Effect of adrenaline on glucose kinetics during exercise in adrenalectomised humans

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1. The role of adrenaline in regulating hepatic glucose production and muscle glucose uptake during exercise was examined in six adrenaline-deficient, bilaterally adrenalectomised humans. Six sex- and age-matched healthy individuals served as controls (CON).

2. Adrenalectomised subjects cycled for 45 min at $68 \pm 1\%$ maximum pulmonary O_2 uptake ($\dot{V}_{O_2,max}$), followed by 15 min at $84 \pm 2\%$ $\dot{V}_{O_2,max}$ without (−ADR) or with (+ADR) adrenaline infusion, which elevated plasma adrenaline levels (45 min, $4\cdot49 \pm 0\cdot69$ nmol l^{-1}; 60 min, $12\cdot41 \pm 1\cdot80$ nmol l^{-1}; means $\pm$ S.E.M.). Glucose kinetics were measured using [3-^{3}H]glucose.

3. Euglycaemia was maintained during exercise in CON and −ADR, whilst in +ADR plasma glucose was elevated. The exercise-induced increase in hepatic glucose production was similar in +ADR and −ADR; however, adrenaline infusion augmented the rise in hepatic glucose production early in exercise. Glucose uptake increased during exercise in +ADR and −ADR, but was lower and metabolic clearance rate was reduced in +ADR.

4. During exercise noradrenaline and glucagon concentrations increased, and insulin and cortisol concentrations decreased, but plasma levels were similar between trials. Adrenaline infusion suppressed growth hormone and elevated plasma free fatty acids, glycerol and lactate. Alanine and β-hydroxybutyrate levels were similar between trials.

5. The results demonstrate that glucose homeostasis was maintained during exercise in adrenalectomised subjects. Adrenaline does not appear to play a major role in matching hepatic glucose production to the increase in glucose clearance. In contrast, adrenaline infusion results in a mismatch by simultaneously enhancing hepatic glucose production and inhibiting glucose clearance.

The rise in plasma adrenaline that occurs during exercise has been suggested to play an important role in mediating the increase in hepatic glucose production. In accordance with this, studies have demonstrated that liver glycogen breakdown was attenuated during exercise in adreno-demedullated animals when compared with that of control animals with normal adrenomedullary secretion (Richter *et al.* 1981*a*; Sonne *et al.* 1985). Somewhat in contrast to this, other studies in adrenodemedullated animals have shown that hepatic glucose production and liver glycogen breakdown were not affected during exercise (Carlson *et al.* 1985; Arnall *et al.* 1986; Marker *et al.* 1986; Winder *et al.* 1987). However, since adrenaline stimulates glucose production late in prolonged exercise when gluconeogenesis is accelerated (Moates *et al.* 1988), it has been suggested that the role of adrenaline during exercise is to facilitate gluconeogenic substrate mobilisation from peripheral sites (Richter *et al.* 1981*b*; Winder *et al.* 1985).

Studies in adrenaline-deficient bilaterally adrenalectomised humans during moderate intensity exercise have shown that euglycaemia was maintained (Järhult & Holst, 1979) and that the exercise-induced increase in hepatic glucose output was similar when compared with that in normal subjects (Hoelzer *et al.* 1986*b*). It should be noted that results from the latter paper were partly retracted (Cryer, 1989); however, this was only in reference to the experiments performed

with an islet clamp. Although these studies suggest that adrenaline does not play an essential role in mediating the increase in hepatic glucose output during moderate intensity exercise, control experiments in which adrenaline was replaced were not performed. Thus, it cannot be ruled out that the apparent normal exercise-induced increase in glucose production in adrenalectomised subjects could be due either to compensatory changes in other hormonal systems influencing glucoregulation, or to development of adrenergic receptor hypersensitivity in combination with other remaining adrenaline-secreting tissue. It is possible that the tissue could secrete adrenaline into the portal area and changes in circulating adrenaline may be difficult to detect due to clearance by the liver. Therefore, it is important to determine the role of glucoregulatory hormones, other than catecholamines, during exercise. In addition, it is important to infuse adrenaline at rest in both adrenalectomised and control subjects, and during exercise in adrenalectomised individuals. In a previous study in exercising humans, pharmacological blockade of the coeliac ganglion was employed to inhibit sympathetic neural activity to the liver, adrenal medulla and pancreas (Kjær *et al.* 1993). The effects of liver nerve blockade were separated from the effects of impaired adrenaline secretion by infusion of adrenaline during exercise. It was concluded that although high physiological concentrations of adrenaline could enhance glucose production in exercising humans, normally adrenaline was not a major stimulus (Kjær *et al.* 1993). However, coeliac ganglion blockade does not completely inhibit adrenaline secretion, and although somatostatin, insulin and glucagon were infused to compensate for the sympathetic neural blockade to the pancreas, this experimental approach does not yield optimal conditions for evaluation of the physiological role of adrenaline.

In addition to regulation of hepatic glucose production, it has been suggested that adrenaline may affect the exercise-induced increase in muscle glucose uptake; however, the results are conflicting. Indeed, in animal studies infusion of adrenaline resulted in both a decrease (Issekutz, 1985) and an increase (Richter *et al.* 1982) in glucose uptake. In humans, infusion of adrenaline into one leg reduced muscle glucose uptake compared with the contralateral leg during two-legged cycling (Jansson *et al.* 1986). Furthermore, β-adrenergic receptor blockade during intense exercise in humans resulted in an increase in glucose disappearance (Sigal *et al.* 1994). In line with these findings, glucose clearance was higher and plasma glucose concentration decreased more rapidly during exercise in experiments in which adrenaline secretion was inhibited by pharmacological coeliac ganglion blockade than when compared with control experiments with a normal adrenaline response (Kjær *et al.* 1993). Taken together these findings support the hypothesis that adrenaline can inhibit glucose uptake during exercise.

The aim of the present study, therefore, was to examine the effect of adrenaline on hepatic glucose production and muscle glucose uptake during exercise. Bilaterally adrenalectomised

humans were examined during both moderate and high intensity exercise by infusing adrenaline in an attempt to obtain plasma levels similar to those observed during exercise in normal humans with intact adrenal glands. Results were compared with healthy, sex- and age-matched control individuals. Finally, all individuals underwent adrenaline infusion at rest to determine whether adrenalectomised individuals have altered adrenergic receptor sensitivity.

