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## Influence of peri-arterial hepatic denervation on the glycemc response to exercise in rats

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### Abstract

Exercise is known to increase hepatic glucose production. Previous studies have suggested that the sympathetic nerves only marginally contribute to this process. This study examined whether increased catecholamine response or increased adrenoceptor sensitivity might have affected previous results showing no effect of hepatic denervation on the increased hepatic glucose production during exercise. Hepatic sympathetic denervated rats, sham-operated rats and control rats were forced to swim against a counter current for 15 minutes. Denervations and sham operations were performed 9 days prior to swimming. The results show that denervation did not affect the changes in levels of blood glucose, plasma FFA, and catecholamines before, during and after swimming. Furthermore, hepatic adrenoceptor sensitivity was not altered in denervated rats, since intravenous infusions of epinephrine (20 ng/min) and norepinephrine (50 ng/min) similarly changed blood glucose and plasma FFA levels in liver-denervated, sham-operated and control rats. Thus, the increase in blood glucose levels during intravenous infusion of epinephrine and norepinephrine in the respective groups was  $1.2 \pm 0.3$  and  $1.0 \pm 0.3$  mmol/l (liver-denervated rats),  $1.6 \pm 0.4$  and  $0.7 \pm 0.3$  mmol/l (sham-operated rats) and  $1.3 \pm 0.3$  and  $0.8 \pm 0.3$  mmol/l (control rats), respectively. After adrenalectomy, however, the rise of glucose levels during swimming in liver-denervated and control rats was completely abolished. Thus, the glucose response to swimming with and without adrenalectomy was  $0.1 \pm 0.4$  and  $1.7 \pm 0.4$  mmol/l in liver-denervated rats ( $P < 0.01$ ) and  $-0.2 \pm 0.4$  and  $2.2 \pm 0.2$  mmol/l in control rats ( $P < 0.001$ ), respectively. The study therefore suggests that the peri-arterial hepatic nerves have a negligible influence on the glycemc response to exercise in rats. Instead, the glycemc response seems to be mediated mainly by the adrenal medulla.

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### Introduction

Hepatic glucose metabolism is profoundly influenced by hepatic autonomic nerves [7,11,22] and exercise is accompanied by increased hepatic

glucose production, resulting in increased plasma levels of glucose [2]. The glycemc response to exercise might be mediated by activation of the sympathetic liver nerves. Evidence for this is provided by a study in which hepatic norepinephrine content was reduced by exercise [21]. Furthermore, another study has shown that electrical stimulation of the sympathetic nerves to the liver results in transition of the inactive phosphorylase

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complex to the active state and, consequently, in increased blood glucose levels [16]. On the other hand, a number of studies have revealed that hepatic denervation fails to diminish hepatic glucose mobilization under different circumstances, such as exercise and insulin-induced hypoglycemia [8–10,17,21]. These data seemingly suggest that the physiological significance of the sympathetic hepatic nerves on peripheral glucose metabolism is negligible. Alternatively, it might be hypothesized that other mechanisms, such as increased epinephrine (E) release or altered adrenoceptor sensitivity, might have masked the effect of liver denervation on hepatic glucose production in the aforementioned studies. In particular, high levels of plasma E, as seen during emotional stress and anesthesia, can directly influence hepatic glucose production [20], potentially compensating for the effects of hepatic denervation. To test this hypothesis, we investigated the effect of peri-arterial hepatic denervation on glucose mobilization in rats well-accustomed to the exercise procedure. The experiment was based on our previous observation that rats accustomed to swimming have relatively low levels of circulating E and high levels of norepinephrine (NE) in comparison to first time swimmers [15]. In a second set of experiments, the effect of hepatic denervation on glucose mobilization was investigated in adrenodemedullated exercising rats. Adrenodemedullation was performed to exclude a possible influence of the adrenal medulla on hepatic glucose production.

