Effects of prolonged elevation of plasma adrenaline concentration *in vivo* on insulin-sensitivity in soleus muscle of the rat*

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1. Prolonged elevation of the plasma adrenaline concentration was produced in rats by implantation of adrenaline-releasing retard-tablets. With this technique, a hyperadrenalinaemic state is maintained for at least 5 days. 2. At 6 h after implantation of the retard-tablet it was found that plasma glucose and fatty acid concentrations increased and insulin concentration decreased compared with values obtained from placebo-tablet-implanted rats. Administration of a subcutaneous glucose load demonstrated an impaired glucose tolerance *in vivo*, and incubation of soleus muscle strips from 6 h-hyperadrenalinaemic rats *in vitro* demonstrated a decreased sensitivity of the rates of glycolysis and glucose transport to insulin. 3. The sensitivities of the rates of glycolysis, glucose transport and glycogen synthesis to insulin were determined for the incubated soleus muscle preparation isolated from animals after 48 h, 72 h and 120 h duration of hyperadrenalinaemia. At 48 h after retard-tablet implantation, the sensitivity of the processes of glucose transport and glycolysis was decreased; at 72 h, the insulin-sensitivities of the rates of glycolysis and glucose transport in skeletal muscle were similar to those determined for control animals; at 120 h, however, the sensitivities of the processes of glucose transport and glycolysis were both statistically significantly increased. In contrast, no changes in the sensitivity of the process of glycogen synthesis were observed at any of the time intervals studied. 4. The possible biochemical basis for the observed changes in skeletal-muscle insulin-sensitivity with prolonged hyperadrenalinaemia is discussed.

INTRODUCTION

The acute administration of β -adrenoceptor agonists to animals has profound effects on glucose metabolism. Adrenaline infusion induces hyperglycaemia in both man and experimental animals, due, at least in part, to stimulation of hepatic glucose output (Sherline *et al.*, 1972; Kneer *et al.*, 1974) and inhibition of peripheral glucose utilization (Deibert & DeFronzo, 1980; Sacca *et al.*, 1982). In addition, acute hyperadrenalinaemia inhibits insulin secretion (Coore & Randle, 1964; Porte, 1967; Altszuler *et al.*, 1967).

Acute exposure of isolated muscle to adrenaline or the β -adrenoceptor agonist isoprenaline causes an activation of glycogenolysis, an elevation of hexose monophosphate concentrations and a consequent inhibition of the rate of glucose phosphorylation (Sloan *et al.*, 1978; Chiasson *et al.*, 1981; Challiss *et al.*, 1986). This may be one mechanism by which the rate of peripheral glucose utilization is decreased *in vivo*.

Little information is available on the effects of prolonged administration of catecholamines on the effects of insulin on glucose metabolism. Chronic administration of the β_2 -adrenoceptor agonist terbutaline sulphate to humans increased insulin-stimulated glucose utilization (Scheidegger *et al.*, 1984). In lean and obese rats of the Zucker strain, chronic treatment with a novel β -adrenoceptor agonist (BRL 26830A) increased glucose tolerance and insulin-sensitivity *in vivo* (Cawthorne *et al.*, 1984; Smith *et al.*, 1985). These effects are considered to

be due to an adaptive increase in peripheral glucose utilization (Scheidegger *et al.*, 1984; Smith *et al.*, 1985). Furthermore, in skeletal muscle isolated from animals treated chronically with the β -adrenoceptor agonist BRL 26830A and incubated *in vitro*, there was a profound increase in the sensitivity of the rate of glucose utilization to insulin (Challiss *et al.*, 1985). For this reason the effect of chronically elevated blood adrenaline concentration in rats on the sensitivity of glucose utilization, glucose transport and glycogen synthesis to insulin in the incubated soleus muscle from these animals has been studied. The hyperadrenalinaemia was achieved by implanting adrenaline-releasing retard-tablets subcutaneously (Porta *et al.*, 1979; Korsatko *et al.*, 1982).

METHODS

Animal manipulations

Male Wistar rats (160–200 g) were used for the study. Under light diethyl ether anaesthesia, a small dorso-lateral incision was made and a retard-tablet was implanted subcutaneously at least 3 cm below the interscapular brown adipose tissue; the wound was sutured, and animals recovered within 15 min. Control animals received a placebo tablet. The preparation of the adrenaline-releasing retard-tablets and the time course and rate of adrenaline release have been reported previously (Korsatko *et al.*, 1982; Porta *et al.*, 1984). In the present study retard-tablets that release adrenaline at

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a constant rate of 1.1 $\mu\text{g}/\text{min}$ were used. After the operation, animals were given free access to food and water, except for animals studied 6 h after implantation, from which food was withheld.

