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Catecholamine-induced lipolysis in obesity

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Catecholamines are the only hormones with pronounced lipolytic action in man. A number of *in vivo* and *in vitro* studies suggest that there is lipolytic resistance to catecholamines in subcutaneous adipose tissue, which is the major fat depot in obese subjects. This is due to multiple alterations in catecholamine signal transduction, involving decreased expression and function of β_2-adrenoceptors, increased function of α_2-adrenoceptors and decreased ability of cyclic monophosphate (AMP) to stimulate hormone sensitive lipase. A sedentary life-style, which usually characterizes obesity, may contribute to the catecholamine resistance. However, hereditary/genetic factors may also be involved. Recently, decreased expression and function of hormone sensitive lipase has been found in subcutaneous adipocytes of non-obese subjects with heredity for obesity. In addition, polymorphisms in the genes for β_2-adrenoceptors, β_3-adrenoceptors and hormone sensitive lipase, associate with obesity. On the other hand, catecholamine-induced lipolysis in visceral adipose tissue is increased in obesity due to increased function of β_3-adrenoceptors (major finding), decreased function of α_2-adrenoceptors and increased ability of cyclic AMP to stimulate lipolysis. When the findings in different adipose regions are considered together, it appears that there is a re-distribution of lipolysis and thereby fatty acid mobilization in obesity, favouring the visceral fat depot. This leads to an increase in the circulating fatty acid levels in the portal vein, which connects visceral fat with the liver. As a consequence, the liver function may be altered leading to hyperinsulinemia, hyperglycemia and dyslipidemia, which usually accompany the obese state.

Keywords: fat cells; adrenergic receptors; fat acids; insulin; adipose tissue; diet; exercise; genes

Introduction

Adipose tissue plays a central role in energy homeostasis through its ability to store and release large amounts of energy rich fatty acids. Alterations in these processes are important for the development of obesity and many obesity complications, as reviewed in detail recently.[1]

Fatty acids are mobilized from the fat depots through hydrolysis (lipolysis) of triglycerides in fat cells. In humans, only catecholamines have a pronounced acute stimulatory effect on lipolysis.[2] Recent data suggest that alterations in this hormonal regulation may be of importance for the development of obesity and several of its metabolic complications. This review deals with recent findings, as regards catecholamines induced lipolysis in relationship to obesity in man. Lipolysis has been discussed in detail as regards earlier findings in man.[2] In the interest of space, review articles rather than original publications will be cited as often as possible

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Mechanisms of catecholamine action

The mechanisms by which catecholamines regulate lipolysis in human fat cells are known in some detail.[2] At the cellular level, the hormones first bind to four different adrenoceptor subtypes on the cell surface. Beta$_1$, beta$_2$ and beta$_3$ (β_1, β_2 and β_3)-receptors are coupled to stimulatory GTP sensitive proteins and activate the membrane bound enzyme adenylyl cyclase which enhances the breakdown of intracellular adenosine triphosphate (ATP) to cyclic AMP. The latter nucleotide activates protein kinase A, which in turn phosphorylates hormone sensitive lipase (HSL). Thereby HSL becomes activated and catalyzes the breakdown of triglycerides (lipolysis), whereafter fatty acids are liberated and can leave the fat cells to be transported by the blood stream for utilization in other organs (mainly the liver and the muscle). α_2-A-adrenoceptors have opposite effects on lipolysis. They couple to inhibitory GTP sensitive proteins so that adenylyl cyclase, cyclic AMP formation, protein kinase A activation, HSL phosphorylation and lipolysis are inhibited.

It is unknown so far why human fat cells need three stimulatory and one inhibitory receptor for such a relatively simple process as catecholamine-regulation of lipolysis. In most other species only one or two

Table 1 Factors modulating catecholamine-induced lipolysis in human fat cells

Non-hormonal	*Hormonal*
Age	Insulin
Exercise	Thyroid hormones
Fasting	Growth hormone
Trauma	Sex hormones
Adipose region	Glucocorticosteroids

(usually β_1 and β_2) adrenoceptors subtypes are expressed in fat cells. Anyhow the net action of catecholamines depends on the balance between β- and α-receptors. Normally the β-mediated lipolytic action dominates.

A number of physiological factors modulate catecholamine action on lipolysis in fat cells (Table 1). Several other hormones have permissive (usually stimulatory) effects. Aging, fasting, trauma and exercise, modulate catecholamine-induced lipolysis, usually exerting a stimulatory effect, except for aging which has an inhibitory effect.

As discussed in detail later in this review, the regional variations in catecholamine-induced lipolysis are of great potential importance for obesity. Using different approaches, such as microdialysis and isotopic infusion in combination with selective blood vessel catheterization, it is firmly established that the *in vivo* lipolytic response to catecholamines differs between central and peripheral subcutaneous adipose tissue as reviewed recently.[3] It has been suggested that regional variations in subcutaneous lipolysis could be of importance for body fat distribution (see Ref. 4 for a detailed discussion). Catecholamine-induced lipolysis is more marked in abdominal, as compared to gluteofemoral, subcutaneous fat and this difference is more marked in women than in men and also maintained in obesity. Thus, catecholamines could play a role for the development of certain obese phenotypes such as upper-body obesity (usually occurring in men) and peripheral obesity (usually occurring in women).

