Adrenoceptor Interplay in the Regulation of Adipocyte Metabolism

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Abstract

Catecholamines affect fat metabolism in a variety of ways through the mobilisation of five adrenoceptor subtypes (β_1, β_2, β_3, α_1 & α_2). Selective and non-selective β adrenoceptor agonists stimulate lipolysis while α_2 adrenoceptor agonists inhibit lipolysis. Since β and α_2 adrenoceptors produce antagonistic effects, the balance between activation and inactivation of these adrenoceptors defines the net outcome of catecholamine-induced adipocyte metabolism in humans. The coexistence of these receptors on the same cell is puzzling and raises a question about its functional significance. Since α_2 adrenoceptors can be activated at low catecholamine concentrations, a plausible theory regarding this question is that a permanent inhibition of lipolysis exists during basal conditions. Analysis of factors like the count of adrenoceptors on a cell, their differential affinities, and their susceptibility to desensitisation backs up this theory. Another possibility is that these adrenoceptors may have distinct roles in different adipose tissue depots and under different pathophysiological conditions. The existence of catecholamine resistance in the adipocytes of obese subjects is well documented. It can be attributed, in part, to a major decrease in the cell-surface density of β_2 adrenoceptors. Similar differences in adipose tissue metabolism have been observed in conditions which include different body states (resting and exercise), locations of fat (subcutaneous and omental fat) and sexes etc. Many of these anomalies can be traced back to discrepancies in adrenoceptor activity. In this review, two hypotheses explaining the coexistence of five adrenoceptor subtypes on adipose tissue are discussed. Furthermore, the interplay of adrenoceptors that generates variations in lipolysis between subcutaneous and omental fat, peripheral and abdominal fat, men and women, and non-obese and obese people is analysed in the context of the physiology of these conditions.

Introduction

Adipocytes are the energy reserves of the body. They store energy mainly in the form of triglycerides which can be released as free fatty acids according to the energy demands of the body. This regulation of fat metabolism is fundamental to the maintenance of body homeostasis. The disruption of this balance between energy storage and mobilisation may result in diseases like type 2 diabetes, cancer cachexia and obesity (Li et al., 2022).

Ample studies have shown that fat metabolism is under immense hormonal-control. Its modulation by catecholamines (a family of neurotransmitters that include epinephrine, norepinephrine and dopamine) is very complex and employs five types of adrenoceptors (α_1, α_2, β_1, β_2 , β_3). Adrenoceptors are a class of G protein-coupled receptors or GPCRs that are linked to three types of G proteins: $G_{\alpha s}$, $G_{\alpha i}$ and $G_{\alpha q}$.

1. Receptors with $G_{\alpha s}$: Stimulate Lipolysis

β_1, β_2 and β_3 adrenoceptors associate with the $G_{\alpha s}$ G protein. Binding of catecholamines to these adrenoceptors activates adenylyl cyclase. This enzyme catalyses the formation of

