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Metabolic consequences of hyperinsulinaemia imposed on normal rats on glucose handling by white adipose tissue, muscles and liver

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The effects of hyperinsulinaemia imposed on normal rats on the subsequent insulin-responsiveness *in vivo* of 2-deoxy-D-glucose uptake of white adipose tissue and of various muscle types were investigated. This was done by treating normal rats with insulin via osmotic minipumps, and by comparing them with saline-infused controls. Hyperinsulinaemia produced by prior insulin treatment resulted in a well-tolerated hypoglycaemia. At the end of the treatment, the glucose utilization index of individual tissues was determined by euglycaemic/hyperinsulinaemic clamps associated with the labelled 2-deoxy-D-glucose method. Prior insulin treatment resulted in increased insulin-responsiveness of the glucose utilization index of white adipose tissue, and in increased total lipogenesis in white adipose tissue and fat-pad weight. In contrast, prior insulin treatment resulted in a decreased glucose utilization index of several muscles. These opposite effects of hyperinsulinaemia on glucose utilization in white adipose tissue and muscles persisted when the hypoglycaemia-induced catecholamine output was prevented (adrenomedullectomy, propranolol treatment), as well as when hypoglycaemia was normalized by concomitant insulin treatment and glucose infusion. Insulin suppressed hepatic glucose production during the clamps in insulin-treated rats as in the respective controls, whereas total hepatic lipid synthesis and liver fat content were greater in rats treated with insulin than in controls. It is concluded that hyperinsulinaemia itself could be one of the driving forces responsible for producing increased glucose utilization by white adipose tissue, increased total lipid synthesis with fat accumulation in adipose tissue and the liver, together with an insulin-resistant state at the muscular level.

INTRODUCTION

Previous experiments have been carried out in an attempt to decide whether tissues become insulin-resistant or insulin-hyper-responsive when exposed to hyperinsulinaemia. In adipose tissue, a decrease in the sensitivity of the glucose-transport process to insulin was observed in isolated cells obtained from normal humans or rodents previously exposed to hyperinsulinaemia for 6 h or 14 days [1–3]. Decreased sensitivity and responsiveness of glucose transport to insulin were also observed in cultured rat adipocytes after exposure (6–24 h) to insulin [4]. In contrast, other studies have reported the occurrence of increased sensitivity and/or responsiveness of the glucose-transport process to insulin in isolated adipocytes obtained from normal rats made hyperinsulinaemic for 1–2 weeks [5–7].

In muscle (epitrochlearis), exposure to insulin *in vitro* for 1–5 h led to an increased responsiveness of glucose transport to insulin [8]. Analogous data were obtained for glucose utilization in incubated soleus muscles obtained from normal rats treated for 2 weeks with insulin [5]. When, however, such an insulin treatment was prolonged to 6 weeks, the stimulatory effect just noted was no longer present [5].

The above-mentioned data are conflicting, possibly because the degree of hyperinsulinaemia, the duration of the latter, the target tissue considered and other unknown variables may all be of importance in altering tissue sensitivity and/or responsiveness to the hormone [1–8]. Owing to these considerations, the present work was undertaken to attempt to study the relationship between hyperinsulinaemia and glucose uptake by white adipose tissue and by various muscles, as well as that between hyperinsulinaemia and hepatic glucose metabolism. For this purpose, normal rats infused with saline or insulin (both delivered by minipumps) were compared. At the end of the respective saline or insulin infusion, euglycaemic/hyperinsulinaemic clamps associated with the labelled 2-deoxy-D-glucose method were performed to measure, in particular, maximal insulin-stimulated glucose utilization *in vivo* (i.e. responsiveness of this process to the hormone) of white adipose tissue, as well as that of muscles.

MATERIALS AND METHODS

Lean female heterozygote Zucker (FA/?) rats, weighing about 200 g, were used throughout the study. The animals were housed in individual cages. Control and insulin-treated rats (2 units/day) had free access to water and a standard laboratory chow (Lacta 299; Provimi-Lacta S.A., Cossonay, Switzerland). When insulin-treated rats received 4 units of insulin per day they had, like their respective saline-infused controls, free access to chow and water containing 10% (w/v) sucrose. Body weight, food and (when added) sucrose intake were measured daily.

