Influence of physical training on adipose tissue metabolism – with special focus on effects of insulin and epinephrine

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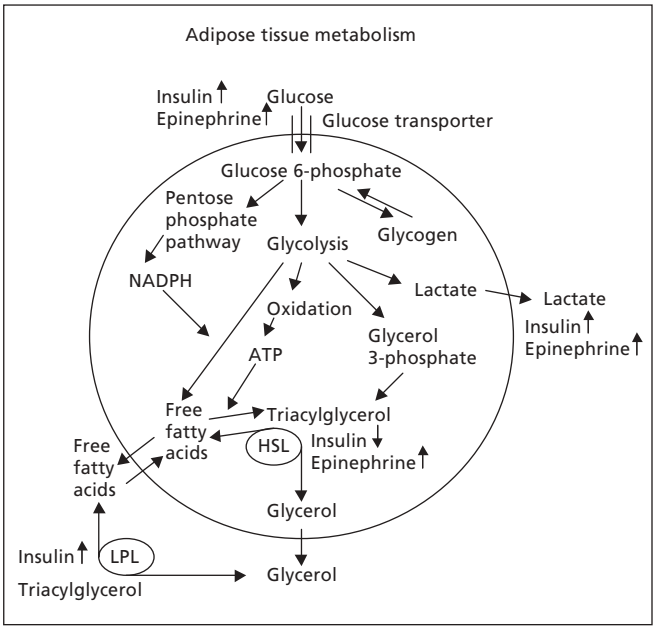

Figure 1. Schematic view of adipose tissue metabolism.

I. INTRODUCTION

A. ADIPOSE TISSUE

Adipose tissue is very variable in size, within as well as between individuals (66, 363). Adipose tissue contains by far the largest energy depot in the body and is an active metabolic organ taking up lipid and glucose and releasing free fatty acids (FFA), glycerol and lactate (125, 130). Lately, adipose tissue has also been recognized as an endocrine/paracrine organ (213, 277) secreting e.g. estrogen (51), prostaglandins (318), adiponectin (256), leptin (73, 218), acylation stimulating protein (334), plasminogen activator inhibitor-1 (8), interleukin-6 (276), insulin-like growth factor I (395), interleukin-8 (53) and resistin (373). Excess amounts of adipose tissue, i.e. as in obese subjects, impose significant health risks and are related to diseases such as type II diabetes, hypertension, coronary heart disease, stroke, osteoarthritis and some types of cancer (1, 3, 353). In addition to the degree of obesity, the regional distribution of adipose tissue is an important predictor of obesity-associated morbidities (202, 214, 278).

B. ADIPOSE TISSUE METABOLISM

The adipose tissue energy depot consists of triacylglycerol (TG), which can be hydrolyzed into glycerol and three FFA by the enzyme hormone sensitive lipase (HSL) (235) (Figure 1). This process is termed lipolysis, and the activity of HSL is considered to be rate limiting for adipose tissue lipolysis (235). As glycerol is not reutilized in the adipocyte to any significant extent (20, 107), adipocyte glycerol release is a marker of lipolysis. When extra energy supply is needed by the rest of the body, as during fasting or exercise, the rate of lipolysis is increased (12, 19, 126, 127, 178, 337). The FFA generated during lipolysis are either released from the adipocyte or reesterified to TG in the adipocyte.

After a meal, uptake of FFA in adipose tissue is stimulated (68, 125, 126, 313). The FFA are released from plasma TG in the adipose tissue capillaries by the enzyme lipoprotein lipase (LPL) and are subsequently stored in the adipose tissue as TG (Figure 1). Furthermore, adipose tissue takes up glucose, which is transported over the plasma membrane by a glucose transporter protein (210, 279) (Figure 1). In the adipocyte, glucose either enters the glycolysis, the pentose phosphate pathway or is stored as glycogen (243). Glucose is via the glycolysis converted to glycerol-3-phosphate or FFA (the latter process is termed de novo lipogenesis and does not occur to any significant degree in humans (6, 125, 126, 359)), metabolized to lactate or oxidized to provide ATP for the adipocyte (243). The pentose phosphate pathway produces NADPH, which is used during de novo lipogenesis (243). Glycogen stores are low in adipose tissue, but have been shown to increase after eating a high-carbohydrate diet for 2.5 days (324).

C. INFLUENCE OF HORMONES ON ADIPOSE TISSUE METABOLISM

Insulin and epinephrine are the two major hormones influencing adipose tissue metabolism (71, 125, 126) (Figure 1). Insulin inhibits lipolysis (56, 60, 69, 150, 241) and stimulates glucose uptake (69, 150, 225, 241, 253) and lactate release (69, 85). Epinephrine stimulates lipolysis (139, 241), glucose uptake (IV) (241, 253) and lactate release (IV) (85). In rats, β-agonists inhibit insulin-stimulated glucose transport in adipocytes in vitro (209) and there are also indications of a β-adrenergic inhibition of insulin-stimulated glucose uptake in adipose tissue in vivo in humans (154) and rats (196).

It has been extensively examined which adrenergic receptors that are responsible for regulation of human adipose tissue lipolysis, and most agree that β_1-, β_2- and β_3-receptors stimulate lipolysis with the β_2-receptor being the most important and the β_3-receptor being the least important (36, 113, 153), whereas α_2-receptors inhibit lipolysis (17, 19, 138). Species differences with respect to the adrenergic activation of lipolysis have been reported with rats having more β_3- and less α_2-receptors compared with humans (229, 230, 364).

Also other hormones than insulin and epinephrine influence adipose tissue metabolism. Evidence exists for a stimulation of adipose tissue lipolysis by cortisol (106, 335, 338) and growth hormone (GH) (149, 319, 336) at physiological concentrations in humans in vivo. However, effects of cortisol and GH on adipose tissue lipolysis are delayed (149, 336, 338), whereas insulin and epinephrine are immediate regulators of adipose tissue metabolism. Glucagon does not seem to regulate human adipose tissue lipolysis in vivo (205).

D. INFLUENCE OF PHYSICAL TRAINING ON IN VITRO LIPOLYSIS IN ADIPOCYTES

The influence of physical training on skeletal muscle metabolism has been examined extensively (2). However, when the studies presented in this thesis were initiated (late 1980's), most knowledge about the influence of physical training on adipose tissue metabolism came from in vitro studies and many of these were performed on epididymal adipose tissue from rats. Far most experiments had

Table 1. Influence of physical training on in vitro basal and epinephrine-stimulated lipolysis in adipocytes.

						Effect of training on	
Reference	**Publication year**	**Gender**	**Region**	**Type of training**	**Expressed per**	**Basal lipolysis**	**Epinephrine-stimulated lipolysis**
Rats:							
(309)	1964	Male	Epididymal	29 wk running	gram AT		⇑ (AT)
(26)	1972	Male	Epididymal	7-12 wk running	gram AT fat pad mg protein	⇔(AT)	⇑ (AT) ⇔ (AT) ⇔ (AT)
(134)	1972	Male	Epididymal	15 wk running	mg DNA gram AT	⇓ (AT) ⇑ (AT)	⇔ (norepinephrine, AT) ⇑ (norepinephrine, AT)
(31)	1975	Male	Epididymal	13 wk running	adipocyte gram AT fat pad mg protein		⇑ ⇑ ⇑ ⇑
(27)	1976	Male Male	Epididymal Epididymal	12 wk long running 12 wk moderate running	fat pad fat pad		⇑ ⇑
(269)	1976	Male	Epididymal	12 wk running	adipocyte gram AT	⇔ ⇑	⇔ ⇑
(301)	1977	Male	Epididymal	12 wk running	adipocyte	⇓	⇑
(54)	1980	Male Female	Epididymal Parametrial	7-11 wk swimming 7-11 wk swimming	adipocyte adipocyte	⇔ ⇑	⇑ ⇑
(298)	1981	Male	Epididymal	12 wk running	adipocyte gram AT	⇔ (cells and AT) ⇔ (cells and AT)	⇔(cells)/ ⇓ (AT) ⇑ (cells)/ ⇔ (AT)
(406)	1982	Male	Epididymal	14 wk swimming	μg DNA	⇔	10^{-7} M: ⇔ Above 10^{-7} M: ⇑
(354)	1986	Female	Perirenal and parametrial	16 wk running	adipocyte	⇔	⇑ (β-agonist)
(358)	1989	Male	Epididymal	9 wk running	adipocyte	⇔	Below 10^{-7} M norepinephrine: ⇔ 10^{-7} M and above: ⇑
(388)	1993	Male	Intraabdominal	6 wk swimming	adipocyte	⇔	⇔
(379)	1993	Male	Epididymal	9 wk running	adipocyte	⇔	10^{-7} M norepinephrine: ⇔ 10^{-6} M and above: ⇑
(192)	1994	Male	Epididymal	9 wk running	adipocyte	⇑	⇑ (norepinephrine)
Humans:							
(100)	1984	Male Female	Gluteal Gluteal	20 wk bicycling	adipocyte adipocyte	⇔ ⇔	⇑ ⇔
(102)	1984	Male Female	Gluteal Gluteal	20 wk bicycling	adipocyte adipocyte	⇔ ⇔	⇑ ⇑
(98)	1984	Mixed	Gluteal	20 wk bicycling	adipocyte	⇑	⇑
(101)	1984	Male Male	Gluteal Gluteal	4 months bicycling Marathon runners	adipocyte adipocyte	⇑ ⇑	⇑ ⇑
(407)	1985	Males with hyperlipemia	Abdominal	4 months jogging, ball games, gymnastics	gram AT	⇔	
(99)	1985	Male	Gluteal	20 wk bicycling	adipocyte		⇑
(226)	1985	Mixed, obese and type II diabetics	Abdominal	3 months walking, jogging, gymnastics, bicycling	adipocyte	⇔	⇔ (norepinephrine)
(82)	1986	Male	Abdominal	Marathon runners	gram lipid	⇔	Percentage increase: Below 10^{-6} M: ⇔ 10^{-6} M and above: ⇑
(312)	1987	Male	Gluteal	22 days bicycling (~2 h/day)	adipocyte	⇔	⇔
(83)	1988	Female	Abdominal	Runners	gram lipid	⇔	Below 10^{-7} M: ⇔ 10^{-7} M and above: ⇑
(84)	1989	Mixed	Abdominal	Long-distance athletes	gram lipid	⇔	Percentage increase: Below 10^{-7} M: ⇔ 10^{-7} M and above: ⇑ Female > Male

Table 1. cont.

Reference	Publication year	Gender	Region	Type of training	Expressed per	Effect of training on: Basal lipolysis	Effect of training on: Epinephrine-stimulated lipolysis
(325)	1989	Female	Abdominal	Long-distance runners	gram lipid	⇓	Percentage increase: Below 10^{-6} M: ⇔ 10^{-6} M and above: ⇑
(394)	1992	Male	Gluteal	Endurance athletes	adipocyte	⇓	Absolute: ⇔ Percentage increase: ⇑
(265)	1997	Female	Abdominal	Runners and skiers	adipocyte surface area	⇑ ⇑	Delta increase: Below 10^{-7} M: ⇔ 10^{-7} M and above: ⇑
			Gluteal		adipocyte surface area	⇔ ⇔	Delta increase: ⇔
(90)	1998	Obese males	Abdominal	12 wk bicycling	gram lipid	⇓	Delta increase: Below 10^{-7} M: ⇔ 10^{-7} M and above: ⇑
Miniature swine:							
(63)	1994	Male	Subcutaneous	12 wk running	adipocyte surface area	Mixed gender, per adipocyte: ⇔	Delta increase: ⇔ Delta increase: ⇔
		Female	Subcutaneous	12 wk running	adipocyte surface area		Delta increase: ⇔ Delta increase: ⇑
(271)	1994	Female	Interscapular	12 wk running	surface area		⇑
(62)	2000	Female	Subcutaneous	12 wk running	surface area		Below 10^{-6} M: ⇔ 10^{-6} M and above: ⇑

AT: Adipose tissue.

examined the influence of training on in vitro lipolysis (Table 1). In rats, many experiments showed no training-induced change in basal adipose tissue lipolysis per adipocyte (54, 269, 298, 354, 358, 406) or per gram of adipose tissue (26, 298), but some found a training-induced decrease in basal lipolysis per adipocyte (134, 301) and some found a training-induced increase per gram of adipose tissue (134, 269). Training often increases number of adipocytes per gram of adipose tissue (III), and, accordingly, there is not necessarily a contrast between a training-induced increase in lipolysis per gram of adipose tissue and a training-induced decrease in lipolysis per adipocyte. Also in humans, most experiments showed no training-induced change in basal lipolysis per adipocyte (100, 102, 226, 312) or per gram of lipid (82-84, 407), although some found an increase per adipocyte (98, 101) and some found a decrease per gram of lipid (325).

Epinephrine-stimulated adipose tissue lipolysis was increased by training in most studies in rats both when expressed per adipocyte (31, 54, 301, 406), per gram of adipose tissue (26, 31, 269, 298, 309) and per fat pad (27, 31). Some, however, found no change per adipocyte (269, 298) or per fat pad (26). Also in humans, most experiments showed a training-induced increase in epinephrine-stimulated adipose tissue lipolysis per adipocyte (98-102) although some found no change (312). Crampes and coworkers most often expressed the epinephrine-stimulated lipolysis as percentage increase relative to basal lipolysis and they found a training-induced increase in lipolysis at supraphysiological (10^{-7} M and above), but not at physiological, epinephrine concentrations in human adipocytes (82-84, 325). It should be noted that all the above-cited studies used supraphysiological epinephrine concentrations (range: 10^{-6}-10^{-4} M) for stimulation of lipolysis.

Training also increased adipocyte lipolysis stimulated at the post-receptor level (by e.g. dibutyryl cAMP) when expressed per adipocyte (54, 354), per mg of lipid (83) and as percentage of basal lipolysis (325). The inhibition of lipolysis by α_2-stimulation (82, 84), adenosine (358) or insulin (226) was not changed by training.

E. INFLUENCE OF PHYSICAL TRAINING ON IN VITRO GLUCOSE UPTAKE IN ADIPOCYTES

When this thesis was initiated, controversy existed to whether basal glucose transport in adipose tissue is changed by training (Table 2). Expressed per adipocyte, some had found no change (392), some had found a decrease (175) and some had found an increase (398) in basal glucose transport in trained compared with sedentary age-matched rats. In the study, in which an increase was found, the rats were fed and, accordingly, the adipocytes had been exposed to insulin before removal from the rat (398). When glucose transport data were normalized for adipocyte size by expressing data per adipocyte surface area, basal glucose transport did not differ between trained and sedentary age-matched rats (175). Glucose transport was estimated from the initial influx of either 3-O-^{14}C-methylglucose (3-MG) (175, 392) or ^{14}C-glucose (398) into adipocytes. 3-MG is not metabolized in the adipocyte and, accordingly, uptake of this substance reflects glucose transport into the cell as long as efflux can be considered negligible (404). It was claimed that the ^{14}C-glucose method gave results similar to the 3-MG method (175).

Craig and coworkers had estimated glucose uptake in adipocytes by measuring the accumulation of the glucose analogue 2-deoxy-^{3}H-glucose (2-DG) (76-81) (Table 2). 2-DG is transported across the cell membrane and phosphorylated in the adipocyte, but it is not metabolized further. Caution has been suggested in using 2-DG accumulation as an estimate of glucose transport as its accumulation after a few minutes mainly is limited by its phosphorylation, when glucose is present (123, 124). Furthermore, the initial influx of 2-DG was found to be approximately 2-fold lower than that of 3-MG (123, 124). In all studies, but one (76), Craig and coworkers found an increased basal 2-DG uptake per adipocyte in trained compared with sedentary fed rats (77-81).

Insulin-stimulated glucose transport per adipocyte had without exception been found to be higher in trained compared with sedentary age-matched and younger control rats as estimated by the initial influx of 3-MG (392, 398) or ^{14}C-glucose (175) (Table 2). The fold increase in glucose transport induced by a maximal insulin

concentration (estimated from graphs) was much higher in adipocytes from trained (8- to 10-fold) compared with adipocytes from sedentary age-matched (2- to 8-fold) rats (175, 392, 398). Also when expressed per adipocyte surface area the insulin-stimulated glucose transport was higher in trained compared with both sedentary age-matched and younger control rats (175). Maximally insulin-stimulated 2-DG uptake per adipocyte had also consistently been found to be increased in trained compared with sedentary age-matched rats with estimated insulin-stimulated fold increases of 1-5 and 0.1-0.5, respectively (76-81) (Table 2). The relatively small fold-stimulation by insulin in the latter studies might be due to the rats being killed in the fed state and that adipocytes, accordingly, had been exposed to insulin before removal from the rat. In many studies, the 2-DG uptake was measured at a number of insulin concentrations both in the physiological and in the supraphysiological insulin concentration range, and 2-DG uptake was higher in adipocytes from trained compared with sedentary rats also at physiological insulin concentrations (76-78, 80, 81). The insulin-stimulated 2-DG uptake in adi-

Table 2. Influence of physical training on in vitro basal and insulin-stimulated glucose uptake in adipocytes.

									Effect of training on	
Reference	**Publication year**	**Gender**	**Region**	**Type of training**	**Expressed per**	**Control group**	**Method**	**Nutritional state**	**Basal glucose uptake**	**Insulin-stimulated glucose uptake**
Rats:										
(78)	1981	Female	Parametrial	12 wk swimming	adipocyte	Age	2-DG	Fed	⇑	⇑
						Adipocyte size			⇔	⇑
(398)	1982	Female	Parametrial	6 wk running	adipocyte	Age	3-MG	Fed	⇑	⇑
(392)	1983	Male	Epididymal	11 wk swimming	adipocyte	Age	3-MG	?	⇔	⇑
						Body weight (food-restricted)			⇔	⇑
						Adipocyte size (food-restricted)			⇔	⇑
(80)	1983	Female	Parametrial	10 wk swimming	adipocyte	Age	2-DG	Fed	⇑	⇑
(76)	1984	Female	Parametrial	10 wk swimming	adipocyte	Age	2-DG	Fed	⇔	⇑
						Adipocyte size			⇔	⇑
(81)	1986	Female (pregnant)	Parametrial	11 wk running	adipocyte	Age	2-DG	Fed	⇑	⇑
(77)	1987	Male	Epididymal	6 months voluntary running	adipocyte	Age	2-DG	Fed	⇑	⇑
						Body weight (food-restricted)			⇔	⇑
				22 months voluntary running		Age			⇑	⇑
						Body weight (food-restricted)			⇔	⇑
(175)	1989	Female	Parametrial	6 wk voluntary running	adipocyte	Age	Initial influx of labeled glucose	?	⇓	⇑
						Adipocyte size			⇑	⇑
					surface area	Age			⇔	⇑
						Adipocyte size			⇑	⇑
(147)	1991	Female	Parametrial	10 wk voluntary running	surface area	Age (normal and impaired glucose tolerance)	60 min incubation with labeled glucose	Fasted	⇑	⇑
(79)	1991	Female	Parametrial	10 wk swimming	adipocyte	Age	2-DG	Fed	⇑	⇑
(III)	1993	Male	Epididymal	10 wk swimming	adipocyte	Age	3-MG	Fasted	⇔	⇑
						Body weight			⇔	⇑
						Adipocyte size			⇔	⇑
					surface area	Age			⇑	⇑
						Body weight			⇑	⇑
						Adipocyte size			⇔	⇑
					volume	Age			⇑	⇑
						Body weight			⇑	⇑
						Adipocyte size			⇔	⇑
(V)	1996	Male	Epididymal	10 wk swimming	relative to basal	Age (± adrenodemedullation, ± sympathectomy)	3-MG	Fasted		⇑
Humans:										
(327)	1987	Male	Abdominal	Runners	adipocyte	Age	60 min incubation with labeled glucose	Fasted	⇔	⇑

2-DG: 3 min incubation with labeled 2-deoxyglucose.
3-MG: Initial influx of labeled 3-O-methylglucose.

pocytes decreased with detraining, but the training effect was nevertheless long-lived as 2-DG uptake was still increased compared with findings in sedentary rats 7 (79) and 9 days (80) after the last exercise bout. However, the physiological mechanism behind the ability of physical training to increase the insulin-stimulated glucose transport in adipocytes was not known.

Only one study had examined the influence of training on glucose transport in humans (327). In this study glucose transport was estimated from uptake of trace amounts of ^{14}C-glucose into adipocytes during 1 hour, and the method was claimed to give results similar to those of the 3-MG method (327). Training did not change basal glucose transport per adipocyte, but insulin-stimulated glucose transport was increased in trained compared with sedentary humans (327).