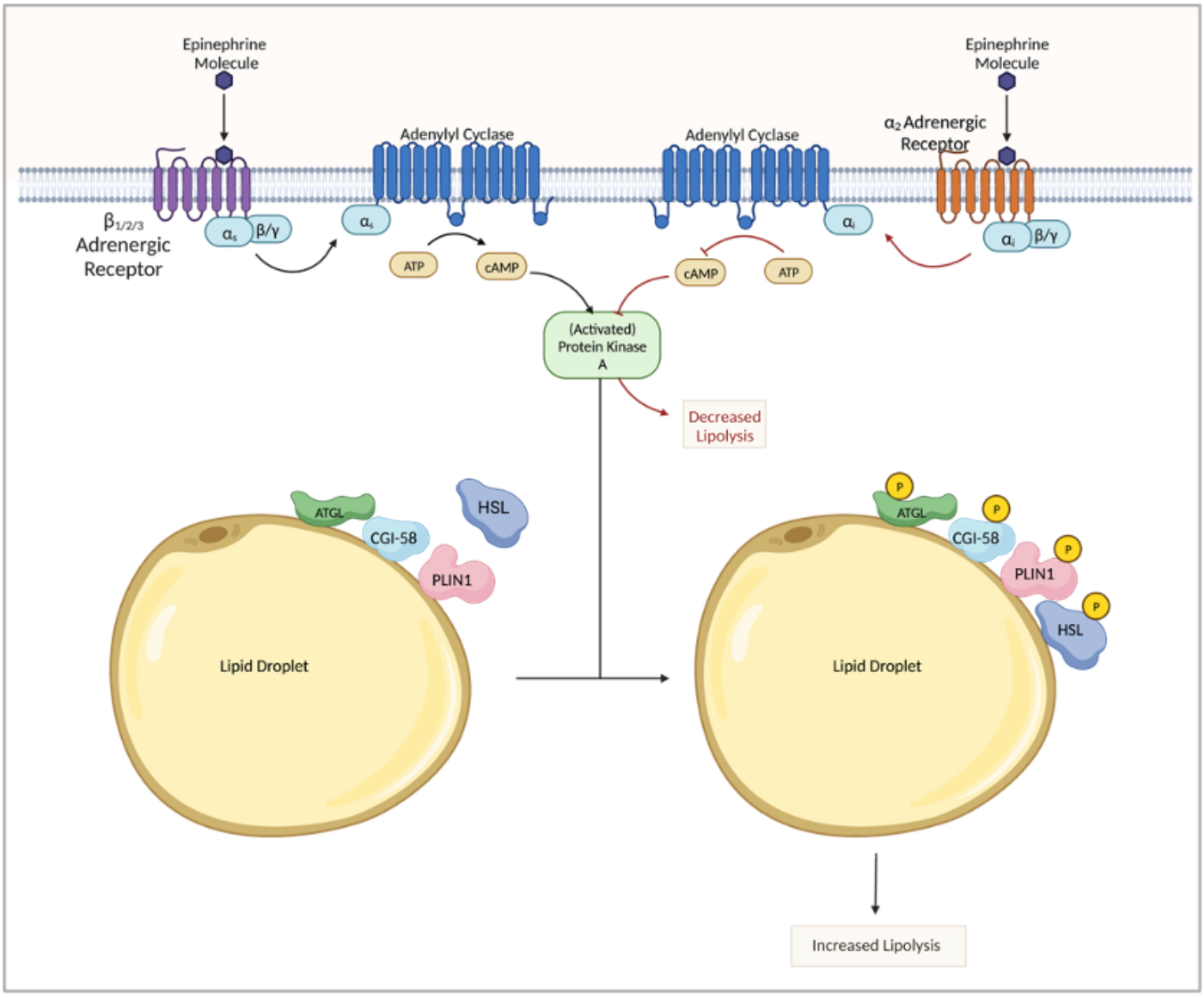
cAMP which further activates PKA. This leads to the phosphorylation and activation of proteins adipose triglyceride lipase (ATGL), comparative gene identification-58 (CGI-58), perilipin 1 (PLIN1) as well as hormone-sensitive lipase (HSL).

ATGL catalyses the first step of lipolysis. It cleaves free fatty acids from triglycerides and converts them into diglycerides. This reaction is followed by the hydrolysis of diglycerides to monoglycerides catalysed by HSL. Finally, the free fatty acids and glycerol molecules are released into the bloodstream (Kintscher et al., 2020).

2. *Receptors with $G_{\alpha i}$: Inhibit Lipolysis*

α_2 adrenoceptors associate with the $G_{\alpha i}$ G protein. Binding of catecholamines to α_2 adrenoceptors leads to the release of inhibitory $G_{\alpha i}$ subunit of the GPCR. This α subunit binds to adenylyl cyclase thereby inhibiting its activity. This decreases the production of cAMP, the activation of PKA and the phosphorylation of enzymes involved in lipolysis, thereby inhibiting lipolysis (Carmen & Víctor, 2006). A visualisation of the mechanisms of action of β as well as α_2 receptors is shown in Figure 1.