Five groups of rats were included in the study: control rats that were infused with iso-osmotic saline; rats that were treated with insulin (2 units of insulin/day or more, as treatment with 1 unit of insulin/day was ineffective in modifying most of the parameters measured, although it increased glucose utilization by white adipose tissue; results not shown); rats that were treated with insulin and adrenomedullectomized; rats that were treated with insulin and propranolol; rats that were treated with insulin and infused with glucose to maintain normoglycaemia. All the rats were anaesthetized with diethyl ether and implanted subcutaneously with osmotic minipump(s) (Alzet 2001; Alza Corp., Palo Alto, CA, U.S.A.) containing either saline or insulin. Insulin was the U-400 human insulin (Hoe 21 PH; Hoechst A.G., Frankfurt am Main, Germany; kindly provided by Mr. M. Zoltobrocki), and insulin treatment consisted of the infusion of 2 or 4 units of the hormone/day at a rate of 1 μl/h for 3 or 4 days, as indicated in Table 1. Adrenomedullectomy was performed as described elsewhere [9]. When propranolol treatment (via minipumps) was made (1 mg/kg per day), ascorbic

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acid (0.1 mg/ml) was added to the solution to prevent its oxidation [10]. In adrenomedullectomized or propranolol-treated rats, the high insulin doses (4 units/day) were purposely infused to produce the occurrence of maximal adrenergic responses. When glucose was infused to prevent the insulin-induced hypoglycaemia of animals treated with insulin, chronic jugular catheters were implanted to allow for the infusion of a glucose solution (400 mg/ml), as well as for blood sampling to measure plasma glucose. This was done by using a home-made device consisting of a swivel and an oscillating arm allowing the animals to move freely.

The glucose utilization index was measured in fed rats during euglycaemic/hyperinsulinaemic clamps associated with the 2-deoxy-D-[1-^{3}H]glucose technique [11]. For the clamps, rats were anaesthetized with Nembutal (50 mg/kg, intraperitoneally), and catheters were inserted into the right jugular vein for infusions and into the left carotid artery for blood sampling [12]. All minipumps were removed just before the clamps were started. Body temperature was maintained at 37 °C with a heating blanket connected to a rectal probe. Blood was sampled via the carotid catheter for measurements of blood glucose and tracer specific radioactivities. After killing, the parametrial white adipose tissue, the soleus, the extensor digitorum longus, the epitrochlearis, the tibialis and the diaphragm were removed, and their content of 2-deoxy[1-^{3}H]glucose 6-phosphate was determined, as previously described [11,13]. The glucose utilization index was derived from the amount of 2-deoxy[1-^{3}H]glucose 6-phosphate measured in the various tissues and is expressed as ng/mg per min, as justified elsewhere [14,15]. Mean steady-state insulinaemia values achieved during the clamps were 876 ± 83 μunits/ml in saline-treated controls and 1163 ± 72 μunits/ml in the various insulin-treated groups ($P < 0.05$). These insulinaemia values enabled study of tissue responsiveness (i.e. maximal response), not tissue sensitivity to the hormone.

In separate experiments, [^{14}C]glucose incorporation rate into muscle glycogen was measured in saline- or insulin-treated fed rats during euglycaemic/hyperinsulinaemic clamps, as reported elsewhere [15], by using the same protocol as that described above for determination of the glucose utilization index, but with D-[U-^{14}C]glucose (50 μCi/rat) being administered as a bolus instead of 2-deoxy-D-[^{3}H]glucose. At the end of the clamps, rats were killed, and muscles were removed and frozen to measure [^{14}C]glucose carbon incorporation rate into glycogen (ng/mg per min), as previously described [15]. Independent groups of fed saline-infused or insulin-treated rats (2 units/day) were also killed at the end of the respective treatment to determine basal (i.e. without carrying out clamps) unlabelled glycogen content of muscles and of the liver, hepatic triacylglycerol content, and total inguinal fat-pad weight.

In additional experiments, total lipid synthesis was studied in saline-infused or insulin-treated fed rats, again during euglycaemic/hyperinsulinaemic clamps and via the incorporation of ^{3}H from ^3H_2O into total lipids of white adipose tissue and of th[illegible] 16,17]. Then 4 mCi of ^3H_2O was administered as a bolus 30 min after the initiation of the clamps. Blood samples were taken to measure the specific radioactivity of ^3H_2O. Liver and white adipose tissue were removed and frozen to measure the rate of ^{3}H incorporation into total lipids, expressed as μg-atoms of ^{3}H/h per g, by taking a plasma water content of 55 M [18].