F. INFLUENCE OF PHYSICAL TRAINING ON NUMBER OF GLUCOSE TRANSPORTERS AND INSULIN- AND B-RECEPTORS IN ADIPOCYTES

The increased insulin-stimulated glucose transport in adipocytes from trained compared with sedentary individuals could be due to an increased number of glucose transporters in the adipocyte plasma membrane of trained individuals and/or an increased activity of an unchanged number of glucose transporters. In the non-stimulated state most of the glucose transporters are stored in the interior of the adipocyte (in low-density microsomes) and upon stimulation by insulin a fraction of these glucose transporters are recruited to the plasma membrane (88, 262). Number of glucose transporters in the membranes can be estimated by cytochalasin B binding (89, 399).

In the non-stimulated state, the number of glucose transporters per adipocyte was higher in the low-density microsome fraction in trained compared with sedentary age-matched rats (175, 393). In the insulin-stimulated state, the number of glucose transporters per adipocyte was higher in the plasma membrane in trained compared with sedentary age-matched food-restricted (393) and younger control rats (175), but not compared with sedentary age-matched freely eating rats (175). Adipocytes from trained rats were significantly smaller than adipocytes from sedentary age-matched rats and when expressed per adipocyte surface area, the insulin-stimulated number of glucose transporters in the plasma membrane was higher in trained compared with sedentary age-matched rats (175).

In the late 1980's, it became clear that many classes of glucose transporters exist of which two, termed GLUT-4 and GLUT-1, are present in adipocytes (208, 211, 279). The GLUT-4 is responsible for most of the insulin-stimulated glucose transport in adipocytes and it is much more abundant than GLUT-1 in adipocytes (211, 279). When this thesis was initiated, the effect of training on number of GLUT-4 and GLUT-1 in adipose tissue and on the amount of mRNA coding for these proteins was not known.

Training increased (78, 392) or did not change (398) number of insulin receptors per adipocyte in rats and did not change number of insulin receptors per adipocyte in humans (226). Number of β-adrenergic receptors per rat adipocyte was not changed by training (54, 354). However, the number per adipocyte of β-adrenergic receptors, which are present at the cell surface, has now been found to be decreased in trained compared with sedentary rats (379). Some had found no training-induced change in number of β-adrenergic receptors per mg of membrane protein with an increase in high-affinity receptors (406), but others have now found a training-induced increase in number of β-adrenergic receptors per mg of membrane protein with no change in receptor affinity (290).

G. INFLUENCE OF PHYSICAL TRAINING ON IN VIVO ADIPOSE TISSUE METABOLISM

Only a few in vivo studies examining the influence of physical training on adipose tissue metabolism had been published when the studies presented in this thesis were initiated. In adipose tissue of rats, training had been found to increase (387) or not influence (383) basal de novo lipogenesis (estimated by incorporation of $^{3}H_2O$ into FFA) and to increase TG synthesis (383) and degradation (29) in vivo. In adipose tissue of mice, training had been found to decrease basal de novo lipogenesis (317). In vivo insulin-stimulated glucose uptake per gram of epididymal adipose tissue had been found to be increased in trained rats (197) and a significantly higher proportion of the glucose was used for de novo lipogenesis in the adipose tissue of the trained rats during insulin stimulation (197). However, the effect of training on in vivo insulin-stimulated glucose uptake in adipose tissue from different locations (site-differences) had not been examined. Furthermore, the effect of training on in vivo insulin-stimulated glucose uptake in adipose tissue had not been examined in humans.

The norepinephrine-stimulated rise in plasma FFA turnover was decreased after training in male rats, and basal and norepinephrine-stimulated plasma FFA concentrations were lower in trained compared with sedentary female rats (386). Likewise, norepinephrine-stimulated plasma FFA and glycerol concentrations were lower in trained compared with sedentary humans (239). These in vivo data are apparently in contrast to in vitro data showing a training-induced increase in epinephrine-stimulated lipolysis in adipose tissue (Table 1). The difference could depend on the methods, as several assumptions are needed for plasma FFA turnover and concentrations to be measures of adipose tissue lipolysis. Also, in vitro adipose tissue lipolysis might not equal in vivo adipose tissue lipolysis, and site-differences in the effect of training on adipose tissue lipolysis might also contribute to the difference. When the present thesis was initiated, the effect of training on in vivo lipolysis had not been examined directly in the adipose tissue in either rats or humans. Also, site-differences in the effect of training on in vivo adipose tissue lipolysis had not been examined.

H. INFLUENCE OF PHYSICAL TRAINING ON THE SECRETION OF INSULIN AND EPINEPHRINE

When evaluating the influence of training on the effects of insulin and epinephrine in adipose tissue, it is also important to evaluate the influence of training on the secretion of these hormones. When the present thesis was initiated, it was well known, that the glucose-stimulated insulin secretion is lower in pancreatic islets from trained compared with sedentary rats (136, 413). However, the mechanism behind this phenomenon was not known.

It has also been known for long, that training is capable of increasing the adrenal gland weight in rats (160, 206, 240, 247, 302, 303, 347, 367). Moreover, it was known that the adrenal gland catecholamine content was higher in trained compared with sedentary rats (206, 302, 303). In trained humans, Kjær et al. had found an increased epinephrine response to insulin-induced hypoglycemia (216) and various other stressors indicating that training results in the development of a "sports adrenal medulla" (215). It was not known, however, whether the size of the adrenal medulla actually increased with training. Moreover, it was not known if the increased epinephrine response to hypoglycemia in trained subjects was due to training per se or could be ascribed to selection, i.e. an effect of training because of a genetically determined high epinephrine secretion capacity.

II. AIM

The aim of the present thesis was to further elucidate the influence of physical training on adipose tissue metabolism, with special focus on the effects of insulin and epinephrine. More specifically the aims were:

1. To reveal the influence of training on adipose tissue metabolism in vivo in rats (VII, IX) as well as in humans (IV, VIII).
2. To evaluate the microdialysis technique (VI), as it was the main

technique that I used for estimating adipose tissue metabolism in vivo.
3. To examine the influence of training on adipose tissue glucose metabolism in vitro in greater detail including the physiological and molecular mechanisms behind the training-induced adaptations (III, V).
4. To examine the effect of training on the oxidative capacity in adipose tissue (II).
5. To add to existing knowledge about the influence of training on the secretion of insulin and epinephrine (I, V).

Unless explicitly stated, the adipose tissue examined and discussed is white adipose tissue and the training mode studied is endurance training.

III. MATERIALS AND METHODS

Adipose tissue, especially from rats, has been extensively studied in vitro, but the tissue is difficult to study in vivo, especially in man, because most depots do not have a vein that selectively drains the tissue and which is easy to cannulate (125). In the late 1980's, however, two new techniques for studying human adipose tissue metabolism in vivo emerged. Frayn and coworkers developed a method for sampling the venous drainage from the subcutaneous adipose tissue of the anterior abdominal wall (128, 130) and they have since then evaluated many aspects of adipose tissue metabolism using this technique (129, 178). The vein cannulation, however, is difficult to perform and it can be difficult to draw blood from the vein. This is probably why only a few research groups have applied the technique. We aimed at cannulating an abdominal vein in the subjects from two of the present studies (IV, VIII). However, as our success rate was low, the data have not been published, but they will be shown in this thesis.

The other new in vivo technique for studying adipose tissue metabolism was the microdialysis technique, which was first used in human adipose tissue by Lönnroth and coworkers (251) and in rat adipose tissue by Arner and coworkers (15). Since then, the microdialysis technique has been widely applied for studies of human and rat adipose tissue (14, 91, 170, 250, 285), and we have used the technique in several of the present studies (IV, VI, VII, VIII, IX).

A practical guide presenting techniques for the measurement of white adipose tissue metabolism in vitro and in vivo has been published (13).

A. INDIVIDUALS

The present studies comprise experiments on rats (I, II, III, V, VII, IX), dogs (VI) and humans (IV, VIII). Training studies are cross-sectional comparing different groups of trained and sedentary rats (I, II, III, V, VII, IX) or humans (IV, VIII). In the human studies, differences between trained and sedentary subjects could be due to genetic factors or other factors than training per se. The rats, however, were randomly divided into the various groups and hence genetic factors were eliminated. This means that the rat studies had advantages similar to those of longitudinal studies with respect to the effect of training.

B. INTERVENTIONS

1. Exercise training

a) Rats

Rats were trained by swimming simultaneously in a tank for up to 6 $h \times day^{-1}$, 5 $days \times week^{-1}$ for either 10 (I, II, III, V) or 15 (VII, IX) weeks. Water temperature was kept at 36 °C by a thermostat. After each training session rats were dried in a towel and placed under a lamp in a drying chamber at 31-35 °C for 30-60 min. The effect of the training program was verified by an increase in heart weight (I, II), heart/body weight (I, II, III, V, VII, IX) and skeletal muscle mitochondrial enzyme activity (I, II, V).

It has been suggested that swim training imposes cold stress on rats (160). However, we measured colonic temperature in rats before, immediately after and for up to 50 min in the drying chamber, and colonic temperature was changed neither after swimming nor during drying (II). Weight of interscapular brown adipose tissue (ISBAT), which is believed to be increased specifically by cold stress (160), was increased in trained female rats, but not in trained male rats (II). It is unlikely that female rats were cold-stressed and male rats were not, as female and male rats followed the same swim training protocol. In two of our studies, a group of rats was handled like trained rats, but they swam for only 2 $min \times day^{-1}$ (I, II). These "sham-trained" rats served as controls for the stress of handling and water exposure and for cold stress during drying. Sham-trained rats differed from sedentary control rats in none of the parameters measured (body weight, heart weight, adrenal gland weight, adrenal medulla volume, weight of ISBAT, white or brown adipose tissue mitochondrial enzyme activity) (I, II) indicating that swim trained rats were not stressed by the mentioned factors. It is, however, not possible to design control experiments which can fully eliminate the psychological influence on adaptations developed during training.

b) Humans

Subjects were regarded as trained if they competed in elite-class endurance sports and their Vo_2peak exceeded 60 $ml \times kg^{-1} \times min^{-1}$ determined during a cycling test in which the load was increased stepwise (IV, VIII). Subjects were regarded as sedentary if they did not participate in any regular exercise and their Vo_2peak was below 50 $ml \times kg^{-1} \times min^{-1}$ (IV, VIII).

c) Effect of last bout of exercise

It is a classic question if differences between trained and sedentary individuals are due to the long-term training or to the last bout of exercise (296). The answer is difficult to give as long-term training consists of repeated bouts of acute exercise sessions and, accordingly, individuals training regularly are always more or less affected by the last bout of exercise. In our human studies, trained subjects did not perform any exercise on the day preceding the experiment (IV ,VIII). In our rat studies, the trained rats performed the last bout of exercise on the day preceding the experiment (female rats: I, II) or 2 days prior to the experiment (male rats: I, II, III, V; female rats: VII, IX). Hence, trained humans and rats were studied in their "habitual state".

2. Sedentary control groups

Trained male rats gain less body weight during the course of a swim training program compared with sedentary male rats (I, II, III, V) (74, 295, 299). Adipocyte size is lower in trained compared with sedentary male and female rats (III, V) (10, 27, 31, 33, 48, 54, 76-80, 136, 175, 232, 269, 296, 298, 308; 343, 347, 387, 392). In order to control for these factors, body weight and/or adipocyte size-matched control groups were used in some of our studies (I, III). In studies involving male rats, matching of body weight was performed either by food restriction (I) or by using control rats younger than the trained rats (9 vs. 14 weeks) (III). Adipocyte size matching was aimed at by using even younger control rats, but even though control rats were only 6 weeks old (2 weeks older than the age at which trained rats entered the swimming protocol), adipocyte size was smaller in trained compared with adipocyte size-matched rats (III). As indicated above, swim training has been suggested to impose cold stress on rats (160). Accordingly, a group of rats were kept in a cold room (4 °C) for 10 weeks to elucidate cold-induced changes in measured parameters (I, II).

Sedentary humans were matched with trained humans for sex, age, weight and height (IV, VIII). All subjects were healthy and non-obese (IV, VIII).

3. Adrenodemedullation and sympathectomy

Rats were adrenodemedullated and/or unilaterally sympathect-

omized before start of exercise training in one of our studies to evaluate if the sympathoadrenergic system is involved in mechanisms behind training-induced adaptations (V). In pentobarbital anesthesia, an incision was made in the adrenal cortex, and the adrenal medulla was squeezed out of the gland. Furthermore, a part of the sympathetic chain on one side was extirpated. Twelve weeks after the operation, adrenal gland epinephrine contents in adrenodemedullated trained and sedentary rats were 53% and 22%, respectively, of contents in sham-adrenodemedullated trained and sedentary rats. Epinephrine content was significantly higher in both groups of trained compared with both groups of sedentary rats. The presence of epinephrine in the adrenal gland in adrenodemedullated trained and sedentary rats indicates either that the adrenodemedullation was incomplete or that the adrenal medulla was partly regenerated after the operation. At rest, plasma epinephrine concentrations in adrenodemedullated trained and sedentary rats were 36% and 29%, respectively, of concentrations in sham-adrenodemedullated trained and sedentary rats. The presence of epinephrine in plasma indicates either that the adrenodemedullation was incomplete, that the adrenal medulla was partly regenerated after the operation or that extra-adrenal epinephrine secretion was present.

In a previous study, adrenodemedullation reduced resting plasma epinephrine concentration to 5% one day after the operation, but during the following 4 weeks the epinephrine concentration increased continuously to 13% of the pre-operation concentration (322). In the mentioned study, the adrenals were studied histologically and the authors stated that no adrenomedullary cells were present indicating that the epinephrine secretion was extra-adrenal (322). In another study, trained and sedentary rats were examined at rest 14 weeks after adrenodemedullation or sham-operation and plasma epinephrine concentrations in adrenodemedullated rats were similar to those found in our study, being 30-35% of concentrations in sham-operated rats with no difference between trained and sedentary rats (201). In response to acute exercise, the plasma epinephrine concentration did not increase in the adrenodemedullated rats, but in the sham-operated rats, the concentration increased 10-15 fold (201). This suggests that even though epinephrine was not completely eliminated from plasma at rest in our adrenodemedullated rats, during the training sessions the adrenodemedullated rats were exposed to much lower epinephrine concentrations compared with the sham-operated rats (V).

Our preliminary experiments showed that epididymal fat pad norepinephrine content was reduced to 17% after sympathectomy, which is similar to what has been found after denervation of the inguinal fat pad of hamsters in a previous study (411). In our main experiment, fat pads were used for other purposes, but hindlimb muscle norepinephrine content was reduced to 9% on the sympathectomized side when evaluated in the end of the study (V), which is similar to what was found in a previous study (321).

C. IN VITRO STUDIES

1. Glucose transport

We estimated glucose transport by the 3-O-^{14}C-methylglucose technique (404). Adipocytes were isolated from epididymal fat pads by collagenase treatment and adipocyte glucose transport was estimated from the initial influx of 3-O-^{14}C-methylglucose with or without a maximally effective insulin concentration (III, V).

2. Glucose transporter protein and mRNA

In previous studies regarding the influence of training on number of glucose transporters in adipose tissue membranes (175, 393), the cytochalasin B binding technique (89, 399) was used to quantitate the number of glucose transporters. Cytochalasin B binds to membranes at several sites, one of which can be inhibited by D-glucose, and this site has been shown to be the glucose transporter (89, 399). However, different isoforms of glucose transporters cannot be distinguished by the cytochalasin B binding technique.

We estimated amounts of glucose transporter isoforms 4 (GLUT-4) and 1 (GLUT-1) protein and mRNA by Western and slot blot analysis, respectively (III). For analysis of glucose transporter protein, whole adipocyte membranes were prepared by homogenization and centrifugation. Subsequently, protein was denatured and subjected to SDS-gel electrophoresis. Then, proteins were transferred to nitrocellulose paper, which was incubated with antibodies against the GLUT-4 and the GLUT-1 glucose transporters, respectively. Antibody-antigen complexes were visualized by coupling a phosphatase-linked secondary antibody to the primary antibody and adding a substrate, which becomes colored upon reaction with the phosphatase. Last, glucose transporters were quantitated by quantitative densitometry. For analysis of glucose transporter mRNA, total RNA was extracted from isolated adipocytes. The integrity of the RNA was checked by visualization of ribosomal bands and no signs of degradation were found. Denatured RNA was applied to slots, blotted and fixed onto nylon membranes. Membranes were hybridized with ^{32}P-labeled cRNA probes for GLUT-4 and GLUT-1 and exposed to a film at –80 °C after which amounts of GLUT-4 and GLUT-1 mRNA were quantitated by quantitative densitometry.

D. IN VIVO STUDIES

1. Microdialysis

The microdialysis technique can be used to estimate interstitial concentrations of various substances in a variety of tissues in humans and animals (14, 15, 64, 91, 170, 250, 251, 285). I evaluated the microdialysis technique for estimation of interstitial concentrations of metabolites and hormones in adipose tissue in my Ph.D. thesis (368). I concluded that the microdialysis technique can be used to estimate interstitial concentrations of glucose, lactate, glycerol and epinephrine in human abdominal subcutaneous adipose tissue, when appropriate calibration procedures are performed (368). Furthermore, I concluded that adipose venous glucose, lactate and glycerol concentrations calculated from interstitial concentrations are positively correlated with glucose, lactate and glycerol concentrations, respectively, measured in veins draining human and dog adipose tissue (368).

a) Principles of microdialysis

The microdialysis probe consists of a semi permeable membrane, which is connected to inflow and outflow tubings (Figure 2). The probe is inserted in the tissue and perfused by an isotonic fluid termed the perfusate, which during perfusion partly equilibrates with the interstitial fluid surrounding the probe. Concentrations of substances in the fluid coming out of the probe, which is termed dialysate, mirrors concentrations of substances in the interstitial fluid. The dialysate is analyzed for the substances of interest. If the microdialysis probe is perfused at a rate close to zero, concentrations of small water-soluble substances in the dialysate will approach inter-

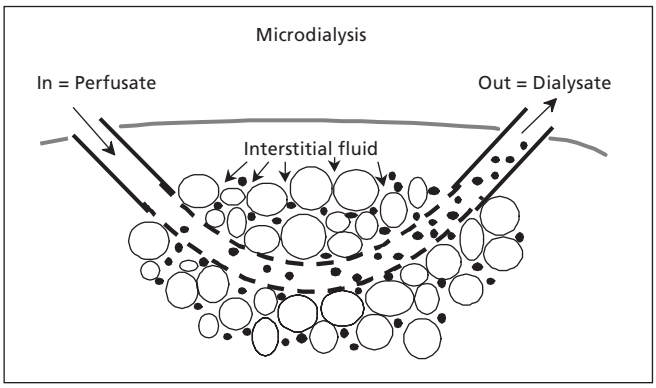

Figure 2. Schematic view of a microdialysis probe placed in subcutaneous adipose tissue. Black dots represent molecules.

stitial concentrations (330). A very low flow rate, however, creates a very low time resolution because long time is needed to sample the volume necessary for analysis. Thus, in our microdialysis studies we used a flow rate at which concentrations of metabolites in dialysate did not equal interstitial metabolite concentrations (IV, VI, VII, VIII, IX). Hence, the relative recovery (RR) of the substance of interest, which is defined as the dialysate concentration relative to the interstitial concentration, must be known to calculate the interstitial concentration from the dialysate concentration.

The microdialysis probe is inserted by use of a cannula, which inevitably will lead to some damage of the tissue. Indeed, elevated ATP concentrations have been measured in the dialysate up to 15 min after insertion of a microdialysis probe in adipose tissue (46). In our experiments we waited at least 60 min from insertion of the probe to the experiment was begun (IV, VI, VII, VIII, IX).

Also, the probe itself is a foreign body, which may elicit a tissue reaction. In our dog experiment (VI), the adipose tissue surrounding the microdialysis probes was histologically examined. The tissue showed no sign of cellular reaction or edema according to the pathologist, but around some of the probes there was an accumulation of erythrocytes. Carey histologically examined miniature swine adipose tissue surrounding microdialysis probes and found mild perivascular inflammation around less than half of the probes (62).

b) Calibration of microdialysis probes

In our microdialysis studies, RR was estimated either by no-net-flux (251) or by internal reference technique (344). Doing no-net-flux calibration, the microdialysis probe is prior to the experiment sequentially perfused with 4-5 different concentrations of the substance of interest. The concentration of substance in the dialysate is determined and the concentration difference between dialysate and perfusate is plotted against the perfusate concentration. This gives a straight line, and the negative slope of this line equals the RR (251, 368).