Glucose tolerance tests

These were performed on 12 h-starved rats at 6, 24, 48, 72 or 120 h after retard-tablet implantation; for each group, animals with placebo tablets implanted for similar periods were also studied. Before glucose administration, a 200 μl blood sample was obtained from the tail artery for metabolite and hormone determinations. A subcutaneous dose of glucose (1 g/kg body wt.) was given, as a 50% (w/v) glucose solution, and plasma glucose concentrations were determined for the subsequent 2 h period by using 20 μl blood samples obtained from the tail artery.

Skeletal-muscle incubations

Rats were starved for 12 h before the experiment. Experiments were performed in rats 6, 48, 72 or 120 h after adrenaline-tablet implantation. Stripped soleus muscles were prepared and incubated as described by Crettaz *et al.* (1980), with the modifications given by Challiss *et al.* (1983). Additions of insulin (1–10000 $\mu\text{units}/\text{ml}$) were made at the start of the incubation period. Rates of lactate production, [^{14}C]lactate production and ^{14}C incorporation into glycogen were measured as described previously (Espinal *et al.*, 1983a; Challiss *et al.*, 1984). The rate of hexose oxidation to CO_2 was measured as described by Leighton *et al.* (1985), and was never greater than 15% of the rate of lactate formation under any of the incubation conditions investigated (results not shown).

For the investigation of glucose transport into soleus muscle strips, using 3-*O*-methyl[^{14}C]glucose, it was considered important to carry out experiments under conditions identical with those used previously. Thus the radiolabelled compounds were added to 5.5 mM-glucose in the incubation medium, so that the actual concentrations of 3-*O*-methylglucose were negligible. [^3H]Inulin was also added to enable the intercellular space in muscle to be measured (for details, see Challiss *et al.*, 1986). Preliminary experiments established that the rates of lactate formation, glycogen synthesis and 3-*O*-methyl[^{14}C]glucose transport increased linearly over the 60 min time course of the experiment (results not shown).

Metabolite and hormone determinations

Insulin concentrations were determined in plasma samples (Hales & Randle, 1963). For other assays, blood samples were deproteinized with 4% (w/v) HClO_4 . Glucose concentration was determined by the method of Bergmeyer *et al.* (1973); fatty acid concentration was measured by the method of Shimizu *et al.* (1979). The concentrations of adrenaline and noradrenaline were determined after extraction on alumina of 250 μl plasma samples, by the h.p.l.c. method of Bouloux *et al.* (1985). Glycogen content in soleus muscle was determined by the method of Keppler & Decker (1973). Intramuscular triacylglycerol was measured by chloroform/methanol extraction (Folch *et al.*, 1957) of soleus muscle after freeze-drying and removal of residual extracellular adipose tissue. After an overnight extraction, the organic phase was dried by nitrogen evaporation, and the

Table 1. Effects of adrenaline retard-tablet implantation on plasma concentrations of metabolites and hormones, and glycogen and triacylglycerol concentrations in soleus muscle

Results are presented as means $\pm$ S.E.M., with numbers of observations given in parentheses. Statistical significance was established by Student's *t* test for unpaired observations for comparison of each time point versus values for placebo implantation; * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$; n.d., not determined.

