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## Sympatho-adrenal regulation of energy metabolism

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## SUMMARY

The role of the sympatho-adrenal system in energy metabolism during exercise has been studied extensively for the last decades. Experiments with chemical and electrical stimulation of the sympatho-adrenal system have yielded considerable insight into the control of circulating glucose and free fatty acid (FFA) concentrations. Most studies, however, were focussed on the levels of nutrients and their regulatory hormones, rather than on the utilization of these nutrients. An increased concentration of a nutrient in the blood was usually explained by an increase in release, rather than by a decrease in utilization. Conversely, a decrease in circulating concentrations was often explained as a result of diminished release rather than increased utilization. To distinguish between the two determinants of the concentration of energy substrates in the blood - release and utilization - at least one of them should be measured.

For this purpose an experimental set-up has been designed for the application of indirect calorimetry during exercise in rats (**chapter 2**). Swimming was chosen as the method of exercise, instead of treadmill running, to eliminate unspecific stress elements. Swimming was performed in an airtight swimming pool, at its top provided with a metabolic chamber. The bottom of the chamber was a platform, which could be lowered into the pool, so that the rat was forced to swim in order to keep his head in the metabolic chamber. Indirect calorimetry was applied to determine energy expenditure (EE) and the contribution of carbohydrates (CHO-ox) and fat (fat-ox) to EE. A high accuracy and precision of the experimental set-up was attained by measuring room air for 20 s after each 100 s of measuring air from the metabolic chamber. Also the use of de-mineralized water to fill up the swimming pool proved to be important, because it contains much less CO<sub>2</sub> than tap water.

The rats were fitted with an indwelling catheter with its tip at the entrance of the right atrium for repeated stress-free sampling of well-mixed central venous blood before, during and after swimming. Glucose and lactate were determined in whole blood; free fatty acids (FFA), epinephrine (EPI), norepinephrine (NOR) and insulin were determined in plasma. After blood sampling the animals received an equal amount of donor blood to avoid hemodilution. The catheter was also used for the administration of adrenoceptor blocking agents. Phentolamine and timolol were used as  $\alpha$ - and  $\beta$ -adrenoceptor blocker, respectively.

By the use of the adrenoceptor blockers, the role of the peripheral adrenoceptors in the regulation of energy metabolism has been studied (**chapter 3**). Both  $\alpha$ - and  $\beta$ -adrenoceptor blockade in swimming rats led to a significant reduction of the exercise-induced increase in EE and fat-ox. Although, in comparison with the control

experiment, the rate of CHO-ox was increased in both experiments, this increase did not make up for the fall in fat-ox. The fall in EE and the shift in nutrient utilization could not fully be explained by changed levels of circulating nutrients or hormones.

In case of  $\beta$ -blockade, the lowered rate of EE may be due to a lack of energy substrates.  $\beta$ -Blockade prevents the exercise-induced increase in both glucose and FFA. However, blood glucose did not decline below the baseline, and thus seems to have been available as substrate. Therefore, it might be that an insufficient oxygen supply contributed to the reduction in EE in addition to the reduced energy substrate availability. The exercise-induced increase in cardiac output is to a large extent due to  $\beta$ -adrenergic chronotropic and inotropic effects on the heart. Moreover, exercise-induced vasodilatation in muscles is partly under  $\beta$ -adrenergic control. Therefore, the increase in blood flow rate and oxygen supply to the working muscles may fall short of the increase in metabolic demand.

In case of  $\alpha$ -blockade, the reduction in EE could definitely not be explained by an insufficient supply of nutrients. The exercise-induced increase in blood glucose was prevented, but plasma FFA concentration was not affected by  $\alpha$ -blockade. It is hypothesized that the reduction in energy expenditure during swimming was due to a limited oxygen supply to the working muscles. The increase in lactate, the product of anaerobic glycolysis, after  $\alpha$ -blockade points in this direction. The re-distribution of cardiac output during exercise in favor of the working muscles depends to a considerable extent on the  $\alpha$ -adrenergic constriction of visceral blood vessels.  $\alpha$ -Blockade prevents adequate re-distribution of blood flow. A large part of the increased cardiac output thus does not pass through the active muscles. Consequently, the ensuing reduction in oxygen supply may restrict the increase in muscular energy release.

To test whether an insufficient oxygen supply to the working muscles contributes to the alterations in energy metabolism induced by adrenoceptor blockade, pH, blood gases, and hemoglobin concentration were measured in central venous blood (**chapter 4**). It appeared that during swimming after  $\beta$ -blockade, venous  $sO_2$  and  $PO_2$  dropped more and  $PCO_2$  rose more than in the control experiment.  $\alpha$ -Blockade caused a less pronounced fall in venous  $sO_2$  and  $PO_2$  than in the control experiment. The exercise-induced rise in  $PCO_2$  tension was almost absent. From these results, it is concluded that after  $\beta$ -blockade the oxygen supply to the active muscles may be limited by inhibition of the exercise-induced rise in cardiac output and prevention of  $\beta$ -adrenergically mediated vasodilation in the working muscles. After  $\alpha$ -blockade, the oxygen supply is restricted through prevention of the necessary re-distribution of cardiac output, mainly from insufficient vasoconstriction in the visceral bed.