When internal reference calibration is applied, an indicator substance, which resembles the substance of interest, is added to the perfusate used during the experiment (344, 368). The indicator substance is often a radioactive form of the substance of interest. It is assumed that the percentage of indicator substance diffusing out through the microdialysis membrane is identical to the percentage of substance of interest diffusing into the microdialysis probe. This has been verified in vitro (344, 368) and the no-net-flux and the internal reference calibration techniques have been shown to give similar results both in vitro and in vivo (171, 199, 252, 368, 369).

c) Calculation of venous metabolite concentration

If the concentration of the substance of interest is higher in the arterial blood than in the interstitial fluid, it diffuses from the blood to the interstitial space and is hence taken up in the tissue. If, on the other hand, the concentration of the substance of interest is lower in the arterial blood than in the interstitial fluid, it diffuses from the interstitial space to the blood and is hence released from the tissue. The size of the concentration difference gives an indication of the metabolism of the tissue studied. However, the concentration difference could be unaltered in face of a changed metabolism if blood flow had changed. In line with this, the adipose tissue dialysate glycerol concentration has been shown to decrease during a selective increase in adipose tissue blood flow (114) and to increase paradoxically during local α_2-stimulation (138).

If one wants to quantitate the exchange of substances over the tissue, one needs to know the permeability of the substance through the capillaries and the capillary surface area in addition to the interstitial and the arterial concentrations of the substance of interest and the blood flow (190, 368). The capillary permeability (P) and surface area (S) product is most often assumed to equal previously determined PS products. In our dog study (VI), however, we determined PS products for lactate and glycerol in the fat pad to be 1.0 ± 0.5 (mean ± SE) and 1.3 ± 0.6 ml × 100 g^{-1} × min^{-1}, respectively. We injected radioactively labeled lactate, glycerol and albumin in the artery feeding the fat pad and calculated the extraction of lactate and glycerol from concentrations in venous blood. Subsequently, the PS products were calculated from extractions and adipose tissue blood flow (237). Others have determined PS products for ^{51}Cr-EDTA (305) and ^{14}C-sucrose (245), which have molecular weights similar to lactate and glycerol, and found PS products of approximately 2 ml × 100 g^{-1} × min^{-1}. The slightly lower PS products, that we found, might be due to the relatively low blood flow in the fat pads of the dogs (VI).

The calculation of venous blood concentration from measurements of interstitial concentrations is based on Fick's law of diffusion for a thin membrane as described by Intaglietta and Johnson (190). This model assumes that each capillary is a uniform cylinder with constant permeability along the length of the capillary and, furthermore, that all capillaries are situated in parallel and homogeneously perfused. Moreover, it is assumed that no precapillary exchange takes place and that the concentration of the substance of interest in the tissue space outside the capillary is uniform (190).

We compared venous glucose, lactate and glycerol concentrations calculated as described by Intaglietta and Johnson (190) with concentrations measured directly in venous outflow from an isolated autoperfused dog fat pad (VI). We found, that calculated and measured concentrations were well correlated with slopes of regression lines close to 1 (VI). Calculated and measured venous concentrations did not differ significantly for either glucose or lactate, but calculated glycerol concentrations were on average 76% of measured concentrations (VI). Others have compared calculated and measured venous glucose, lactate and glycerol concentrations in human abdominal subcutaneous adipose tissue (362, 381). This tissue, however, is not isolated from overlying skin and surrounding adipose tissue as the dog fat pad is, and, accordingly, it is not known if the abdominal vein drains exactly the tissue in which the microdialysis probe is placed. Simonsen et al. found good agreement between calculated and measured venous glucose and glycerol concentrations, but calculated venous lactate concentrations were much higher than measured concentrations (362). Summers et al. found, as we did, that calculated venous glycerol concentrations were systematically lower than measured concentrations (381). They suggest that the difference reflects that calculated venous glycerol concentrations depend upon intracellular HSL action whereas measured concentrations depend upon both HSL and intravascular LPL actions (381).

d) Calculation of exchange

The exchange of a metabolite in the tissue can be calculated by Fick's principle as the arterio-venous (uptake) or veno-arterial (release) concentration difference multiplied by blood flow. In our dog study (VI) this was done using calculated (as described in section c) as well as directly measured venous metabolite concentrations. Surprisingly, we found poor (glucose and lactate), or even negative (glycerol), correlations between calculated and measured metabolite exchange. This can probably be ascribed to the fact that a minor uncertainty in the calculation of the venous concentration has a large influence on the arterio-venous or veno-arterial concentration difference, if this concentration difference is small. Simonsen et al. also found that calculated and measured metabolite fluxes differed markedly (362). When Summers et al. corrected the measured glycerol release for intravascular lipolysis, as we also did, calculated and measured glycerol release did not differ significantly (381). The better agreement between calculated and measured glycerol concentrations in the study by Summers et al. (381) compared with our dog study (VI) might be due to different properties of microdialysis probes used. Summers et al. used the commonly used CMA 60 catheter (CMA, Stockholm, Sweden) (381), whereas we used homemade probes manufactured from artificial kidneys (Alwall GFS+12, Gam-

bro AB, Lund, Sweden) (VI). We suspect that the homemade probes bind glycerol (368) and, accordingly, we do not use these probes for determination of glycerol concentrations any more.

e) Lipolysis equals glycerol release

For lipolysis to equal glycerol release, TG must be fully hydrolyzed in the cell (i.e. broken down to 3 FFA and 1 glycerol molecule) and all glycerol must be released from the tissue. These assumptions are most often considered to be fulfilled for adipose tissue. If TG was not fully hydrolyzed, mono- or diacylglycerol would be released from or accumulate in the tissue. In the basal state, Arner et al. found low concentrations of mono- and diacylglycerol in human adipose tissue (20, 21). During in vitro stimulation of lipolysis, Arner et al. found accumulation of diacylglycerol in adipose tissue (1 diacylglycerol per 4 TG molecules being hydrolyzed), but no measurable concentration of mono- or diacylglycerol in the medium (20, 21). Fielding et al. measured concentrations of mono- and diacylglycerol in arterial and adipose tissue venous plasma in humans before and after a meal and found that these substances accounted for less than 3% of total acylglycerol concentrations (120, 121). This evidence suggests, that TG is almost totally hydrolyzed in human adipose tissue.

In vitro utilization of glycerol in adipose tissue was very low compared with glycerol release (20, 107). Only traces of glycerol were oxidized in human adipose tissue in vitro (20), and the activity of the enzyme necessary for phosphorylation of glycerol (if glycerol was to be used for oxidation or TG synthesis), glycerol kinase, was low in rat (326, 372) as well as in human adipose tissue (224, 333). Also in vivo extraction of glycerol by human subcutaneous adipose tissue (determined by tracer technique) was very low compared with in vivo glycerol release both in the postabsorptive state and during i.v. glucose infusion (72). Moreover, free glycerol did not accumulate in human adipose tissue segments in vitro either in the basal state or during β-adrenergic stimulation (20).

In contrast, data are emerging indicating usage of glycerol in skeletal muscle. Although glycerol kinase activity is low in rat (283) and human (351) skeletal muscle, glycerol kinase activity might nevertheless be of quantitative importance in skeletal muscle (400). In 24-hour fasted rats, more glycerol than glucose was incorporated in TG in both soleus and gastrocnemius muscles in vivo (151). Moreover, glycerol was taken up by lower-extremity tissue in humans in vivo, implying that glycerol might be reused in muscle tissue (204). Furthermore, we found lower glycerol concentrations in the extracellular space of exercising human muscle than in arterial plasma water indicating net uptake of glycerol (Stallknecht et al., unpublished observations).

2. Adipose tissue blood flow

We estimated adipose tissue blood flow (ATBF) by the ^{133}Xe washout technique (236, 350) in human studies (IV, VIII) and by the ^{133}Xe washout technique as well as by direct weighing of venous outflow from the isolated autoperfused fat pad in the dog study (VI). In rat studies (VII, IX), we estimated ATBF by the radioactively labeled microsphere technique (169, 314).

When using the ^{133}Xe washout technique, the ^{133}Xe is injected into the adipose tissue, and washout of ^{133}Xe is followed by external gamma counting (236, 350). ATBF is calculated as the rate constant of the washout (k) multiplied by the tissue-to-blood distribution coefficient for ^{133}Xe at equilibrium (λ). In human studies, we estimated λ from a previously determined formula (57) taking into account the thickness of the adipose tissue in which the blood flow was estimated. In dog studies, we calculated λ for each fat pad after estimation of water, lipid and protein content of samples from the fat pad (255). Data from the dog study (VI) can be used to compare ATBF estimated by ^{133}Xe washout and by direct weighing of outflow from the fat pad, respectively. Blood flows calculated from ^{133}Xe washout rates were positively correlated with directly measured blood flows ($r = 0.72$, $P < 0.0001$, $n = 30$, range: 1-10 ml × 100 $g^{-1} \times min^{-1}$), and calculated blood flow was on average $^2/_3$ of measured blood flow (2.9 ± 1.8 vs. 4.4 ± 3.0 ml × 100 $g^{-1} \times min^{-1}$, $P < 0.01$, $n = 30$). Previously, a close correlation has been found between ATBF estimated by ^{133}Xe washout and measured directly by weighing of venous outflow from the rabbit fat pad ($r = 0.997$, $P < 0.001$, $n = 9$, range: 7-53 ml × 100 $g^{-1} \times min^{-1}$) with no systematic difference between ATBF determined by the two methods (286). A close correlation has also been found between values of brown ATBF estimated by ^{133}Xe washout and microsphere technique, respectively, in rats ($r = 0.96$, $P < 0.001$, $n = 27$, range: 10-600 ml × 100 $g^{-1} \times min^{-1}$) with no difference between ATBF determined by the two methods (32).

A prerequisite for estimating blood flow by the ^{133}Xe washout technique is that the blood flow in the area of interest is evenly distributed and that the tissue is homogenous. This may not have been fulfilled in our dog study (VI), and we could by chance have injected the ^{133}Xe in hypoperfused areas. Alternatively, capillary blood flow may at low overall flow rates be relatively low compared with flow through shunt vessels. As the ^{133}Xe washout technique estimates capillary blood flow this may imply that the total flow is underestimated by the ^{133}Xe washout technique. Also, ATBF as measured by the ^{133}Xe washout technique is known to show a significant day-to-day, regional and inter-individual variation when used for estimating human ATBF (112, 287, 380).

When using the radioactive microsphere technique, a bolus of microspheres is injected into the heart or the aortic arch, and it is assumed that the microspheres are uniformly mixed with the arterial blood and distributed in the body in proportion to the blood flow (169, 314). Most often microspheres with a diameter of 15 mm are used, which should ascertain lodging of the microspheres in small arterioles and capillaries. Blood flow to individual tissues is calculated from radioactivity in tissue samples and in an arterial blood sample drawn at a known rate during and after injection of microspheres. We checked for mixing of microspheres with arterial blood by calculating the coefficient of variation (CV) for distribution of microspheres between the right and the left kidney as the difference between kidneys divided by the kidney mean. We found a mean CV of 16%, which was considered to indicate sufficient mixing (VII, IX).

A third method for estimating tissue blood flow is the microdialysis outflow-inflow ratio technique (117, 173, 370). In short, a blood flow marker, which most often is ethanol, is perfused through the microdialysis probe and the concentration of the marker is measured in the outflow from and the inflow to the probe. The ratio between concentration in outflow and inflow is calculated and as this ratio reflects the amount of blood flow marker *not* washed away by the blood, the outflow-inflow ratio is inversely related to tissue blood flow. Reassuring, the ethanol outflow-inflow ratio determined by microdialysis technique was inversely correlated with ATBF estimated by ^{133}Xe washout technique ($r = -0.81$, $P < 0.01$, $n = 8$, range: 1-6 ml × 100 $g^{-1} \times min^{-1}$) (117). Moreover, local heating increased ATBF estimated by the ^{133}Xe washout technique and decreased ethanol outflow-inflow ratio (117). The main advantage of the microdialysis outflow-inflow ratio technique is that, in microdialysis studies, changes in blood flow are determined in the same area in which changes in metabolite or hormone concentrations are determined. The main disadvantage is that the technique is not quantitative, i.e. absolute tissue blood flow is not determined.

3. Body composition

In vivo adipose tissue metabolism is often expressed per 100 g of adipose tissue. Thus, if one wants to estimate whole body adipose tissue metabolism, it is necessary to determine the whole body adipose tissue mass. In humans, we estimated adipose tissue mass by bioelectrical impedance analysis (BIA) (IV) or dual-energy X-ray absorptiometry (DEXA) scanning (VIII). In rats and dogs, we did

not estimate whole body adipose tissue mass, but we weighed individual adipose tissues (III, V, VI, VII, IX).

When using the BIA technique, electrodes are placed on a hand and a foot and the resistance of the body to a test current is determined (165, 348). The resistance and the height, the body weight, the age and the sex of the subject is inserted in an equation which has been developed from calibration of the BIA technique against another technique which provides a more direct assessment of body composition (e.g. measurement of body density). From this equation the lean body mass, and subsequently the fat percentage, is calculated. The BIA technique is easy to use, but the theoretical background for the technique is not clear (346) and it has been suggested that BIA is not a valid technique in athletes (341).

During DEXA scanning, the body is divided into a large number of pixels in which the attenuation of X-rays of two different energy levels is measured. The attenuation of X-rays varies between fat and lean tissues, and this fact is used to calculate the fat percentage in soft tissue pixels. The fat percentage for pixels containing both soft tissue and bone is extrapolated from measurements in soft tissue pixels (152). Estimates of body fat percentage from DEXA scanning has been validated against estimates from a four-compartment model (which is considered the most accurate way of estimating body composition) in a population of young adults who, among other things, varied in athletic status (315). It was concluded that body fatness estimates by DEXA are accurate with no systematic error (315).

4. Catheterization and blood sampling

In humans, a catheter was introduced into the radial artery of the non-dominant arm during local analgesia for blood sampling (IV, VIII). The catheter was kept patent by regular flushing with isotonic saline containing heparin (5 IU $\times$ ml^{-1}) (IV) or by isotonic saline delivered by an automatic flushing device (VIII). Also, we aimed at catheterizing a vein draining the subcutaneous adipose tissue of the anterior abdominal wall (128, 130) in the subjects in our two human studies (IV, VIII), and we succeeded in 10 out of 28 subjects. The catheters were kept patent by continuous infusion of isotonic saline (30 ml $\times$ h^{-1}). Additionally, catheters were introduced in antecubital veins for infusion of epinephrine (IV), insulin and glucose (VIII). Heparin is known to activate the enzyme LPL, and after intravenous infusion of heparin (50 IU $\times$ kg body weight^{-1}) in humans, plasma TG was found to decrease and plasma FFA was found to increase (120). In the present experiments (IV), we injected less than 5 IU heparin per kg body weight, and we found no decrease in plasma TG (data not shown).

In dogs, blood was sampled from an artery as well as from the external pudendal vein (VI). The dog was anticoagulated with 5000 IU of heparin to allow collection of blood from the external pudendal vein during the experiment (VI).

In the in vivo rat studies, catheters were inserted into aorta via a common carotid artery for blood sampling (I, VII, IX), into a jugular vein for infusion of epinephrine (IX), insulin (I, VII) and glucose (VII) and into a tail artery for microsphere reference blood sampling (VII, IX). All catheters were heparinized before insertion. The erythrocytes removed from the rat during blood sampling were replaced by erythrocytes obtained from a donor rat (I, VII, IX).

Blood was always sampled into iced tubes containing preservative and usually centrifuged immediately. Glucose and lactate concentrations were usually determined at once and other samples were kept at –20 °C until analysis, except samples for FFA and catecholamines, which were kept at –80 °C.

5. Metabolite and hormone analyses

All analyses on blood/plasma were run in duplicate. Microdialysis samples were run in singular due to shortage of dialysate. Glucose and lactate concentrations were determined by an automated analyzer (YSI, Yellow Springs, USA). Glycerol and β-hydroxybutyrate concentrations were determined by fluorometry (130, 137). TG (187) and urea (93) concentrations were determined spectrophotometrically. FFA concentrations were determined using a commercial enzymatic kit (Wako, Neuss, Germany). Insulin concentrations were determined using a commercial ELISA (DAKO, Cambridgeshire, UK) or RIA (NOVO, Bagsværd, Denmark or Linco Research, St. Charles, USA) kit. Catecholamine concentrations were determined by a single-isotope radioenzymatic assay (9, 37, 217).

6. Anesthesia of rats and dogs

During in vivo rat (VII, IX) and dog (VI) studies, animals had to be anesthetized due to the experimental design. Rats were anesthetized by halothane gas and dogs were anesthetized by thiopental and pentobarbital. All were supplemented with 50% O_2, 50% N_2O. In the rats, we surprisingly found that ATBF fell in response to insulin infusion (VII) and was unaltered in response to epinephrine infusion (IX). This might be the physiological response to these hormones in rat adipose tissue, but it might also be an artifact due to the anesthesia. Halothane anesthesia is known both to affect tissue metabolism (119) and to decrease blood flow (179, 274). That metabolism is influenced by anesthesia was also likely in our dog study (VI). In the first 3 dogs, we aimed at performing no-net-flux calibration of microdialysis probes, but this was not successful as basal metabolite concentrations were not stable (368).

E. COMPARISON BETWEEN IN VITRO AND IN VIVO MEASUREMENTS

The studies in the present thesis comprise both in vitro (II, III, V) and in vivo (I, IV, VI, VII, VIII, IX) measurements, but no attempt was made to compare in vitro and in vivo measurements directly. However, others have tried to do that.

One study found a weak correlation (r = 0.36) between in vitro insulin-stimulated glucose transport in adipocytes and in vivo whole body insulin-stimulated glucose uptake during a hyperinsulinemic, euglycemic clamp in a group of men with normal glucose tolerance (45). Moreover, aging induced a 35% decrease in the in vitro insulin-stimulated adipocyte glucose transport but no change in the in vivo whole body insulin-stimulated glucose uptake (410). However, only few percent of an in vivo glucose load is taken up in adipose tissue (43) and, accordingly, concordant changes in the in vitro insulin-stimulated glucose transport in adipocytes and in the in vivo whole body insulin-stimulated glucose uptake are not necessarily to be expected.

In contrast, the major part of FFA and glycerol releases takes place in adipose tissue and, accordingly, it can be relevant to compare in vitro adipocyte lipolysis with whole body FFA and glycerol turnover. In the basal state, whole body lipolytic rate (estimated from lipolytic rate in abdominal subcutaneous adipocytes in vitro and fat mass) and whole body plasma FFA turnover (estimated by tracer technique) were both correlated positively with percentage body fat in a group of healthy women with a wide range of fatness (244). However, there was not a positive correlation between in vitro and in vivo assessments of fat metabolism when these were compared directly (244).

The plasma glycerol concentration is a simple measure of in vivo whole body lipolytic rate as removal of glycerol from plasma is proportional with the plasma glycerol concentration (352). The responsiveness of abdominal subcutaneous adipocytes to in vitro catecholamine stimulation has been found to be positively correlated (r = 0.84, P < 0.005, n = 16) with the plasma glycerol concentration during exercise performed at 67% of Vo_2max in a group of healthy men (248). In another study, 65 healthy subjects of both sexes were divided into two groups on the basis of their in vitro lipolytic sensitivity to β-agonist stimulation in abdominal subcutaneous adipocytes (249). During exercise and mental stress tests, subjects with high in vitro β-adrenergic sensitivity had higher plasma glycerol concentrations compared with subjects with low in vitro β-adrenergic sensi-

tivity despite of lower norepinephrine (during exercise) and epinephrine (during mental stress) concentrations in the former subjects (249). A study by Carey found a training-induced increase in epinephrine-stimulated in vitro lipolysis, but no effect of training on epinephrine-stimulated plasma FFA or glycerol response in miniature swine (62). The in vitro and the in vivo measures of lipolysis were not compared directly. In response to a 4-week very-low-calorie diet, Stich et al. found an increase in both in vitro abdominal subcutaneous adipocyte lipolysis during β-adrenergic stimulation and plasma glycerol concentration during β-adrenergic stimulation (378). Furthermore, in vitro basal HSL activity and protein level increased in response to the diet (378). Again, the in vitro and the in vivo measures of lipolysis were not compared directly.