METHODS

Subjects

Six adrenaline-deficient bilaterally adrenalectomised subjects (5 females, 1 male; age, $45\cdot8 \pm 5\cdot8$ years; weight, $75\cdot2 \pm 8\cdot0$ kg; means $\pm$ S.E.M.) volunteered to participate in the experiment. Subjects were in good health and taking adrenocortical replacement medications (hydrocortisone and aldosterone), which were not altered for the purpose of this study. In addition, six normal healthy untrained individuals with intact adrenal glands who were sex and age matched ($47\cdot0 \pm 4\cdot7$ years, $69\cdot3 \pm 2\cdot4$ kg) to the adrenalectomised subjects also volunteered to participate in the experiment. The experimental procedures and possible risks of the study were explained to each subject verbally and in writing. All subjects gave their informed, written consent to the experiment, which was approved by the Ethical Committee of Copenhagen.

Pre-experimental protocol

In order to determine maximum pulmonary oxygen uptake ($\dot{V}_{O_2,max}$) and to establish the relationship between workload and oxygen uptake ($\dot{V}_{O_2}$) all subjects performed an incremental workload test to exhaustion on a modified electromagnetically braked Krogh cycle ergometer. The subjects lay behind the cycle ergometer on a couch in a semi-recumbent position with the upper part of the body forming an angle of $\sim$45 deg with the couch. Maximum $\dot{V}_{O_2}$ was the highest $\dot{V}_{O_2}$ attained during the latter stages of the test and was accompanied by a respiratory exchange ratio (RER) that was greater than $1\cdot1$ and a heart rate (in beats per minute, bpm) that was close to the age-predicted maximum (220 bpm − age). Mean $\dot{V}_{O_2,max}$ was $1\cdot46 \pm 0\cdot19$ and $2\cdot30 \pm 0\cdot31$ l min^{-1} for the adrenalectomised and normal subjects, respectively. For the day preceding each trial the subjects were instructed to abstain from strenuous exercise, tobacco, caffeine and alcohol. The subjects reported to the exercise laboratory in the morning after a 10–12 h overnight fast.

Experimental protocol

Adrenalectomised subjects. The adrenalectomised subjects were studied during two exercise periods, separated by at least 14 days. During exercise either isotonic saline (−ADR) or adrenaline (+ADR) was infused. The exercise trials were performed on the same modified cycle ergometer as used for $\dot{V}_{O_2,max}$ determination.

On arrival at the exercise laboratory, the adrenalectomised subjects rested quietly on the modified cycle ergometer. Following local anaesthesia ($0\cdot5$ ml lidocaine, 10 mg ml^{-1}) a catheter was introduced percutaneously into the radial artery for blood sampling and continuous measurement of blood pressure. The catheter for blood sampling was kept patent by regular flushing with saline. In addition, a catheter was inserted into a contralateral forearm vein and a three-way stop cock was attached to allow for simultaneous infusion of tracer and isotonic saline or adrenaline. Following a priming dose of 24 μCi, D-[3-^{3}H]glucose (pharmaceutically prepared and dissolved in isotonic saline; Isotopapoteket, Amersham, Denmark) was infused continuously at a rate of $0\cdot24$ μCi min^{-1} by

a syringe pump (P4000 anaesthesia syringe pump, IVAC, Damca) for the duration of the 2 h rest period and exercise. On completion of the rest period the adrenalectomised subjects commenced exercise at a workload that elicited an exercise intensity of $68 \pm 1\%$ $\dot{V}_{O_2,max}$ for 45 min, immediately followed by a 15 min bout of exercise at $84 \pm 2\%$ $\dot{V}_{O_2,max}$. At the onset of exercise either isotonic saline or adrenaline was infused continuously via a volumetric infusion pump (IMED 960, San Diego, CA, USA). In the first trial (−ADR), isotonic saline was infused at a similar rate to +ADR. In the subsequent trial (+ADR), an adrenaline solution ($2\ \mu g\ ml^{-1}$) was infused at a rate of $0\cdot15\ nmol\ kg^{-1}\ min^{-1}$ for 45 min and the rate was then increased to $0\cdot40\ nmol\ kg^{-1}\ min^{-1}$ for the final 15 min of exercise. The infusion rates were based on expected increases in plasma concentrations obtained in previous experiments with adrenaline infusion (Kjær *et al.* 1993). Arterial blood was sampled at 5 min intervals for the last 15 min of the rest period and throughout exercise for later analysis of plasma glucose, lactate and $[3\text{-}^3H]$glucose specific activity. Arterial samples were also obtained immediately prior to the commencement of exercise, at 10, 20, 30 and 45 min of exercise, and at the completion of the exercise period for analysis of catecholamines. Additional samples were taken at 0, 20, 45 and 60 min for analysis of insulin, glucagon, cortisol, growth hormone, free fatty acids (FFA), glycerol, β-hydroxybutyrate, alanine, haematocrit and oxygen saturation. Blood for analysis was collected in chilled tubes containing EGTA and glutathione for catecholamines, in heparinised tubes for the metabolites and in tubes containing aprotinin and EDTA for the other hormones. The blood samples were centrifuged immediately and the plasma removed and stored at $-20\ ^\circ C$ for later analysis. Plasma for catecholamine and FFA analysis was stored at $-80\ ^\circ C$. In preparation for hormone analysis the plasma was deproteinised in perchloric acid, centrifuged again and the supernatant removed and stored at $-20\ ^\circ C$. Expired gases were sampled during exercise for measurement of oxygen consumption and carbon dioxide production by an Oxycon chamber system (Jaeger Instruments). Heart rate was measured continuously using electrocardiography. During exercise the intensity of effort was quantified by a rating of perceived exertion on a scale from 6 (minimum effort) to 20 (maximum effort).

