

Browning and activation of brown adipose tissue as an anti-obesity treatment

Introduction

Obesity is caused by an energy imbalance when energy intake exceeds energy expenditure. It is characterized by excessive accumulation of adipose tissue, which might impair health. It is the most common metabolic disorder in the world and, according to the WHO, in 2014 more than **1.9 billion** adults were overweight and of these over **600 million** were classified as **obese**.

Currently, the therapeutic strategy that seems to be more promising and powerful to prevent obesity is to **increase energy expenditure** by activating the **brown adipose tissue (BAT)**. This tissue has been recently identified in adults. BAT is the main effector organ of the adaptive thermogenesis and it is specialized in dissipating chemical energy in the form of heat.[1] Therefore, the activation of BAT could enable to oxidize energy reserves and increase energy expenditure, thus promoting weight loss.

Aims and methods

The objectives of this project are:

- To describe the **3 types of adipocytes**, specifying their origin as well as their main features and functions.
- To study the main regulation of BAT: the **sympathetic nervous system (SNS)**.
- To study **irisin, FGF21, NP i BMP7**, endogenous molecules which regulate BAT and are considered possible targets for the anti-obesity treatment.

The methodology used was a literature research. Firstly, recent Reviews regarding BAT were searched in Pubmed. And then, based on their references, specific articles on endogenous molecules that regulate this tissue were used.

Adipose tissue

It is an organ which plays a role in energy homeostasis. Specifically, there are 3 types of tissues: **white adipose tissue (WAT)**, **classic BAT** and **beige**. Beige is a subtype of BAT, which was discovered in 2010, and it is scattered within WAT.

1. Origin and differentiation

Adipose tissue has a mesodermal origin, but 2 types of precursors are derived from mesenchymal stem cells: (Fig.1) [1]

- WAT and beige are derived from **Myf5-precursor**. It is unknown whether beige arises from the transdifferentiation of mature WAT in response to some stimulus or it originates from the differentiation of specific precursors within WAT (CD137+ i TMEM26+). [2] The development process of beige is called **browning**.
- **Myf5+ precursors** are induced to transform into classic BAT.

PPAR-γ is an indispensable factor for the adipogenesis

PRDM16, which modulates PGC-1α, is essential for BAT differentiation

PGC-1α regulates:
✓ Mitochondrial biogenesis
✓ Oxidative metabolism
✓ Thermogenesis