Figure 1
*Signal Transduction Pathways of Epinephrine with β and α_2 Adrenoceptors in an Adip*ocyte.



Note. Adapted from Mechanism of Odorant Signal Transduction, by BioRender.com, 2023 (https://app.biorender.com/biorender-templates).

3. *Receptors with $G_{\alpha q}$: Exhibit No Explicit Effect on Lipolysis*

α_1 adrenoceptors associate with the $G_{\alpha q}$ G protein. Binding of catecholamines to α_1 adrenoceptors leads to the stimulation of phosphoinositidase C activity, leading to inositol 1,4,5-trisphosphate and diacylglycerol synthesis. This causes mobilisation of intracellular Ca2+ stores and activation of protein kinase C. In white fat cells, these changes lead to the stimulation of glycogenolysis. In brown fat cells, these changes lead to an increase in heat production (Lafontan & Berlan, 1993).

Research to understand the lipolytic effects of catecholamines continually underscores the heterogeneity of adipose tissue. The rate of lipolysis varies depending on the nature of the

fat depot, physiological/pathological conditions and sex. Recent data suggests that regional variations in lipolysis might be of pathophysiological importance for the development of different types of regional obesity as well as for the complications arising from excess body fat (Arner, 1995; Wahrenberg et al., 1989).

The relative contribution of adrenoceptors in these conditions remains elusive. In this review, we provide hypotheses for the existence of five adrenoceptor subtypes on adipose tissue. We also aim to move a step closer to untangling the mechanisms that produce the aforementioned regional as well as sex-based differences by thoroughly discussing these anomalies and the interplay of adrenoceptors underlying them.

Role of the Five Adrenoceptor Subtypes

Several hypotheses have been generated to understand the reason behind the existence of two opposing mechanisms regulating lipolysis in adipocytes. Although these hypotheses do not fully encompass the relationship between all adrenoceptors, they provide an important beginning to delineate the relative contribution of different adrenoceptors in the regulation of adipocyte metabolism.

Possible Hypothesis #1- Basal Lipolysis Inhibition

An in vivo microdialysis study by Arner et al. (1990) investigated the effects of adrenergic blocking agents on subcutaneous adipose tissue glycerol levels at rest and during exercise. While addition of the nonselective α adrenergic blocking agent phentolamine to the dialysis perfusate did not influence exercise-induced adipose tissue dialysate glycerol levels, it resulted in a rapid and marked increase in the dialysate glycerol concentration at rest. On the contrary, exposure of the extracellular space of adipose tissue to a nonselective β adrenergic blocking agent markedly inhibited the exercise-induced increased lipolysis in subcutaneous adipose tissue but it did not alter lipolysis at rest. This indicates that resting lipolysis in subcutaneous adipose tissue is modulated by α adrenergic inhibition while β adrenergic mechanisms modulate lipolysis during physical exercise.

One possible explanation arising from this data is that a permanent, basal inhibition is exerted on lipolysis (Arner et al., 1990; Lafontan et al., 1997). α_2 adrenoceptors must be the primary lipolysis-regulators, modulating lipolysis when the sympathetic nervous system is weakly active. This allows the adipose tissue to store energy when an organism is at rest. Having the default mechanism set to inhibit lipolysis is a way to reserve energy until there is a need for it to be used (for example, during fight-flight-fright response).

Other findings that support this hypothesis are as follows.