In the experiments described in **chapter 5**, the importance of hepatic glycogen, the major source of circulating glucose, in the supply of nutrients during exercise was investigated. For this purpose, rats were studied after 48 h starvation. Hepatic glycogen stores have been reported to be nearly depleted after 48 h starvation. Hepatic glycogen depletion is accompanied by a decrease in blood glucose concentrations. Starved rats were studied with and without adrenoceptor blockade to test whether the alterations in blood glucose after adrenoceptor blockade might have been induced by changes in the utilization of blood-borne glucose. In starved rats baseline EE was reduced. This was accompanied by a shift in nutrient utilization towards fat-ox. The exercise-induced responses in EE, fat-ox and CHO-ox were not different from those in fed rats. The sympatho-adrenal system showed a stronger response to exercise. As in the case of adrenoceptor blockade in fed rats, blockade of  $\alpha$ - and of  $\beta$ -adrenoceptors led to a reduction in the exercise-induced increase in EE and fat-ox, when compared with starved control rats. The rate of CHO-ox was slightly reduced after blockade of either adrenoceptor type.  $\alpha$ -Blockade prevented the exercise-induced increase in blood glucose. Plasma FFA was not affected. Blood lactate, plasma insulin, NOR, and EPI were increased after  $\alpha$ -blockade. Due to  $\beta$ -blockade, the exercise-induced increases in glucose and FFA were prevented. Blood glucose even declined below the baseline value. EPI showed an exaggerated increase, NOR rose less. The results support the idea that  $\alpha$ -adrenoceptor blockade-induced changes in energy metabolism are the result of a diminished oxygen supply. In case of  $\beta$ -blockade, changes in energy metabolism are mainly induced by a fall in energy substrate availability.

In rats, EPI is of adrenomedullar origin. The effect of extirpation of the adrenal medulla (ADM) was studied to elucidate the role of EPI in the regulation of energy metabolism (**chapter 6**). ADM rats were studied in an *ad-lib*-fed state and after 48 h of starvation. Starvation in intact rats introduced an exaggeration of the exercise-induced increase in EPI, suggesting an important role for EPI in the regulation of energy metabolism. Both in fed and starved ADM rats, EE was reduced during swimming and early recovery. In fed ADM rats, this decrease in EE was accompanied by a reduction in CHO-ox. In starved ADM rats, fat-ox was reduced during recovery. In both cases, the exercise-induced increase in blood glucose was reduced; in starved ADM rats, blood glucose even declined below the baseline. The decline in blood glucose will mainly be the result of an increased uptake of glucose from the blood, resulting from the absence of adrenergic stimulation of muscular glycogenolysis.

The effects of chronic intragastric administration of dex-fenfluramine (d-FFL), an anorectic agent that increases serotonergic transmission, upon energy metabolism and nutrient concentrations were investigated at rest and during swimming. Rats were provided with a permanent cannula for intragastric d-FFL or saline administration, additionally to the cannula for blood sampling. One group of animals received 1 mg/kg of d-FFL, twice a day. The control group received saline.

In **chapter 7**, a longitudinal study of the effects of d-FFL treatment is presented. In this experiment, all animals were submitted to swimming for 15 min at -2, 1, 4, and 7 days relative to the onset of d-FFL administration. On days 12 and 14, the animals received an intravenous infusion of NOR and EPI, respectively, to identify possible d-FFL-induced changes in catecholamine-sensitivity in liver and adipose tissue. Finally, after 20 days of d-FFL-treatment, energy metabolism was studied by means of indirect calorimetry. Chronic treatment with d-FFL led to a transient reduction in the exercise-induced increase in blood glucose. This effect was most striking on day 1 of treatment. Plasma NOR responses to exercise gradually increased in the d-FFL-treated animals in comparison to the control rats. Baseline RQ was markedly increased in the d-FFL-treated animals, while EE was not changed, indicating an increase in CHO-ox and a decrease in fat-ox. Infusion of NOR induced a stronger response in FFA in the d-FFL group, while EPI had no effect. Baseline concentrations of FFA were lower after d-FFL-treatment.

In the experiment described in **chapter 8**, energy metabolism and nutrient and hormone concentrations were studied after 20 to 25 days of intragastric d-FFL treatment under baseline conditions, during swimming and during recovery. Under baseline conditions, d-FFL induced an increase in CHO-ox, and a decrease in fat-ox. Plasma FFA concentration was decreased, lactate and insulin were increased after d-FFL treatment. The shift in nutrient utilization remained present during swimming. The exercise-induced increase in blood glucose was reduced after d-FFL. During swimming, FFA, lactate and insulin concentrations were similar in the two groups. It is concluded that chronic d-FFL treatment leads to an increase in the oxidation of carbohydrates and a decrease in the oxidation of fat as a result of a decrease in transport of fatty acids over the mitochondrial membrane.

The results of the present study suggest that the role of sympatho-adrenal system in energy metabolism during exercise has a facilitating character. It plays a key role in the control of nutrient and oxygen supply to the working muscles. Deficiencies in the supply of nutrients and oxygen are accompanied by increased sym-

Summary

patho-adrenal activity. Partial lack of sympatho-adrenal activity at target tissue level through peripheral adrenoceptor blockade causes a significant disturbance of energy metabolism during exercise. Elimination of the hormonal branch of the sympatho-adrenal system (adrenomedullation) introduces a shift in carbohydrate utilization from muscular sources to blood-borne glucose. Therefore, it is concluded that the main action of EPI is the stimulation of muscle glycogenolysis rather than the enhancement of hepatic glycogenolysis.