## Materials and Methods

### *Animals and housing*

Male Wistar rats weighing 300–330 g at the beginning of the experiments were used. The animals were individually housed in Plexiglass cages (25 × 25 × 30 cm) at room temperature (20 ± 2°C), and had continuous access to food (Hope Farm chow) and water. The rats were maintained on a 12:12 h light-dark regime (0700–1900 h: lights on), and they were handled and weighed every day at 0900 h.

### *Surgery*

All animals were provided with two permanent heart catheters two weeks before the experiments. This and all other surgery was performed under light ether anaesthesia. The heart catheters allowed blood sampling and infusion of liquids in freely moving, undisturbed rats. The method has been described extensively before [18]. One week after insertion of the heart catheters, eight rats were denervated, eight rats were sham operated and eight rats served as controls.

### *Denervation and adrenodemedullation*

A laparotomy was performed in the midline. Using micro-surgical instruments under an operating microscope (Leitz), the hepatic artery was denervated close to the hilum, but deliberately sparing the hepatic vagal nerves [6] and the sympathetic pancreatic nerves. A myelin specific dye (Toluidin blue) was used to stain the nerves peri-arterially. Sham-operated animals were treated similarly except for cutting the nerves. Bilateral adrenodemedullation was performed by flank incisions. The adrenal medullas were removed by surgical enucleation of the medulla.

### *Physical exercise*

Exercise was performed in a pool made of stainless steel (length 3.00 m, width 0.40 m and depth 0.90 m) filled to 70% with water with a temperature of 33 ± 2°C. The pool was equipped with a starting platform (33 × 37 cm) placed 2 cm above the water level. This platform could be lowered into the water down to the bottom of the swimming pool. A water pump (Loewe Silenta, FRG) provided a counter current of 0.22 m/s that forced the animal to swim continuously. At the end of the exercise period, a removable resting platform (20 × 37 cm) at the upstream side of the swimming pool was offered to the swimming rat. The rats were accustomed to swimming and blood sampling several times to eliminate emotional stress of novelty. The rats readily learned to climb on this lit and warmed platform within 2 min after presentation.

### *Experimental set-up*

In experiment I, all animals were challenged with an intravenous infusion of physiological doses

of E and NE, respectively, on the fourth and sixth day after hepatic sympathetic denervation to investigate possible changes in catecholamine sensitivity. The doses of E and NE were selected to mimic elevated physiological concentrations in plasma E and NE levels [13,18]. Thereafter, the rats were submitted to exercise on the tenth day after hepatic sympathetic denervation (experiment II). The animals were adrenalectomized on day eleven after denervation to investigate a possible compensatory mechanism of adrenal medullary origin. At day nineteen, the animals were again submitted to exercise (experiment III).

All experiments were performed during the light period between 0900 and 1200 h. On experimental days, food was removed from the home cages 1.5 h before the start of the experiment. Forty minutes before the first blood sample was taken, the animals were connected to tubing (in mm: 300 length, 1.25 OD, and 0.75 ID) to allow blood sampling. After each sample, a transfusion of a similar amount of citrated donor blood was given to avoid diminution of the blood volume and related changes in haemodynamics. Donor blood was obtained from undisturbed rats with permanent heart catheters.

In experiment I, a second tube was connected for infusion of the catecholamine solution. The catecholamine infusion experiments were carried out in the home cage of the animals. Solutions of E (20 ng/min) and NE (50 ng/min) were intravenously infused over a 20-min period at a rate of 0.075 ml/min. A small amount of ascorbic acid (0.01%) was added to the infusates as an antioxidant. Throughout the experiments, seven blood samples (0.6 ml each) were taken for determination of blood glucose, plasma FFA, and plasma catecholamine levels. After two baseline samples (time points  $t = -11$  and  $t = -1$  min), the infusion pump was switched on (time point  $t = 0$ ) and was stopped at time point  $t = 20$  min. During infusion, blood samples were taken at time points  $t = 2, 10$  and  $17$  min. After the infusion two additional samples were taken at time points  $t = 22$  and  $30$  min.

In experiments II and III, 12 blood samples (0.6 ml each) were taken for determination of the glucose, FFA, and catecholamine concentrations.