Relative affinities of adrenoceptors. Based on the measurements of some in vitro experiments, it has been found that catecholamines have a higher affinity for α_2 adrenoceptors relative to β adrenoceptors. The relative affinity of adrenoceptors for norepinephrine is $\alpha_2 > \beta_1 \geq \beta_2 > \beta_3$ (Lafontan et al., 1997). Also, α_2 adrenoceptors are found to greatly outnumber β-adrenoceptors in human adipocytes (Li et al., 2022). Thus, at very low catecholamine concentrations, α_2 adrenoceptors are mainly activated which inhibit lipolysis. β adrenoceptors start stimulating lipolysis only at higher agonist concentrations (under physiological conditions of acute stress). This result supports the aforementioned speculation.

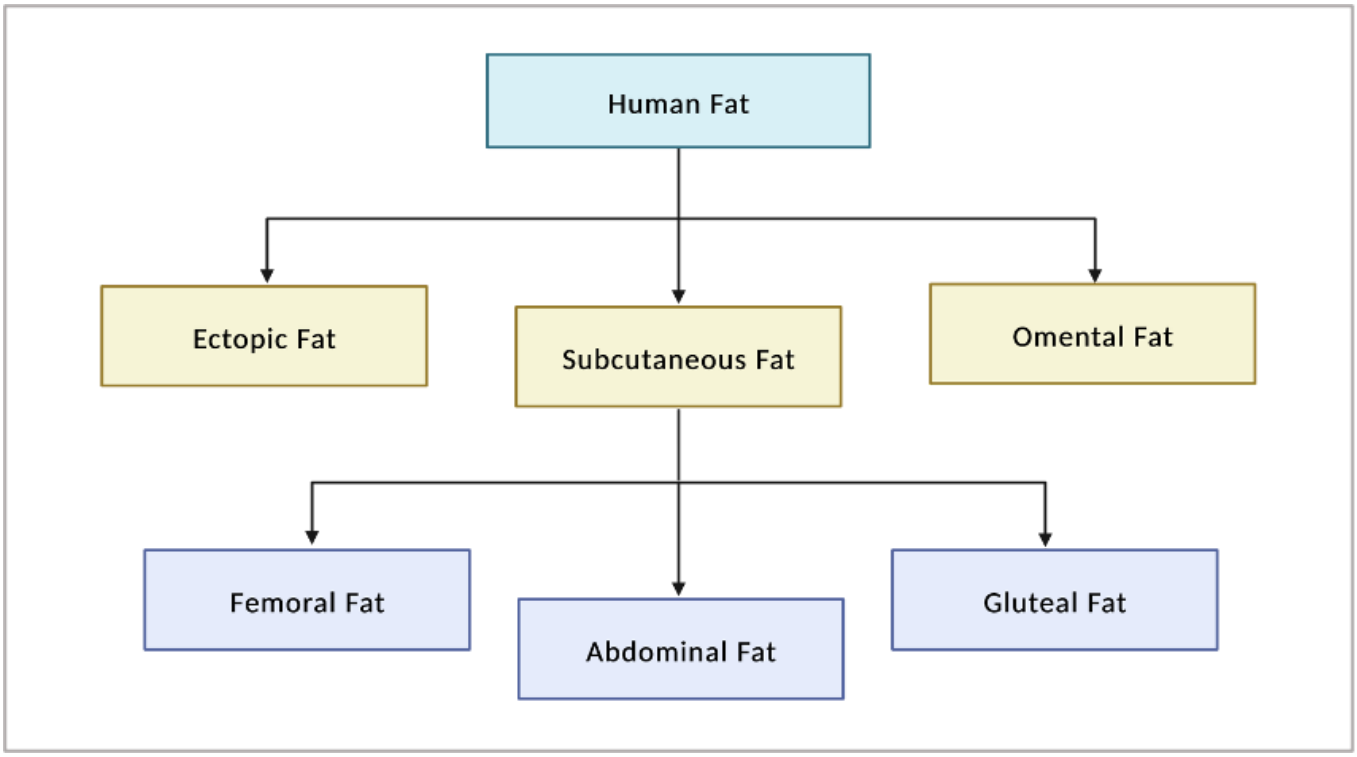
Desensitisation of adrenoceptors. The desensitisation of adrenoceptors in adipocytes has been thoroughly studied and it has been found that α_2 adrenoceptors are quite refractory to desensitisation. Short-term as well as long-term exposure of fat cells to natural catecholamines or selective α_2-agonists in vitro, in vivo, and in situ does not alter $\alpha_2$receptor number or function in fat cells (Arner, 1992; Lafontan & Berlan, 1993). If the aforementioned hypothesis is considered to be true, α_2 adrenoceptors are activated at almost all times to maintain lipolysis inhibition. Thus, their low susceptibility to desensitisation can be considered an adaptation to maintain the default, inhibited state of lipolysis in basal conditions.

