

Physiological regulation of NEFA availability: lipolysis pathway

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Plasma NEFA are an important energy substrate and, furthermore, play a key role in the induction of insulin resistance in the body. The availability of NEFA is determined predominantly by their mobilization from adipose tissue triacylglycerol stores by the process of lipolysis. Adipose tissue lipolysis in man is regulated by a number of hormonal and paracrine and/or autocrine signals. The main hormonal signals may be represented by catecholamines, insulin, growth hormone, natriuretic peptides and some adipocytokines. The absolute levels and relative importance and contribution of these signals vary in different physiological situations, with diet and physical exercise being the main physiological variables that affect the hormonal signalling. Thus, modulations in hormonal signals induce an increase in NEFA mobilization in the post-absorptive state and during an acute bout of exercise, and suppress NEFA mobilization in the postprandial state. In addition, hormonal regulation is modified by long-term interventions in energy balance, such as dietary restriction and/or physical training, and is disturbed in some pathological states, such as obesity or diabetes. The question that remains is whether disturbances in lipolysis regulation in obese and diabetic subjects may be 'corrected' by the long-term interventions in diet and physical activity.

Adipose tissue: Lipolysis

Plasma NEFA are primarily an important energy substrate for a number of organs. NEFA are also precursors for the formation of triacylglycerol (TAG) stores in adipose tissue, liver and muscle through esterification. In addition, it appears that NEFA may be involved in the regulation of a number of metabolic processes in the body; for example, NEFA have been shown to control the expression of genes encoding uncoupling protein 3 in skeletal muscle (Khalfallah *et al.* 2000) and muscle carnitine palmitoyl-transferase 1 in cardiac myocytes (Brandt *et al.* 1998). If they are present in excess, NEFA are involved directly in the pathogenesis of metabolic disturbances leading to insulin resistance and metabolic syndrome, and they may also exert adverse effects on heart chronotropic function. The availability of NEFA for all these processes is governed mainly by their release from the major TAG store in the body, the adipose tissue. NEFA are liberated from intracellular TAG by the process of lipolysis and released from adipose cells into the interstitial space and, ultimately, into the circulation. A proportion of NEFA

liberated from TAG during lipolysis may be re-esterified and thus form TAG in the adipocytes. Consequently, the net release of NEFA from adipose tissue is a result of the contribution of lipolysis and NEFA re-esterification, the lipolysis being, in most physiological situations, dominant in the control of NEFA release. Thus, the present overview will focus mainly on the physiological regulation of lipolysis, but will mention the other relevant pathways in connection with physiological conditions in which they appear relevant.

Adipose tissue lipolysis and its regulation

In view of the multiple metabolic functions of NEFA it is obvious that the fine regulation of lipolysis is important for the maintenance of body energy homeostasis as well as for the prevention of systemic metabolic disorders. In the process of lipolysis the TAG in the adipocyte are hydrolysed into three molecules of NEFA and one molecule of glycerol. As the liberated NEFA may be used in the

Abbreviations: HSL, hormone-sensitive lipase; TAG, triacylglycerols.

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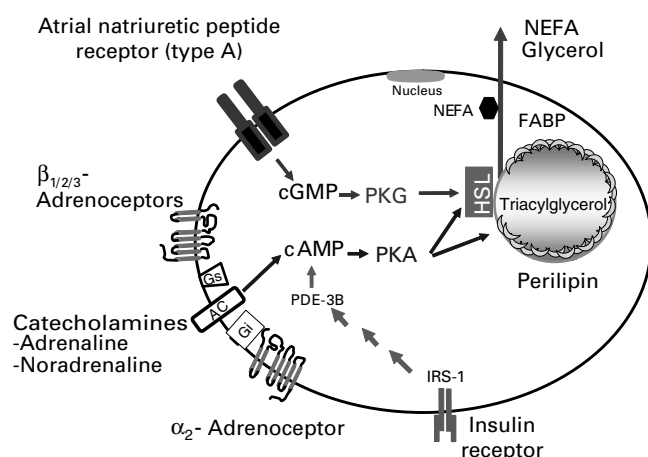


Fig. 1. Regulation of human fat cell lipolysis. HSL, hormone-sensitive lipase; FABP, fatty acid-binding protein; PKA, PKG, protein kinase A and G respectively; PDE-3B, phosphodiesterase 3B; IRS-1, insulin receptor substrate 1; AC, adenylylcyclase; Gs, Gs protein; Gi, Gi protein.