Control subjects. The sex- and age-matched normal subjects with intact adrenal glands were studied during one exercise period (CON). On arrival at the exercise laboratory, the subjects rested quietly on the cycle ergometer and a catheter was inserted into the radial artery of one arm for blood sampling. The subjects exercised at a workload that required $73 \pm 3\%$ $\dot{V}_{O_2,max}$ for 45 min, immediately followed by a 15 min bout of exercise at $90 \pm 4\%$ $\dot{V}_{O_2,max}$. The exercise intensity and duration were not significantly different from those of the adrenalectomised subjects. Arterial blood samples were taken at 0, 10, 20, 30, 45 and 60 min of exercise for analysis of catecholamines, glucose and lactate. Haematocrit and oxygen saturation were measured at 0, 20, 45 and 60 min of exercise. Expired gases were sampled during exercise. Heart rate and blood pressure were measured continuously.

Sensitivity test. Each subject (both controls and adrenalectomised subjects) was infused with adrenaline in the resting state to test for adrenergic receptor sensitivity. After completion of the exercise trial (CON and −ADR for adrenalectomised subjects) subjects rested for 30 min and then adrenaline was infused at a rate of $0\cdot15\ nmol\ kg^{-1}\ min^{-1}$ for 15 min followed by $0\cdot40\ nmol\ kg^{-1}\ min^{-1}$ for another 15 min to simulate adrenaline levels during exercise. Arterial blood was sampled before infusion, and at 15 and 30 min for analysis of catecholamines, glucose and lactate. Heart rate and blood pressure responses were recorded every minute.

Table 1. Oxygen uptake, RER, heart rate, MAP and perceived exertion during 60 min of cycling exercise in normal (CON) and adrenalectomised subjects with saline (−ADR) or adrenaline (+ADR) infusion commencing at the onset of exercise

	0–45 min	45–60 min
Oxygen uptake (l min^{-1})		
−ADR	$0\cdot97 \pm 0\cdot13$	$1\cdot28 \pm 0\cdot20$
+ADR	$1\cdot02 \pm 0\cdot12$	$1\cdot17 \pm 0\cdot13$
CON	$1\cdot68 \pm 0\cdot23$	$2\cdot15 \pm 0\cdot27$
RER		
−ADR	$0\cdot82 \pm 0\cdot02$	$0\cdot86 \pm 0\cdot02$
+ADR	$0\cdot87 \pm 0\cdot02$	$0\cdot87 \pm 0\cdot02$
CON	$0\cdot86 \pm 0\cdot01$	$0\cdot94 \pm 0\cdot02$
Heart rate (bpm)		
−ADR	113 ± 12	141 ± 13
+ADR	124 ± 14	144 ± 11
CON	$136 \pm 13*$	$166 \pm 6*$
MAP (mmHg)		
−ADR	108 ± 6	107 ± 7
+ADR	107 ± 6	104 ± 5
CON	112 ± 4	109 ± 4
Perceived exertion		
−ADR	12 ± 1	18 ± 1
+ADR	13 ± 1	17 ± 1
CON	12 ± 1	16 ± 1

Values are means $\pm$ S.E.M. ($n = 6$). RER, respiratory exchange ratio; MAP, mean arterial pressure. *Significantly different ($P < 0\cdot05$) from −ADR.

Analytical techniques

Plasma glucose and lactate were measured using an automated glucose–lactate analyser (YSI 23 AM; Yellow Springs Instruments, Yellow Springs, OH, USA). Catecholamine concentrations were determined by a single-isotope radioenzymatic method (Ben-Jonathan & Porter, 1976). The concentrations of insulin, glucagon, cortisol and growth hormone were determined by radioimmuno-asssay as previously described (Galbo *et al.* 1979). Plasma FFA, glycerol, β-hydroxybutyrate and alanine concentrations were measured by enzymatic fluorometric methods. Haematocrit was determined by the microhaematocrit method. Blood oxygen saturation was measured by an automated blood gas microanalyser (OSM 3; Acid-Base Laboratory, Radiometer, Denmark) immediately after blood samples had been drawn. Plasma $[3\text{-}^3H]$glucose radioactivity was determined as described by Kjær *et al.* (1984). Specific activity was calculated from the $[3\text{-}^3H]$glucose activity divided by the corresponding plasma glucose concentration. The measured variables were smoothed by a sliding fit technique that employed three consecutive glucose or specific activity values (Cherrington & Vranic, 1973). From measurement of plasma glucose concentration and determination of specific activity in the pre-exercise period the individual distribution volumes for glucose were calculated according to Hentenyi & Norwich (1974). The mean distribution volume for glucose was determined to be $19\cdot9 \pm 1\cdot7\%$ and was not different between −ADR and +ADR. The non-steady state equations of Steele *et al.* (1956) were used to calculate the rate of glucose appearance (R_a: hepatic glucose production) and disappearance (R_d). The metabolic clearance rate for glucose was

calculated as glucose R_d divided by the corresponding plasma glucose concentration. Results from the adrenalectomised ($-$ADR and $+$ADR) subjects were compared using a two-way analysis of variance (ANOVA) for repeated measures (cross-over design); results from the normal (CON) and adrenalectomised ($-$ADR) subjects were compared using a two-way ANOVA for repeated measures (parallel design). The level of significance was set at $P < 0.05$ in two-tailed tests. Specific differences were determined using the Student–Newman–Keuls *post hoc* test. All data are reported as means $\pm$ S.E.M.

RESULTS

Adrenalectomised subjects

Plasma adrenaline concentrations were similar at rest between $-$ADR $(0.04 \pm 0.02 \text{ nmol l}^{-1})$ and $+$ADR $(0.03 \pm 0.01 \text{ nmol l}^{-1})$. During exercise in $-$ADR, plasma adrenaline did not change from resting levels. In $+$ADR, infusion of adrenaline during exercise resulted in a marked increase $(P < 0.05)$ in plasma arterial levels to 4.49 ± 0.69 and $12.41 \pm 1.80 \text{ nmol l}^{-1}$ at 45 and 60 min, respectively (Fig. 1). Plasma noradrenaline concentrations were similar

at rest between $-$ADR and $+$ADR, and increased during exercise $(P < 0.05$, time effect), but were not different between trials (Fig. 1).

During exercise oxygen uptake, RER and heart rate were similar between $-$ADR and $+$ADR. However, there was an increase $(P < 0.05$, time effect) in these variables when the exercise intensity was raised from 68 to 84% $\dot{V}_{O_2,max}$ (Table 1). Perceived exertion increased $(P < 0.05$, time effect) similarly during exercise in $-$ADR and $+$ADR (Table 1). Mean arterial pressure (Table 1), haematocrit and oxygen saturation (data not shown) remained constant throughout exercise and were similar between the two trials.