Time after implantation (h)	Glucose (mM)	Fatty acid (mM)	Insulin ($\mu\text{units}/\text{ml}$)	Adrenaline (pg/ml)	Noradrenaline (pg/ml)	Glycogen ($\mu\text{mol}/\text{g dry wt.}$)	Triacylglycerol ($\mu\text{mol}/\text{g dry wt.}$)
0	3.7 $\pm$ 0.2 (15)	0.51 $\pm$ 0.02 (15)	37 $\pm$ 3 (9)	13 $\pm$ 4 (5)	14 $\pm$ 5 (5)	130 $\pm$ 12 (6)	12 $\pm$ 2 (6)
6	7.2 $\pm$ 0.6 (15)***	0.76 $\pm$ 0.05 (7)**	16 $\pm$ 3 (9)***	n.d.	n.d.	47 $\pm$ 7 (6)***	12 $\pm$ 1 (6)
24	3.9 $\pm$ 0.3 (15)	0.91 $\pm$ 0.06 (16)***	29 $\pm$ 3 (9)	n.d.	n.d.	69 $\pm$ 13 (6)**	n.d.
48	4.1 $\pm$ 0.2 (8)	1.0 $\pm$ 0.06 (11)***	39 $\pm$ 4 (9)	n.d.	n.d.	88 $\pm$ 4 (6)*	10 $\pm$ 3 (6)
72	3.2 $\pm$ 0.3 (8)	1.2 $\pm$ 0.06 (10)***	38 $\pm$ 4 (9)	46 $\pm$ 11 (5)*	15 $\pm$ 1 (5)	112 $\pm$ 8 (6)	9 $\pm$ 1 (6)
120	3.2 $\pm$ 0.3 (7)	0.90 $\pm$ 0.08 (5)**	46 $\pm$ 8 (9)	120 $\pm$ 7 (5)***	19 $\pm$ 5 (5)	138 $\pm$ 5 (6)	5 $\pm$ 2 (6)*

Table 2. Effect of adrenaline retard-tablet implantation on glucose tolerance

Rats received 1 g of glucose/kg body wt. subcutaneously at zero time. Blood samples were withdrawn from the tip of the tail at regular intervals for the subsequent 120 min period. Each result (mM) is given as mean $\pm$ S.E.M.; the numbers of animals studied for each time point after retard-tablet implantation are given in parentheses. For each response curve an integral was calculated, and the control response was set to 100%. Significant changes in areas under the response curves were assigned by using Student's *t* test for unpaired observations: ***P* < 0.01.

Time after glucose administration (min)	Time after retard-tablet implantation (h) . . .	Glucose (mM)					
		0 (15)	6 (15)	24 (15)	48 (6)	72 (7)	120 (7)
0		2.92 $\pm$ 0.23	7.16 $\pm$ 0.43	3.92 $\pm$ 0.32	4.08 $\pm$ 0.15	2.71 $\pm$ 0.24	3.21 $\pm$ 0.30
15		5.16 $\pm$ 0.45	9.02 $\pm$ 0.47	5.94 $\pm$ 0.28	5.81 $\pm$ 0.35	4.51 $\pm$ 0.33	4.87 $\pm$ 0.41
30		4.89 $\pm$ 0.21	9.39 $\pm$ 0.61	5.34 $\pm$ 0.31	5.44 $\pm$ 0.23	3.94 $\pm$ 0.47	4.65 $\pm$ 0.34
45		3.91 $\pm$ 0.16	9.18 $\pm$ 0.61	5.16 $\pm$ 0.31	5.26 $\pm$ 0.26	3.66 $\pm$ 0.32	4.49 $\pm$ 0.30
60		3.50 $\pm$ 0.17	8.73 $\pm$ 0.72	5.08 $\pm$ 0.40	4.88 $\pm$ 0.28	3.36 $\pm$ 0.39	4.00 $\pm$ 0.27
90		3.15 $\pm$ 0.17	7.67 $\pm$ 0.58	4.41 $\pm$ 0.32	4.41 $\pm$ 0.32	2.83 $\pm$ 0.33	3.17 $\pm$ 0.40
120		3.05 $\pm$ 0.16	6.94 $\pm$ 0.58	3.91 $\pm$ 0.34	4.20 $\pm$ 0.21	2.67 $\pm$ 0.26	3.00 $\pm$ 0.20
Area under curve $\int_0^{120}$		100 $\pm$ 7	139 $\pm$ 12**	110 $\pm$ 8	94 $\pm$ 7	86 $\pm$ 11	84 $\pm$ 7

concentration of glycerol was determined after alkaline-ethanol hydrolysis (Eggstein & Kuhlmann, 1973).

RESULTS

It has previously been demonstrated that plasma adrenaline concentrations are elevated for at least 48 h after implantation of adrenaline-releasing retard-tablets into rats (Korsatko *et al.*, 1982). The concentration of plasma adrenaline was also elevated 72 h and 120 h after retard-tablet implantation, but there was no change in plasma noradrenaline concentration (Table 1).

Preliminary experiments showed that implantation of the placebo tablet into animals had no effect on any of the parameters at any of the time points investigated, and therefore data from animals receiving the placebo pellet for 6–120 h were 'pooled' to provide a single control group.

Retard-tablet implantation for 6 h increased the plasma concentrations of glucose and fatty acids and decreased that of insulin. For longer periods of time after implantation, the concentrations of plasma glucose and insulin were normal, but that of plasma non-esterified fatty acids was increased throughout the time course of investigation (Table 1).