Finally, other saline- or insulin-treated rats were used to assess hepatic glucose production and total glucose metabolism during euglycaemic/hyperinsulinaemic clamps, as described above, but in this instance 2 h after food removal. Hepatic glucose production and total glucose turnover rate were measured by infusing D-[6-^{3}H]glucose and were calculated as previously described [12].

Plasma glucose was determined by the glucose oxidase method (Beckman glucose analyser 2). Plasma insulin was measured by radioimmunoassay, with dextran-coated charcoal to separate free from bound insulin [19]. Human standards were used to determine the insulinaemia reached either during insulin treatment of the rats or during the clamps. Rat insulin standards were used to determine basal insulinaemia of control rats.

For measurements of the specific radioactivity of 2-deoxy-D-[1-^{3}H]glucose, D-[U-^{14}C]glucose, ^3H_2O or [6-^{3}H]glucose, 50 μl of arterial blood was deproteinized in 250 μl of $ZnSO_4$ (0.3 M) and 250 μl of $Ba(OH)_2$ (0.3 M). D-[U-^{14}C]Glucose was separated from [^{14}C]lactate with an anion-exchange resin column (AG2-X8; Bio-Rad Laboratories A.G., Glattburg, Switzerland). Glucose concentration was determined in the supernatant by a glucose oxidase kit (Boehringer, Mannheim, Germany). Glycogen and [^{14}C]glycogen were measured as previously reported [20]. Lipids were extracted by the method of Folch *et al.* [21].

Comparisons between experimental groups were made by Student's *t* test for unpaired data.

RESULTS

Energy intake, body-weight gain, glycaemia and insulinaemia in rats treated with insulin

Treatment of normal rats with insulin alone (2 units/day) produced significant increases in energy intake, body-weight gain and basal plasma insulin levels, while resulting in marked, though well tolerated, hypoglycaemia (Table 1). As hypoglycaemia is known to produce adrenergic responses that could influence the glucose utilization (see below), groups of adrenomedullectomized or propranolol-treated rats were studied with or without insulin treatment (4 units/day), with the same consequences on the parameters just mentioned (Table 1). The actual sucrose intake was not different in groups B and C (Table 1). When insulin-treated rats were simultaneously infused with glucose to avoid hypoglycaemia, the energy intake was the same as that of controls. However, body-weight gain was increased in insulin-treated rats and a basal hyperinsulinaemia was achieved, without lowering basal glycaemia when compared with saline-infused controls.

Glucose utilization index of white adipose tissue and of various muscles from rats treated with insulin

As shown in Table 2, the glucose utilization index (i.e. the tissue responsiveness of this process to insulin) of white parametrial adipose tissue was higher in rats previously treated with insulin than in controls. In contrast, the glucose utilization index of several muscle types was lower in the insulin-treated group than in controls (Table 2).

As further depicted by Table 3, the stimulatory effect of prior insulin treatment on the glucose utilization index of white adipose tissue remained present in rats in which the adrenergic responses (owning to hypoglycaemia) were blockaded (adrenomedullectomy; infusion of the β-adrenergic antagonist propranolol), or when hypoglycaemia of insulin-treated rats was prevented by a concomitant glucose infusion (Table 3). Again, an analogous decrease in the glucose utilization index of several muscles from insulin-treated hypoglycaemic rats was obtained after adrenergic blockade, as well as when the hypoglycaemia of insulin-treated animals was corrected by simultaneous glucose infusion (Table 3).

No intergroup difference was observed when the glucose utilization index was measured in non-insulin-dependent tissues such as the skin, the gut and the brain (results not shown).

Table 1. Main characteristics of insulin-treated normal rats and their respective saline-infused controls

Abbreviation: ADMX, adrenomedullectomy. Duration of insulin treatment: 4 days (groups A and D) or 3 days (groups B and C). Values are means ± S.E.M. of 4–8 experiments. Inter-group differences: $*P < 0.025$; $**P < 0.005$; $***P < 0.0005$. See the Materials and methods section for details.

