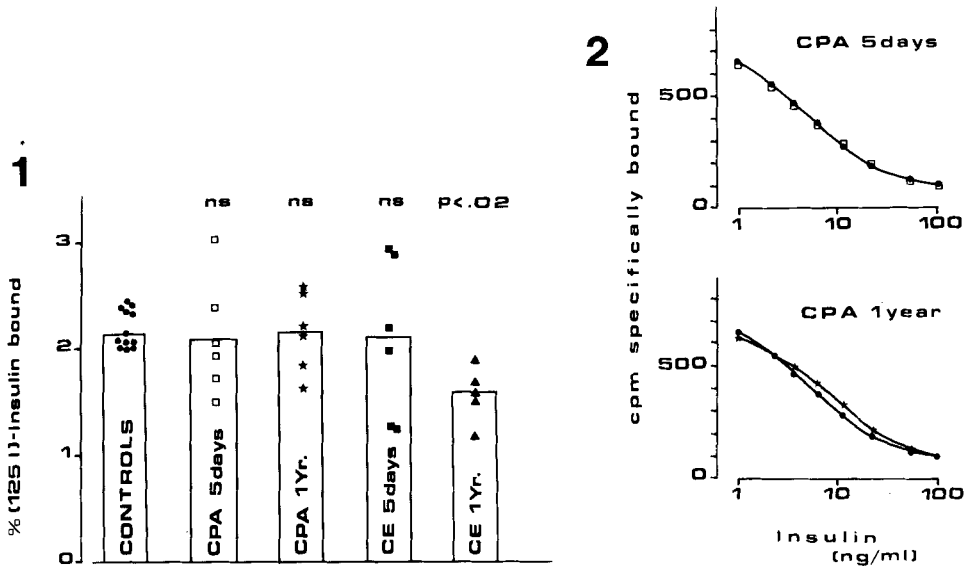

Fig. 1. Effect of cyproterone acetate (CPA) and conjugated estrogens (CE) treatment on [^{125}I]insulin (1 ng/ml) specific binding to 4 × 10^6 monocytes/ml. Mononuclear cells were incubated in Tris-HCl, 0.1% BSA (pH 7.8) buffer for 100 min at 15°C.

Fig. 2. Effect of cyproterone acetate (CPA) treatment on competition-inhibition effect of porcine insulin on [^{125}I]insulin binding to 4 × 10^6 monocytes/ml. Controls (●); treated 5 days (□); treated 1 year (*).

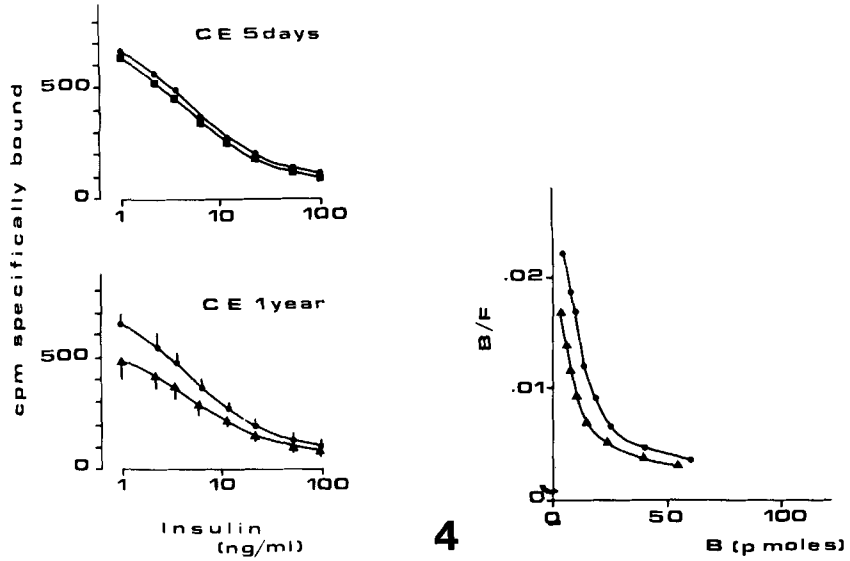

Fig. 3. Effect of conjugated estrogens (CE) treatment on competition-inhibition effect of porcine insulin on [^{125}I]insulin binding to 4 × 10^6 monocytes/ml. Controls (●); treated 5 days (■); treated 1 year (▲).

Fig. 4. Scatchard analysis [Scatchard, 1949] of data presented in Figure 3, lower panel. Controls (●); 1 year of conjugated estrogens treatment (▲).

Nielsen et al., 1980; De Pirro et al., 1981b], on the other hand, has suggested that the effect of steroids upon the receptor molecule may differ depending upon their chemical structure. The present data demonstrate and confirm that the steroid effect on the insulin receptor differs according to the compound and the length of treatment; in fact decreased binding has been reported within a few hours of treatment with cortisone and dexamethasone [De Pirro et al., 1980b] but only after several days treatment with estrogens. No effect has been found after treatment with cyproterone acetate and increased binding has been reported after prednisone or prednisolone administration [Beck-Nielsen et al., 1980; De Pirro et al., 1981b]. This would be in keeping with some observations appearing in the literature some years ago on the different effect of steroids on glucose metabolism; for example, it has been reported that medroxyprogesterone acetate impairs, whereas 17α-hydroxyprogesterone enhances, glucose tolerance [Benjamin and Casper, 1966; Muggia et al., 1968].

It has been demonstrated that during the menstrual cycle, insulin binding is higher in the follicular than in the luteal phase [De Pirro et al., 1978] and that an inverse relationship exists between these insulin binding changes and serum estradiol, 17α-hydroxyprogesterone, or progesterone variations [Bertoli et al., 1980b]; furthermore, it has been reported that women taking estrogen/progestagen compounds for contraceptive purposes have decreased insulin binding [De Pirro et al., 1981a]. The present data appear to suggest that estrogens may play a role and progestagens might have a minor effect in these receptor changes.

ACKNOWLEDGMENTS

This study was performed in part with a grant from ISIS, Sezione Scientifica.

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