During exercise in $-$ADR the plasma glucose concentration did not change significantly from resting levels, whilst in $+$ADR there was a marked increase $(P < 0.05)$ in plasma glucose which was significantly higher than that in $-$ADR, except for the first 5 min (Fig. 2). Glucose concentration in $+$ADR reached steady state after 30 min of moderate intensity exercise, reflecting a match between hepatic glucose production and glucose uptake. When the adrenaline infusion rate and intensity of exercise were further increased,
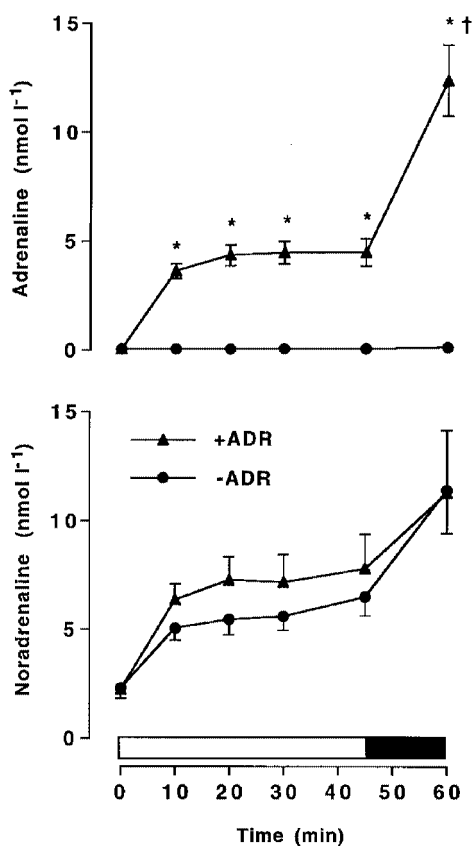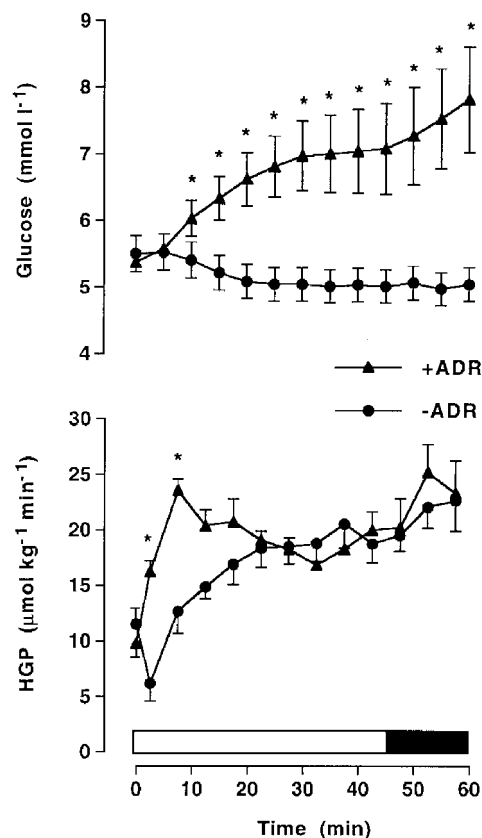

Figure 1. Catecholamines and exercise

Plasma adrenaline and noradrenaline during cycling exercise at 68% $\dot{V}_{O_2,max}$ for 45 min, followed by 15 min at 84% $\dot{V}_{O_2,max}$ in adrenalectomised subjects with saline ($-$ADR) or adrenaline ($+$ADR) infusion commencing at the onset of exercise and increased after 45 min. Values are means $\pm$ S.E.M. ($n = 6$). * Significantly different ($P < 0.05$) from $-$ADR; † significantly different ($P < 0.05$) from 45 min.

Figure 2. Glucose concentration and production

Plasma glucose and hepatic glucose production (HGP) during cycling exercise at 68% $\dot{V}_{O_2,max}$ for 45 min, followed by 15 min at 84% $\dot{V}_{O_2,max}$ in adrenalectomised subjects with saline ($-$ADR) or adrenaline ($+$ADR) infusion commencing at the onset of exercise and increased after 45 min. Values are means $\pm$ S.E.M. ($n = 6$). * Significantly different ($P < 0.05$) from $-$ADR.

there was a tendency for the glucose concentration to increase further, reflecting a more rapid rise in glucose production than in glucose uptake. Hepatic glucose production increased ($P < 0.05$) during exercise in both −ADR and +ADR; however, infusion of adrenaline augmented the rise ($P < 0.05$) in hepatic glucose production during the first 10 min of exercise (Fig. 2). When the exercise intensity was raised at 45 min, there was a tendency for hepatic glucose production to increase more so in +ADR than in −ADR (Fig. 2). Glucose R_d increased ($P < 0.05$) during exercise in both trials, but was lower ($P < 0.05$, main effect) in +ADR compared with that in −ADR (Fig. 3). There was an increase ($P < 0.05$) in metabolic clearance rate during exercise in −ADR, although this was significantly reduced ($P < 0.05$) with infusion of adrenaline (Fig. 3).