re-esterification process whereas glycerol appears not to be utilized (because glycerol kinase, the enzyme controlling the esterification of NEFA and glycerol into TAG, is absent in the adipocytes), it is the rate of glycerol release that has been taken as an index of the rate of lipolysis. However, the validity of this index has been put in doubt by some recent studies that suggest that there is utilization of glycerol in the adipose tissue (Kurpad *et al.* 1994; Samra *et al.* 1999; Blaak, 2003), but the level of utilization does not exceed approximately 10–20% of the released glycerol.

The key rate-limiting enzyme of the reaction is hormone-sensitive lipase (HSL). The activation of HSL, as suggested by the name of the enzyme, is associated with a broad spectrum of hormonal signals (Langin *et al.* 1996; Lafontan *et al.* 1997; Fig. 1). The main hormones involved in the regulation of HSL activity are catecholamines and insulin. Catecholamines stimulate lipolysis through the activation of β_1 and β_2 adrenoceptors and inhibit lipolysis through activation of the α_2 adrenoceptor. HSL activation is mediated by a cascade beginning with coupling to Gs or Gi protein and subsequent formation of cAMP through the adenylylcyclase system and subsequent activation of protein kinase A and phosphorylation of HSL. Insulin is a potent inhibitor of lipolysis and acts primarily through its effect on phosphodiesterase and subsequent suppression of the formation of cAMP.

Recently, it has been demonstrated *in vivo* and *in vitro* that atrial natriuretic peptide has a powerful stimulatory effect on lipolysis in adipose tissue (Sengenès *et al.* 2000). In contrast to the effect of catecholamines and insulin, this effect is mediated by a cGMP-dependent pathway, also leading presumably, via protein kinase G, to phosphorylation of HSL.

Lipolysis in man is also stimulated by growth hormone, although its lipolytic action is delayed and not as well understood, and is modulated by a number of signals that have autocrine or paracrine characteristics, such as

adenosine, prostaglandins etc. Recently, the lipolysis-stimulating actions of a number of cytokines secreted in the adipose tissue have been described, including those of leptin (Fruhbeck *et al.* 2001), TNF- α and IL-6 (Lyngso *et al.* 2002). The physiological relevance of the lipolytic action of these substances remains to be elucidated.

The rate of lipolysis may be regulated on two levels: (1) variation in the regulating signal, i.e. regulating hormone; (2) variation in the responsiveness to the action of hormones.

Receptor densities and characteristics vary greatly depending on the location of adipose tissue; for example, when comparing abdominal subcutaneous with gluteal subcutaneous or abdominal intra-peritoneal tissues. Consequently, the lipolytic rates differ substantially in various adipose tissue regions and, thus, various adipose tissue depots may contribute to NEFA availability to a quite different extent. This aspect will be discussed in relation to the relevant physiological situations.

Methods for investigating lipolysis and NEFA release

Whole-body lipolysis and NEFA release *in vivo* have been studied by measuring glycerol and NEFA turnover using stable-isotope-labelled glycerol and NEFA respectively.

Regional lipolysis and/or NEFA release *in vivo* have been investigated by: (1) direct measure of arterio-venous differences using simultaneous catheterization of the artery and outflowing vein (used primarily in subcutaneous adipose tissue); (2) the method of microdialysis (in subcutaneous adipose tissue only; NEFA kinetics cannot be estimated with this method); (3) in all adipose tissues the combination of catheterization of the supplying artery and outflowing vein and measures of turnover with stable isotopes provides evaluation of regional lipid metabolism.

In vitro, lipolysis is investigated in isolated adipocytes obtained from biopsy samples taken by either needle biopsy (subcutaneous tissue) or surgical procedures (visceral adipose tissue). In the biopsy samples concentrations or activities of proteins involved in the regulation of lipolysis or the expression of relevant genes may also be determined.