The muscle glycogen contents of soleus muscle were decreased at 6 h, 24 h and 48 h after retard-tablet implantation, but at 72 h and 120 h were not significantly different from the glycogen content of soleus muscles taken from animals receiving placebo tablets (Table 1). In contrast, triacylglycerol content of soleus muscle was decreased only 120 h after implantation of the adrenaline retard-tablet.

The results of glucose tolerance tests performed 0, 6, 24, 48, 72 and 120 h after adrenaline-pellet implantation are shown in Table 2. The simplest indicator of the hyperglycaemic response to a subcutaneous glucose load is the area under the response curve, taking the plasma glucose concentration at zero time as the baseline. The integral values are given in Table 2: glucose tolerance was impaired 6 h after adrenaline-pellet implantation; the area under the glucose tolerance curve was 39%

greater after hyperadrenalinaemia for 6 h than that of animals receiving the placebo implant. However, with longer duration of hyperadrenalinaemia, glucose tolerance was normal; indeed after 72 and 120 h there was an improvement in tolerance, although it did not reach statistical significance (Table 2).

We have previously used the isolated incubated stripped soleus muscle as a skeletal-muscle preparation *in vitro* to investigate physiological changes in the sensitivity of the rates of glycolysis and glycogen synthesis to insulin (Budohoski *et al.*, 1984a; Challiss *et al.*, 1984). For control muscle incubations insulin increased the rate of lactate formation about 2-fold, and the concentration of insulin that produced a half-maximal stimulation of the rate of lactate formation was about 75 μ units/ml; the rate of glycogen synthesis was increased about 3-fold by a maximal concentration of insulin, with a half-maximal effect achieved at about 125 μ units of insulin/ml (Table 3). These results are similar to those obtained in previous studies (Budohoski *et al.*, 1984a,b; Challiss *et al.*, 1984, 1986).

Adrenaline retard-tablet implantation for 6 h produced a dramatic effect on the sensitivity of the rate of lactate formation to insulin; the concentration of insulin required to produce half-maximal stimulation was increased to about 750 μ units/ml. In contrast, neither the basal nor the maximal rates of lactate formation were altered, so that it was the sensitivity and not the range of response to insulin that was affected by acute hyperadrenalinaemia. There was no effect on the sensitivity of glycogen synthesis to insulin (Table 3), but there was an increase in the rates of glycogen synthesis at 100, 1000 and 10000 μ units of insulin/ml. This may be a consequence of the low content of glycogen in the soleus muscles of these animals (Table 1), since glycogen content can be an important determinant of its own rate of synthesis (Danforth, 1965; Fell *et al.*, 1982). The decrease in sensitivity of the rate of lactate formation to insulin was present in muscles from animals 48 h after adrenaline-tablet implantation (Table 3), approx. 600 μ units of insulin/ml being required to elicit a half-maximal stimulation.

Table 3. Effects of insulin on rates of lactate and glycogen formation by the stripped-soleus-muscle preparation isolated from rats which had received adrenaline retard-tablets implanted 0–120 h before study

Results are presented as means $\pm$ S.E.M., with the minimum number of separate muscle incubations for each condition in parentheses. Statistical significance was established by Student's *t* test (for unpaired observations); comparisons are for each hyperadrenalinaemic period with control values at each given insulin concentrations: **P* < 0.05, ***P* < 0.01, ****P* < 0.001.