Groups of animals	Energy intake [kJ (kcal)/day]	Body-weight gain during treatment (g)	Basal insulinaemia (μunits/ml)	Basal glycaemia (mmol/l)
A. Saline-infused	260±8.4 (62±2)	5.2±0.5	65.0±6.5	7.1±0.4
Insulin-treated (2 units/day)	390±4.2 (93±1)***	9.8±1.4*	145.5±42.5*	3.9±0.9**
B. Saline-infused, ADMX	319±12.6 (76±3)	2.0±1.1	93.7±12.5	7.4±0.1
Insulin-treated (4 units/day), ADMX	390±16.8 (93±4)**	12.0±1.2***	385.0±70.0**	1.3±0.1***
C. Saline- and propranolol-infused	332±12.6 (79±3)	2.6±1.1	70.0±12.5	7.7±0.2
Insulin (4 units/day)- and propranolol-infused	466±12.6 (111±3)***	9.8±1.2***	502.5±65.0***	1.8±0.1***
D. Saline-infused	256±8.4 (61±2)	6.9±1.4	62.0±8.2	6.5±0.2
Insulin (2 units/day)- and glucose-infused	269±12.6 (64±3)	9.6±1.2*	301.8±70.6***	6.3±0.3

Table 2. Insulin-stimulated glucose utilization index of white adipose tissue and of various muscles obtained from saline-infused or insulin-treated rats and measured during euglycaemic/hyperinsulinaemic clamps

Rats were saline-infused or insulin-treated (2 units/day) for 4 days (see group A, Table 1). Mean steady-state insulinaemia reached during clamps was: controls, 817.5±37.5 μunits/ml; insulin-treated, 965±110 μunits/ml; not significant. Mean steady-state glycaemia was: controls, 6.8±0.2 mmol/l; insulin-treated, 6.9±0.2 mmol/l. Values are means ± S.E.M. of six experiments. Inter-group differences: $*P < 0.05$, $**P < 0.01$, $***P < 0.0005$. Abbreviations: WAT, white adipose tissue: EDL, extensor digitorum longus; EPI, epitrochlearis. See the Materials and methods section for details.

Tissues	Glucose utilization index (ng/mg per min)	
	No treatment	Insulin
WAT	2.0±0.2	10.6±1.0***
Soleus	24.8±2.6	21.9±3.5
EDL	19.2±1.5	10.1±1.8*
EPI	20.6±2.4	11.4±1.9**
Tibialis	16.8±1.0	8.2±0.6***
Diaphragm	75.0±3.4	50.1±2.0***

Glycogen content and glycogen synthesis *de novo* in muscles from rats treated with insulin

The observed decrease in the glucose utilization index of muscles obtained from rats treated with insulin (see Table 2) could conceivably be due to an intramuscular accumulation of glycogen produced by such treatment. This situation would limit the capacity of the respective muscles to take up glucose during the clamps. That such was not the case is shown by Table 4; glycogen content, measured at the end of the saline infusion or of the insulin treatment, was either not different or actually decreased in muscles of insulin-treated rats compared with those of controls (except for the soleus). As further shown by Table 4, when synthesis of glycogen *de novo* from [^{14}C]glucose was measured in muscles during the clamps, it followed the same pattern as that of the glucose utilization index, i.e. unchanged in soleus and decreased in other muscles, thereby suggesting that glucose uptake was the rate-limiting step of the glycogen synthesis *de novo*.

Hepatic glucose production and total glucose metabolism in rats treated with insulin

The hepatic glucose production, as determined during euglycaemic/hyperinsulinaemic clamps, was inhibited to the

Table 3. Insulin-stimulated glucose utilization index of white adipose tissue and of various muscles obtained from saline-infused or insulin-treated rats after adrenergic blockade or glucose infusion and measured during euglycaemic/hyperinsulinaemic clamps

Rats were treated as described in Table 1 (groups B–D). Mean steady-state insulinaemia reached during clamps was: controls, 896±114 μunits/ml; insulin-treated, 1230±41 μunits/ml; $P < 0.05$. Mean steady-state glycaemia was: 6.9±0.1 mmol/l; insulin-treated, 6.8±0.3 mmol/l. Values are means ± S.E.M. of 4–8 experiments. Inter-group differences: $*P < 0.05$, $**P < 0.01$, $***P < 0.0005$. Abbreviations: WAT, white adipose tissue; EDL, extensor digitorum longus; EPI, epitrochlearis; ADMX, adrenomedullectomy. See the Materials and methods section for details.