Plasma insulin and glucagon concentrations, and the glucagon:insulin molar ratio were similar between −ADR and +ADR at rest and during exercise. However, during exercise there was an increase ($P < 0.05$, time effect) and a decrease ($P 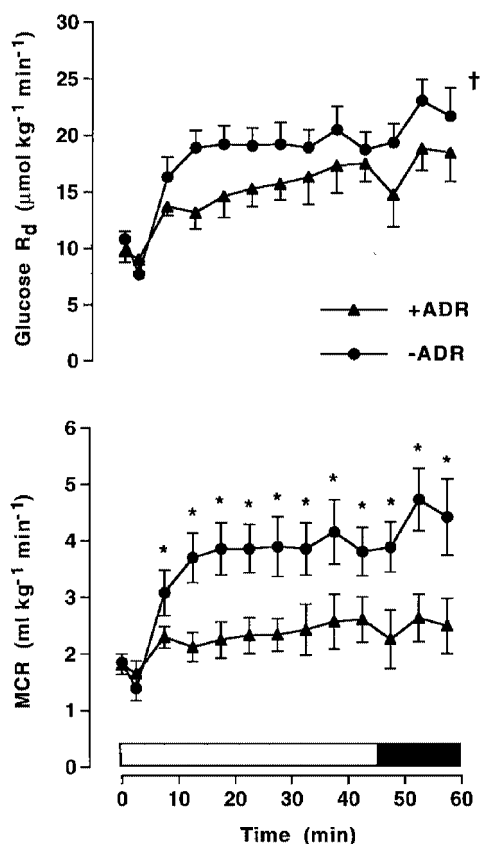< 0.05$, time effect) in plasma glucagon and insulin, respectively, which resulted in an elevated ($P < 0.05$, time effect) glucagon:insulin molar ratio (Table 2). Plasma cortisol was not different between −ADR and +ADR trials at rest and during exercise. However, during exercise there was a decrease ($P < 0.05$, time effect) in the cortisol concentration (Table 2). During exercise infusion of adrenaline suppressed the increase in plasma growth hormone (Table 2).

Plasma FFA and glycerol concentrations were similar at rest between the trials. During exercise, infusion of adrenaline increased ($P < 0.05$) plasma levels of FFA and glycerol (Table 3). β-Hydroxybutyrate and alanine concentrations were similar between −ADR and +ADR at rest and during exercise; however, alanine increased ($P < 0.05$, time effect) during exercise (Table 3). Lactate increased ($P < 0.05$) during exercise in both trials, but was significantly higher with adrenaline infusion from 10 min (Fig. 4).

Control subjects

At rest the plasma adrenaline concentration was ∼10-fold lower in bilaterally adrenalectomised subjects (0.04 ± 0.02 nmol l^{-1}) when compared with that in normal subjects (0.35 ± 0.03 nmol l^{-1}). During exercise in CON, plasma adrenaline levels increased ($P < 0.05$) to a peak of 2.20 ± 0.58 nmol l^{-1} at 60 min. Plasma adrenaline levels were significantly greater in CON when compared with those in −ADR, but were somewhat lower than levels obtained in +ADR during exercise (Figs 1 and 5). Plasma noradrenaline concentration increased ($P < 0.05$, time effect) during exercise in CON, but was not significantly different from that in −ADR (Fig. 5).

Relative oxygen uptake (percentage $\dot{V}_{O_2,max}$) was not different between CON and adrenalectomised subjects

Figure 3. Glucose uptake and clearance

Whole-body glucose uptake (Glucose R_d) and metabolic clearance rate (MCR) during cycling exercise at 68% $\dot{V}_{O_2,max}$ for 45 min, followed by 15 min at 84% $\dot{V}_{O_2,max}$ in adrenalectomised subjects with saline (−ADR) or adrenaline (+ADR) infusion commencing at the onset of exercise and increased after 45 min. Values are means ± s.e.m. ($n = 6$).
* Significantly different ($P < 0.05$) from +ADR;
† significantly different ($P < 0.05$, main effect) from +ADR.

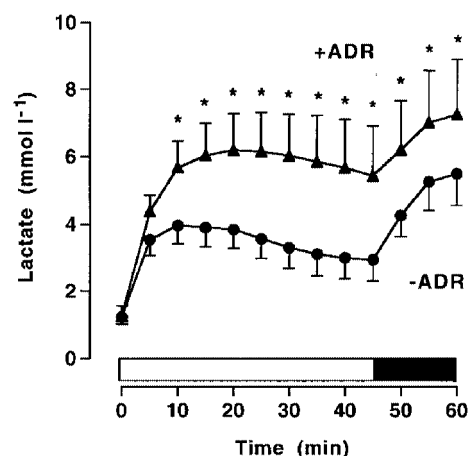**Figure 4. Lactate in exercising adrenalectomised humans**

Plasma lactate during cycling exercise at 68% $\dot{V}_{O_2,max}$ for 45 min, followed by 15 min at 84% $\dot{V}_{O_2,max}$ in adrenalectomised subjects with saline (−ADR) or adrenaline (+ADR) infusion commencing at the onset of exercise and increased after 45 min. Values are means ± s.e.m. ($n = 6$).
* Significantly different ($P < 0.05$) from −ADR.

during exercise, whereas absolute $\dot{V}_{O_2}$, RER and heart rate were all higher ($P < 0.05$) in CON compared with both −ADR and +ADR (Table 1). Mean arterial pressure, perceived exertion (Table 1), haematocrit and oxygen saturation (data not shown) were similar between the two subject groups.

Euglycaemia was maintained throughout exercise and plasma glucose was not different between CON and −ADR (Fig. 6). Plasma lactate increased ($P < 0.05$) during exercise and was similar between the two subject groups, except at 60 min when lactate was higher ($P < 0.05$) in CON (7.68 ± 0.97 mmol l^{-1}) than in −ADR (5.49 ± 0.94 mmol l^{-1}) (Fig. 6).

Sensitivity test

Infusion of adrenaline at a rate of 0.15 nmol kg^{-1} min^{-1} increased ($P < 0.05$) the plasma adrenaline concentration to a similar level in the two subject groups (Table 4). When the adrenaline infusion rate was increased to 0.40 nmol kg^{-1} min^{-1} the plasma adrenaline concentration was further elevated ($P < 0.05$), but was higher ($P < 0.05$) in

adrenalectomised subjects (11.9 ± 1.12 nmol l^{-1}) compared with CON (9.17 ± 0.83 nmol l^{-1}). In adrenalectomised subjects plasma adrenaline concentrations were similar regardless of whether adrenaline was infused at rest (Table 4) or during exercise (Fig. 1). Plasma noradrenaline was not different between subject groups prior to and during adrenaline infusion (Table 4). Infusion of adrenaline increased ($P < 0.05$, time effect) plasma glucose, but this was not different between subject groups (Table 4). Adrenaline infusion at rest had no significant effect on plasma lactate concentration, heart rate and mean arterial blood pressure (Table 4).