	Time after retard-tablet implantation (h) ...	Rate (μ mol/h per g of tissue)				
		Insulin (μ units/ml)				
		0 (control)	6	48	72	120
Lactate formation	1	6.91 $\pm$ 0.63 (19)	6.58 $\pm$ 0.73 (7)	7.95 $\pm$ 0.48 (7)	8.99 $\pm$ 0.76 (8)*	8.30 $\pm$ 0.44 (13)
	10	8.62 $\pm$ 0.35	6.58 $\pm$ 1.03	8.05 $\pm$ 0.47	9.90 $\pm$ 0.67	11.88 $\pm$ 0.74**
	100	12.10 $\pm$ 0.43	5.66 $\pm$ 0.82**	8.15 $\pm$ 0.64**	11.77 $\pm$ 0.67	14.07 $\pm$ 0.60**
	1000	15.39 $\pm$ 0.52	11.91 $\pm$ 0.49**	13.30 $\pm$ 0.75*	13.65 $\pm$ 0.86	14.61 $\pm$ 0.80
	10000	15.24 $\pm$ 1.03	15.33 $\pm$ 0.33	15.85 $\pm$ 1.45	15.98 $\pm$ 0.95	13.99 $\pm$ 1.54
Glycogen synthesis	1	1.65 $\pm$ 0.11 (14)	1.72 $\pm$ 0.20 (7)	1.49 $\pm$ 0.18 (6)	1.44 $\pm$ 0.05 (5)	2.37 $\pm$ 0.18 (6)**
	10	1.62 $\pm$ 0.10	1.96 $\pm$ 0.27	1.94 $\pm$ 0.21	2.10 $\pm$ 0.07**	2.62 $\pm$ 0.30**
	100	2.82 $\pm$ 0.08	3.87 $\pm$ 0.40**	2.76 $\pm$ 0.68	3.88 $\pm$ 0.15**	4.92 $\pm$ 0.51**
	1000	4.07 $\pm$ 0.35	6.57 $\pm$ 0.90**	3.35 $\pm$ 0.53	4.72 $\pm$ 0.50	6.02 $\pm$ 0.33**
	10000	4.51 $\pm$ 0.14	6.10 $\pm$ 0.30**	4.52 $\pm$ 0.48	5.02 $\pm$ 0.36	6.73 $\pm$ 0.61**

Fig. 1. Effects of insulin on rates of 3-O-methyl-D-[14 C]glucose uptake by the stripped-soleus-muscle preparation isolated from rats receiving adrenaline retard-tablets for 0–120 h before investigation *in vitro*

Each data point represents the mean of at least six separate muscle-strip incubations for control (○) or 6 h (△), 48 h (□), 72 h (●) and 120 h (▲) after retard-tablet implantation. Error bars have been omitted for clarity, but the S.E.M. was never greater than 8% of the mean. Statistical significance of differences between experimental and control values for each concentration of insulin investigated was determined by Student's *t* test for unpaired observations: **P* < 0.05; ***P* < 0.01; ****P* < 0.001.

Hyperadrenalinaemia for 72 h resulted in less marked effects on insulin-stimulated rates of lactate formation, but the sensitivity of the process was still greater than 100 μ units of insulin/ml (Table 3).

Prolonged hyperadrenalinaemia (120 h) had profound effects on the rates of insulin-stimulated lactate formation; the half-maximal concentration of insulin required to stimulate the rate of lactate formation was less than 10 μ units/ml. In contrast, the sensitivity of the rate of glycogen synthesis to insulin was similar to that observed for muscles from control animals.

The rate of lactate formation is an indicator of the rate of glucose transport in the incubated stripped soleus muscle (Challiss *et al.*, 1986). However, because of the possibility that this may not hold for muscles isolated from hyperadrenalinaemic animals, it was considered important to show that the changes in sensitivity of the rate of lactate formation to insulin were indeed a measure of changes in the sensitivity of glucose transport to insulin. The effects of hyperadrenalinaemia for 0–120 h on the rates of insulin-stimulated 3-O-methylglucose transport in the incubated muscle preparation are shown in Fig. 1.

The range of response was unaffected by hyperadrenalinaemia for any of the times investigated (Fig. 1). The concentration of insulin that stimulated the rate of 3-*O*-methylglucose transport half-maximally varied dramatically: 6 and 48 h after implantation of adrenaline retard-tablet, the sensitivity of glucose transport was decreased; after 72 h the sensitivity was similar to that observed for muscle strips from control rats, and after 120 h sensitivity to insulin was dramatically increased (Fig. 1).

DISCUSSION

Plasma catecholamine concentrations may be elevated under various physiological conditions, e.g. exercise-training (Galbo *et al.*, 1975; Maron *et al.*, 1977; Winder *et al.*, 1978) and cold-exposure (Leduc, 1961; Depocas & Behrens, 1978; Picotti *et al.*, 1981); several studies have addressed the question of whether increased catecholamine concentrations are responsible for some of the changes seen in these conditions. These studies have involved decreasing the 'effectiveness' of catecholamines by surgical (Galbo *et al.*, 1978; Richter, 1984; Henriksson *et al.*, 1985), chemical (Galbo *et al.*, 1978; Richter *et al.*, 1980) or pharmacological (Irving *et al.*, 1974; Galbo *et al.*, 1975; Ji *et al.*, 1986) methods, or by increasing the 'effectiveness' of catecholamines by administration of adrenoceptor agonists (Harri & Valtola, 1975; Thibault *et al.*, 1979; Fell *et al.*, 1981; Racotta *et al.*, 1986). The role of catecholamines in causing changes in glucose metabolism and tissue sensitivity to insulin has received little attention, which is surprising, since exercise-training (Richter *et al.*, 1982; Espinal *et al.*, 1983b) and cold-exposure (Vallerand *et al.*, 1983; Budohoski *et al.*, 1984b) are characterized by an increased peripheral sensitivity to insulin.