Of greater pathophysiological importance than variation in lipolysis between subcutaneous fat depots is probably the lipolytic differences between subcutaneous and visceral adipose tissue (see Ref. 5 for detailed information). Only visceral adipose tissue is in direct contact with the liver, since it is drained by the portal vein. A high fatty acid concentration in the liver, for example induced by excess 'portal' delivery, has a number of undesirable effects on the organ. Gluconeogenesis and triglyceride production are stimulated. Insulin breakdown is inhibited. Thus, high 'portal' fatty acids may induce hyperglycemia, dyslipidemia and hyperinsulinemia, which all are common abnormalities in obese subjects. It should be stressed that the evidence for a difference in lipolysis between visceral and subcutaneous adipose tissue is based on *in vitro* studies. For ethical reasons it is not possible to directly study the visceral lipolysis rate with current techniques. The rate of lipolysis is much higher in visceral as compared to subcutaneous fat cells *in vitro*. This is due to regional variations in the action of a number of hormones. For catecholamines, the lipolytic action of the β-adrenoreceptor subtypes are more pronounced and the antilipolytic action of α_2-receptors less pronounced in visceral as compared to subcutaneous adipocytes. Recent studies suggest that, in men, these regional variations in catecholamine action are more pronounced in obese as compared to non-obese subjects.[6]

Regional variations in catecholamine-induced lipolysis may have physiological as well as pathophysiological (see below) implications. Gluteofemoral lipolysis is enhanced in lactating women and fatty acids from this depot could serve as energy substrate during lactation. Visceral fatty acid mobilization could be of importance in situations when there is rapid need for excess endogenous energy supply such as during physical work.

Catecholamine action in obesity

As reviewed earlier,[2,3] a number of *in vivo* studies have shown that the lipolytic action of catecholamines is blunted *in vivo* in obese subjects. This defect might be an early event in obesity, since it is observed in obese adolescents.[7] On the basis of *in vitro* studies on subcutaneous fat cells (see reference 2 for details) it can be concluded that the catecholamine resistance is caused by multiple defects in signal transduction (Table 2). Decreased expression and function of β_2-adrenoceptors, increased antilipolytic action of α_2-adrenoceptors and impaired ability of cyclic AMP to activate lipolysis are found in subcutaneous fat cells of obese subjects.

The findings of visceral adipocytes in obesity (Table 2) are, on the other hand, much different from those with subcutaneous fat cells. In the visceral fat depot catecholamine-induced lipolysis is increased (see reference 2 for details). The mechanisms seem to be enhanced lipolytic function of β_3-adrenoceptors, decreased antilipolytic function of α_2-adrenoceptors and increased ability of cyclic AMP to activate lipolysis. These findings at large opposite to those found in subcutaneous fat cells of obese subjects.

Table 2 Catecholamine-induced lipolysis in fat cells of obese subjects

Action	*Subcutaneous adipocytes*	*Visceral adipocytes*
Lipolysis	decreased	increased
β_2-adrenoceptor function	decreased	no change
β_3-adrenoceptor function	no change	increased
α_2-adrenoceptor function	increased	decreased
Ability of cyclic AMP to stimulate lipolysis	decreased	increased

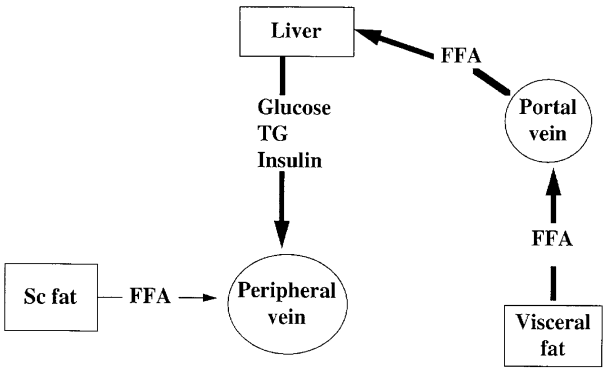

Figure 1 Proposed role of free fatty acid (FFA) mobilization from different fat depots in obesity. The rate of catecholamine-induced lipolysis is decreased in the subcutaneous (Sc) fat cells, but increased in the visceral fat cells. This favor mobilization of FFA to the portal vein as compared to peripheral veins. A high portal FFA concentration impairs liver function, so that the production of glucose and triglycerides (TG) is increased and the breakdown of insulin decreased in the liver. The latter results in hyperglycemia, dyslipidemia and hyperinsulinemia.

Recent studies suggest that gender is also of importance for catecholamine action on visceral fat cell lipolysis in obesity.[8] The rate of lipolysis is much higher in visceral fat cells of obese men in comparison with obese women; the mechanism for the observed differences are the same as those described above.