Lately, the relative stimulation of lipolysis by catecholamines in vitro and during microdialysis in abdominal subcutaneous adipose tissue has been compared in a group of obese but otherwise healthy men and women (223). The values of relative stimulation of lipolysis in vitro and during microdialysis, respectively, were positively correlated (223).

From the above it is evident that there is coherence between in vitro and in vivo measurements of adipose tissue lipolysis, but that this coherence is not absolute. Obviously major differences exist between the in vitro and the in vivo situation. One important factor is that the blood supplies and removes substances during the in vivo but not during the in vitro situation. If the concentration of substances as e.g. adenosine, FFA and lactate are allowed to build up during in vitro experiments, this might change the metabolism. Lately, adipose tissue has been shown to secrete many other endocrine/paracrine substances and differences in concentration of these substances between the in vitro and the in vivo situation might also change the metabolism. Furthermore, site differences in adipose tissue lipolysis are well known (203). In vitro measurements typically represent lipolysis at only a single adipose tissue site, whereas in vivo measurements often represent mean whole body lipolysis (including lipolysis in non-adipose tissues).

At present many more in vitro than in vivo studies of the influence of physical training on adipose tissue metabolism have been performed and therefore conclusions based on the in vitro evidence are established "truths". However, the in vivo situation is the "real thing". In conclusion, in vitro experiments are important to elucidate specific questions in a well-controlled setting, but if the question allows the use of an in vivo technique, this must be preferred.

F. ETHICAL CONSIDERATIONS

All animal experiments were performed in accordance with national ethical guidelines for use of animals in research, and the Ethics Committee for Medical Research in Copenhagen had approved all human experiments. Rats were swim trained after a protocol accepted by the Danish Animal Experiments Inspectorate.

In human experiments, radioisotopes were used for estimating ATBF (^{133}Xe) and for estimating recovery in microdialysis probes (^{3}H-glucose, ^{3}H-glycerol and ^{14}C-lactate). Furthermore, subjects were examined by DEXA scanning in one study (VIII). Subjects received a total radiation dosage of less than 0.5 mSv, which corresponds to an X-ray of thorax.

Human subjects, who had a catheter in the radial artery during the experiment, were instructed not to lift heavy things on the day following the experiment. One subject reported the development of a haematoma over the radial artery two days after the experiment during lifting of a piano. The subject used manual compression to stop the bleeding. No other untoward episodes were reported.

IV. RESULTS AND DISCUSSION

A. TRAINING-INDUCED ADAPTATIONS IN ADIPOSE TISSUE

1. Adipose tissue mass

a) Effect of training on white adipose tissue

Vigorous endurance training is capable of reducing adipose tissue mass in humans. This has been confirmed in both cross-sectional (5, 38, 239, 265, 327, 342, 394) and longitudinal studies (4, 90, 99, 102, 133, 312, 377, 403). In rats, adipose tissue mass is reduced by training irrespective of site, age and gender (10, 24-31, 33, 54, 74, 96, 136, 160, 232, 240, 267, 269, 292, 295, 298, 300, 306, 309, 323, 347; 386, 387). As little as 4 days of swim training was sufficient to reduce fat pad weight and adipocyte size significantly (~20%) in male rats (118).

In accordance with the above-mentioned findings, we found a 50% lower fat percentage (estimated by DEXA scanning) (VIII) and a ~55% smaller abdominal skinfold thickness (IV, VIII) in endurance-trained compared with sedentary male subjects. When estimated by BIA technique, fat percentage did not differ between trained and sedentary subjects (IV), which probably reflects that BIA is not a valid technique in athletes (341). In endurance-trained male and female rats, we found reductions in mass of various adipose tissue depots (epididymal fat: ~60% (III, V), retroperitoneal fat: ~60% (VII, IX), parametrial fat: ~45% (VII, IX), mesenteric (visceral) fat: ~40% (VII, IX)). We did not weigh the subcutaneous adipose tissue depot in the rats, as the depot is difficult to dissect out.

The visceral fat mass is considered to be especially important in relation to major diseases such as type II diabetes and cardiovascular disease (202, 214, 278). In the rats, we did not find a greater reduction of the visceral fat mass relative to the other adipose tissue depots in response to training (VII, IX). However, according to a recent review, visceral fat mass is reduced relatively more than total fat mass in humans whether weight loss is induced by training, dieting or pharmacological means (365). Both according to the mentioned review and according to a recent study directly comparing effects of training and diet, visceral fat mass is not reduced relatively more by training than by diet (332, 365).

Strangely, endurance training of free-living overweight or obese humans results in only a minor fat loss according to several metaanalyses (34, 140, 275). The discrepancy between studies in lean and overweight individuals can probably be ascribed to the low amount of calories most obese humans are able or willing to expend by exercising. Furthermore, overweight people may compensate for the extra energy expenditure during training sessions by reducing their normal activity level. This has been found to be the case in elderly subjects (148, 270). However, that some obese subjects during well-controlled circumstances are able to loose a considerably amount of fat by exercising (without dieting) is confirmed in a study in which obese subjects reduced their adipose tissue mass by 18% by exercising approximately 1 hour daily for 12 weeks (332).

In conclusion, training is capable of reducing adipose tissue mass in both humans and rats.

b) Effect of adrenodemedullation and sympathectomy on white adipose tissue

The sympathoadrenergic system is of major importance for the increase in lipid mobilization from adipose tissue during exercise (12, 19) and it was therefore likely that the sympathoadrenergic system is involved in the training-induced decrease in fat mass. However, we found no effect of adrenodemedullation and/or sympathetic denervation on the training-induced reduction in epididymal fat pad weight in rats (V). This implies that an intact sympathoadrenergic system is not of major importance for the training-induced decrease in adipose tissue mass. Nevertheless, when trained and sedentary rats were evaluated together, adrenodemedullation tended to increase (13%) and sympathetic denervation significantly increased (8%) epididymal fat pad mass (V). This indicates that the sympathoadrenergic system is of some importance for the regulation of adipose tissue mass. Sympathetic denervation of adipose tissue has previously been shown to increase fat mass in rodents (75, 242, 411). Also, unilateral denervation of the lumbar fat depot in rats, but not adrenodemedullation, has been shown to partially prevent

the decrease in adipose tissue weight that is induced by a 48-hour fast (61).

In conclusion, the sympathoadrenergic system is not of major importance for the training-induced decrease in adipose tissue mass in rats. The factors regulating this decrease remain to be determined, but GH might be a candidate.

c) Effect of training on brown adipose tissue

Cold exposure increases brown adipose tissue mass in rats (II) (23, 96, 159, 160, 240), but controversy exists with respect to the effect of training. We found a swim training-induced increase in interscapular brown adipose tissue (ISBAT) mass in female but not in male rats (water 36 °C) (II). In male rats, Harri & Kuusela found no change in ISBAT mass when trained by swimming in water at 38 °C, a small increase ISBAT mass when trained by swimming at 36 °C and a large increase in ISBAT mass when trained by swimming at 30 °C (160). In another study, swim training at 37 °C did not change ISBAT mass in male rats (240). Running training has in some studies been found to decrease ISBAT mass in both female (386) and male rats (23, 160, 292, 408), but other studies found no run training-induced change in ISBAT mass of female (143, 387) or male rats (96, 159, 268, 349, 405). Overall, it seems that both training and low body temperatures may increase ISBAT mass in rats. However, the reason for the varying effect of training on ISBAT mass is not completely understood, but differences in training regimen and rat sex and strain might influence results although no unambiguous differences exist between studies.

In conclusion, training may increase the amount of brown adipose tissue particularly in female rats. However, available evidence is ambiguous.

d) Effect of training on body weight

We found a reduction in body weight in swim trained compared with sedentary male rats (I, II, III, V). In contrast, body weight did not differ between swim trained and sedentary female rats (I, II, VII, IX). This gender difference has also been noted by others (74, 295, 299). Theoretically, the difference could be due to female rats swimming less vigorously than male rats in the bathtub. Inspection of the rats during swimming, however, did not indicate that. Moreover, female rats have been found spontaneously to run twice the distance as male rats when given free access to running wheels indicating that female rats are not lazier than male rats (74). Furthermore, a gender difference has also been found in rats trained by forced running during conditions in which the running distance was controlled for (281). If energy expenditure is increased identically during training in female and male rats, the lower body weight in trained male compared with female rats must be due to a lower energy intake in trained male compared with trained female rats. In fact, female rats have been found to increase food intake in response to exercise training (175, 266, 267, 281, 295, 299), whereas male rats decreased or did not change food intake (10, 87, 96, 232, 281, 292, 295, 299, 323, 347).

In overweight and obese humans, training resulted in a modest decrease in body weight which was not influenced by sex of the subjects (34, 140, 275).

In conclusion, training decreases body weight gain in male but not in female rats. In overweight and obese humans, training is capable of reducing body weight.

2. Adipocyte size and number

a) Adipocyte size

Endurance training is capable of decreasing adipocyte size in humans in both cross-sectional (40, 82, 84, 101, 265, 325, 342) and longitudinal studies (99, 102). Adipocyte size is also smaller in trained compared with sedentary rats (III, V) (10, 27, 31, 33, 48, 54, 76-80, 136, 175, 232, 269, 296, 298; 308, 343, 347, 387, 392). As seen with respect to adipose tissue mass, the sympathoadrenergic system is not of major importance for the training-induced decrease in adipocyte size in rats (V).

The lower adipose tissue mass and adipocyte size after training makes it difficult to compare adipose tissue metabolism between trained and sedentary individuals. No standard way of expressing adipose tissue metabolism exists and, accordingly, many different expressions have been used in the literature: per subject, per kg body weight, per whole body adipose tissue, per fat pad, per gram of adipose tissue, per mg of adipose tissue protein, per adipocyte, per adipocyte surface area and per adipocyte weight or volume. Often the conclusion of a study will vary depending on which expression has been used (26, 134, 175, 246, 269, 298). Traditionally, the expression "per mg of protein" has been used when enzyme activity is measured and often "per cell" has been used for measurements of metabolite uptake, release and metabolism. However, both basal and hormone-stimulated adipocyte metabolism increase with adipocyte size (in sedentary individuals of similar age) (16, 22, 31, 39, 41, 42, 52, 142, 144, 146, 157, 158, 183, 194, 195, 304, 366, 387, 392, 414). When metabolism depends on adipocyte size it would seem logical to express adipocyte metabolism per adipocyte volume. The adipocyte, however, contains a large fat droplet and most of the adipocyte metabolism takes place in the thin cytoplasm rim between the plasma membrane and the fat droplet. Accordingly, it would be logical to express adipocyte metabolism relative to adipocyte cytoplasm water content which varies with adipocyte volume and hence with adipocyte surface area except when adipocyte volume is extremely small (≤100 pl) (105). Adipocyte metabolism expressed per cell has been shown to correlate better with the adipocyte surface area than with the adipocyte diameter or weight (42, 195). Correspondingly, catecholamine-stimulated lipolysis expressed per adipocyte surface area was independent of adipocyte diameter indicating that hormone-stimulated metabolism expressed per adipocyte surface area is independent of cell size per se (195, 414).

In rats, adipocyte size increases with age during maturation (145, 158), and as age per se most often has been found to decrease adipocyte metabolism (146, 157, 158, 183), the effect of adipocyte size per se is often obscured by the effect of age.

In conclusion, training decreases adipocyte size in humans and rats. This complicates comparisons of adipocyte metabolism between trained and sedentary individuals as basal and hormone-stimulated adipocyte metabolism increase with adipocyte size per se. The sympathoadrenergic system is not of major importance for the training-induced decrease in adipocyte size in rats.

b) Adipocyte number

In rats, we and most other investigators found no major changes in adipocyte number with training (III) (10, 24, 27, 31, 33, 48, 54, 175, 269, 298, 301, 343, 387, 392). One study, however, found a decrease in epididymal adipocyte number in rats trained by long-term (6-22 months) voluntary running (77). Another study found that training commenced early in rat life (5 days old) reduced number of adipocytes and fat pad weight later in life (297). A third study found that training reduced adipocyte number in obese but not in lean rats (347). In humans, training did not influence adipocyte number significantly (102, 226).

In conclusion, most often training does not influence adipocyte number, but in rats a reduction may be induced by long-term training, by training commenced early in life or by training in obese individuals.

3. Enzymes

a) White adipose tissue

We found a higher activity of the mitochondrial enzymes cytochrome-c oxidase (CCO) and malate dehydrogenase (MDH) in white adipose tissue in swim trained compared with sedentary rats of both genders when expressed per gram of adipose tissue (males: CCO: 16-fold, MDH: 10-fold; females: CCO: 10-fold) as well as per mg protein

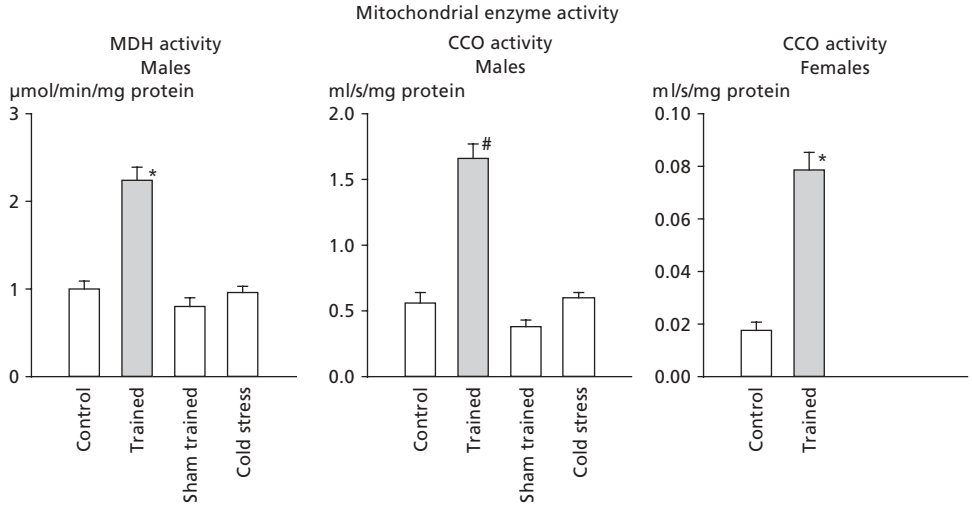

Figure 3. Influence of physical training, sham swim training and cold stress on activity of malate dehydrogenase (MDH) and cytochrome-c oxidase (CCO) in rat white adipose tissue. Values are means ± SE, n = 8-12. * $P < 0.05$ vs. all other groups. # $P < 0.05$ vs. sham-trained and control groups.

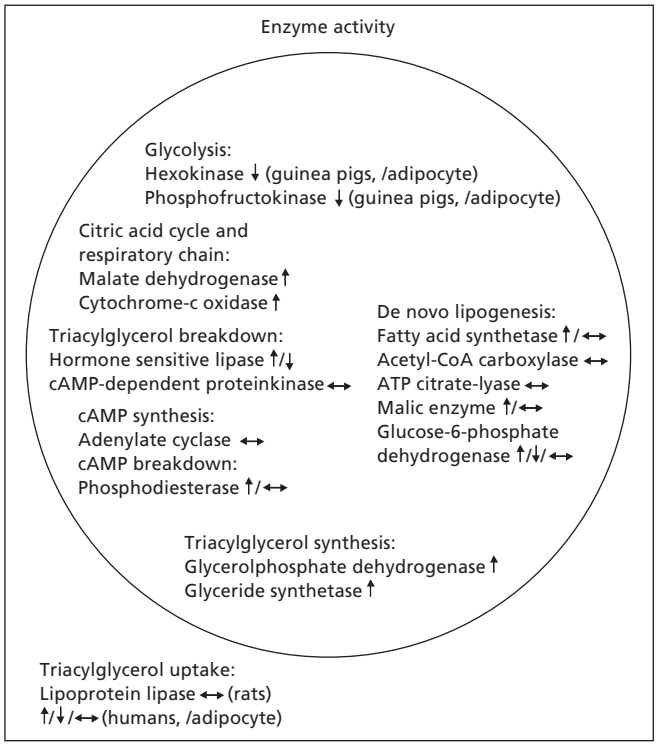

Figure 4. Influence of physical training on enzyme activity in white adipose tissue. Unless explicitly stated, the enzyme activity is expressed per mg protein and is measured in rat adipose tissue homogenate.

in adipose tissue homogenate (II) (Figure 3 and Figure 4). Neither sham-training nor cold-stress changed adipose tissue CCO or MDH activities (II). CCO participates in the respiratory chain, which synthesizes ATP (243). MDH participates in the citric acid cycle, which also contributes to ATP synthesis (243). Moreover, MDH participates in transport of reducing equivalents for ATP synthesis from the cytosol to the mitochondrial matrix and in transport of acetyl-groups for de novo lipogenesis from the mitochondrial matrix to the cytosol and is furthermore involved in gluconeogenesis (243). Accordingly, trained rats might be better to synthesize ATP in adipose tissue compared with sedentary rats. In the adipocyte, ATP is among other things used for synthesis of glycerol 3-phosphate, which is necessary for TG synthesis (243). Also the activation of FFA during TG synthesis as well as de novo lipogenesis requires ATP (243). A training-induced increase in mitochondrial enzyme activity has not previously been found in adipose tissue, but an increase in mitochondrial enzyme activity in skeletal muscle after training is well known (181, 182).

In the following, the enzyme activity is expressed per mg protein in adipose tissue homogenate unless explicitly stated. It should be noted, that the amount of protein per gram of adipose tissue often is increased with training (II) (25, 28, 307). Accordingly, the finding of no training-induced change in enzyme activity expressed per mg of protein can be equivalent with a training-induced increase in enzyme activity when expressed per gram of adipose tissue.

Interestingly, training of rats has been found to increase the activity of the multienzyme complex glyceride synthetase, which catalyzes TG synthesis from glycerol 3-phosphate and FFA (25, 30, 35) (Figure 4). Training of rats also increased the activity of glycerol phosphate dehydrogenase, which catalyzes glycerol 3-phosphate synthesis from dihydroxyacetone phosphate that is generated during glycolysis (247). On the other hand, training of guinea pigs decreased the activity of the glycolytic enzymes, hexokinase and phosphofructokinase, when expressed per adipocyte (264). The activity of fatty acid synthetase, which catalyzes de novo lipogenesis, has been found to increase (35) or not to change (24) after training of rats. Two other enzymes involved in de novo lipogenesis by supplying substrates (acetyl-CoA carboxylase and ATP citrate-lyase) were found not to change after training of rats (25, 35). The activity of malic enzyme, which produces NADPH used during de novo lipogenesis, increased (164) or was not changed (25, 35) in rat adipose tissue after training. The activity of the enzyme glucose-6-phosphate dehydrogenase from the pentose phosphate pathway, which also produces NADPH, was found to increase (164), decrease (25) or not to change (35) after training of rats. The described training-induced enhancement of activity of enzymes involved in TG synthesis probably explains the increase in insulin-mediated incorporation of glucose into lipids in adipocytes after training (392, 393).

We have recently found a training-induced increase in HSL protein in retroperitoneal adipose tissue and in epinephrine-stimulated HSL activity in retroperitoneal and mesenteric adipose tissues of rats (110) (Figure 4). Previously, however, others had found a training-induced decrease in basal and cAMP-stimulated HSL activity in parametrial adipose tissue of rats (355) and a training-induced decrease in basal HSL activity in abdominal subcutaneous adipose tissue of obese male subjects (90). Further studies are needed to clarify the effect of training on HSL activity in adipose tissue.

The HSL activity is stimulated by cAMP via phosphorylation by a cAMP-dependent protein kinase (235). Basal and cAMP-stimulated protein kinase activity did not differ between trained and sedentary rats (192, 356) (Figure 4). Formation of cAMP is catalyzed by the enzyme adenylate cyclase, which in the basal state has been found not to change in rat adipose tissue by training (354, 356, 406). However, the percentage stimulation of adenylate cyclase by epinephrine was increased in adipocyte membranes from trained compared with sedentary rats (406), whereas the change due to norepinephrine was decreased (356). The enzyme phosphodiesterase, which degrades

cAMP, was increased (28, 212, 355, 356) or unchanged (307) in rat adipose tissue after training.