Groups of animals	Glucose utilization index (ng/mg per min)					
	WAT	Soleus	EDL	EPI	Tibialis	Diaphragm
Saline-infused, ADMX	2.0±0.2	10.9±1.4	13.6±0.8	9.4±0.8	11.1±0.5	57.6±4.3
Insulin-treated (4 units/day), ADMX	9.9±1.1***	7.4±0.5	5.9±0.8***	4.1±0.8***	5.0±1.0***	35.1±3.3**
Saline- and propranolol-infused	1.8±0.1	17.0±2.1	17.6±1.8	9.1±1.3	12.4±1.2	52.4±7.5
Insulin (4 units/day)- and propranolol-treated	10.1±1.0***	12.4±1.4	8.2±0.9**	5.4±1.1	6.1±0.5**	31.6±3.0*
Saline-infused	2.4±0.3	33.0±2.4	26.7±1.2	11.6±1.9	16.0±1.1	87.1±9.2
Insulin (2 units/day)- and glucose-treated	5.0±0.8*	16.7±2.1**	20.1±3.6	6.6±1.9*	13.0±1.9	57.2±8.5*

Table 4. Glycogen content and [^{14}C]glucose carbon incorporation into glycogen in muscles from saline-infused or insulin-treated rats measured at the end of respective treatments

Rats were treated as described in Table 1 (group A). Saline or insulin (2 units/day) was infused via minipumps. Values are means ± S.E.M. of 4–8 experiments. Inter-group differences: *$P < 0.025$; **$P < 0.01$; ***$P < 0.001$. Abbreviation: EDL, extensor digitorum longus. See the Materials and methods section for details.

Muscle	Glycogen content before clamps (mg/g of tissue)		[^{14}C]Glucose carbon incorporation into glycogen during clamps (ng/mg per min)	
	Saline-infused rats	Insulin-treated rats	Saline-infused rats	Insulin-treated rats
Soleus	4.1 ± 0.3	4.0 ± 0.3	18.6 ± 2.6	22.8 ± 3.0
EDL	4.0 ± 0.1	3.0 ± 0.1***	12.4 ± 2.0	4.9 ± 1.0**
Tibialis	3.7 ± 0.1	2.4 ± 0.3*	8.9 ± 0.9	3.0 ± 0.5***
Diaphragm	4.8 ± 0.7	3.5 ± 0.3	91.4 ± 9.8	60.1 ± 8.3*

same extent in rats previously treated with insulin for 4 days (Table 1, group A) and in those infused with saline (−0.48 ± 0.2 mg/min and −0.41 ± 0.11 mg/min respectively; not significant). Total glucose metabolism measured during the clamps was higher in insulin-treated rats than in saline-infused controls (5.6 ± 0.3 mg/min versus 4.1 ± 0.14 mg/min respectively; $P < 0.01$).

The hepatic glycogen content was markedly lower in the insulin-treated rats than in the saline-infused controls when measured before the clamps (20.1 ± 2.8 mg/g for the saline-treated and 6.7 ± 1.8 mg/g for the insulin-treated rats; $P < 0.001$). It was restored toward normal during the clamps (18.5 ± 1.8 mg/g for the saline-infused and 12.3 ± 1.2 mg/g for the insulin-treated rats; $P < 0.01$).

Total lipid synthesis in liver and white adipose tissue in rats treated with insulin

Total lipid synthesis in liver and white adipose tissue was also studied, during euglycaemic/hyperinsulinaemic clamps, in insulin-treated rats (2 units/day; see Table 1) and saline-infused controls. It was observed that this process was higher in the liver of insulin-treated rats than in that of saline-infused controls (89.6 ± 7.7 and 58.1 ± 4.8 μg-atoms/h per g respectively; $P < 0.05$). This was in keeping with the increased hepatic fat content measured in the insulin-treated group (30.4 ± 2 mg/g in the insulin-treated rats, 26.0 ± 0.7 mg/g in the controls; $P < 0.05$). Similar results were obtained in white adipose tissue of insulin-treated rats compared with saline-infused controls (133.8 ± 37.9 and 56.2 ± 11.3 μg-atoms/h per g respectively; $P < 0.05$), an observation in keeping with the increased total inguinal fat-pad weight of insulin-treated rats (2.8 ± 0.1 g in insulin-treated rats, 1.8 ± 0.5 g in controls; $P < 0.001$).

DISCUSSION

A state of increased insulin-responsiveness of some metabolic pathways (i.e. liver and adipose-tissue lipogenesis), together with a state of insulin-resistance of others, often coincide in animal models of hyperinsulinaemia and obesity [22–24]. The reason for such divergence is not clearly established. Moreover, when various animal models are studied longitudinally, it has usually been observed that hyperinsulinaemia increases with the duration of the syndrome and that tissues that ultimately become insulin-resistant may become so after a state of hypersensitivity and hyper-responsiveness to the hormone [22–25]. From these observations, it has been suggested that hyperinsulinaemia could be one of the causes that would bring about insulin-resistance, at least in some tissues [24].