DISCUSSION

The results from the present study demonstrate that in adrenaline-deficient bilaterally adrenalectomised humans, infusion of adrenaline that resulted in plasma levels within the physiological range augmented the rise in hepatic glucose output early during exercise. However, the overall magnitude of the exercise-induced increase in hepatic glucose production was not significantly different regardless
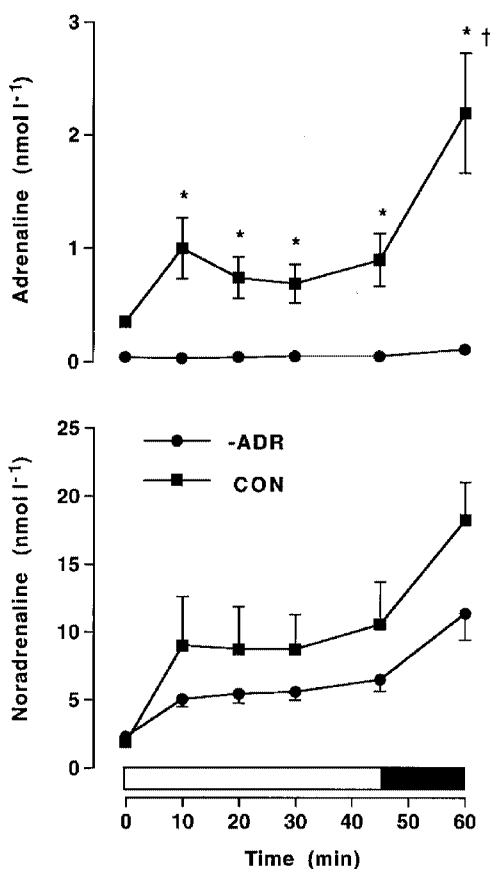
Figure 5. Catecholamines in adrenalectomised humans and controls

Plasma adrenaline and noradrenaline during cycling exercise at $\sim70\%$ $\dot{V}_{O_2,max}$ for 45 min, followed by 15 min at $\sim86\%$ $\dot{V}_{O_2,max}$ in normal control (CON) or adrenalectomised subjects with saline infusion (−ADR). Values are means $\pm$ s.e.m. ($n = 6$). * Significantly different ($P < 0.05$) from −ADR; † significantly different ($P < 0.05$) from 45 min.

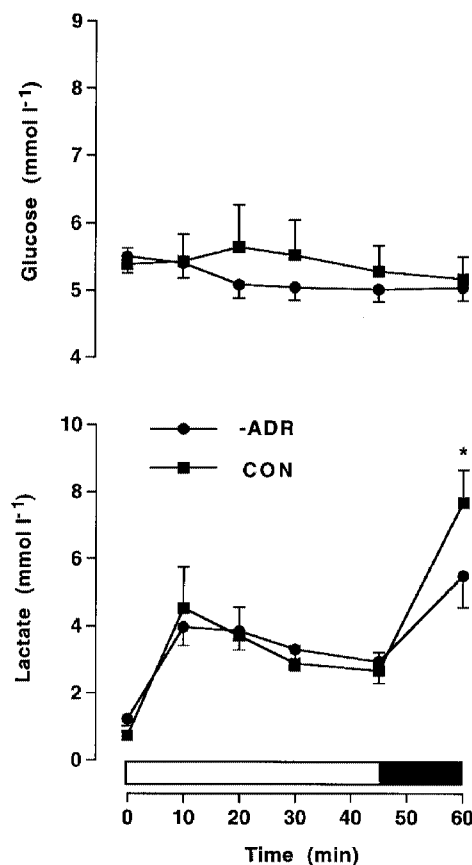**Figure 6. Glucose and lactate in adrenalectomised humans**

Plasma glucose and lactate during cycling exercise at $\sim70\%$ $\dot{V}_{O_2,max}$ for 45 min, followed by 15 min at $\sim86\%$ $\dot{V}_{O_2,max}$ in normal control (CON) or adrenalectomised subjects with saline infusion (−ADR). Values are means $\pm$ s.e.m. ($n = 6$). * Significantly different ($P < 0.05$) from −ADR.

Table 2. Plasma hormones during 60 min of cycling exercise in adrenalectomised subjects with saline (−ADR) or adrenaline (+ADR) infusion commencing at the onset of exercise

	Rest	20 min	45 min	60 min
Insulin (pmol l^{-1})				
−ADR	87·8 ± 37·1	57·9 ± 22·8	43·0 ± 16·3	36·6 ± 10·6
+ADR	66·8 ± 23·1	62·2 ± 15·6	61·6 ± 14·5	32·1 ± 6·9
Glucagon (ng l^{-1})				
−ADR	62·6 ± 10·7	64·5 ± 11·8	69·4 ± 12·9	70·8 ± 11·8
+ADR	65·1 ± 10·7	75·0 ± 14·6	71·4 ± 15·4	78·1 ± 16·4
G:I molar ratio				
−ADR	0·35 ± 0·08	0·47 ± 0·09	0·63 ± 0·10	0·76 ± 0·15
+ADR	0·39 ± 0·08	0·46 ± 0·13	0·41 ± 0·11	0·90 ± 0·25
Cortisol (nmol l^{-1})				
−ADR	441 ± 120	411 ± 123	336 ± 102	298 ± 91
+ADR	428 ± 58	391 ± 57	333 ± 50	308 ± 50
GH (ng ml^{-1})				
−ADR	1·02 ± 0·44	5·32 ± 2·65	6·63 ± 2·53*	6·59 ± 2·89*
+ADR	1·18 ± 0·44	2·99 ± 1·40	2·22 ± 1·16	1·75 ± 0·76

Values are means ± s.e.m. ($n = 6$; except for growth hormone (GH), $n = 5$). NA, noradrenaline; G:I, glucagon:insulin. * Significantly different ($P < 0·05$) from +ADR.

