# OBESITY: BROWN, WHITE OR BRITE?

## *Different types of adipose tissue and their implications in the treatment of obesity*

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## 1.Introduction

Obesity is the epidemic of our century and its prevalence is increasing. The imbalance between food intake and energy expenditure leads to the accumulation of lipids in the adipose tissue, resulting in obesity and other associated disorders. Because of their role in energy homeostasis, brown and beige fat tissue are powerful targets to fight against obesity. In this work, I collected data from different scientific reports to describe the most powerful treatments of obesity involving fat tissue.

## 2.Matherials and methods

To do this work I have search scientific manuscripts in the PubMed and Web of Knowledge. Moreover, information and images books, web sites and a thesis have been used. Afterwards, I have read all the information and summarized the most relevant data.

## 3. Adipose Tissue

### White Adipose Tissue (WAT)

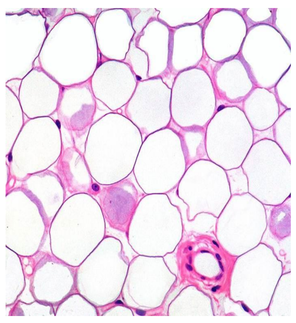

*Image adapted from www.studyblue.com*

**Features**:
-Round cells
-Unilocular lipid droplet
-Thin cytoplasm with few mitochondria
-Peripheral nucleus
**Origin:**
-Myf5- mesenchymal precursor cell
**Function:**
-Stores energy in the form of triglycerides
-Acts as a secretory organ

### Brown Adipose Tissue (BAT)

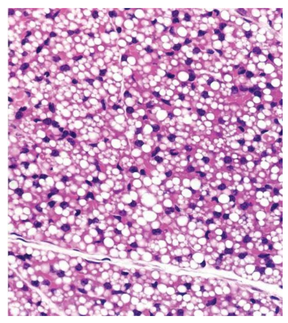

*Image adapted from www.galleryhip.com*

**Features:**
-Polygonal shape
-Multilocular lipid droplet
-Normal cytoplasm with many mitochondria
-Central nucleus
-Express UCP1
**Origin:**
-Myf5 mesenchymal precursor cell
**Function:**
-Combusts energy
-Thermogenesis

### Beige Adipose Tissue

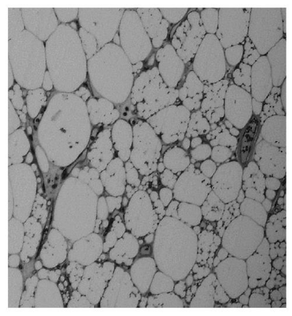

*Image adapted from reference 1*

**Features:**
-Multilocular lipid droplet
-High mitochondrial content
-Express UCP1
**Origin:**
-Two hypothesis:
-Transdifferentiation through white adipocytes
-Myf5- mesenchymal precursor cell
**Function:**
-Stores energy
-Thermogenesis