Regulation of lipolysis in physiological conditions

The regulation of NEFA release and lipolysis is tuned in order to respond to the actual energy needs of the body organ in a given physiological situation. If this tuning fails, not only are the energy needs not adequately satisfied, but eventually there is an excess of NEFA release that causes systemic metabolic disturbances. The tuning is mediated by modulations in hormonal signalling and by changes in the responsiveness to hormonal action. In relation to energy needs and hormonal signalling in the control of the lipolysis and NEFA release, the basic physiological conditions that should be differentiated are: (1) the resting post-absorptive state; (2) the resting postprandial state; (3) an acute bout of exercise, or the response to other stressors, in the post-absorptive state; (4) exercise and food

intake. In addition, the regulation of lipolysis and NEFA release in these basic physiological conditions may be modulated by a number of variables; mainly those that are related to a longer-term dietary and/or physical activity regimen.

Post-absorptive state

The post-absorptive state is characterized by a requirement to mobilize energy stores. The increase in the release of NEFA is primarily determined by an increase in the rate of lipolysis in adipocytes, i.e. by an increase in HSL activity. The proportion of NEFA that is re-esterified within adipose tissue is low (Samra *et al.* 1996). A healthy normal-weight individual having 15 kg body fat (>50 mol fatty acids) releases <0.4 mmol fatty acids/min into the circulation. The post-absorptive phase represents a short-term (10–14 h) period of fasting within the 24 h cycle. The principles associated with the effects of short-term fasting are well demonstrated if fasting is prolonged to 22 h. Fasting for 22 h induces an increase in whole-body and regional lipolysis, demonstrated by both the whole-body rate of appearance of glycerol and the regional output of glycerol from subcutaneous adipose tissue, as well as an increase in the rate of NEFA release (Horowitz *et al.* 1999b). The main stimulus for the fasting-induced increase in lipolysis appears to be a reduction in plasma insulin levels (there is a correlation between the decrease in insulin levels and the increase in lipolytic rates). Systemic nerve activity does not play a role as the spill over of noradrenaline is reduced during fasting (Horowitz *et al.* 1999b). However, the results of Nielsen *et al.* (2003), which show a correlation between fasting plasma adrenaline concentrations and mean 4 d palmitate release, suggest that catecholamine levels may also contribute to ‘setting’ the level of post-absorptive NEFA release.

There is a variation in the contribution of different adipose tissue regions to whole-body NEFA release. In non-obese subjects NEFA release by the upper-body subcutaneous adipose tissue represents >50% of the overall release when compared with that of the leg and splanchnic regions (Jensen & Johnson, 1996). This finding is in accordance with regional variations in the responsiveness to catecholamine stimulation of lipolysis, showing constantly higher values for subcutaneous abdominal adipose tissue compared with femoral adipose tissue (for review, see Lafontan *et al.* 1997), and with regional variations in responsiveness to the anti-lipolytic action of insulin (Zierath *et al.* 1998).

Postprandial state

The postprandial state represents the opposite side of the spectrum. In the presence of the exogenous energy substrate the need for endogenous substrate mobilization is reduced. This state is represented by a marked suppression of HSL activity and lipolytic rate. The main hormonal signal mediating this suppression is elevation of insulin, which is typical after a mixed meal. The sensitivity to

insulin anti-lipolytic action is high. The 50% suppression of NEFA (palmitate) release is achieved with a concentration of free insulin of about 12 pmol/l (Jensen *et al.* 1989). In addition, hyperinsulinaemia induces a reduction in the lipolysis-stimulating action of catecholamines (Stich *et al.* 2003). Furthermore, insulin stimulates re-esterification of NEFA released from the adipocyte (stimulating the uptake of glucose and formation of glycerol-6-phosphate). Nevertheless, insulin is probably not the only mediator of postprandial suppression of NEFA release. After intake of a high-fat meal or an intravenous TAG load insulin levels are not markedly changed and NEFA release and calculated HSL activity are still suppressed (Evans *et al.* 1999). A direct action of NEFA on lipolysis regulation has been suggested, although the hypothesis has not been verified in *in vitro* conditions.

In the postprandial situation, particularly after a high-fat meal, a major proportion of the NEFA appearing in the circulation is derived from intravascular lipolysis associated with lipoprotein lipase activity. Lipoprotein lipase action is stimulated by a postprandial increase in insulin levels and, in the presence of an increased inflow of dietary TAG, not all NEFA mobilized from dietary TAG are ‘trapped’ in the adipose tissue through the esterification process and ‘leak’ into the circulation (Frayn *et al.* 1997). The proportion of the lipoprotein lipase-derived NEFA in plasma increases with time, peaks at about 3–5 h after the meal and reaches >80% of the total plasma NEFA (Frayn *et al.* 1997).