Table 3. Plasma substrates during 60 min of cycling exercise in adrenalectomised subjects with saline (−ADR) or adrenaline (+ADR) infusion commencing at the onset of exercise

	Rest	20 min	45 min	60 min
FFA (mmol l^{-1})				
−ADR	0·67 ± 0·06	0·53 ± 0·07*	0·76 ± 0·08*	0·68 ± 0·08*
+ADR	0·63 ± 0·07	0·92 ± 0·11	1·04 ± 0·06	1·05 ± 0·09
Glycerol (μmol l^{-1})				
−ADR	107 ± 21	152 ± 17*	250 ± 23*	272 ± 35*
+ADR	98 ± 10	237 ± 12	296 ± 36	333 ± 42
β-Hydroxybutyrate (mmol l^{-1})				
−ADR	0·23 ± 0·09	0·17 ± 0·05	0·21 ± 0·07	0·22 ± 0·08
+ADR	0·35 ± 0·11	0·25 ± 0·06	0·33 ± 0·09	0·38 ± 0·11
Alanine (μmol l^{-1})				
−ADR	122 ± 22	156 ± 11	172 ± 17	178 ± 11
+ADR	113 ± 19	166 ± 18	167 ± 17	173 ± 18

Values are means ± s.e.m. ($n = 6$). * Significantly different ($P < 0·05$) from +ADR.

of whether or not adrenaline was replaced. Elevated plasma adrenaline levels also attenuated the exercise-induced increase in peripheral glucose uptake. Furthermore, glucose homeostasis was maintained during exercise in adrenalectomised subjects infused with saline. Taken together, the results indicate that normally adrenaline does not play a major role in matching glucose production to the increase in glucose clearance during exercise. Rather, adrenaline infusion results in a mismatch by simultaneously enhancing glucose production and inhibiting glucose clearance.

Comparisons between experiments with and without adrenaline infusion in adrenalectomised subjects suggest that increases in adrenaline concentration, as seen during transition from rest to exercise and from moderate to intense exercise, may enhance glucose production (Figs 1 and 2). The increase in glucose production during exercise in +ADR was accompanied by increases in plasma glucose concentration (Fig. 2) which suggests that adrenaline may cause a mismatch between glucose production and clearance. Indeed, the findings indicate that the increase in plasma glucose reflects both an increase in glucose production (Fig. 2) and a reduction in glucose clearance (Fig. 3). During steady-state periods of exercise, glucose production was similar in +ADR and −ADR. However, given that elevated plasma glucose (Fig. 2), *per se*, can inhibit glucose production (Jenkins *et al.* 1985), this suggests that during

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Table 4. Sensitivity test: response to adrenaline infusion at rest in normal (CON) and
adrenalectomised (−ADR) subjects

	0 min	15 min (0·15 nmol kg^{-1} min^{-1})	30 min (0·40 nmol kg^{-1} min^{-1})
Adrenaline (nmol l^{-1})			
CON	0·85 ± 0·61	3·73 ± 0·29†	9·17 ± 0·83*‡
−ADR	0·07 ± 0·02	4·57 ± 0·37†	11·90 ± 1·12‡
Nordrenaline (nmol l^{-1})			
CON	1·85 ± 0·30	1·77 ± 0·20	1·74 ± 0·24
−ADR	2·52 ± 0·44	2·70 ± 0·45	2·50 ± 0·40
Glucose (mmol l^{-1})			
CON	5·07 ± 0·33	5·83 ± 0·33	7·24 ± 0·42
−ADR	5·27 ± 0·27	6·16 ± 0·23	7·57 ± 0·33
Lactate (mmol l^{-1})			
CON	1·73 ± 0·24	1·42 ± 0·21	1·64 ± 0·26
−ADR	1·97 ± 0·47	1·79 ± 0·34	2·16 ± 0·33
Heart rate (bpm)			
CON	84 ± 6	89 ± 6	96 ± 7
−ADR	84 ± 5	87 ± 6	91 ± 7
MAP (mmHg)			
CON	78 ± 4	72 ± 3	74 ± 3
−ADR	82 ± 2	75 ± 3	76 ± 3

Values are means ± S.E.M. ($n = 6$). MAP, mean arterial pressure. * Significantly different ($P < 0·05$) from
−ADR; † significantly different ($P < 0·05$) from 0 min; ‡ significantly different ($P < 0·05$) from 15 min.

the steady state, adrenaline may also enhance glucose production.

The observed differences in glucose kinetics between −ADR and +ADR during exercise are unlikely to be elicited by glucoregulatory hormones other than adrenaline, as plasma levels of glucagon, insulin and cortisol were not different between trials (Table 2). Furthermore, during exercise the growth hormone concentration was lower in +ADR than in −ADR, a difference which *per se* would tend to cause changes in glucose kinetics opposite to those observed (that is, lower glucose production and higher glucose clearance). The fact that the exercise-induced increase in growth hormone was suppressed by adrenaline infusion probably reflects reduced secretion as a result of increased plasma glucose levels (Galbo, 1983). The finding that plasma cortisol concentration always decreased during exercise in hydrocortisone-substituted, adrenalectomised subjects (Table 2) is in accordance with the fact that cortisol clearance is increased by exercise (Galbo, 1983).

The finding that adrenaline can stimulate hepatic glucose production during exercise has previously been demonstrated for other experimental conditions. Indeed, when adrenaline was infused at rates that resulted in high physiological concentrations hepatic glucose production was enhanced in healthy subjects (Kjær *et al.* 1993; Howlett *et al.* 1999). However, when adrenaline was accurately replaced by infusion during exercise in coeliac ganglion-

blocked humans there was no effect on hepatic glucose output (Kjær *et al.* 1993). Although in some studies adrenodemedullated animals have been shown to display reduced hepatic glycogenolysis (Richter *et al.* 1981*a*) and tracer-determined glucose production (Sonne *et al.* 1985) during exercise, other studies find no effect on the decrease in liver glycogen content during exercise (Winder *et al.* 1985; Arnall *et al.* 1986). In other animal studies, adrenaline has been shown to indirectly stimulate hepatic glucose production by increased gluconeogenesis as a result of accelerated muscle glycogenolysis and subsequent lactate release (Sonne *et al.* 1987; Wasserman *et al.* 1987). In the present study, adrenaline infusion increased plasma lactate levels (Fig. 4); however, the time course of the increase in lactate during exercise differed from that of the increase in glucose production. This suggests that adrenaline increased glucose production primarily by stimulating hepatic glycogenolysis.