In the home cage of the rat, two blood samples were taken in a 10-min interval (at time points  $t = -11$  and  $t = -1$  min) to measure baseline levels of blood components. The animals were then transferred to the starting platform (time point  $t = 0$  min) of the swimming pool after withdrawal of the last blood sample in the home cage. Blood samples were taken at time points  $t = 1.5$  min and  $10$  min. Immediately thereafter, the starting platform was lowered to the bottom of the pool and the rat was forced to swim for  $15$  min. Blood samples were taken at time points  $t = 11, 15, 20$  and  $25$  min. The rats were then allowed to climb onto the resting platform. Blood samples on the resting platform were taken at time points  $t = 27, 30, 37$  and  $47$  min.

#### *Chemical determinations*

Blood samples were immediately transferred to chilled ( $0^{\circ}\text{C}$ ) centrifuge tubes containing EDTA as antioxidant and  $10\ \mu\text{l}$  heparin solution ( $500\ \text{U}/\text{ml}$ ) as anticoagulant. Blood glucose ( $50\ \mu\text{l}$  blood) was measured by the ferricyanide method of Hoffman (Technicon Auto Analyzer TMII). The remaining volume was centrifuged for  $15$  min at  $5000$  rpm at  $4^{\circ}\text{C}$ . The supernatant was divided into two parts:  $100\ \mu\text{l}$  were immediately stored at  $-80^{\circ}\text{C}$  for catecholamine measurements and  $100\ \mu\text{l}$  were used for the FFA assay.

Determination of plasma catecholamine concentrations was performed by high-pressure liquid chromatography (HPLC) in combination with electro-chemical detection (ECD). This method has been described in detail before [13]. For determination of tissue NE concentrations,  $10$ – $25\ \mu\text{g}$  of the liver were cut from frozen tissue and were homogenized in  $300\ \mu\text{l}$   $\text{HClO}_4$  ( $0.1\ \text{N} + 0.05\%$  EDTA) for  $5$  min ( $0^{\circ}\text{C}$ ). The homogenate was centrifuged for  $10$  min at  $10000$  rpm and NE concentrations were determined by HPLC/ECD. Plasma FFA were extracted and photometrically determined [1].

#### *Data analysis, statistics and ethics*

Concentrations of blood components are expressed as mean changes  $\pm$  S.E. compared to baseline levels at time point  $t = -1$  min. Within each experiment, the Wilcoxon matched-pairs

signed rank test was used when the levels of the blood components at a certain time during the experiments were compared with baseline values in the home cage. Two-way analysis of variance followed by a Mann Whitney U-test were applied to determine for each sample point the significant differences between definitive experiments and control experiments. A probability level of  $P < 0.05$  was regarded as statistical significance for all tests. The study was approved by the local ethics committee for animal studies.

## Results

Table I presents the basal concentrations of blood glucose and plasma FFA in control, sham-operated, and liver-denervated animals in experiment I. Baseline levels of blood glucose and plasma FFA were similar in the three groups. The results of experiment I, in which control, sham-operated, and liver-denervated animals were subjected to intravenous infusions of E (20 ng/min) and NE (50 ng/min), are presented in Fig. 1. In the control group, infusion of E caused an increase in the concentration of blood glucose of  $1.3 \pm 0.3$  mmol/l ( $P < 0.01$ ). No significant changes were found in concentrations of plasma FFA in control animals during or after infusion of E compared to the baseline levels. Infusion of NE (50 ng/min) led to an increase in blood glucose levels of  $0.8 \pm 0.3$  mmol/l ( $P < 0.05$ ) and

TABLE I

Basal values of blood glucose and plasma FFA in control, sham-operated and liver-denervated rats (experiment I)