Exercise

The delivery of excess NEFA to meet the increased energy demands of the body during physical exercise is provided by an increase in adipose tissue lipolysis. The increase in lipolysis has been assumed to be controlled mainly by the increase in activation of β receptors produced by an exercise-induced rise in circulating catecholamines and sympathetic nerve activity and by the decrease in insulin secretion.

In addition, it has been demonstrated that the anti-lipolytic activity of catecholamines mediated by α_2 adrenoceptors is also involved in the regulation of exercise-induced lipolysis. *In situ* investigation with microdialysis has shown that the blockade of the α_2 adrenoceptor with the α adrenoceptor inhibitor phentolamine results in a rise in lipolytic response during exercise (Stich *et al.* 1999). The involvement of the α_2 adrenoceptor in the control of exercise-induced lipolysis does demonstrate the physiological relevance of this pathway of catecholamine lipolysis regulation and may be responsible for changes in lipolysis regulation during various physiological and pathological states, e.g. impairment of exercise-induced lipolysis observed in obese subjects (Stich *et al.* 2000).

A number of recent findings have cast some doubt on the accepted view that β adrenergic stimulation has a decisive role in the control of lipolysis during exercise. Stallknecht *et al.* (2001) have shown that sympathetic nerve activity plays a minor role in exercise-induced lipolysis in adipose tissue. In paraplegic subjects with

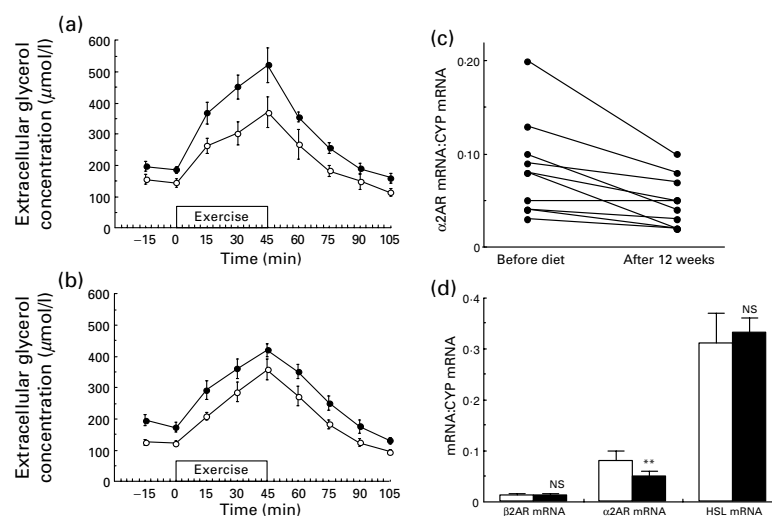


Fig. 2. Effect of 12 weeks on a low-energy diet on the α_2 adrenergic anti-lipolytic pathway. (a, b) Time-course of extracellular glycerol concentration in subcutaneous adipose tissue during the 45 min cycle-ergometer exercise before (a) and during the 12th week (b) on the low-energy diet in obese women, in the presence (●) or absence (○) of the α adrenoreceptor (AR) antagonist phenolamine in the perfusion medium. Values are means with their standard errors represented by vertical bars. The response in the presence of phenolamine was higher than that in the controls. The difference between the two time response curves before dietary treatment was significant (ANOVA; $P = 0.04$). The difference between the two time response curves after dietary treatment was not significant (ANOVA; $P = 0.32$). (c) Changes in α_2 AR mRNA values for the individual subjects during the 12 weeks on the low-energy diet. The amounts of α_2 AR mRNA were determined using RT-competitive PCR. The level of mRNA was related to the housekeeping gene CYP mRNA level. (d) The effect of the low-energy diet on α_2 AR, β_2 AR, and hormone-sensitive lipase (HSL) mRNA levels in subcutaneous adipose tissue of the ten obese women. (□), Before commencing the diet; (■), during the 12th week of dietary treatment. Values are means with their standard errors represented by vertical bars. Mean values for α AR mRNA were significantly different from those before dietary treatment: ** $P = 0.01$. (From Stich *et al.* 2002.)

spinal cord injuries there is no difference between the exercise-induced lipolysis in the upper innervated part of the body and the abdominal denervated part.