The present experiments were undertaken in an attempt to answer the following question: does a short-term hyperinsulinaemia bring about an overstimulation of glucose metabolism in some tissues and an insulin-resistance in others? This hypothesis was tested by treating normal rats with saline or insulin for a few days, and then measuring glucose utilization by adipose tissue and different muscles, by using the euglycaemic/hyperinsulinaemic clamps associated with the labelled 2-deoxy-D-glucose technique.

It was observed that, in white adipose tissue of normal rats treated with insulin for a few days, the glucose utilization index was increased in response to an acute insulin exposure during hyperinsulinaemic/euglycaemic clamps, compared with that of saline-infused controls. This was accompanied by an actual increase in total inguinal fat-pad weight and by an increased adipose-tissue lipogenic activity (Tables 2 and 3, and the Results section).

It was also observed that, in several muscles from normal rats treated with insulin, the glucose utilization index was decreased in response to an acute insulin exposure during the clamps, compared with that of saline-infused controls (Table 2). Such inhibitory effects were not due to an increased adrenergic/noradrenergic activity of rats made hypoglycaemic, as they persisted upon removal of adrenergic and noradrenergic stimulations (Table 3). The decreased responsiveness to insulin of glucose utilization observed in muscles obtained from rats previously treated with insulin alone was not due to increased muscle glycogen content (that would inhibit the uptake of the hexose), as such content was the same or smaller in insulin-treated rats than that of the respective controls (Table 4). Furthermore, the glycogen synthesis *de novo* measured in the various muscles studied closely followed the changes observed in glucose uptake, suggesting that the glucose transport was the likely rate-limiting step that was influenced by prior insulin treatment (Table 4).

The inhibitory effect of prior insulin treatment on muscle glucose utilization was not related to insulin-induced hypoglycaemia, since analogous results were obtained when glycaemia was normalized by a superimposed glucose infusion (Table 3). Preliminary data on basal corticosteronaemia indicated analogous values in saline-infused or insulin-treated rats, making the participation of this hormone in the effects observed unlikely. As a whole, chronic insulin infusion resulted in a decrease in the glucose utilization index of several muscles that occurred concomitantly with an increase in that of white adipose tissue.

Chronic hyperinsulinaemia imposed on normal rats also resulted in a marked increase in liver glucose utilization (as estimated by changes in liver glycogen content measured before

and after the clamps), and in an increased hepatic total lipid synthesis, producing fat accumulation in the hepatic parenchyma. However, prior insulin treatment of normal rats did not alter the inhibitory effect of insulin on hepatic glucose production measured during the clamps (Tables 2 and 3; the Results section).

The present study shows that hyperinsulinaemia provoked in normal rats by chronic insulin infusion produces, within a few days, some of the abnormalities seen in animal models of obesity linked with hyperinsulinaemia: the appearance of increased glucose utilization and lipogenesis with actual fat accumulation in adipose tissue and the liver, together with an insulin-resistant state at the muscular level [24].

It should be recalled here that, in 16-day-old obese Zucker (*fa/fa*) rats, high values of glucose transport have been observed in their adipose tissue, when basal insulinaemia was still normal [26]. However, other data have indicated that although basal insulinaemia was normal in 17-day-old *fa/fa* rats, substrate-induced insulin secretion was increased [27]. When basal hyperinsulinaemia was present in 30-day-old obese (*fa/fa*) rats, glucose utilization was still increased in white adipose tissue [28], but most muscles had become insulin-resistant [13,29]. Similar results have been obtained in rats that were studied 1 week after ventromedial hypothalamic lesions [30]. These data together are suggestive of a putative effect of hyperinsulinaemia on the occurrence of insulin-resistance, at least in some tissues.

The present study shows that chronic hyperinsulinaemia itself imposed on normal rats appears to have a dual effect, stimulating glucose utilization in adipose tissue, but decreasing it in several muscle types, leaving, in particular, the hepatic glucose production unaltered. The underlying mechanism(s) of these differential effects have yet to be defined at the cellular or molecular level. They could be related to different modulations of the glucose-transporter system described previously [6], to different regulations of the insulin-receptor-complex autophosphorylation, or of some as yet undefined steps. Whatever the underlying factor(s) implicated, hyperinsulinaemia may be a relevant factor in bringing about increased body weight and abnormal glucose handling via stimulating lipogenic pathways (liver, adipose tissue), as well as producing insulin-resistance, at least at the level of some muscles.

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