Conversely, β adrenoceptors are shown to be desensitised in different ways from both short-term and long-term agonist exposures. Immediately after catecholamine-interaction, β adrenoceptors are phosphorylated which uncouples them from Gαs G proteins. Long-term exposure leads to a down-regulation in the cell-surface count of β adrenoceptors (Arner, 1992). Since activation of β adrenoceptors promotes lipolysis, the β receptors' high susceptibility to desensitisation likely represents a regulatory mechanism to prevent over-stimulation of lipolysis.

Possible Hypothesis #2- Distinct Adrenoceptor Roles in Different Conditions

Human adipose tissue can be categorised into different depots based on the region where it is present in the body (as depicted in Figure 2). In addition to differences in adrenoceptor behaviour within an adipocyte, adrenoceptors may have distinct roles in different adipose tissue depots and under different pathophysiological situations as exemplified in the following sections.

Figure 2
Classification of Human Fat Based on Region.



Note. Adapted from Flow Chart (5 Levels, Vertical, Black and White) 3, by BioRender.com, 2023 (https://app.biorender.com/biorender-templates).

Adrenoceptor Interplay in Regional Variations

Subcutaneous vs. Omental Adipose Tissue

Although in basal conditions, the rate of lipolysis is higher in subcutaneous than in omental fat cells, catecholamine-induced lipolysis is higher in omental than in subcutaneous fat cells. To find out the mechanisms underlying these differences, dose-response experiments were conducted using specific α and β agonists. While the role of α adrenoceptors was limited, a five to ten times increase was observed in β_1 and β_2 adrenoceptor sensitivity in omental cells. This is because β_1 and β_2 adrenoceptor count was found to be twice in omental fat cells (Hellmér et al., 1992). Arner (1995) as well as Hoffstedt et al. (1995) demonstrated that omental cells also have an increased β_3 adrenoceptor action. Thus, β adrenoceptors (but not the α adrenoceptors) contribute to the lipolysis rate being higher in omental as compared to subcutaneous fat.

Table 1
Summary of Regional Variations in Lipolysis between Subcutaneous and Omental Adipose Tissue.

Fat Depot	Catecholamine-induced Lipolysis Rate	Major Mechanisms	
		β sensitivity	α sensitivity
Subcutaneous Fat	Low	Normal	Normal
Omental Fat	High	Increased β_1, β_2 , β_3 count and sensitivity.	No change

Peripheral vs. Abdominal Adipose Tissue

Within subcutaneous adipose tissue, the lipolytic rate is low in the peripheral regions (i.e. gluteal and femoral) and higher in the abdominal regions (Arner, 1992). In non-obese, resting people, a ten to twenty times increase in β adrenoceptor sensitivity was found in abdominal than in gluteal cells (Wahrenberg et al., 1989). This can be explained by a twofold increase in the number of β adrenoceptors found in abdominal adipocytes compared to femoral adipocytes. Women, but not men, also exhibited a reduction in α_2 adrenoceptor effect in abdominal fat cells (Wahrenberg et al., 1989). An in situ microdialysis study showed similar results in lipid mobilisation from gluteal versus abdominal adipose tissue during exercise. α adrenoceptors were not found to be involved in creating these differences (Arner et al., 1990).