	Infusion of E (20 ng/min)		Infusion of NE (50 ng/min)	
	Blood glucose (mmol/l)	Plasma FFA ( $\mu$ eq/ml)	Blood glucose (mmol/l)	Plasma FFA ( $\mu$ eq/ml)
Control rats ( $n = 6$ )	5.9 $\pm 0.2$	263.5 $\pm 66.1$	5.7 $\pm 0.4$	126.7 $\pm 17.0$
Sham-operated rats ( $n = 5$ )	5.9 $\pm 0.2$	181.9 $\pm 34.9$	5.8 $\pm 0.2$	170.0 $\pm 26.1$
Liver-denervated rats ( $n = 7$ )	6.1 $\pm 0.2$	189.2 $\pm 26.2$	6.1 $\pm 0.2$	122.6 $\pm 22.9$

Values are mean  $\pm$  SE of concentrations of blood glucose and plasma FFA as measured at  $t = -1$  min before infusion of physiological amounts of E (20 ng/min) or NE (50 ng/min).

an increase of plasma FFA of  $75 \pm 23$   $\mu$ eq/ml ( $P < 0.05$ ). In the sham-operated and liver-denervated animals, infusion of E and NE resulted in similar changes in blood glucose and plasma FFA levels as observed in the control group.

The results of experiment II, in which control, sham-operated, and liver-denervated animals were subjected to exercise, are presented in Fig. 2. Baseline levels of blood components are shown in Table II and were similar in the three groups. Compared to baseline levels, exercise resulted in increases in blood glucose, plasma FFA, NE and

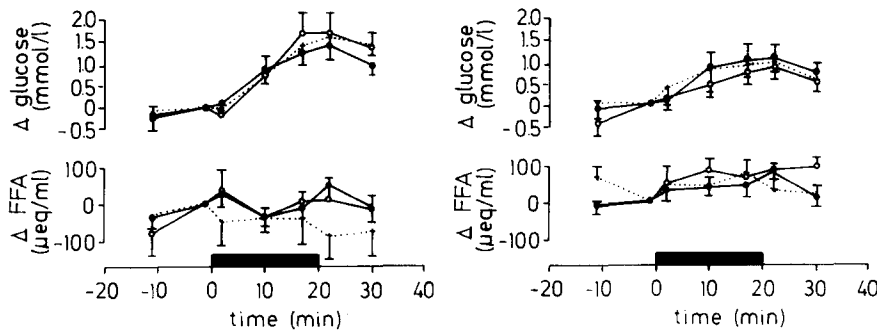


Fig. 1. Effect of infusion of epinephrine (20 ng/min) (left graph) and norepinephrine (50 ng/min) (right graph) on concentrations of blood glucose and plasma FFA in liver-denervated rats ( $\bullet$ — $\bullet$ ;  $n = 7$ ), sham-operated rats ( $\circ$ — $\circ$ ;  $n = 5$ ) and control rats ( $+ - - - +$ ;  $n = 6$ ). Data are expressed as mean  $\pm$  S.E. The infusion period is depicted by a black bar at the bottom axes.

TABLE II

Basal values of blood glucose, plasma FFA, NE and E in control, sham-operated, and liver-denervated rats before (control swimming) and after adrenodemedullation (admx swimming) (experiments II and III)

	Blood glucose (mmol/l)	Plasma FFA ( $\mu$ eq/ml)	Plasma NE (nmol/l)	Plasma E (pmol/l)
Control swimming				
Control rats (n = 6)	5.9 $\pm$ 0.1	153.3 $\pm$ 15.6	1.28 $\pm$ 0.16	203 $\pm$ 40
Sham-operated rats (n = 5)	5.5 $\pm$ 0.1	212.7 $\pm$ 41.7	1.50 $\pm$ 0.13	332 $\pm$ 78
Liver-denervated rats (n = 6)	5.8 $\pm$ 0.1	120.5 $\pm$ 32.6	1.73 $\pm$ 0.14	410 $\pm$ 148
Admx swimming				
Control rats (n = 6)	5.6 $\pm$ 0.2	176.0 $\pm$ 40.7	1.78 $\pm$ 0.27	n.d.
Sham-operated rats (n = 5)	5.5 $\pm$ 0.2	171.0 $\pm$ 20.4	1.85 $\pm$ 0.40	n.d.
Liver-denervated rats (n = 7)	5.6 $\pm$ 0.2	145.0 $\pm$ 17.6	2.12 $\pm$ 0.21	n.d.