In rats, training did not change LPL activity when expressed per gram of adipose tissue (96, 97, 232, 412), per mg of adipose tissue protein (26, 35, 97) or per adipocyte (10, 293, 343) (Figure 4). Also the amount of LPL protein and mRNA did not change after training of rats (293). In contrast, most cross-sectional studies in humans found a training-induced increase in LPL activity expressed per gram of adipose tissue (261, 291, 342) although one study found a lower LPL activity in endurance trained compared with sedentary subjects (265). Expressed per adipocyte in humans, cross-sectional studies showed a training-induced increase (342) or decrease (265) in LPL activity, whereas longitudinal studies showed a decrease (231) or no change (312). A recent cross-sectional study in humans found no difference in LPL activity per adipocyte between middle-aged trained and sedentary lean men, but sedentary lean men had lower LPL activity compared with obese men indicating that a major determinant of adipose tissue LPL-activity in humans is the degree of fatness, not training (38). Discrepancies between studies do not appear to be due to sex of subjects or adipose tissue site.

In conclusion, training increases the mitochondrial enzyme activity markedly in rat adipose tissue both when expressed per gram of adipose tissue and per mg protein in adipose tissue homogenate. Furthermore, training increases the activity of enzymes involved in triacylglycerol synthesis, does not change basal adenylate cyclase activity, increases phosphodiesterase activity, does not change cAMP dependent protein kinase activity and does not change lipoprotein lipase activity in rat adipose tissue.

b) Brown adipose tissue

We found neither a training- nor a cold-induced change in the activity of the mitochondrial enzymes CCO and MDH when expressed per g of brown adipose tissue or per mg protein in brown adipose tissue homogenate in male rats (II). As we found no effect of training on the weight of ISBAT in male rats, also the total activities of CCO and MDH in ISBAT were not changed by training (II). However, the total activities of CCO and MDH in ISBAT were increased 3-fold in the cold-stressed rats due to the cold-induced increase in weight of ISBAT (II). Also Harri et al. did not find an influence of training on mitochondrial enzyme activity expressed per mg protein in ISBAT or expressed as total enzyme activity in ISBAT (159). However, in their study, cold-stress markedly increased the activity of many mitochondrial enzymes, including CCO, when expressed per mg protein (159). This discrepancy between the two studies is difficult to explain but could be related to the age of the animals as our rats weighed approximately 100 g at the beginning of the experiment whereas the rats of Harri et al. weighed approximately 200 g (II) (159). Harri et al. (159) and we (II) studied male Wistar rats. In female Sprague-Dawley rats, training has been found to markedly decrease CCO activity expressed per g of ISBAT (143, 385) as well as per total ISBAT (143).

Mitochondria in brown adipose tissue contain uncoupling proteins (UCP1, 2 and 3), which increase heat production by uncoupling respiration from ATP synthesis (50). Boss et al. examined if endurance training of rats changes the amount of mRNA coding for UCP1, 2 and 3 in ISBAT and found no training-induced change (50). In contrast, others have found a training-induced decrease in mRNA coding for UCP1 in ISBAT (349, 408), but no change in UCP1 protein in ISBAT (349).

In conclusion, training does not change or decreases the mitochondrial enzyme activity in rat brown adipose tissue. Cold-stress increases the mitochondrial enzyme activity in total interscapular brown adipose tissue.

4. Blood flow

a) Basal

Adipose tissue is often thought of as a poorly perfused tissue, but in fact the capillary bed of white adipose tissue of rats has approximately the same size as that of resting skeletal muscle when expressed per gram of tissue (163). Moreover, in resting humans, adipose tissue blood flow (ATBF) is twice skeletal muscle blood flow when expressed per gram of tissue (109).

We found that basal blood flow per gram of adipose tissue was increased at least twofold in trained compared with sedentary humans (IV, VIII) and rats (VII, IX) (Figure 5). In humans, we only examined abdominal subcutaneous ATBF (IV, VIII), but in rats, the training-induced increase in blood flow was a general adipose tissue adaptation as subcutaneous, retroperitoneal, parametrial and mesenteric adipose tissues were examined (VII, IX).

Only few other studies have examined the effect of training on basal ATBF. In young male rats, training increased blood flow per gram of retroperitoneal and epididymal adipose tissue two-fold when estimated by the microsphere technique, but in old male rats, training did not modify ATBF (268). Training for 12-16 weeks did not change ATBF per gram of tissue in young male subjects (185), obese male subjects (377) or old female subjects (234). In our human studies (IV, VIII), trained subjects were elite-class athletes whereas relatively short term training was used in the mentioned studies (185, 234, 377). The degree of training might explain the discrepancy in results. Moreover, in the mentioned human studies, body fat percentage did not change (185, 234) or decreased only marginally (377) after training. A decrease in fat mass might be a prerequisite for a training-induced increase in ATBF. This is also suggested in a study by Hickner et al. in which they compared abdominal subcutaneous ATBF estimated by microdialysis outflow-inflow ratio technique in lean trained and sedentary women and in obese sedentary women (172). ATBF was lower in obese compared with lean women, but ATBF did not differ between lean trained and lean sedentary women (172). It is well known, that ATBF per gram of tissue is higher in lean compared with obese subjects (44, 288, 380). Gersh and Still noted already in 1945 that capillaries formed loose meshes around the adipocytes in rat adipose tissue, the smaller the adipocytes the smaller the meshes and, accordingly, the higher the capillary density (141). In accordance with this, Di Girolamo et al. found in dogs, that basal ATBF per gram was higher in fat pads with small compared with large adipocytes and calculated that basal blood flow per adipocyte was constant (104). It is not possible to tell whether the higher ATBF per gram of tissue in endurance-trained compared with sedentary individuals in our studies (IV, VII, VIII, IX) is due to training per se or to the training-induced decrease in adipose tissue mass.

In rats, basal ATBF per gram of tissue was higher in mesenteric compared with other adipose tissues (VII, IX) (Figure 5). This has also been noted by others (401, 402), and it might be due to the smaller size of mesenteric compared with other adipocytes (86, 282, 401). However, when ATBF was expressed per adipocyte surface area, i.e. correcting for differences in adipocyte size, ATBF was still higher in mesenteric compared with other adipose tissues (86, 401).

In conclusion, basal blood flow per gram of adipose tissue is higher or the same in trained compared with sedentary individuals. A difference may be secondary to a reduction in adipocyte volume. In rats, blood flow is higher in mesenteric compared with other adipose tissues.

b) Effect of insulin

We found no effect of physiological or supraphysiological levels of insulin on ATBF in trained or sedentary male subjects (VIII) (Figure 5). Also in a previous study carried out in sedentary subjects, the ^{133}Xe washout technique was used for estimating ATBF during a hyperinsulinemic, euglycemic clamp, and also in that study insulin did not influence ATBF (115). Other previous studies in humans estimated insulin-induced changes in ATBF by the microdialysis outflow-inflow ratio technique and found either no change (155, 156, 193) or an increase in ATBF (168, 331). One study found an increase

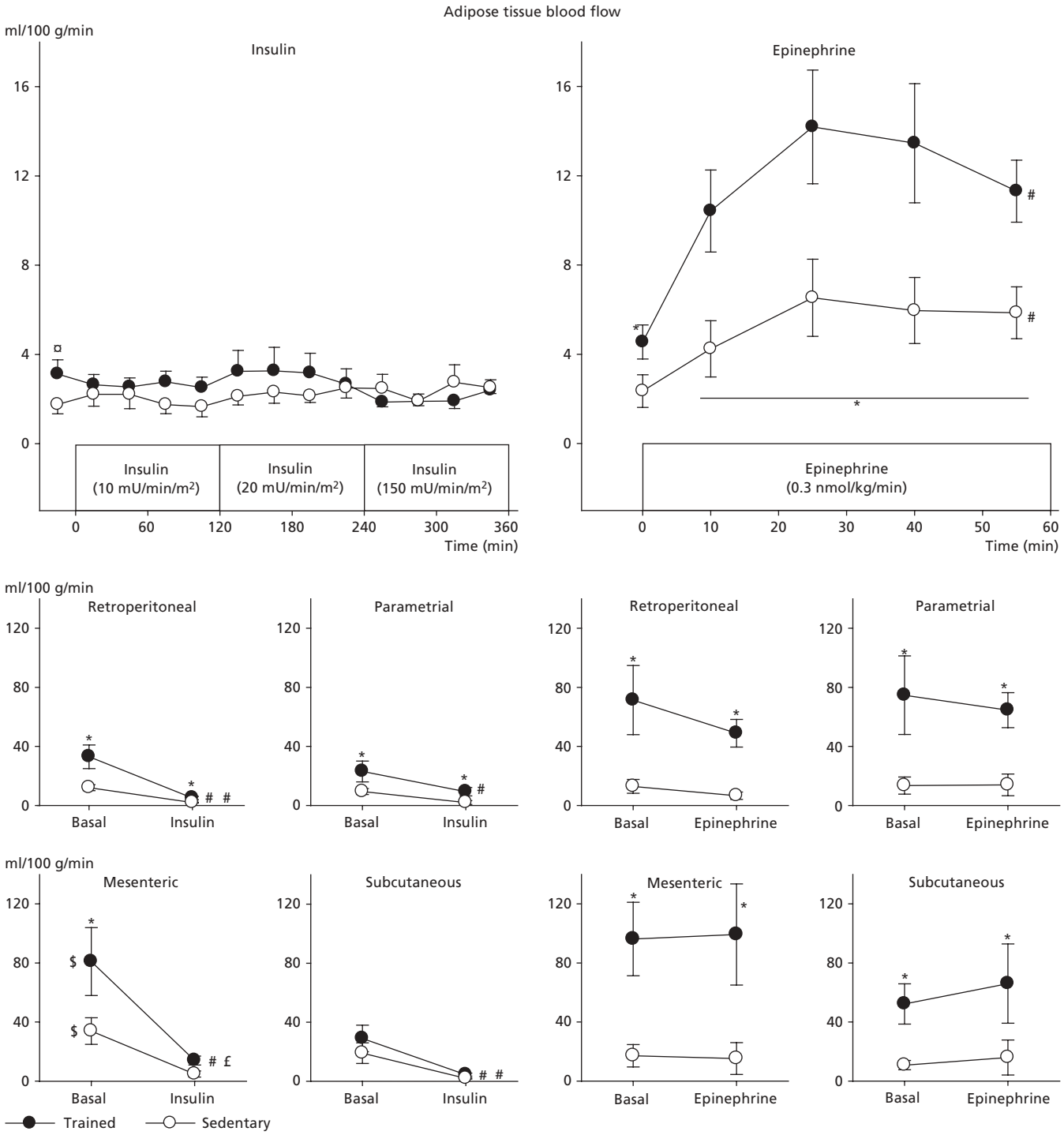

Figure 5. Influence of physical training on adipose tissue blood flow. Top panel: Blood flow in human abdominal subcutaneous adipose tissue measured by the ^{133}Xe washout technique in the basal state as well as during intravenous insulin (left panel) or epinephrine (right panel) infusion. Bottom panels: Blood flow in rat intra-abdominal and subcutaneous adipose tissue measured by the microsphere technique in the basal state as well as during intravenous insulin (left panels) or epinephrine (right panels) infusion. Values are means ± SE, n = 4-15. * $P < 0.05$ vs. sedentary group. ¤ $P < 0.1$ vs. sedentary group. # Significant change with time. $ $P < 0.05$ vs. retroperitoneal, parametrial and subcutaneous adipose tissue. £ $P < 0.05$ vs. retroperitoneal and subcutaneous adipose tissue.

in ATBF in sedentary but no change in ATBF in trained subjects (172).

In contrast to the mentioned studies, in both trained and sedentary female rats we found a decrease in ATBF estimated by the microsphere technique during a hyperinsulinemic, euglycemic clamp (VII) (Figure 5). The reason for the different effects of insulin on ATBF in our human (VIII) and rat studies (VII) is not clear. Obviously, insulin could have different effects on ATBF in different species. In fact, in response to a carbohydrate-rich meal ATBF has been shown to increase in humans (361) and to decrease in rats (402). Also the anesthesia could have influenced ATBF in the rats as halothane anesthesia has been found to decrease cardiac output and blood flow in skeletal muscle and skin (179, 274). ATBF estimated by the microdialysis outflow-inflow ratio technique did not change during a hyperinsulinemic, euglycemic clamp in male rats anesthetized by pentobarbital (65). In contrast, ATBF measured by the ^{133}Xe washout technique decreased during combined insulin and glucose infusion in female rats, which were anesthetized by pentobarbital too (254). The difference between the two last mentioned studies probably reflects that the ^{133}Xe washout technique is more sensitive than the microdialysis technique but may also reflect that sex is of importance for ATBF responses.

In conclusion, insulin does not change adipose tissue blood flow in either trained or sedentary humans but decreases adipose tissue blood flow in anesthetized trained and sedentary rats.

c) Effect of epinephrine

Physiological concentrations of epinephrine increase ATBF in humans (IV) (131, 176, 185, 340, 369) and a dose-dependency exists at lower concentrations of epinephrine (0.5-2 nM) (131, 176, 185). We did not find a dose-dependency of epinephrine at high physiological concentrations (3-6 nM) on abdominal subcutaneous ATBF (369), and this might be due to a ceiling effect.

We found an increase in abdominal subcutaneous ATBF during an intravenous epinephrine infusion in both trained and sedentary male subjects (IV) (Figure 5). During the epinephrine infusion, ATBF was higher in endurance-trained compared with sedentary male subjects (IV). In contrast to this, Horowitz et al. found no training-induced increase in epinephrine-stimulated ATBF in male subjects (185). Moreover, Stich et al. found no effect of training on locally β-stimulated ATBF in obese males (377). As in the basal state, the difference might be due to the lower amount of abdominal subcutaneous adipose tissue in trained than in sedentary subjects in our study (IV) compared with the similar amounts of adipose tissue before and after training in the other studies (185, 377).

Epinephrine infusion did not change ATBF in either trained or sedentary anesthetized rats (IX) and, accordingly, the ATBF during epinephrine infusion was higher in trained compared with sedentary rats as in the basal state (Figure 5). In anesthetized dogs, we most often found an epinephrine-induced decrease in ATBF (VI). Species differences with respect to the influence of epinephrine on ATBF do exist as epinephrine previously has been found to increase ATBF in humans and to decrease ATBF in dogs (177). This was explained by different subtypes of β-adrenergic receptors being present in human and dog adipose tissue vasculature (177). Rats have been reported to have more β_3- and less α_2-receptors compared with humans (229, 230), but that would be expected to increase rather than decrease epinephrine-induced ATBF in rats compared with humans. Again, the anesthesia of the rats could have influenced ATBF (179, 274). Also sex-differences could be present with respect to the influence of epinephrine on ATBF as sex has been found to influence the epinephrine-induced increase in adipose tissue lipolysis (122) and ATBF has been suggested to increase in response to an increase in adipose tissue lipolysis (289).

In conclusion, epinephrine increases adipose tissue blood flow in both trained and sedentary humans but does not change adipose tissue blood flow in trained and sedentary rats. During epinephrine infusion, blood flow per gram of adipose tissue is higher or the same in trained compared with sedentary humans and higher in trained compared with sedentary rats.

5. Lipolysis

a) Basal

We found no influence of training on basal lipolysis expressed per gram of abdominal subcutaneous adipose tissue in male subjects (IV) (Figure 6). Lipolysis was, as discussed previously, calculated from measurements of interstitial and arterial glycerol concentrations and ATBF. The small number of subjects in each group (n=6) made the risk of a type II statistical error substantial. The power for detection of a 50% difference in basal lipolysis was only 55%. In our rat study, we did not calculate adipose tissue lipolysis but estimated lipolysis from the interstitial-arterial glycerol concentration difference and ATBF (IX). The mean adipose tissue interstitial-arterial glycerol concentration difference did not differ between trained and sedentary rats, but as previously mentioned, mean ATBF expressed per gram of tissue was several fold higher in trained compared with sedentary rats (IX). This probably means that basal lipolysis was higher in adipose tissue of trained compared with sedentary rats as the blood removed glycerol faster from the interstitial space in the trained than in the sedentary rats.

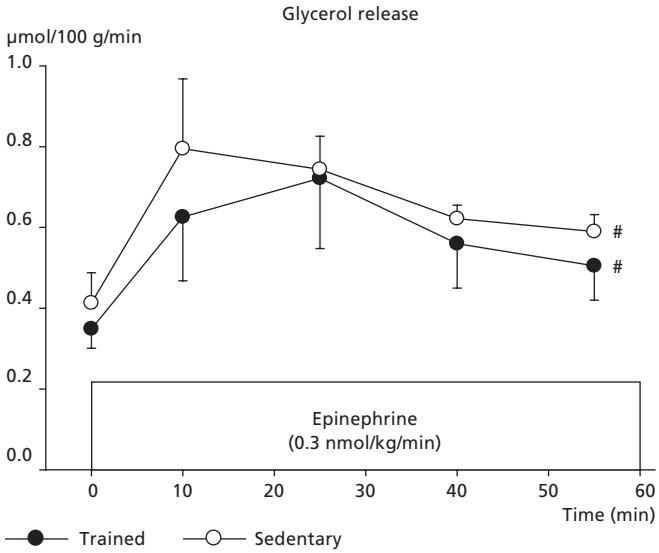

Figure 6. Influence of physical training on glycerol release from human abdominal subcutaneous adipose tissue in the basal state as well as during intravenous epinephrine infusion. Glycerol release was calculated from measurements of interstitial and arterial glycerol concentrations and adipose tissue blood flow. Values are means ± SE, n = 6. # Significant change with time.

Three recent microdialysis studies support the conclusion that training does not influence basal lipolysis expressed per gram of adipose tissue in humans. In lean women, 12 weeks of training influenced neither abdominal nor femoral subcutaneous adipose tissue lipolysis (186). Moreover, in obese male subjects (377) and in old female subjects (234), 12 weeks of training did not influence abdominal subcutaneous adipose tissue lipolysis. Further support for the notion that training does not influence basal adipose tissue lipolysis comes from the fact that also the plasma glycerol concentration, which often has been taken as an indicator of whole body adipose tissue lipolysis, did not differ significantly between trained and sedentary individuals in our (IV, VIII, IX) and in many other studies (93-95, 132, 133, 188, 221, 239, 360, 377). The plasma glycerol concentration, however, reflects both the lipolytic activity per gram of adipose tissue and the amount of adipose tissue in the body. As mentioned previously, adipose tissue mass is often reduced by training, and, accordingly, one would expect a lower plasma glycerol concentration in trained compared with sedentary subjects when adipose tissue lipolysis per gram of adipose tissue does not differ between groups. Site differences in the adipose tissue lipolysis response to training could explain the discrepancy. Moreover, the plasma glycerol concentration reflects both appearance in and disappearance from the plasma of glycerol and is as such only a reflection of whole body lipolysis.

Rate of appearance and disappearance of various substances in plasma can be estimated by isotope turnover techniques (222), and rate of appearance of glycerol or FFA in plasma has been used to estimate whole body lipolysis in trained and sedentary subjects. Results are conflicting showing both a higher (59, 219, 310, 329), the same (67, 132, 172, 185, 186, 221, 311, 360) and a lower (58, 133) basal whole body lipolysis in trained compared with sedentary subjects. In the studies showing a higher whole body lipolysis, however, trained subjects were examined less than 24 hours after the last exercise bout, while sedentary subjects were examined after a day when no or only little exercise was performed (59, 219, 310, 329). Hence, the increased lipolysis found in trained subjects in some studies could be a consequence of the last bout of exercise (220).

The whole body glycerol appearance rate not only represents HSL-activity in adipose tissue but also HSL-activity in skeletal muscle and LPL-activity in adipose tissue and muscle (204). Moreover, a

discrepancy has been found between rate of appearance of glycerol estimated by isotope turnover technique and net release of glycerol estimated by Fick's principle when calculated across abdominal subcutaneous adipose tissue (227). The whole body FFA appearance rate represents whole body lipolysis minus the local reesterification and oxidation of locally mobilized FFA. Nevertheless, glycerol and FFA turnover methods are valuable techniques adding to the knowledge about adipose tissue lipolysis. In some studies, however, adipose tissue lipolysis has been calculated as whole body glycerol appearance rate minus intramuscular lipolysis, which was calculated as total fat oxidation (estimated by indirect calorimetry) minus rate of disappearance of FFA divided by 3 (because only one glycerol molecule is released per three FFA molecules) (310, 328). This calculation does not take hydrolysis of plasma TG into account and it is erroneously assumed that fat oxidation and FFA disappearance only take place in muscle and that FFA mobilized from intramuscular TG or taken up from plasma are directly oxidized. Accordingly, the calculation gives a very indirect measure of adipose tissue lipolysis and results from such calculations should be interpreted with care.