When available data are considered together, the following speculation on catecholamine-induced lipolysis is presented (Figure 1). The action is increased in visceral fat cells, but decreased in subcutaneous fat cells, due to multiple alterations in the catecholamine signal transduction pathway for lipolysis in these two cell types. As a consequence, there is a re-distribution of fatty acid mobilization from adipose tissue, favouring the visceral over the subcutaneous depot. This could be a mechanism behind abdominal obesity since the subcutaneous abdominal fat depot is the largest adipose region in this obese phenotype. It could also be a mechanism for many of the metabolic complications which are caused by abdominal obesity. Increased visceral mobilization of fatty acids resulting in elevated 'portal' fatty acids and impaired liver function may, at least in part, be responsible for the atherogenic metabolic profile in abdominal obesity. It has recently been suggested that an increase in the size of the visceral fat depot is the precursor for elevated 'portal' fatty acids.[9] However, the data reviewed in the present article also support the view that changes in the rate of lipolysis *per se* (independent of the size of the visceral fat depot) contribute to excess mobilization of portal fatty acids in upper-body (abdominal) obesity. However, it should be noted that the theory on regional fat lipolysis is based almost completely on *in vitro* studies.

Primary and secondary events

What comes first, obesity or defects in the action of catecholamines on lipolysis? Although this question cannot be firmly answered yet, it is possible that both primary and secondary factors are of importance (Table 3).

A hen-and egg question regarding obesity can sometimes be answered by investigations performed before and after weight reduction. The information of lipolysis regulation before and after weight reduction is limited as regards earlier studies (see Ref. 2). Recently it was demonstrated that a 20% weight reduction partly normalized lipolysis regulation in subcutaneous fat cells of obese women.[10] Another recent study on formerly obese women showed that *in vivo* lipolysis in subcutaneous adipose tissue during exercise (a condition when lipolysis is accelerated mainly due to increase of circulating catecholamines) was not different from that in never-obese control subjects.[11] However, no information was available in this study on lipolysis before the women lost weight. The question as to whether or not lipolysis abnormalities persist after weight reduction can best be explained by a comparison of the same subjects in the obese and post-obese states.

Most obese subjects have a sedentary life-style and excess caloric intake. Earlier studies (reviewed in reference 2) indicate that exercise and endurance training improves the lipolytic action of catecholamines in subcutaneous fat, whereas over-feeding has no or small effects. Recent data further support the notion that a low level of physical activity, not a high caloric intake, play a role for resistance to the lipolytic action of catecholamine in obesity. Overfeeding for 100 d resulting in 6 kg weight gain did not alter catecholamine-stimulated lipolysis in subcutaneous fat cells of non-obese subjects.[12] Catecholamine-induced lipolysis was more pronounced in subcutaneous adipocytes from endurance-trained women than from sedentary women, owing to increased β-adrenoceptor function and decreased α_2-adrenoceptor function.[13] However, it should be kept in mind that the interactions between lipolysis and exercise have mainly been investigated *in vitro* on fat cells. Recent studies suggest that exercise does not influence catecholamine-induced lipolysis *in vitro*.[14]

Table 3 Evidence for that altered catecholamine induced lipolysis is either a primary or a secondary event in obesity

Primary event	*Secondary event*
1. Abnormal lipolysis in subjects with heredity for obesity.	1. Normal lipolysis in post-obese women.
2. Polymorphisms in genes for β_2-adrenoceptors, β_3-adrenoceptors and hormone sensitive lipase associate with obesity.	2. Improved lipolysis following weight reduction.

There is both direct and indirect evidence that catecholamine-induced lipolysis is under hereditary influence. Earlier studies on subcutaneous fat cells (reviewed in Ref. 2 and Ref. 12) show, first, a resemblance of lipolysis stimulation in homozygous twins and, second, a bimodal distribution of β_2-adrenoceptor sensitivity and liplolytic function in the non-obese population. These data suggest that variations in catecholamine action (in particular *via* β_2-receptor) between individuals are genetically determined. Further support for this notion is the recent finding that a common structural variation in the β_2-adrenoceptor protein is associated with lipolytic variability.[15]

Recent data also argue that hereditary defects in catecholamine-induced lipolysis are linked to obesity. Subcutaneous fat cells of non-obese subjects, who have heredity of obesity among first degree relatives, display resistance to catecholamine-induced lipolysis owing to a defect in hormone sensitive lipase function.[16] Polymorphism in the hormone sensitive lipase gene is more common among obese than among non-obese subjects.[17] Polymorphisms in the β_2-adrenoceptor gene have a strong association to obesity in women.[15] Finally, a coding polymorphism in the β_3-adrenoceptor gene, Trp64Arg, was demonstrated some years ago and has been intensity investigated (see Ref. 18 for details). In some studies, the polymorphism is associated with obesity and altered β_3-receptor function whereas other investigations have failed to demonstrate any phenotypic effects of the polymorphism.

Conclusion

Recent data may indicate that both environmental and genetic factors modify the action of catecholamines on lipolysis in fat cells with consequences for the development of obesity. A sedentary life-style may promote catecholamine-resistance. Structural variations in the genes for β_2-adrenoceptors, β_3-adrenoceptors an hormone-sensitive lipase or in other genes regulating the expression and/or function of the previously mentioned genes could impair lipolysis and promote the development of obesity. Clearly much more information is needed about primary and secondary events in lipolysis regulation in obese subjects.

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