Table 2
Summary of Regional Variations in Lipolysis between Peripheral and Abdominal Adipose Tissue.

Fat Depot	Catecholamine-induced Lipolysis Rate	Major Mechanisms	
		β sensitivity	α_2 sensitivity
Peripheral Fat	Low	No change	No change
Abdominal Fat	High	Increased β_1, β_2 count and sensitivity.	Decreased α_2 sensitivity (only in women).

Adrenoceptor Interplay in Sex-Based Variations

The regional differences in lipolytic effects of catecholamines in gluteal and abdominal regions are more pronounced in women as compared to men in both resting as well as exercise

state (Arner et al., 1990). The major determinant of regional differences in catecholamine action on lipolysis in fat cells is the β adrenergic sensitivity of an adipocyte in both men and women. But as mentioned above, along with an increase in β adrenoceptor sensitivity, a decrease in α_2 adrenoceptor effect was found particularly in women (Wahrenberg et al., 1989). Experiments were conducted by Wahrenberg et al. (1989) to find out whether this decrease was due to a reduced receptor count or decreased receptor sensitivity. The number of α_2 adrenergic binding sites was not different between abdominal and gluteal cells but a marked difference was found in α_2 adrenoceptor affinity between these two regions. Thus, a discrepancy in α_2 adrenoceptor function (but not in β adrenoceptor function) can explain why the regional variations are more apparent in women than in men.

Also, this observed difference between peripheral lipolysis rate and abdominal lipolysis rate being greater in women than in men can explain to some extent why women tend to accumulate more subcutaneous fat around the hips (i.e. gluteo-femoral/peripheral fat) than the abdomen (Arner et al., 1990).

Adrenoceptors in Obesity

Obesity is a chronic disease characterised by excessive fat accumulation which poses a hazard to health. It impacts most body systems including heart, liver, kidneys, joints, and reproductive system (World Health Organisation [WHO], 2022). As reported by WHO, more than 1 billion people worldwide are obese and obesity is now considered to be a global epidemic.

A number of in vivo and in vitro studies have shown that catecholamine-induced lipolysis is blunted in adipose tissue of obese subjects (Arner, 1992; Reynisdottir et al., 1994). Since this diminution of epinephrine activity has also been observed in early-childhood obesity as well as in normal weight first degree relatives of obese adults (Bougnères, 1997), it is hypothesised that this anomaly might predispose to obesity.

On the adrenoceptor level, this catecholamine-resistance in the subcutaneous fat cells can be attributed to an increased α_2 adrenoceptor response in obese males and a decreased β_2 adrenoceptor response in obese females (Arner, 1995). A 70% reduction in the cell surface density of β_2 receptors was found on subcutaneous fat cells in a study with upper-body obese women (Reynisdottir et al., 1994).

On the other hand, the rate of free fatty acid mobilisation from omental fat cells is accelerated in obesity (Bougnères et al., 1997). This could mainly be explained by β_3 adrenoceptors, and not by β_1 or β_2 adrenoceptors. In vivo studies have revealed that obese subjects are fifty times more sensitive to β_3 adrenoceptor agonists (Lönnqvist et al., 1995). The increased β_3 adrenoceptor might relate to the count or affinity of the receptor subtype to the cell but it is suggested by Lönnqvist et al., (1995) that the increased β_3 adrenoceptor activity is due to an enhanced receptor number.

Furthermore, a decreased α_2 adrenoceptor function also contributes, in part, to increased lipolysis in omental fat cells. The sensitivity of α_2 adrenoceptor is six times less in omental fat cells of obese subjects as compared to those of non-obese subjects. Thus, obese subjects

demonstrate a decreased lipolytic rate in subcutaneous fat (explained by abnormal α_2 and β_2 adrenoceptor activity) and an increased lipolytic rate in omental fat (due to increased β_3 adrenoceptor activity).