Microdialysis investigations also support the view that catecholamines are not the only factor promoting the rise in lipolysis during exercise. Administration of the non-selective β -blocker propranolol into the microdialysis probe only partially inhibits the exercise-induced lipolysis (Arner *et al.* 1990). In a search for other promoters of lipolysis during exercise, atrial natriuretic peptide has been suggested as a candidate. The marked lipolytic activity of atrial natriuretic peptide has been demonstrated recently (Sengenès *et al.* 2000). During exercise, if the blockade of β adrenoreceptors is brought about by an oral agent, the exercise-induced rise in extracellular glycerol is correlated with the exercise-induced increase in atrial natriuretic peptide (C Moro, F Crampes and M Berlan, personal communication). Growth hormone, cortisol and cytokine IL-6 are among the other hormones that may contribute to exercise-induced lipolysis.

Exercise-induced lipolysis is modulated by simultaneous nutritional interventions; oral glucose intake before or during exercise reduces the lipolytic response.

Modulation of lipolysis and NEFA release by long-term interventions in energy balance

Restriction of energy intake

Long-term restriction of energy intake creates the need for mobilization of energy stores. A low-energy diet accompanied by weight loss does not result in a modification in resting NEFA release but enhances the NEFA response to low-intensity exercise (Kanaley *et al.* 1993). This outcome may reflect the results of a recent study with obese subjects subjected to a low-energy diet. The expression of HSL in adipose tissue is unchanged, but α_2 adrenoreceptor-mediated anti-lipolytic activity *in situ* during exercise is reduced (Stich *et al.* 2002; Fig. 2). However, during more restrictive diets there appears to be an increase in the lipolytic responsiveness of adipose tissue to adrenergic stimulation as well as an increase in HSL activity (Stich *et al.* 1997). This finding would suggest an increase in resting lipolysis and/or NEFA release *in vivo*. Thus, in obese subjects who show impairments in lipolysis regulation, dietary intervention could lead to 'correction' of the impairment.

Effects of training

In cross-sectional studies *in vitro* results have demonstrated a higher adrenergic lipolytic responsiveness of adipocytes in trained subjects (for example, see Crampes *et al.* 1986, 1989). *In vivo*, training has been shown, again in cross-sectional studies, to enhance the whole-body lipolysis and NEFA release at rest (Romijn *et al.* 1993) and during strenuous exercise (Klein *et al.* 1996). However, the *in situ* lipolytic sensitivity to catecholamine action investigated by microdialysis does not appear to be affected by training status (Stallknecht *et al.* 1995).

In most longitudinal studies endurance training has not been found to change the *in vivo* lipolytic responsiveness to adrenergic stimuli (for example, see Horowitz *et al.* 1999a), although it seems that the response may depend on the intensity of training and the body weight (or adiposity) status of subjects. High-intensity exercise training improves *in situ* β -adrenergic lipolytic sensitivity in obese subjects (van Aggel-Leijssen *et al.* 2001) and 12 weeks training has the same effect on *in vitro* β -adrenergic sensitivity in obese men (De Glisezinski *et al.* 1998). Training has been shown to improve whole-body sensitivity to insulin anti-lipolytic action (Hickner *et al.* 2000) but, taking into account that training often elicits a fall in insulin levels, this improved sensitivity may not lead to a decrease in the overall lipolysis and/or NEFA release. Importantly, in obese subjects, in whom the regulation of lipolysis is disturbed, some longitudinal studies showed improvement of lipolytic responsiveness.

Conclusions

In conclusion, lipolysis in white adipose tissue in man is regulated in order to respond to variations in the energy demands of the body. The adrenergic system and insulin still appear to be principal mediators of regulation in physiological conditions. Recently, the physiological relevance of the anti-lipolytic pathway mediated by α_2 adrenoceptors has been elucidated. Novel pathways of lipolysis regulation, such as that mediated by atrial natriuretic peptide, have been described. Long-term interventions in energy balance by diet or physical training may modify some of the pathways of lipolysis regulation and this approach may be important in subjects with impairments in lipolysis regulation, such as obese or diabetic patients.

Acknowledgements

The authors would like to thank Francois Crampes, Dominique Langin and Max Lafontan from Toulouse, France, for their important role in the studies mentioned in this overview. The studies cited in this article were supported by a grant from the Ministry of Health of Czech Republic IGA 6836-3.

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