Values are mean  $\pm$  S.E. of blood glucose, plasma FFA, NE and E as measured at t = -1 min in the home cage before the rats were placed on the starting platform in swimming pool. n.d. = not detectable

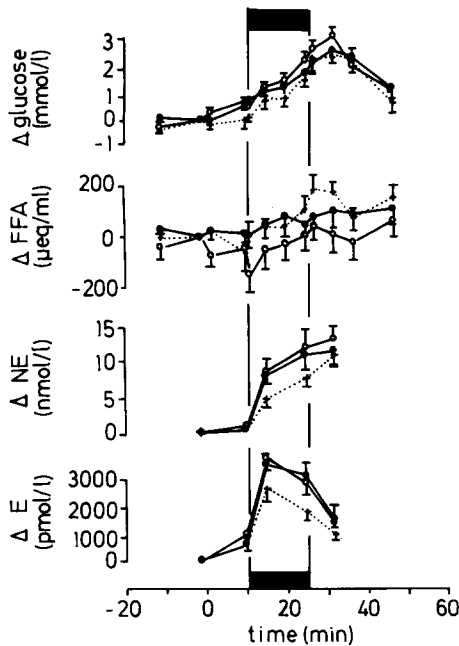


Fig. 2. Effect of swimming exercise on concentrations of blood glucose, plasma FFA, norepinephrine (NE), and epinephrine (E), in liver-denervated rats (●—●; n = 7), sham-operated rats (○—○; n = 5) and control rats (+---+; n = 6). Data are expressed as mean  $\pm$  S.E. The swimming period is depicted by a black bar at the bottom axes.

E. The exercise-induced changes were similar to alterations in previously performed studies [13,14]. The increases in concentrations of blood glucose, plasma FFA, NE and E in control animals were not different from the levels observed in sham-operated and liver-denervated rats.

The results of experiment III, in which adrenodemedullated, sham-operated, and liver-denervated animals were subjected to exercise, are presented in Fig. 3. Baseline levels of blood components are shown in Table II and were similar in control, sham-operated and liver-denervated rats. Plasma concentrations of E were below detection levels (lower than 25 pmol/l). In the control group, adrenodemedullation markedly reduced the exercise-induced increase of blood glucose (significant at time points t = 20, 25, 27, and t = 32 min). The exercise-induced changes from baseline levels in plasma FFA and NE in the control group were not different from the changes in the sham-operated and liver-denervated group.

Tissue NE levels in whole liver were  $0.031 \pm 0.008 \mu\text{g/g}$  in denervated and  $0.076 \pm 0.012 \mu\text{g/g}$  in controls, at day 19 of the study, which corresponds to a 60% reduction by the denervation

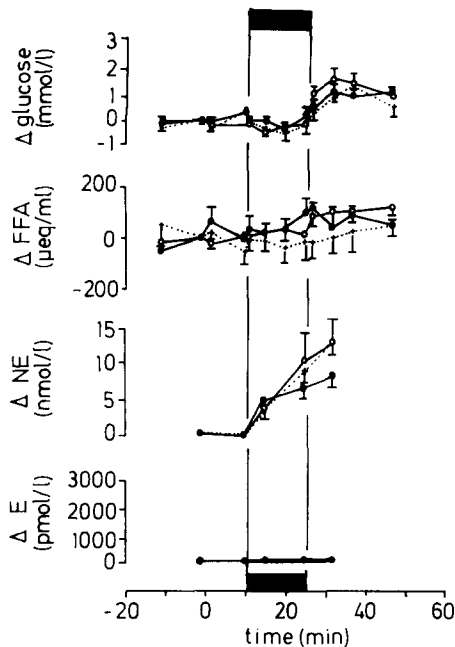


Fig. 3. Effect of swimming exercise on concentrations of blood glucose, plasma FFA, norepinephrine (NE) and epinephrine (E) before, during and after swimming in adrenodemedullated liver-denervated rats (●—●;  $n = 7$ ), adrenodemedullated sham-operated rats (○—○;  $n = 5$ ) and adrenodemedullated control rats (+---+;  $n = 6$ ). Data are expressed as mean  $\pm$  S.E. The swimming period is depicted by a black bar at the bottom axes.