Training did not change basal in vitro adipose tissue lipolysis expressed per adipocyte or per gram of adipose tissue in most studies published before this thesis was initiated (Table 1). In studies published since then, basal in vitro adipose tissue lipolysis was decreased (gluteal) (394), unchanged (gluteal) (265) or increased (abdominal) (265) when expressed per adipocyte in human adipose tissue and decreased when expressed per gram of lipid (abdominal) (90) (Table 1). Training of rats did not change (epididymal and intra-abdominal) (379, 388) or increased (epididymal) (192) basal in vitro adipose tissue lipolysis expressed per adipocyte.

We found a higher basal in vivo lipolysis in intra-abdominal compared with subcutaneous adipose tissue in rats (IX). This is in accordance with other studies in rats which have shown a higher basal in vitro lipolysis in intra-abdominal compared with subcutaneous adipose tissue (162, 228). This inter-site difference is probably related to the enzyme HSL as the HSL-activity and the HSL protein and mRNA levels were higher in epididymal and retroperitoneal compared with subcutaneous adipocytes (382, 384). However, indicating a species difference most studies in humans found a lower basal in vitro lipolysis in intra-abdominal compared with subcutaneous adipocytes (47, 108, 166, 180, 203, 304, 320).

In conclusion, most data suggest no effect of training on basal adipose tissue lipolysis in humans. In rats, we found a training-induced increase in basal in vivo lipolysis per gram of adipose tissue, which is in accordance with in vitro lipolysis expressed per adipocyte being unchanged or higher in trained compared with sedentary rats. Basal in vivo and in vitro lipolysis is higher in intra-abdominal than in subcutaneous adipose tissue in rats. In vitro data suggest that this relationship is not present in humans.

b) Effect of insulin

Insulin inhibits adipose tissue lipolysis (56, 60, 69, 150, 241) (Figure 7 and Figure 8). We found that insulin decreased the interstitial glycerol concentration in abdominal subcutaneous adipose tissue faster in trained compared with sedentary lean male subjects indicating an increased sensitivity of adipose tissue lipolysis to insulin in trained subjects (VIII). An accelerated decrease in plasma glycerol concentration in response to insulin has also been found in trained compared with sedentary lean male subjects (272). Hickner et al. examined lean trained and lean and obese sedentary women by microdialysis and stable isotope technique during a hyperinsulinemic, euglycemic clamp (172). In abdominal subcutaneous adipose tissue, they found no difference in suppression of dialysate glycerol concentration between groups, but in femoral adipose tissue, the dialysate glycerol concentration was not suppressed to the same degree in obese as in lean trained and sedentary subjects at a low insulin concentration (172). The insulin-induced decrease in rate of appearance of glycerol and plasma glycerol concentration was more

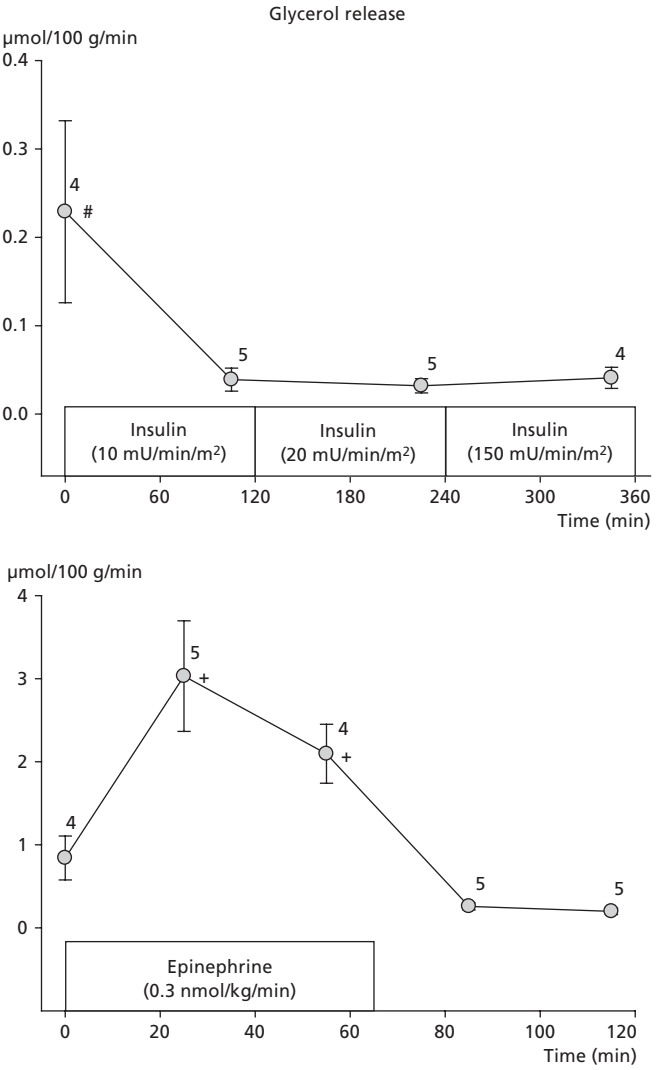

Figure 7. Glycerol release from human abdominal subcutaneous adipose tissue in the basal state as well as during intravenous insulin (top panel) or epinephrine (bottom panel) infusion. Glycerol release was calculated from measurements of abdominal venous and arterial glycerol concentrations and adipose tissue blood flow. Values are means ± SE, n is shown and comprise both trained and sedentary subjects. # $P < 0.05$ vs. other time points. + $P < 0.05$ vs. basal state and time 85 and 115 min.

pronounced in lean trained compared with obese sedentary women, with no difference between lean trained and lean sedentary women (172). This study indicates that the increased insulin-sensitivity with respect to suppression of lipolysis is secondary to the training-induced decrease in fat mass, not to training per se. A study in rats showed that plasma FFA was suppressed 60% in trained compared with only 27% in sedentary rats during a hyperinsulinemic, euglycemic clamp (238). Furthermore, an in vitro study in rats showed a training-induced enhancement of insulin-mediated inhibition of lipolysis in adipocytes (379). However, in vitro studies in obese humans found a blunting (90) or no change (226) in the insulin-mediated inhibition of lipolysis after training.

In conclusion, most evidence suggests that training increases the sensitivity of adipose tissue lipolysis to inhibition by insulin, an effect that may in part be secondary to loss of fat mass.

c) Effect of epinephrine

Epinephrine stimulates adipose tissue lipolysis both in vivo (IV) (339, 340, 369) (Figure 6, 7 and 8) and in vitro (139, 241). We found no effect of training on the epinephrine-stimulated lipolysis estimated by microdialysis technique in abdominal subcutaneous adipose tissue in male subjects (IV) (Figure 6), but as previously discussed, this could be due to a type II error. However, plasma glycerol

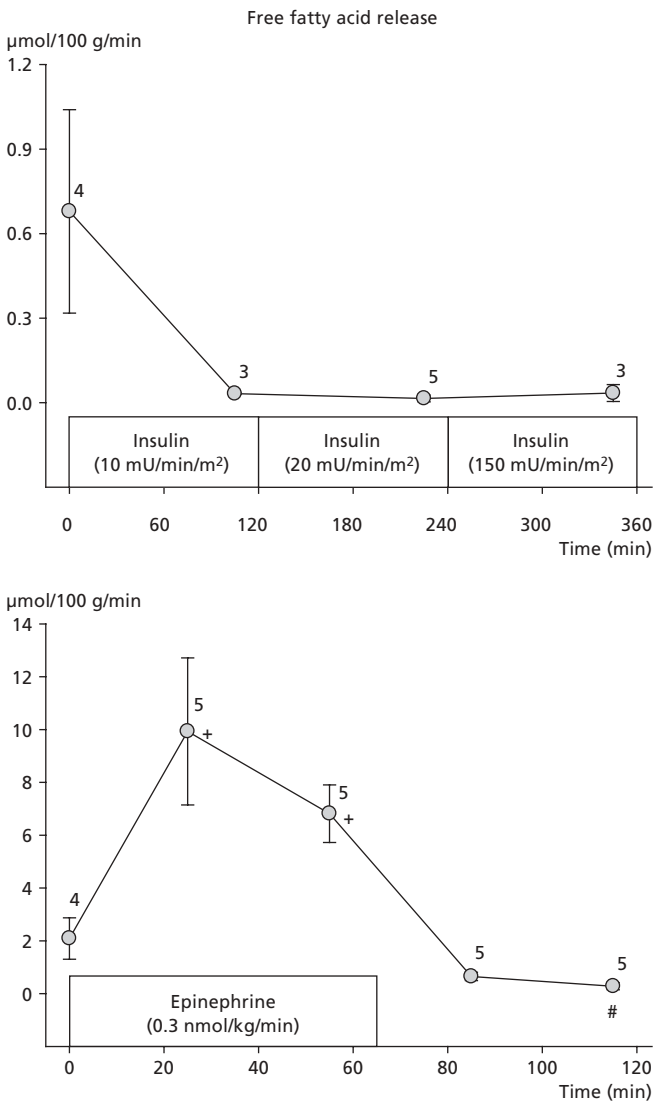

Figure 8. Free fatty acid release from human abdominal subcutaneous adipose tissue in the basal state as well as during intravenous insulin (top panel) or epinephrine (bottom panel) infusion. Free fatty acid release was calculated from measurements of abdominal venous and arterial free fatty acid concentrations and adipose tissue blood flow. Values are means ± SE, n is shown and comprise both trained and sedentary subjects. # $P < 0.05$ vs. other time points. + $P < 0.05$ vs. basal state and time 85 and 115 min.

and FFA concentrations also did not differ between trained and sedentary male subjects during the epinephrine infusion (IV). In contrast, in female rats we found a higher epinephrine-stimulated adipose tissue lipolysis per 100 g estimated by microdialysis technique after training (IX). Interestingly, this was the case in both subcutaneous and intra-abdominal adipose tissues (IX). As in our human study, however, arterial plasma glycerol concentrations did not differ between trained and sedentary rats during the epinephrine infusion (IX). This is probably due to the significant reduction in adipose tissue mass in the trained compared with the sedentary rats (IX).

Stich et al. trained obese men for 3 months and found an increased interstitial glycerol concentration during local microdialysis perfusion with β-agonist in abdominal subcutaneous adipose tissue (377). They furthermore found higher plasma glycerol and FFA concentrations during intravenous β-agonist infusion after compared with before training (377). Supporting our human findings, Horowitz et al. found no difference in whole body rate of appearance of glycerol during graded intravenous epinephrine infusion before and after training of young lean men for 16 weeks (185). Different results between the above-mentioned studies are probably due to differences in design (intravenous versus local administration, epinephrine versus β-agonist, microdialysis versus isotope infusion technique, rat versus human, lean versus obese, males versus females). Too few in vivo studies have been performed to elucidate in which subgroups epinephrine-stimulated lipolysis is changed by training.

In contrast, a tremendous amount of in vitro studies have been performed in which catecholamine-stimulated lipolysis was examined in adipocytes from trained and sedentary rats and humans (Table 1). Most studies showed a training-induced increase in adipose tissue lipolysis at supraphysiological, but not at physiological, catecholamine concentrations. As our human in vivo study was performed at physiological epinephrine concentrations (IV), human in vitro studies performed at physiological catecholamine concentrations and expressed per gram of adipose tissue in fact support the notion that training does not increase epinephrine-stimulated adipose tissue lipolysis in humans (82-84, 90, 325) (Table 1).

The effect of training on whole body lipolysis estimated by tracer infusion technique has also been examined during the "natural" increase in plasma catecholamine concentrations, which is occurring during exercise (67, 132, 133, 186, 219, 221, 263, 310, 360). However, plasma catecholamine concentrations were measured in only some of the studies (67, 186, 310, 360). In studies in which trained and sedentary subjects exercised at the same absolute intensity (and in which plasma catecholamines presumably were lower in trained compared with sedentary subjects (186, 215, 310)), whole body lipolysis was either lower (263, 310) or unchanged (132, 133, 186, 219, 360) in trained compared with sedentary subjects. Also abdominal and femoral subcutaneous adipose tissue lipolysis estimated by microdialysis technique were not changed by 12 weeks of training in women exercising at the same absolute intensity as pre-training (186, 234). In studies in which trained and sedentary subjects exercised at the same relative intensity (and in which plasma catecholamines presumably did not differ much between trained and sedentary subjects (67, 103)), whole body lipolysis was either higher (67, 221) or unchanged (132, 133) in trained compared with sedentary subjects. These findings suggest that training increases or does not change adipose tissue lipolysis at physiological epinephrine concentrations in humans. However, other factors affecting adipose tissue lipolysis than epinephrine, e.g. the insulin concentration, are changed during exercise. Accordingly, exercise studies do not show the pure effect of epinephrine on lipolysis.

In our above-mentioned human study we noted a decrease in adipose tissue lipolysis after the initial epinephrine-induced increase (IV). To further elucidate this phenomenon we performed repeated and graded epinephrine infusions and estimated adipose tissue lipolysis by microdialysis technique in normal subjects (369). We found that adipose tissue lipolysis varied directly with arterial plasma epinephrine concentration but we also found a reduced response upon repeated epinephrine exposure indicating that adipose tissue lipolysis can be desensitized by epinephrine in vivo (369). In vivo desensitization of adipose tissue lipolysis has also been found during local perfusion with catecholamines through a microdialysis catheter (18, 260). During perfusion with β_1-, but not with β_2-agonist, the initial increase in dialysate glycerol concentration was followed by a rapid decrease indicating that β_1-, but not β_2-adrenergic receptors, are desensitized (18). The desensitization might be related to the concentration of the agonist as local microdialysis perfusion with high concentrations of a non-selective β-adrenergic agonist was found to cause a marked and sustained increase in dialysate glycerol concentration in human adipose tissue (154).

The epinephrine concentration, to which the adipocytes are exposed, is the concentration in the interstitial space and as this concentration might differ from the plasma concentration, we estimated the interstitial epinephrine concentration by microdialysis technique (369). In the basal state, the interstitial epinephrine concentration was approximately 60% of the arterial plasma concentra-

tion, but this difference was not statistically significant (369). During epinephrine infusions, interstitial epinephrine concentrations varied in parallel with arterial plasma concentrations, and interstitial epinephrine concentrations were approximately 40% of plasma concentrations (P<0.05) (369). Samra et al. also infused epinephrine intravenously in humans and found an increase in dialysate epinephrine concentration in abdominal subcutaneous adipose tissue during infusion (339). Assuming an epinephrine recovery of 50%, which is the recovery that Samra et al. found for glucose, interstitial epinephrine concentrations were approximately 60% and 15%, respectively, of arterial plasma concentrations in the basal state and during epinephrine infusion (339). Recently, we examined interstitial epinephrine concentrations in clavicular and abdominal subcutaneous adipose tissue in the basal state and during exercise in spinal cord injured and control subjects (371). We found the interstitial epinephrine concentration to be approximately 30% of the arterial plasma concentration in both groups in the basal state as well as during exercise (371). It can be concluded, that the interstitial epinephrine concentration is lower than the arterial plasma concentration, but the magnitude of the difference is not yet well established. Furthermore, the interstitial epinephrine concentration varies in parallel with the arterial epinephrine concentration.

We found a higher epinephrine-stimulated lipolysis estimated by microdialysis technique in intra-abdominal compared with subcutaneous adipose tissue in rats (IX). This is in accordance with previous studies in rats showing higher catecholamine-stimulated dialysate glycerol concentrations in epididymal (65) and mesenteric (191) adipose tissues compared with subcutaneous adipose tissue. Moreover, several in vitro studies in rats have shown that catecholamine-stimulated lipolysis is higher in intra-abdominal compared with subcutaneous adipocytes (161, 162, 228, 384). In humans, the inter-site difference in the in vitro responsiveness to catecholamines varied, but the in vitro sensitivity to catecholamines was consistently higher in intra-abdominal compared with subcutaneous adipocytes (11, 166, 180, 203, 320, 390).

In conclusion, training does not change in vivo or in vitro lipolysis expressed per gram of adipose tissue when stimulated by physiological epinephrine concentrations. However, training increases in vitro lipolysis in adipocytes when stimulated by supraphysiological epinephrine concentrations. In vivo epinephrine-stimulated lipolysis is desensitized by epinephrine in human adipose tissue. Interstitial epinephrine concentrations in human abdominal subcutaneous adipose tissue are lower but vary in parallel with the arterial plasma concentrations. Epinephrine-stimulated lipolysis is higher in intra-abdominal than in subcutaneous adipose tissue.

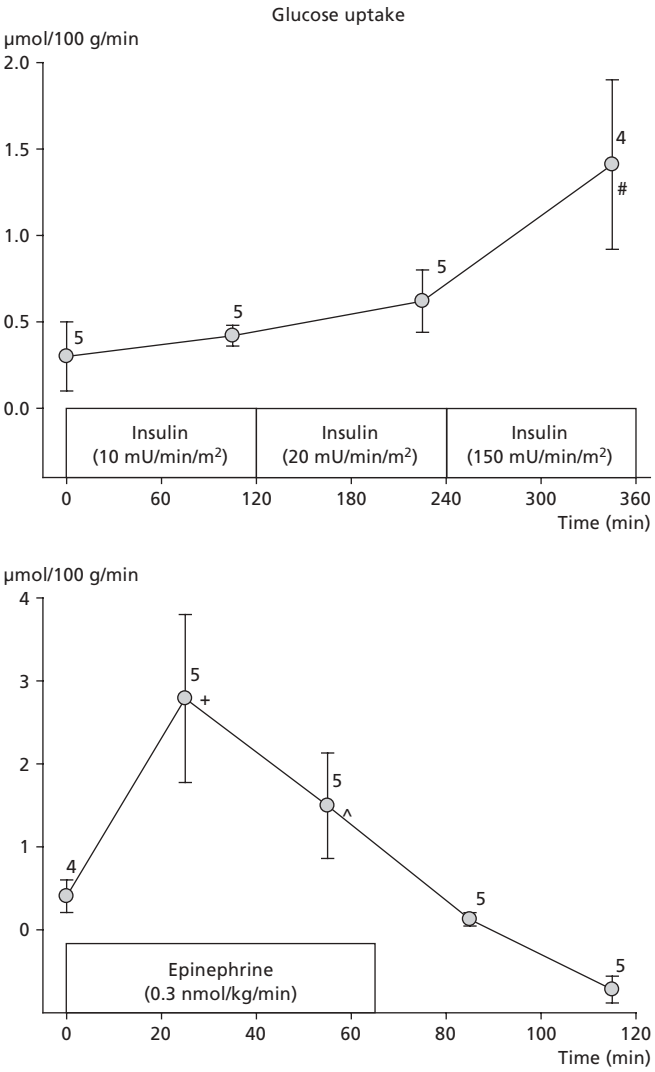

Figure 9. Glucose uptake in human abdominal subcutaneous adipose tissue in the basal state as well as during intravenous insulin (top panel) or epinephrine (bottom panel) infusion. Glucose uptake was calculated from measurements of abdominal venous and arterial glucose concentrations and adipose tissue blood flow. Values are means ± SE, n is shown and comprise both trained and sedentary subjects. # $P < 0.05$ vs. other time points. + $P < 0.05$ vs. basal state and time 85 and 115 min. ^ $P < 0.05$ vs. time 115 min.

6. Glucose uptake

a) Basal

In the overnight fasted state, adipose tissue takes up glucose in vivo (IV, VII, VIII) (70, 369) (Figure 9). However, glucose uptake is low and the arterio-venous glucose difference over abdominal subcutaneous adipose tissue is small (~0.1 mM) (70). That adipose tissue is of minor importance in whole body glucose metabolism is also suggested by Björntorp et al. who demonstrated that adipose tissue takes up only 0.5 and 2% of an intravenous glucose load in lean and obese subjects, respectively (39).

We found no difference in basal glucose uptake per gram of abdominal subcutaneous adipose tissue between trained and sedentary male subjects in vivo (IV). We did not calculate basal glucose uptake in rats, but interstitial glucose concentrations in adipose tissue did not differ significantly between trained and sedentary rats (VII). Interestingly, the interstitial glucose concentration was lower and the ATBF was higher or the same in intra-abdominal compared with subcutaneous adipose tissue in both trained and sedentary rats indicating that basal glucose uptake in vivo is higher in intra-abdominal compared with subcutaneous adipose tissue (VII).

James et al. trained male rats by forced running for 7 weeks and also found no significant effect of training on in vivo basal glucose uptake per gram of epididymal adipose tissue measured by the glucose analogue 2-DG (197). In addition, James et al. estimated in vivo glucose incorporation into the fatty acid and glycerol parts of TG, respectively, in adipose tissue and found lower glucose incorporation into the fatty acid part with no change in glucose incorporation into the glycerol part in trained compared with sedentary rats (197). As discussed previously, training increased basal in vitro 2-DG uptake per adipocyte in fed rats (Table 2). Feeding increases the insulin concentration (68, 126), and, hence, the adipocytes used for the in vitro studies had been insulin-stimulated before removal from the rat, which might partly explain the discrepancy between the mentioned in vivo and in vitro studies.