This data might lead to an initial conclusion that fat accumulation in the omental fat depot is impossible because of an increased lipolysis rate. But fat accumulation is determined by the balance between lipogenesis and lipolysis. So, lipid synthesis rate must also be taken into consideration here. Studies demonstrate that in omental fat cells, fat turnover is balanced when considering both fat storage and mobilisation rates (Arner, 1995).

Discussion

Adrenoceptors play a key role in the regulation of fat cell metabolism. The counter-regulatory, antagonistic actions of β and α_2 adrenoceptors exhibit a system evolved to allow for minimal but sufficient lipolytic stimulation, while protecting against excess activation (Li et al., 2022).

α_2 adrenoceptors have a higher affinity and cell surface count than β receptors. So it has been suggested that α_2 adrenoceptors modulate lipolysis during basal conditions, at very low catecholamine concentrations (Lafontan et al., 1997; Arner et al., 1990). α_2 adrenoceptors are highly resistant to desensitisation while β adrenoceptors are not (Arner, 1992; Lafontan & Berlan, 1993). These findings support the hypothesis that a default inhibition is maintained on lipolysis through the action of α_2 adrenoceptors and β adrenoceptors are only employed during stressful conditions and/or when energy demand of the body is high.

Variations in the expression of adrenoceptor subtypes at different anatomic locations have been described. These may be involved in the development of region-specific differences in lipolysis. The presence of a higher catecholamine-induced lipolytic rate in omental fat cells can be attributed primarily to an increased β adrenoceptor count and increased sensitivity to β agonists (Hellmér et al., 1992). Within the subcutaneous adipose tissue, fat cells in the abdominal region display the highest lipolysis rate, followed by gluteal and femoral fat cells. A heightened β adrenoceptor activity in abdominal adipocytes justifies this observation (Arner, 1995).

Specifically in women, a reduction in α_2 adrenoceptor sensitivity has been observed in abdominal adipocytes (Wahrenberg et al., 1989). This may contribute to the previously seen, greater regional variations present in women as compared to men. Women exhibit a tendency to accumulate more fat around the hips than the abdomen (Arner et al., 1990). This may be because of the decreased α_2 adrenoceptor sensitivity in women, which has not been observed in men.

Many studies have shown that obesity is associated with resistance to catecholamines in subcutaneous fat cells (Arner, 1992; Reynisdottir et al., 1994). Whether this resistance is causative of obesity or a resultant of the same is yet to be established. Increased β_2 and decreased α_2 adrenoceptor activity contribute to produce this effect (Arner, 1995). Conversely, lipolysis rate is increased in the omental fat cells of obese people. Studies show that a high

number of β_3 adrenoceptors are present on these cells (Lönnqvist et al., 1995). A decrease in α_2 adrenoceptor activity partly plays a role as well.

To conclude, several variations in lipolysis in different regions and under various physiological conditions have been observed. The causes of most of these variations can be traced back to discrepancies in the actions of adrenoceptor subtypes. These variations have been highlighted and the role of adrenoceptor subtypes in the development of these differences has been reviewed. While much is known about the changes in adrenoceptor behaviour, the relative contribution of adrenoceptor subtypes to disturbed lipolysis in different metabolic conditions remains to be completely elucidated. But it is important since thorough understanding of lipolysis regulation may be helpful in the study of therapeutics for obesity-related metabolic disorders.