In the present study, we have used adrenaline-releasing retard-tablets (Korsatko *et al.*, 1982), implanted subcutaneously, to bring about a chronic state of hyperadrenalinaemia, which is maintained for at least 5 days after implantation. In common with many other studies (Shikama & Ui, 1975; Deibert & DeFronzo, 1980; Sacca *et al.*, 1982), we found that acute elevation of plasma adrenaline concentrations (6 h) caused an elevation of plasma glucose, a decrease in plasma insulin concentrations, decreased glucose tolerance and a decrease in the sensitivity to insulin of glucose utilization in skeletal muscle. A decrease in insulin-sensitivity of glucose utilization of skeletal muscle exposed to β -adrenoceptor agonists *in vitro* has been shown to be due to an increased rate of glycogenolysis causing an increase in tissue hexose monophosphate concentrations and a consequent inhibition of the rate of glucose phosphorylation (Chiasson *et al.*, 1981; Challiss *et al.*, 1986), but the rate of glucose transport into the muscle is itself not affected by the presence of β -adrenoceptor agonists (Challiss *et al.*, 1986). However, short-term elevation of the adrenaline concentration *in vivo* (6 h and 48 h) resulted in a decrease in the sensitivity not only of glycolysis but also of glucose transport in the isolated soleus muscle preparation. Furthermore, the indirect mechanism by which adrenaline decreases the sensitivity of the glycolytic rate *in vitro* does not provide an explanation of the data presented here: comparison of the rate of lactate formation measured spectrophotometrically and radiochemically suggests that the glycogenolytic

rate observed in incubated muscles from 6 h-hyperadrenalinaemic rats is similar to that observed in muscles from control rats (L. Budohoski, unpublished work).

The quintessential finding in the present study is that, with increasing duration of hyperadrenalinaemia, the initially decreased sensitivity of glucose transport, and hence glycolysis, to insulin is reversed, to produce a dramatic increase in the sensitivity of these processes to insulin. Thus 72 h after retard-tablet implantation the sensitivity of glucose transport in soleus muscle is similar to that observed in muscles from control rats, and after 120 h it is increased. It is important to note that the changes in sensitivity to insulin are observed for the processes of lactate formation and glucose transport, but not for the process of glycogen synthesis, which suggests a post-receptor interaction between the insulin and adrenaline transduction mechanisms. This view is supported by the finding that the number and affinity of insulin receptors in soleus muscle are unaffected by 120 h hyperadrenalinaemia (L. Budohoski, unpublished work).

To our knowledge, this is the first report that prolonged (120 h) elevation of the plasma concentration of adrenaline increased peripheral tissue sensitivity to insulin. Several studies have shown that β -adrenoceptor agonists, when administered chronically, improve insulin-stimulated glucose disposal in man (Scheidegger *et al.*, 1984) and improve glucose tolerance and insulin-sensitivity both *in vivo* in genetically obese rats (Cawthorne *et al.*, 1984; Smith *et al.*, 1985) and in isolated muscles from lean and obese animals *in vitro* (Challiss *et al.*, 1985). Our results therefore suggest that the effects of terbutaline sulphate and BRL 26830A are mediated by the β -adrenoceptor-agonist activity of these agents and that this effect may be a common feature of β -adrenoceptor agonists when administered chronically.

Evidence has been obtained that a decrease in the local concentration of adenosine in isolated soleus muscle increases the sensitivity of the rates of glucose transport, but not glycogen synthesis, to insulin (Espinal *et al.*, 1983b; Budohoski *et al.*, 1984a). Since chronic elevation of plasma adrenaline concentration for 120 h has a similar effect, it is tempting to speculate that adrenaline exerts its effects on the sensitivity of glucose transport to insulin by decreasing the concentration of adenosine in skeletal muscle or changes in the properties of skeletal-muscle adenosine receptors, and this postulate requires investigation.

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