In conclusion, training does not change basal glucose uptake per gram of adipose tissue in short term fasted humans and rats in vivo, but training increases glucose uptake expressed per adipocyte in fed rats in vitro.

b) Effect of insulin

The arterio-venous glucose difference across human abdominal subcutaneous adipose tissue was found to increase little, but significantly, during a hyperinsulinemic, euglycemic clamp (69). In

human microdialysis studies, the dialysate glucose concentration in subcutaneous adipose tissue was found to decrease little (154, 207) or not at all (257, 258, 331) during a hyperinsulinemic, euglycemic clamp. As most studies find no change in ATBF during a hyperinsulinemic, euglycemic clamp (VIII) (115, 155, 156, 193), the insulin-stimulated increase in glucose uptake in adipose tissue must be small. We found a significant stimulation of glucose uptake in human abdominal subcutaneous adipose tissue only at a supraphysiological insulin concentration during a euglycemic clamp (Figure 9). That insulin stimulation of adipose tissue glucose uptake is modest is indirectly suggested by DeFronzo et al. who estimated that skeletal muscle accounts for 85% of the total insulin-stimulated glucose uptake in humans (92). In rats, in vivo evidence for an insulin-mediated increase in glucose uptake in adipose tissue is more convincing (184, 196, 197, 225).

We found an insulin-stimulated increase in glucose uptake in abdominal subcutaneous adipose tissue in male athletes, but no significant stimulation of glucose uptake by insulin in sedentary males (VIII). Furthermore, we found a higher insulin-stimulated glucose uptake per gram of adipose tissue in trained compared with sedentary rats in both subcutaneous and intra-abdominal adipose tissues, with no significant difference between adipose tissues studied (VII) (Figure 10). Our findings confirm and extend previous in vivo (197) and in vitro (Table 2) findings (see introduction). However, whereas in vitro studies suggest an increased whole-body insulin-stimulated glucose uptake in adipose tissue after training (the glucose uptake was increased by training when expressed per adipocyte, and number of adipocytes usually does not differ between trained and sedentary rats), in vivo studies do not suggest that (the glucose uptake per gram of adipose tissue increased approximately the same percentage as the adipose tissue mass decreased) (VII).

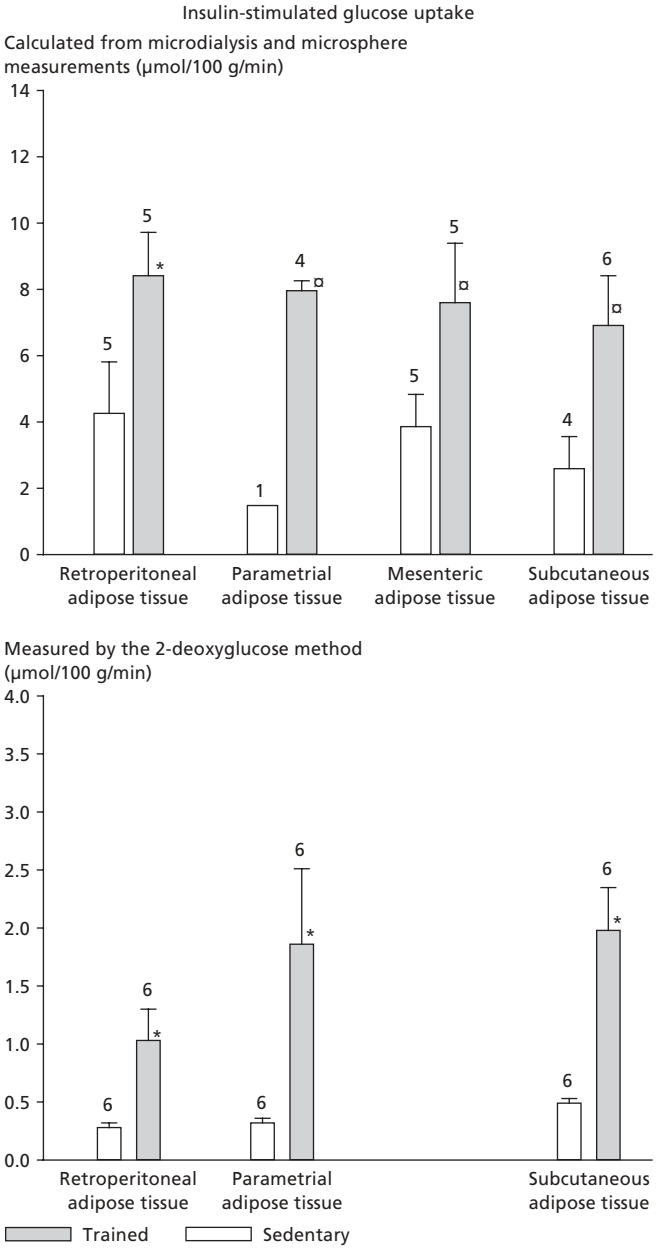

Figure 10. Influence of physical training on in vivo insulin-stimulated glucose uptake in rat intra-abdominal and subcutaneous adipose tissue. Values are means ± SE, n is shown. * $P < 0.05$ vs. sedentary group. ¤ $P < 0.1$ vs. sedentary group.

In conclusion, training increases insulin-stimulated glucose uptake expressed per gram of adipose tissue in vivo and expressed per adipocyte in vitro.

c) Effect of epinephrine

Epinephrine stimulates glucose uptake in adipose tissue in vivo (IV) (Figure 9). However, we found no difference between male athletes and sedentary males in epinephrine-stimulated glucose uptake in abdominal subcutaneous adipose tissue estimated by microdialysis technique (IV).

In conclusion, training does not change epinephrine-stimulated glucose uptake per gram of adipose tissue in vivo.

7. Glucose transport

a) Basal

Controversy exists whether training changes basal glucose transport in adipocytes (see introduction) (Table 2). In male rats, we did not find a difference in basal glucose transport (3-MG technique) expressed per adipocyte between trained and sedentary age-matched or younger control rats (III). However, when normalizing for adipocyte size (and expressing transport per adipocyte surface area or per adipocyte volume), we found a higher basal glucose transport in trained compared with sedentary age- and body weight-matched rats (III). Goodyear et al. measured total glucose metabolism in adipocytes from trained and sedentary age-matched rats, which had either normal or impaired glucose tolerance (147). They claimed that total glucose metabolism reflected glucose transport since at the low glucose concentration, which was used in the assay, the glucose transport was rate limiting for glucose metabolism (147). However, the values for glucose metabolism were less than 10% of the values for glucose transport that we found by the 3-MG method (147) (III). Nevertheless, in accordance with our findings (III), Goodyear et al. found that training increased basal glucose metabolism expressed per surface area in rats with both normal and impaired glucose tolerance (147).

In conclusion, training does not change basal glucose transport per adipocyte, but training increases basal glucose transport when normalized for adipocyte size.

b) Effect of insulin

In accordance with previous findings (see introduction) (Table 2), we found a higher maximally insulin-stimulated glucose transport per adipocyte in trained compared with sedentary age-matched rats (III). Moreover, the insulin-stimulated glucose transport per adipocyte was higher in trained compared with younger rats (III). Also when expressed per adipocyte surface area as well as per adipocyte volume, the insulin-stimulated glucose transport was higher in trained compared with both sedentary age-matched and younger control rats (III) (147) (Figure 11). Interestingly, as little as 4 days of swimming was sufficient to increase the insulin-stimulated 3-MG transport in epididymal adipocytes from rats when measured 18-22 h after the last exercise bout (118).

We studied the mechanism behind the training-induced increase in insulin-stimulated glucose transport in adipocytes (V). We found, that training increased insulin-stimulated 3-MG transport in

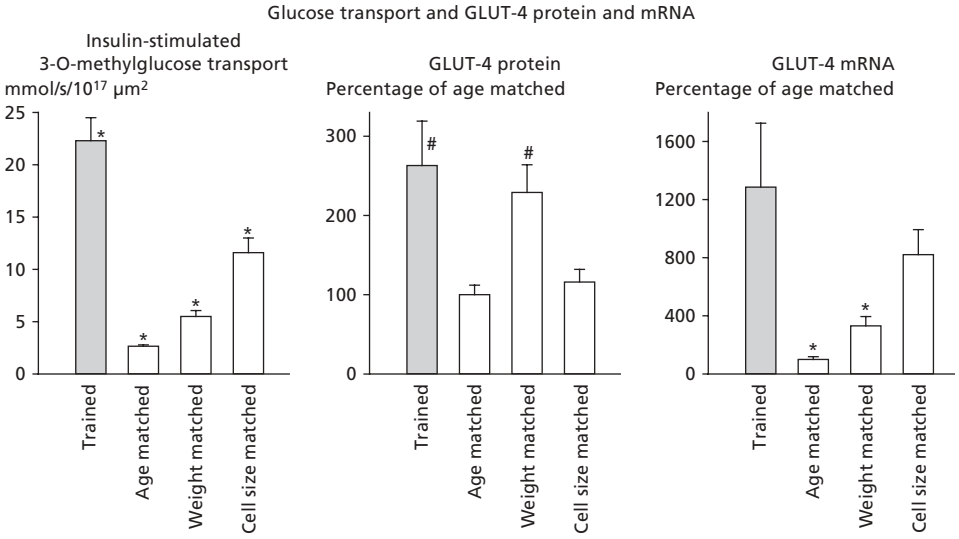

Figure 11. Influence of physical training on insulin-stimulated 3-O-methylglucose transport and amount of GLUT-4 protein and mRNA in rat adipocytes when corrected for adipocyte size. Values are means ± SE, n = 5-11. * $P < 0.05$ vs. all other groups. # $P < 0.05$ vs. age- and cell size-matched control groups.

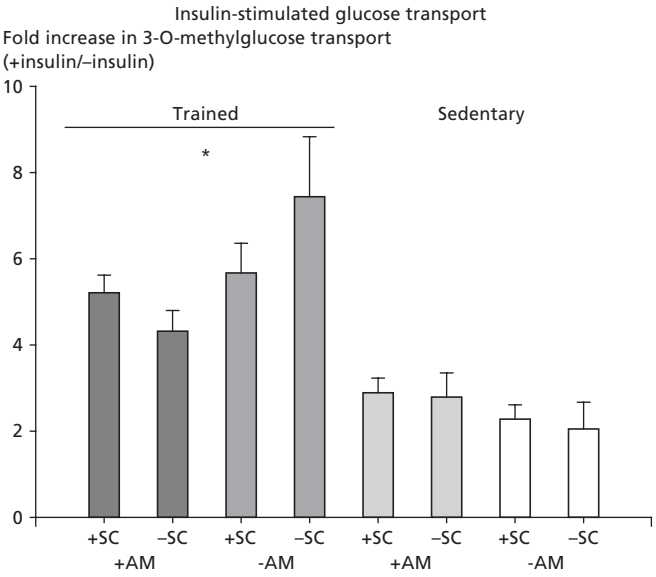

Figure 12. Influence of physical training on the fold increase in 3-O-methylglucose transport above basal values upon maximal insulin stimulation of rat adipocytes. Before training the rats had been either adrenodemedullated (–AM) or sham adrenodemedullated (+AM). Part of the abdominal sympathetic chain had been removed on one side (–SC), and the other side was sham sympathectomized (+SC). Values are means ± SE, n = 4-15. * $P < 0.05$ vs. sedentary group.

epididymal adipocytes, and neither adrenodemedullation nor sympathetic denervation affected the increase indicating that sympathoadrenergic activity is not important for the training-induced increase in insulin-stimulated glucose transport in adipocytes (V) (Figure 12).

In conclusion, insulin-stimulated glucose transport is increased in adipocytes from trained compared with sedentary rats. The sympathoadrenergic system is not important for this training-induced adaptation.

8. Glucose transporter protein and mRNA

We and others found that the number of GLUT-4 per epididymal adipocyte was increased in trained compared with sedentary younger control rats, which had an adipocyte size similar to that of trained rats (III) (174). Furthermore, we found that number of GLUT-4 was increased in trained compared with both sedentary age-matched and younger control rats when normalized for adipocyte size (III) (Figure 11). In contrast, training did not increase the number of GLUT-1 per adipocyte (III) (174) or per adipocyte surface area (III).

Hirshman et al. determined number of GLUT-4 and GLUT-1 separately in plasma membranes and low-density microsomes (174). In plasma membranes they found an increase in basal and insulin-stimulated GLUT-4 protein expressed per adipocyte as well as per adipocyte surface area in trained compared with sedentary younger control rats (174). Compared with sedentary age-matched rats, GLUT-4 per adipocyte surface area was increased in trained rats (174). In low-density microsomes, basal GLUT-4 per adipocyte and per surface area was increased in trained compared with sedentary age-matched rats, but not compared with sedentary younger control rats (174). Training changed GLUT-1 neither in plasma membrane nor in low-density microsomes (174). During in vitro insulin stimulation, 4-day swim trained rats had an increased number of cell surface GLUT-4 per adipocyte compared with sedentary rats, whereas GLUT-1 did not differ between groups (118).

We measured the amount of mRNA coding for GLUT-4 and GLUT-1 in epididymal adipocytes from trained and sedentary male rats and found a large increase in GLUT-4 mRNA in trained compared with sedentary age-matched rats both when expressed per adipocyte and after correction for adipocyte size (III) (Figure 11). On the contrary, GLUT-1 mRNA was not increased by training (III). Later, an increase in both GLUT-4 protein and mRNA in adipose tissue has been found in mice trained for 3 weeks (189). In another study, rats trained by running for seven days had mesenteric and subcutaneous adipose tissue removed immediately after the last exercise bout (357). GLUT-4 mRNA expressed per amount of total RNA was decreased in mesenteric adipose tissue of trained compared with sedentary rats, but GLUT-4 mRNA was not changed in subcutaneous adipose tissue (357). Most likely the last bout of exercise influenced the results of the latter study. Also, studies are difficult to compare, as it is not known if training changed the amount of total RNA (357).

In conclusion, training increases the number of GLUT-4 in rat adipocytes. In the basal state, number of GLUT-4 is increased by training in the membrane depot in the interior of the adipocyte resulting in an increased insulin-mediated translocation of GLUT-4 to the plasma membrane after training. Training does not increase number of GLUT-1. Training increases GLUT-4 mRNA, but not GLUT-1 mRNA, in rat adipocytes.

9. Lactate release

a) Basal

In the overnight fasted state adipose tissue releases lactate in vivo (IV, VIII) (69, 198) (Figure 13). A study by Yang et al. indicated no difference in lactate production in inguinal adipose tissue between trained and sedentary rats as they found no difference in dialysate lactate concentrations between groups, but as neither arterial lactate

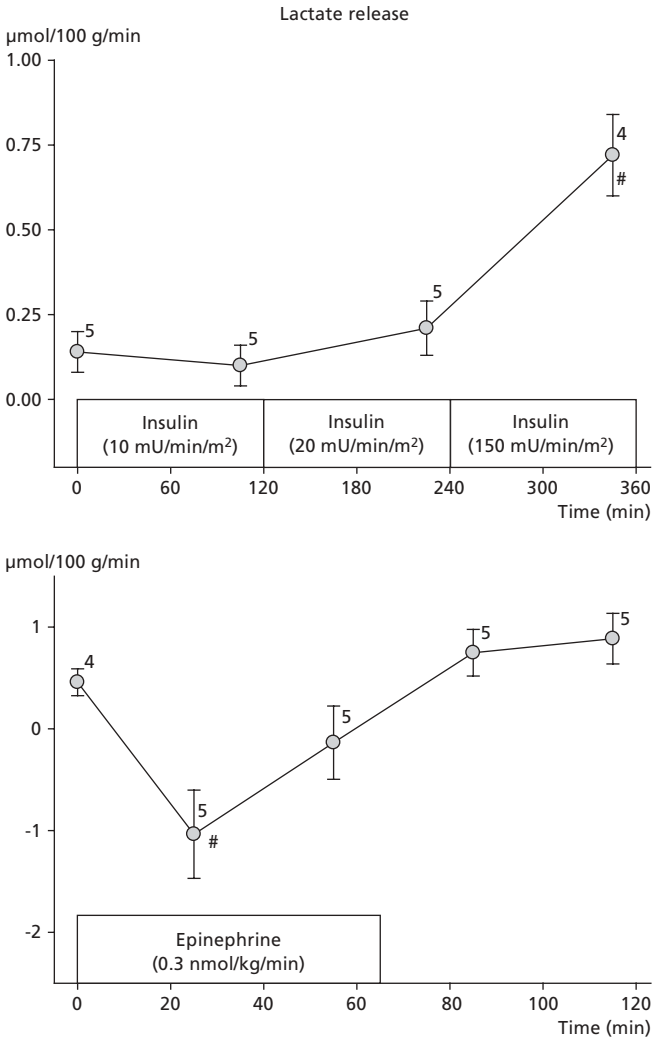

Figure 13. Lactate release from human abdominal subcutaneous adipose tissue in the basal state as well as during intravenous insulin (top panel) or epinephrine (bottom panel) infusion. Lactate release was calculated from measurements of abdominal venous and arterial lactate concentrations and adipose tissue blood flow. Values are means ± SE, n is shown and comprise both trained and sedentary subjects. # $P < 0.05$ vs. other time points.

concentrations nor ATBF was studied, conclusions are difficult to draw (409). We estimated lactate release from adipose tissue using microdialysis technique, too, and found no difference in basal lactate release per gram of adipose tissue in athletes compared with sedentary male subjects (IV). In rats, we did not calculate lactate release from adipose tissue, but basal adipose tissue interstitial lactate concentrations did not differ between trained and sedentary rats (VII). Also, in the basal state interstitial lactate concentrations did not differ between intra-abdominal and subcutaneous adipose tissues (VII).

In conclusion, in line with the effect of training on basal in vivo glucose uptake, training does not change basal lactate release per gram of adipose tissue in vivo.

b) Effect of insulin

We found a significant stimulation of lactate release from human abdominal subcutaneous adipose tissue only at a supraphysiological insulin concentration during euglycemic clamping (Figure 13). Moreover, insulin increased the interstitial-arterial lactate concentration difference similarly in abdominal subcutaneous adipose tissue of trained and sedentary subjects (VIII). In humans, ATBF did not differ between trained and sedentary subjects during insulin infusion, and, accordingly, the stimulation of lactate release by insulin probably did not differ between groups (VIII). This is somewhat surprising as insulin stimulated adipose tissue glucose uptake more in trained than in sedentary subjects (VIII), and the finding might be due to a type II error. Neither we (VII) nor Yang et al. (409) found a difference between trained and sedentary rats in adipose tissue microdialysate lactate concentration during insulin stimulation.

In conclusion, it is at present not clear if training influences insulin-stimulated lactate release from adipose tissue.

c) Effect of epinephrine

Epinephrine stimulates lactate release from adipose tissue along with glucose uptake according to microdialysis (IV) as well as in vitro data (85). However, according to data obtained by catheterizing a vein draining the subcutaneous adipose tissue of the anterior abdominal wall, epinephrine decreases lactate release (Figure 13). The reason for this discrepancy is not clear. In line with the effect of training on glucose uptake, we found no difference between trained and sedentary male subjects in lactate release per gram of adipose tissue in vivo (IV).

B. TRAINING-INDUCED ADAPTATION IN SECRETION OF INSULIN AND EPINEPHRINE

1. Insulin

We found that training decreases the glucose-stimulated insulin secretion from pancreatic islets (V) (Figure 14), which is a confirmation of previous findings (136, 413). Training also decreases glucose-stimulated insulin secretion in single pancreatic β-cells (116), and this in vitro finding is reflected in a lower plasma insulin concentration in trained compared with sedentary rats during an in vivo hyperglycemic clamp (116). In humans, insulin secretion (as reflected by both plasma C-peptide and insulin concentrations) has been shown to be lower in trained compared with sedentary subjects during hyperglycemic clamping (273) as well as after identical oral glucose loads (94). Insulin is secreted in bursts during an oral glucose load, and trained subjects have been shown to secrete less insulin per burst, but to have the same number of bursts compared with sedentary subjects (111).