## 4.Thermogenesis pathway

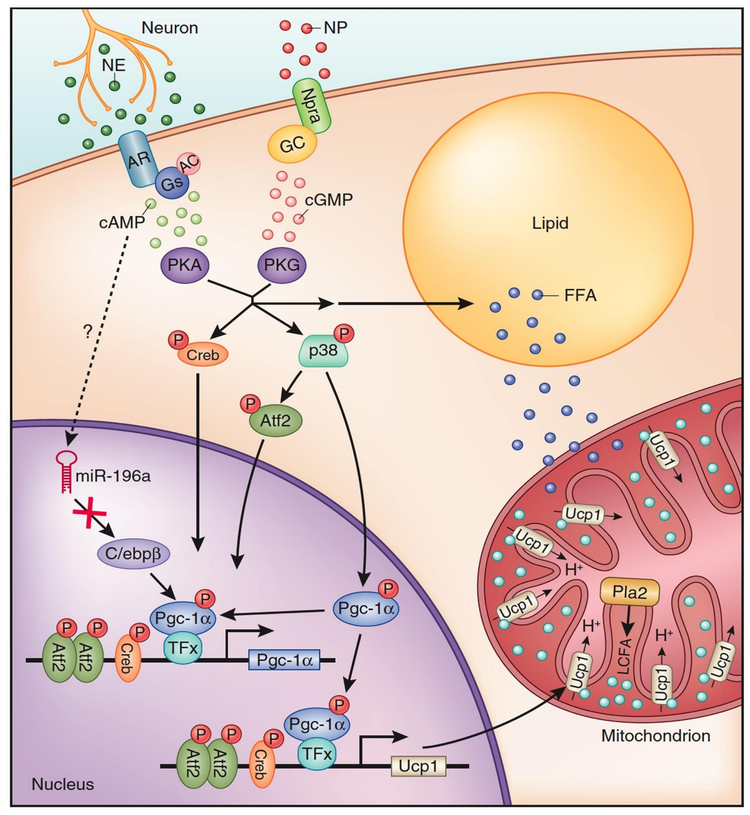


*Image adapted from reference 2*

Adipocytes have an important hormonal role, regulating energy intake and fat storage. In obesity, the adipocytes are enlarged and their functions are dysregulated. Current interest to fight against obesity is focused on the activation of **thermogenesis** in brown and beige adipocytes. Thermogenesis is activated by the sympathetic nervous system, which in turn is activated by cold and diet. Norepinephrine and natriuretic peptides trigger a signalling cascade on adipocyte mediated by PKA and PKG. The effects achieved are, on the one hand, the cleavage of triglycerides from lipids droplets with consequent release of fatty acids, which activates the oxidation of UCP1 protein; on the other hand, thermogenic genes transcription is activated on adipocytes, inducing factors like PGC1-α, PRDM16 and PPARγ, UCP1 expression, mitochondrial biogenesis and enzymatic components involved in oxidation.

## 5. Treatment

| Activation and recruitment of BAT | |
|---|---|
| **Mechanism of action** | **Effect achieved** |
| Cold-sensitive channels (TRP) | The activation of these channels by cold or compounds present on food leads to sympathetic nervous system and thermogenesis activation. |
| Natriuretic peptides(NP) and β-adrenoreceptor (β-AR) agonists | These agonists promote brown adipocytes features and functions in WAT. However, previous therapies have had negative effects because of the lack of organ specificity. |
| Leptin | Central treatment with leptin increase sympathetic activity and norepinephrine, resulting in brown fat activation. |
| **Regulation of lipolysis mechanisms** | |
| **Mechanism of action** | **Effect achieved** |
| Phosphodiesterase PDE3B | This phosphodiesterase controls the regulation of free fatty acids. Its inhibition increase lipolysis, but the release of free fatty acids could lead to side effects. |
| Carnitine palmitoyltransferase (CPT system) | Studies with a non-inhibiting CTP1 isoform shown a reduction in the lipid accumulation in WAT. |
| **Endogenous molecules** | |
| **Mechanism of action** | **Effect achieved** |
| BMP8B | It functions as a thermogenic amplificator in response to adrenergic activators. |
| Sirtuin 1 | It favours PPARγ and PRDM16 interactions, promoting browning. |
| FGF21 | It acts on WAT, increasing PGC-1α amounts and UCP1 expression. |
| Irisin | It is secreted after exercise and it acts recruiting brown adipose tissue to raise energy expenditure. |
| Ghrelin | Ghrelin's receptor ablation favours the sympathetic activation of BAT. |
| BMP7 | It promotes the differentiation of precursor cells into brown adipocytes. |
| RALDH1 (retinaldehyde dehydrogenase) | Its deletion increases the levels of retinaldehyde, which promotes brown fat-like phenotype. |
| Triiodothyronine (T3) | Increase thermogenesis in BAT through the inactivation of AMP-activated protein kinase (AMPK). |
| COX-2 | It acts inducing the expression of thermogenic genes in WAT. |
| **Diet** | |
| **Mechanism of action** | **Effect achieved** |
| Bile acid receptor | Targeting this receptor potentiates the effect of T3, increasing energy expenditure. |
| Capsaicin and capsinoids | It decreases body fat by increasing beige cells activity. |

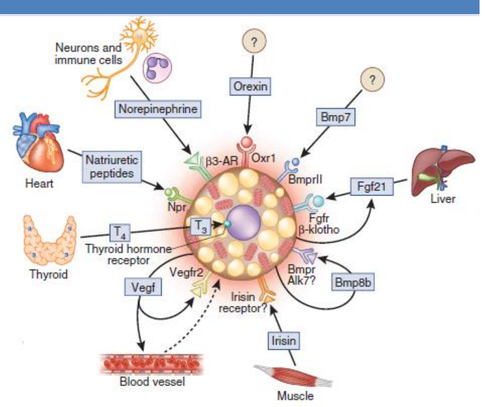


*Image adapted from reference 3*

## 5. Conclusions

A totally unanimous view of the adipocytes differentiation process along with all the molecules involved is necessary to proper address obesity treatment research. Although it is not clear yet if human adults have enough BAT (or its precursor cells) to be activated and thus achieve an important energy expenditure, good pharmacological options arise to target this tissue. Future studies should consider the use of β3-AR agonist in combination with molecules that activate brown and beige cells as treatment. It is also important to find new drugs with safer profiles to individualize obesity therapies.

## 6. References

**[1]:** Giralt, M.; Villarroya, F. ***White, brown, beige/brite: different adipose cells for different functions?***. Endocrinology. 2013 Sep;154(9):2992-3000
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**[3]:** Haas, B ; Schlinkert, P ; Mayer, P ; Eckstein, N. ***Targeting adipose tissue***. Diabetol Metab Syndr. 2012. Oct;4(1):43
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**[5]:** Saito M. ***Brown adipose tissue as a therapeutic target for human obesity***. Obes Res Clin Pract. 2013; 7(6):432-438