References

1. Arner, P. (1992). Adrenergic receptor function in fat cells. *The American Journal of Clinical Nutrition, 55*(1). https://doi.org/10.1093/ajcn/55.1.228s

2. Arner, P. (1995). Differences in lipolysis between human subcutaneous and omental adipose tissues. *Annals of Medicine, 27*(4), 435–438. https://doi.org/10.3109/07853899709002451

3. Arner, P., Kriegholm, E., Engfeldt, P., & Bolinder, J. (1990). Adrenergic regulation of lipolysis in situ at rest and during exercise. *Journal of Clinical Investigation, 85*(3), 893–898. https://doi.org/10.1172/jci114516

4. *BioRender.* BioRender App. (n.d.). Retrieved April 15, 2023, from https://app.biorender.com/biorender-templates

5. Bougnères, P., Stunff, C. L., Pecqueur, C., Pinglier, E., Adnot, P., & Ricquier, D. (1997). In vivo resistance of lipolysis to epinephrine. A new feature of childhood onset obesity. *Journal of Clinical Investigation, 99*(11), 2568–2573. https://doi.org/10.1172/jci119444

6. Carmen, G.-Y., & Víctor, S.-M. (2006). Signalling mechanisms regulating lipolysis. *Cellular Signalling, 18*(4), 401–408. https://doi.org/10.1016/j.cellsig.2005.08.009

7. Hellmér, J., Marcus, C., Sonnenfeld, T., & Arner, P. (1992). Mechanisms for differences in lipolysis between human subcutaneous and omental fat cells. *The Journal of Clinical Endocrinology & Metabolism, 75*(1), 15–20. https://doi.org/10.1210/jcem.75.1.1320047

8. Hoffstedt, J., Shimizu, M., Sjöstedt, S., & Lönnqvist, F. (1995). Determination of β3-adrenoceptor mediated lipolysis in human fat cells. Obesity Research, 3(5), 447–457. https://doi.org/10.1002/j.1550-8528.1995.tb00174.x

9. Kintscher, U., Foryst-Ludwig, A., Haemmerle, G., & Zechner, R. (2020). The role of adipose triglyceride lipase and cytosolic lipolysis in cardiac function and heart failure. *Cell Reports Medicine, 1*(1), 100001. https://doi.org/10.1016/j.xcrm.2020.100001

10. Lafontan, M., & Berlan, M. (1993). Fat cell adrenergic receptors and the control of white and brown fat cell function. *Journal of Lipid Research, 34*(7), 1057–1091. https://doi.org/10.1016/s0022-2275(20)37695-1

11. Lafontan, M., Barbe, P., Galitzky, J., Tavernier, G., Langin, D., Carpene, C., Bousquet-Melou, A., & Berlan, M. (1997). Adrenergic regulation of adipocyte metabolism. *Human Reproduction, 12*(suppl 1), 6–20. https://doi.org/10.1093/humrep/12.suppl_1.6

12. Li, Y., Li, Z., Ngandiri, D. A., Llerins Perez, M., Wolf, A., & Wang, Y. (2022). The molecular brakes of adipose tissue lipolysis. *Frontiers in Physiology, 13*. https://doi.org/10.3389/fphys.2022.826314

13. Lönnqvist, F., Thöme, A., Nilsell, K., Hoffstedt, J., & Arner, P. (1995). A pathogenic role of visceral fat β_3-adrenoceptors in obesity. *Journal of Clinical Investigation, 95*(3), 1109–1116. https://doi.org/10.1172/jci117758

14. Reynisdottir, S., Wahrenberg, H., Carlström, K., Rössner, S., & Arner, P. (1994). Catecholamine resistance in fat cells of women with upper-body obesity due to decreased expression of β_2-adrenoceptors. *Diabetologia, 37*(4), 428–435. https://doi.org/10.1007/bf00408482

15. Wahrenberg, H., Lönnqvist, F., & Arner, P. (1989). Mechanisms underlying regional differences in lipolysis in human adipose tissue. *Journal of Clinical Investigation, 84*(2), 458–467. https://doi.org/10.1172/jci114187

16. World Health Organization. (2022, March 4). *World Obesity Day 2022 – accelerating action to stop obesity.* World Health Organization. Retrieved April 26, 2023, from https://www.who.int/news/item/04-03-2022-world-obesity-day-2022-accelerating-action-to-stop-obesity