( $P < 0.05$ ). Tissue NE levels in the superficial liver tissue were  $0.007 \pm 0.002 \mu\text{g/g}$  in denervated and  $0.042 \pm 0.005 \mu\text{g/g}$  in controls, which corresponds to 84% reduction by the denervation ( $P < 0.05$ ).

## Discussion

Peri-arterial hepatic nerves are supposed to be predominantly sympathetic efferent nerves. Stimulation of these nerves leads to hepatic glucose release by activation of glycogenolysis [7,12,22]. Peri-arterial denervation might therefore impair the glycaemic response to exercise.

In the present experiment, the glycaemic response to exercise was similar in denervated, sham-operated and control rats (experiment II).

Identical blood glucose responses were also seen in the three groups of animals during peripheral infusions of physiological amounts of NE and E (experiment I). These results suggest that the influence of the peri-arterial hepatic nerves on the glycaemic response to exercise is negligible. Instead, adrenal E proved to be a much more powerful mediator of hepatic glucose production, since adrenodemedullation abolished the glycaemic response to exercise in rats (experiment III), which confirms previous reports [14,17]. Finally, no differences in the blood glucose levels were observed between the denervated, sham-operated and control rats after adrenodemedullation. Again, this suggests that peri-arterial hepatic nerves are of minor importance for hepatic glycogenolysis during exercise. The data from the catecholamine infusion experiments revealed also that a counterregulatory mechanism leading to hepatic adrenoceptor hypersensitivity cannot explain the identical glycaemic responses during exercise in denervated rats and control rats.

The difference between the results of this study and previously reported data might be attributed to species-specific variations in the importance of the sympathetic innervation of the liver for glucose production. Thus, direct sympathetic innervation to the liver seems less important for hepatic glucose production in rats in comparison with other species. This might be due to considerable species differences in the pattern of sympathetic innervation of the liver parenchymal cells. For example, in guinea pigs, all liver parenchymal cells are separately innervated whereas in rats only a few cells are innervated. It has been hypothesized that signal transduction in rat liver cells mainly occurs indirectly via gap junctions [4,7]. In other species, such as the dog [3] and the rabbit [16], evidence for a role of hepatic sympathetic mechanisms in this respect is well documented. In humans, a dense sympathetic innervation of the liver has been demonstrated, and electrical stimulation of the liver sympathetic nerves has been shown to stimulate hepatic glucose production in patients undergoing abdominal surgery [12]. However, whether these nerves are of importance for hepatic glucose production during exercise in humans is not known.

This study thus suggests that a major role for the hepatic sympathetic nerves in the regulation of hepatic glucose production seems unlikely in the rat. Nevertheless, a possible additive contribution of hepatic sympathetic nerves to other control mechanisms, like glucagon, cannot be excluded. For example, it is possible that the efficacy of glucagon is potentiated by peri-arterial liver denervation [9], which might account for a compensation for the reduced stimulatory effect of the sympathetic liver nerves in the present study. Such compensatory mechanisms have been described in other situations, e.g. in hypoglycemia [5].

It might be argued that the hepatic denervation was not complete in the present study, since the denervation of the peri-arterial hepatic nerves diminished average hepatic norepinephrine content by only 60%. On the other hand, norepinephrine was almost completely absent in the superficial part of the liver after denervation, indicating that the peri-arterial denervation caused a substantial reduction of the hepatic sympathetic innervation.

In conclusion, the results of the present study do not favor the idea that peri-arterial sympathetic nerves innervating the liver play an important role in hepatic glucose production during exercise in rats. Furthermore, the catecholamine infusion experiments indicate that the effects of hepatic denervation are not counteracted by increased adrenoceptor sensitivity in the liver.

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