The mechanism responsible for the development of the training-induced decrease in glucose-stimulated insulin secretion is not known. The sympathoadrenergic system is activated during exercise (135), and this system could be of importance for the training-induced adaptations. It has previously been found, that plasma concentrations of insulin are higher in adrenodemedullated compared

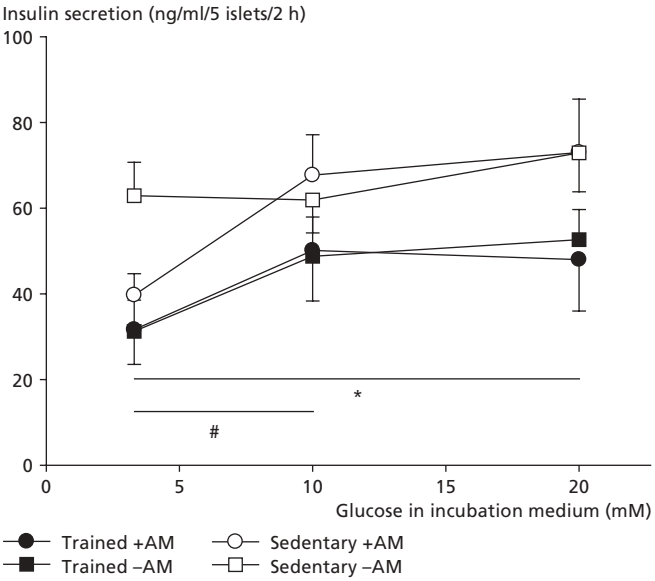

Figure 14. Influence of physical training on glucose-stimulated insulin secretion of pancreatic islets from rats, which had been either adrenodemedullated (–AM) or sham adrenodemedullated (+AM) prior to training. Values are means ± SE, n = 7-9. * $P < 0.05$ vs. sedentary group. # Significant influence of increasing glucose concentrations.

with control rats during acute exercise (321). However, prior adrenodemedullation had no effect on glucose-stimulated insulin secretion from pancreatic islets in either trained or sedentary rats (V) (Figure 14). Moreover, Jean et al. found no effect of prior adrenodemedullation on basal plasma insulin or pancreatic insulin levels in trained or sedentary rats (200).

Insulin secretion is considered to be intimately coupled to glucose metabolism in pancreatic β-cells (259). Hence, the molecular mechanism behind the training-induced decrease in insulin secretion from pancreatic islets could be a decrease in glucose metabolism in pancreatic islets. However, surprisingly we found a training-induced increase in glucose utilization and oxidation in pancreatic islets (V). Prior adrenodemedullation did not influence the glucose metabolism in either trained or sedentary rats (V). Lack of parallelism between changes in insulin secretion and glucose metabolism in pancreatic islets after training has also been found previously as both Zawalich et al. and Villela et al. found a lower glucose-stimulated insulin secretion despite no change in glucose utilization in pancreatic islets of trained compared with sedentary rats (391, 413).

In conclusion, training decreases the glucose-stimulated insulin secretion and may increase glucose-stimulated glucose metabolism in pancreatic islets in vitro. Adrenomedullary hormones are not important for the training-induced changes in insulin secretion and glucose metabolism in pancreatic islets.

2. Epinephrine

Confirming previous findings, we found an increase in both adrenal gland weight (I) (160, 206, 240, 247, 302, 303, 347, 367) and catecholamine content in trained compared with sedentary rats (I) (206, 302, 303, 345). Furthermore, we found that the adrenal medulla volume was increased in trained compared with sedentary age-matched rats (I) (Figure 15), and Schmidt et al. subsequently confirmed this in both young and old rats (345).

We also examined if the training-induced increase in adrenal medulla volume was reflected by a training-induced increase in epinephrine secretion capacity in trained compared with sedentary rats (I). Surprisingly, we found that trained rats had a markedly lower epinephrine response to hypoglycemia compared with sedentary rats (I). The reason for this inconsistency is unknown, but as the blood glucose concentration of the trained rats was markedly lower in the morning on exercise days as well as in the afternoon on non-exercise days compared with the concentration in the sedentary rats (I), the trained rats might have adapted to these frequent hypoglycemic episodes with a reduced nervous stimulation of the adrenal medulla upon hypoglycemic stimulation.

In humans, findings concerning the influence of training on epinephrine response to insulin-induced hypoglycemia are conflicting as both an increased (216) and a decreased (389) response have been found. Interestingly, both in our rat study (I) and in the study by Tremblay et al. (389), a higher insulin dose had to be infused in sedentary compared with trained individuals to achieve a similar level of hypoglycemia, whereas in the study by Kjær et al. (216), the same insulin dose was infused in the two groups. This may reflect that the time elapsed after the last exercise bout in trained individuals could have influenced results, as trained individuals did not train on the 2 days preceding the experiment in the study by Kjær et al. (216) and only abstained from exercise for 1 day in the other experiments (I) (389).

In conclusion, training increases adrenal gland weight and catecholamine content and adrenal medulla volume in rats. Human studies have indicated an increased epinephrine secretion capacity in trained individuals although findings are not consistent. Rat studies suggest a decreased hypoglycemia-induced epinephrine secretion after training.

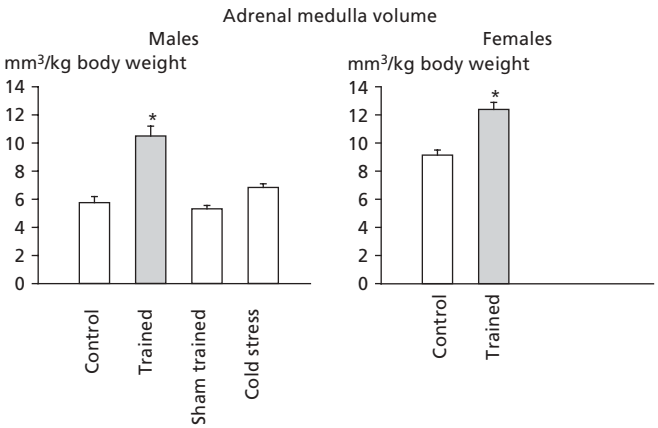

Figure 15. Influence of physical training, sham swim training and cold stress on adrenal medulla volume in rats. Values are means ± SE, n = 7-14. * $P < 0.05$ vs. other groups of same sex.

V. CONCLUSIONS FROM OWN STUDIES

1. The microdialysis technique can be used to estimate adipose tissue venous concentrations of glycerol, glucose and lactate. Thus, the technique can be used to study adipose tissue metabolism in vivo, which is useful as most adipose tissue depots do not have a vein, which readily can be catheterized.
2. Training is capable of reducing adipose tissue mass in both humans and rats. The sympathoadrenergic system is not important for this training-induced adaptation. Brown adipose tissue mass is not changed by swim training in male rats and is increased by training in female rats. Training decreases body weight gain in male but not in female rats.
3. Training decreases adipocyte size and the sympathoadrenergic system is not important for this training-induced adaptation. Training does not influence adipocyte number.
4. Training increases the mitochondrial enzyme activity markedly in rat white adipose tissue both when expressed per gram of adipose tissue and per mg protein in adipose tissue homogenate. Training does not change the mitochondrial enzyme activity in rat brown adipose tissue, but cold-stress increases mitochondrial enzyme activity in total interscapular brown adipose tissue.
5. Basal blood flow per gram of adipose tissue is higher in trained compared with sedentary humans and rats. Blood flow is higher in mesenteric compared with other adipose tissues in both trained and sedentary rats. Insulin does not change adipose tissue blood flow in either trained or sedentary humans and decreases adipose tissue blood flow in trained and sedentary rats. Training increases epinephrine-stimulated blood flow per gram of adipose tissue in humans and rats.
6. In humans, basal adipose tissue lipolysis in vivo is not influenced by training, but training increases basal lipolysis per gram of adipose tissue in rats in vivo. The sensitivity of abdominal subcutaneous adipose tissue anti-lipolysis to insulin is increased in trained compared with sedentary male subjects in vivo. There is no difference between trained and sedentary male subjects in epinephrine-stimulated lipolysis in vivo expressed per gram of abdominal subcutaneous adipose tissue, but training increases lipolysis in female rats. Basal and epinephrine-stimulated in vivo lipolysis is higher in intra-abdominal than in subcutaneous adipose tissue in rats.
7. Training does not change basal adipose tissue glucose uptake per gram of adipose tissue in vivo. Training increases insulin-stimulated glucose uptake in humans and rats, but training does not change epinephrine-stimulated glucose uptake per gram of human adipose tissue in vivo.
8. Basal glucose transport is increased in trained compared with sedentary, age-matched rats when normalized for adipocyte size. Insulin-stimulated glucose transport is increased in adipocytes from trained compared with sedentary rats, and the

sympathoadrenergic system is not important for this adaptation. Training increases the number of GLUT-4 in rat adipocytes. Training does not increase number of GLUT-1. Training increases GLUT-4 mRNA, but not GLUT-1 mRNA, in rat adipocytes.

9. Training does not change basal or epinephrine-stimulated adipose tissue lactate release per gram of adipose tissue in vivo. The influence of training on insulin-mediated lactate release is at present not clear.
10. Training decreases the glucose-stimulated insulin secretion and increases the glucose-stimulated glucose metabolism in rat pancreatic islets in vitro and adrenomedullary hormones do not mediate these adaptations.
11. Training increases adrenal gland weight and catecholamine content and adrenal medulla volume in rats. Nevertheless, training decreases the epinephrine response to hypoglycemia in rats.

VI. CONCLUDING REMARKS AND FUTURE PERSPECTIVES

A. EXTRAPOLATION FROM ADIPOSE TISSUE TO WHOLE BODY

My conclusions concerning the influence of physical training on adipose tissue metabolism in vivo are based on a "per gram of adipose tissue" comparison. Accordingly, an estimate of whole body metabolism can be obtained by multiplying with adipose tissue mass. However, in rat studies we did not measure whole body adipose tissue mass, and in human studies we either used an imprecise method for estimating adipose tissue mass (IV) or we did not calculate adipose tissue metabolism directly (VIII). Nevertheless, based on the unchanged (humans: IV) or increased (rats: IX) basal and epinephrine-stimulated lipolysis per gram of adipose tissue and the generally accepted decrease in adipose tissue mass with training, it can be estimated, that in vivo whole body basal and epinephrine-stimulated adipose tissue lipolysis are either decreased or unchanged with training. Indicating an unchanged whole body adipose tissue lipolysis with training, basal and epinephrine-stimulated arterial plasma glycerol concentrations did not differ between trained and sedentary individuals (IV, VIII, IX). Basal whole body rate of appearance of glycerol or FFA has been found to be higher (59, 219, 310, 329), the same (67, 132, 172, 185, 186, 221, 311, 360) or lower (58, 133) in trained compared with sedentary subjects. Training did not change epinephrine-stimulated whole body rate of appearance of glycerol (185). In conclusion, most evidence suggests that training does not change basal or epinephrine-stimulated whole body lipolysis.

Basal glucose uptake and lactate release per gram of adipose tissue are not changed with training (IV, VII). As the adipose tissue mass probably was decreased in the trained individuals, the in vivo whole body basal adipose tissue glucose uptake and lactate release are decreased with training. Insulin-stimulated glucose uptake per gram of adipose tissue is increased with training (VII, VIII), but the increase is probably outweighed by the decrease in adipose tissue mass and, accordingly, in vivo whole body insulin-stimulated adipose tissue glucose uptake is probably unchanged with training.

B. EFFECTS OF REDUCED ADIPOSITY VERSUS DIRECT EFFECTS OF TRAINING

A question which cannot be answered from the present studies is, if differences in adipose tissue metabolism between trained and sedentary individuals are due to the training per se or to the training-induced decrease in adipose tissue mass. In favor of an effect of training per se is a study that showed that basal and insulin-stimulated in vitro 2-DG uptake in rat adipocytes remained elevated for 7 days after stop of training despite an increase in adipocyte size to the size of adipocytes in age-matched control rats during this time (79). Another study in favor of an effect of training per se showed a higher epinephrine-stimulated in vitro lipolysis in intensively compared with lightly trained rats despite no difference in adipocyte size between groups (27). However, Mauriege et al. found that the increase in the in vitro epinephrine-stimulated lipolysis after training could be ascribed to the training-induced decrease in adipocyte size as they found a negative correlation between adipocyte size and epinephrine-stimulated lipolysis which was not influenced by training (265). Also the decrease in the in vitro adipose tissue LPL activity with training, which has been found in some studies, has been ascribed to the lower fat mass in trained compared with sedentary subjects (38, 265). A study design which could help elucidate whether changes in adipose tissue metabolism after training are due to training per se or to the training-induced reduction in adiposity is one in which adipose tissue metabolism is compared during 4 conditions: 1) training with fat loss, 2) training with no fat loss due to a compensating energy intake, 3) no training but fat loss due to an energy-reduced diet, 4) no training and no fat loss (control group).

C. FUTURE STUDIES

Several clinical, sports-related and methodological studies would be interesting to perform in the future. Obesity is an increasing problem in the affluent part of the world and only few studies have examined the influence of training on adipose tissue metabolism in obese subjects. One interesting study found that the addition of a training program to a hypocaloric diet prevented the decrease in basal and epinephrine-stimulated lipolysis in vitro in overweight and obese women (284). Another study found indications of an enhanced β-adrenergic stimulation of lipolysis after training of obese males (377). It would be interesting to investigate if training influences in vivo adipose tissue metabolism differently in lean and obese subjects. The regional distribution of adipose tissue is an important predictor of obesity-associated morbidities, and although site-related differences in adipose tissue metabolism are well-established, only few studies have examined the influence of training on metabolism simultaneously in more than one adipose tissue depot (VII, IX) (172, 186, 265, 284). Especially, there is a lack of studies examining the influence of training on intra-abdominal adipose tissue metabolism in humans. This tissue has been proposed to be particularly involved in the development of the metabolic syndrome. Accordingly, studies on the effect of training on intra-abdominal adipose tissue metabolism are warranted in healthy subjects as well as in patients suffering from obesity, type II diabetes and hyperlipemia. Such studies should be possible to perform by simultaneously applying isotope turnover and hepatic venous catheterization techniques (7, 396, 397).

The effect of acute exercise on adipose tissue metabolism was not evaluated in this thesis. The influence of acute exercise on whole body lipolysis has been extensively studied in humans (see the section on lipolysis), and a significant number of studies also examined the influence of acute exercise on metabolism in one or two adipose tissue depots in humans in vivo (7, 19, 49, 55, 167, 178, 186, 234, 260, 280, 316, 374-376, 396, 397). However, only one of the latter studies was performed in both trained and sedentary subjects (186). Hence, it would be interesting to further elucidate the influence of training on human adipose tissue metabolism in vivo during and between acute exercise sessions and the effect of e.g. adipose tissue depot, gender and previous meals.

The microdialysis technique has previously mostly been used for determination of the interstitial concentrations of small, water-soluble molecules. However, lately also the interstitial concentrations of larger molecules have been estimated by microdialysis (233). Recently, the interstitial concentrations of FFA, leptin, tumor necrosis factor-α and interleukin-6 have been estimated by open-flow microperfusion technique in human adipose tissue (294). Using microdialysis, open-flow microperfusion or abdominal vein catheterization technique, it would be interesting to estimate the in vivo release from human adipose tissue of some of these newly discovered endocrine/paracrine substances and the influence of physical training and acute exercise on this release.

VII. SUMMARY

The aim of the present thesis was to elucidate the influence of endurance training on adipose tissue metabolism, with special focus on the effects of insulin and epinephrine. Especially, I wanted to reveal the influence of training on adipose tissue metabolism in vivo. Studies comprised experiments on rats, dogs and humans and the microdialysis technique was used in many of the experiments. In an evaluation of the microdialysis technique, we found that the technique can be used to estimate adipose tissue venous concentrations of glycerol, glucose and lactate. Hence, the technique can be used to study adipose tissue metabolism in vivo, which is useful as most adipose tissue depots do not have a vein, which readily can be catheterized.

Training decreased adipose tissue mass and adipocyte size, and the sympathoadrenergic system was not important for these adaptations. Training did not influence adipocyte number. Training markedly increased mitochondrial enzyme activity in white adipose tissue of rats, but did not influence the activity in rat brown adipose tissue. Basal and epinephrine-stimulated blood flow per gram of white adipose tissue were markedly higher in trained compared with sedentary individuals. Insulin did not change adipose tissue blood flow in humans. In rats, both blood flow and lipolysis were higher in intra-abdominal than in subcutaneous adipose tissue.

In vivo basal and epinephrine-stimulated lipolysis per gram of adipose tissue did not differ between trained and sedentary humans, but lipolysis was higher in trained compared with sedentary rats. The sensitivity of adipose tissue anti-lipolysis to insulin was increased in trained compared with sedentary humans in vivo. Training did not change basal or epinephrine-stimulated glucose uptake in adipose tissue in vivo. However, in vivo insulin-stimulated glucose uptake in adipose tissue and in vitro insulin-stimulated glucose transport in rat adipocytes were increased by training. This might be due to the training-induced increase in GLUT-4 mRNA and ensuing GLUT-4 glucose transporter number in adipose tissue. Training did not change number of GLUT-1 glucose transporters or amount of GLUT-1 mRNA in adipose tissue. The sympathoadrenergic system was not important for the training-induced increase in insulin-stimulated glucose transport in rat adipocytes. Training did not change basal or epinephrine-stimulated lactate release per gram of adipose tissue in vivo.

Training decreased the glucose-stimulated insulin secretion and increased the glucose-stimulated glucose metabolism in pancreatic islets in vitro, and adrenomedullary hormones were not important for these adaptations. Training increased adrenal gland weight and catecholamine content and adrenal medulla volume but reduced hypoglycemia-induced epinephrine secretion in rats.

In conclusion, endurance training is capable of decreasing adipose tissue mass and increasing adipose tissue blood flow and oxidative capacity. Furthermore, training changes several aspects of insulin- and epinephrine-stimulated adipose tissue metabolism in vitro as well as in vivo. The training-induced decrease in adipose tissue mass and associated metabolic adaptations might be beneficial from a health perspective.

THE PRESENT PUBLICATION IS BASED ON THE FOLLOWING PUBLICATIONS:

I. Stallknecht, B., M. Kjær, K.J. Mikines, L. Maroun, T. Ploug, T. Ohkuwa, J. Vinten, and H. Galbo. Diminished epinephrine response to hypoglycemia despite enlarged adrenal medulla in trained rats. Am. J. Physiol. 259: R998-R1003, 1990.

II. Stallknecht, B., J. Vinten, T. Ploug, and H. Galbo. Increased activities of mitochondrial enzymes in white adipose tissue in trained rats. Am. J. Physiol. 261: E410-E414, 1991.

III. Stallknecht, B., P.H. Andersen, J. Vinten, L.L. Bendtsen, J. Sibbersen, O. Pedersen, and H. Galbo. Effect of physical training on glucose transporter protein and mRNA levels in rat adipocytes. Am. J. Physiol. 265: E128-E134, 1993.

IV. Stallknecht, B., L. Simonsen, J. Bülow, J. Vinten, and H. Galbo. Effect of training on epinephrine-stimulated lipolysis determined by microdialysis in human adipose tissue. Am. J. Physiol. 269: E1059-E1066, 1995.

V. Stallknecht, B., M. Roesdahl, J. Vinten, K. Capito, and H. Galbo. The effect of lesions of the sympathoadrenal system on training induced adaptations in adipocytes and pancreatic islets in rats. Acta Physiol. Scand.156: 465-473, 1996.

VI. Stallknecht, B., J. Madsen, H. Galbo, and J. Bülow. Evaluation of the microdialysis technique in the dog fat pad. Am. J. Physiol. 276: E588-E595, 1999.

VII. Enevoldsen, L.H., B. Stallknecht, J.D. Fluckey, and H. Galbo. Effect of exercise training on in vivo insulin-stimulated glucose uptake in intra-abdominal adipose tissue in rats. Am. J. Physiol. 278: E25-E34, 2000.

VIII. Stallknecht, B., J.J. Larsen, K.J. Mikines, L. Simonsen, J. Bülow, and H. Galbo. Effect of training on insulin sensitivity of glucose uptake and lipolysis in human adipose tissue. Am. J. Physiol. 279: E376-E385, 2000.

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The publications are in the text referred to by their roman numerals.

Publication no. VI is based on the results, which form part of the basis for my Ph.D. thesis (Estimation of interstitial concentrations of metabolites and hormones in adipose tissue by means of microdialysis – method evaluation, 1997). Results from the remainder of the publications (no. I-V and VII-IX) have not previously been evaluated with the purpose of achieving an academic degree.

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