Despite the fact that elevated levels of adrenaline can stimulate hepatic glucose production, it appears that in the absence of adrenaline, glucose production was not impaired during moderate and high intensity exercise. In the present study, euglycaemia was maintained during exercise in adrenalectomised humans and the plasma glucose response was similar when compared with that of normal subjects (Fig. 6). Similar findings have also been demonstrated during moderate exercise in adrenalectomised humans

(Järhult & Holst, 1979; Hoelzer *et al.* 1986*b*), and in normal subjects following anaesthetic blockade of the coeliac ganglion (Kjaer *et al.* 1993) and adrenergic receptor blockade (Simonson *et al.* 1984; Hoelzer *et al.* 1986*a*). This study also provides further support for the suggestion that adrenaline is not essential for regulating hepatic glucose production even at high exercise intensities (Kjær *et al.* 1993; Coker *et al.* 1997*b*; Howlett *et al.* 1999). However, these findings do not exclude the possibility that adrenaline may play a role during more prolonged exercise in humans. Indeed, in adrenalectomised dogs the effect of adrenaline on hepatic glucose production was not seen until late during prolonged moderate-intensity exercise (Moates *et al.* 1988).

The exercise-induced increase in hepatic glucose production in the adrenalectomised humans was probably stimulated by changes in the pancreatic hormones. Indeed, during exercise there was a decrease and an increase in insulin and glucagon, respectively ($P < 0.05$). Sympathetic neural activity may also have contributed to the increase in glucose production; however, previous studies in exercising humans (Kjær *et al.* 1993, 1995) and dogs (Coker *et al.* 1997*b*) suggest that this is not the case. The changes in plasma cortisol and growth hormone concentration are probably too slow to account for glucose production during exercise in the present study. Furthermore, glucose production increased despite a reduction in cortisol during exercise (Table 2).

Although extra-adrenomedullary adrenaline secretion occurs in bilaterally adrenalectomised humans (Shah *et al.* 1984; Hoelzer *et al.* 1986*b*), this is likely to be minimal as plasma adrenaline levels were ~10-fold lower in adrenalectomised subjects than in healthy control subjects (Figs 1 and 5). However, it cannot be completely ruled out that adrenaline secreted from other tissues into the portal area is cleared by the liver, and subsequently does not result in a notable increase in peripheral circulating levels of adrenaline during exercise (Coker *et al.* 1997*a*). Plasma adrenaline did not rise above resting levels during exercise in adrenalectomised subjects (−ADR), whereas infusion of adrenaline elevated plasma levels to concentrations that are normally observed during intense exercise. However, the adrenaline levels in +ADR were somewhat higher than those measured during exercise in the control subjects who exercised at a comparable relative workload. As adrenaline infusion rates were calculated based on findings in healthy young individuals (Kjær *et al.* 1993) it is likely that the rate of adrenaline clearance was lower in the adrenalectomised subjects. This could be due to the fact that the individuals in the present study were older than those in the study by Kjær *et al.* (1993), as it has recently been found that adrenaline clearance decreases with ageing (Marker *et al.* 1998). In the present study, adrenaline infusion resulted in a comparable rise in plasma levels at rest and during exercise (Table 4 and Fig. 1). This agrees with our previous observation that adrenaline clearance is only minimally affected by exercise (Kjær *et al.* 1985). In the present study

there was no indication that adrenalectomised subjects had developed adrenergic receptor hypersensitivity, similar to that seen in spinal cord injured subjects with impaired sympathetic activity (Mathias *et al.* 1976), as adrenaline infusion at rest resulted in metabolic and circulatory responses that were similar in adrenalectomised and control subjects.

The exercise-induced increase in glucose uptake was significantly reduced in adrenalectomised subjects when adrenaline was infused (Fig. 3). Furthermore, as plasma glucose levels increased markedly during exercise with adrenaline infusion, glucose clearance was even more diminished than glucose uptake (Fig. 3). The conclusion that adrenaline inhibits glucose clearance during exercise is in agreement with a previous study in which plasma adrenaline levels were manipulated by coeliac ganglion blockade and adrenaline infusion (Kjær *et al.* 1993). The mechanism responsible for this reduction in glucose clearance may be related to reduced glucose utilisation in muscle secondary to an increase in muscle glycogenolysis, as a result of adrenergic receptor stimulation (Raz *et al.* 1991). Adrenaline-mediated muscle glycogen breakdown is supported by some (Richter *et al.* 1981*a,b*, 1982; Katz *et al.* 1986; Jansson *et al.* 1986; Febbraio *et al.* 1998), but not all studies (Chesley *et al.* 1995; Wendling *et al.* 1996). In the present study higher plasma lactate levels in +ADR compared with those in −ADR are compatible with stimulation of muscle glycogen breakdown during exercise (Fig. 4). Other possible mechanisms that may account for the reduction in muscle glucose uptake with adrenaline infusion include effects on muscle glucose transport and/or fat metabolism. Under resting conditions adrenaline has been shown to decrease muscle glucose transport despite an increase in glucose transporter (GLUT4) translocation to the plasma membrane, which suggests a reduction in GLUT4 intrinsic activity (Bonen *et al.* 1992). Elevated plasma FFA may contribute to a reduction in leg glucose uptake during exercise (Hargreaves *et al.* 1991) although this remains controversial (Romijn *et al.* 1995; Odland *et al.* 1997). In the present study, lipolysis and the supply of FFA to the muscle were increased by adrenaline infusion as indicated by higher plasma glycerol and FFA levels in +ADR compared with those in −ADR (Table 3). However, it is unlikely that an adrenaline-mediated increase in fat mobilisation influenced glucose uptake because fat oxidation, as determined from oxygen consumption and RER measurements, was not different between trials (Table 1).

In summary, in adrenaline-deficient bilaterally adrenalectomised humans, infusion of adrenaline augmented the rise in hepatic glucose production early in exercise. However, overall levels of glucose production were not different during exercise in adrenalectomised subjects regardless of whether or not adrenaline was infused. Infusion of adrenaline also markedly attenuated the exercise-induced rise in muscle

glucose uptake and clearance. Furthermore, glucose homeostasis was maintained during exercise in adrenalectomised subjects infused with saline. The results suggest that during exercise adrenaline does not play an essential role in matching hepatic glucose production to an increase in glucose clearance. In contrast, adrenaline infusion tends to result in a mismatch by simultaneously enhancing glucose production and inhibiting glucose clearance.

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