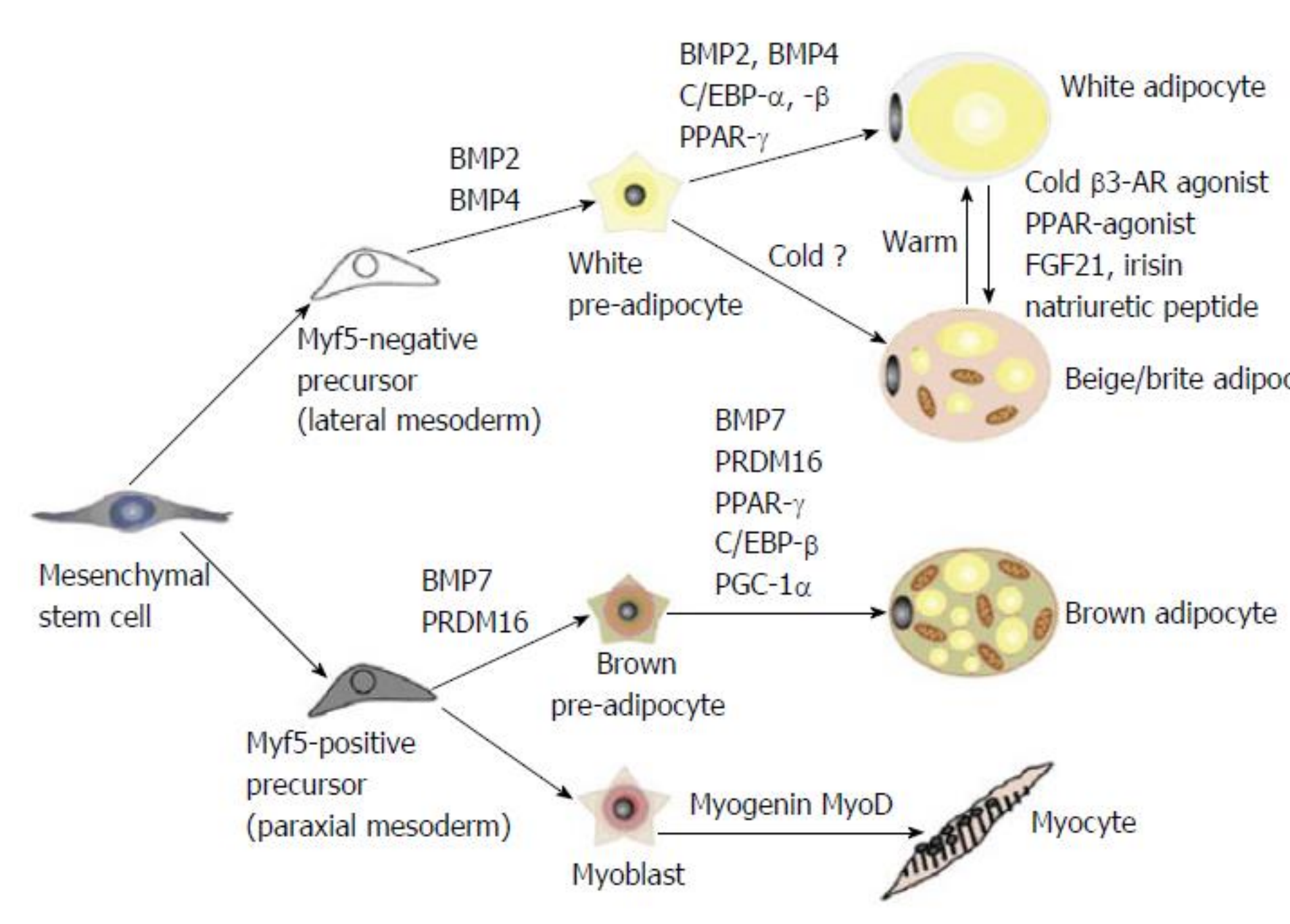
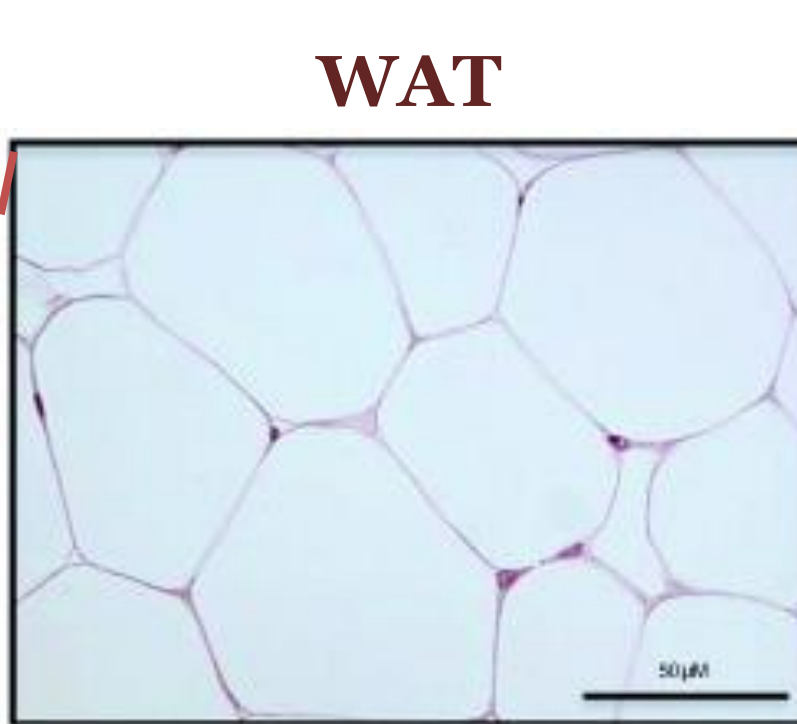


Fig.1 Differentiation into 3 types of adipocytes. [1]

2. Features of the 3 types of adipocytes [1]



Throughout the body there are 2 types of WAT: subcutaneous WAT (sWAT) and visceral WAT.

- Round shape
- A large single lipid droplet
- Nucleus is displaced to periphery
- Few mitochondria
- Yellowish colouring

Storage of energy

Endocrine activity

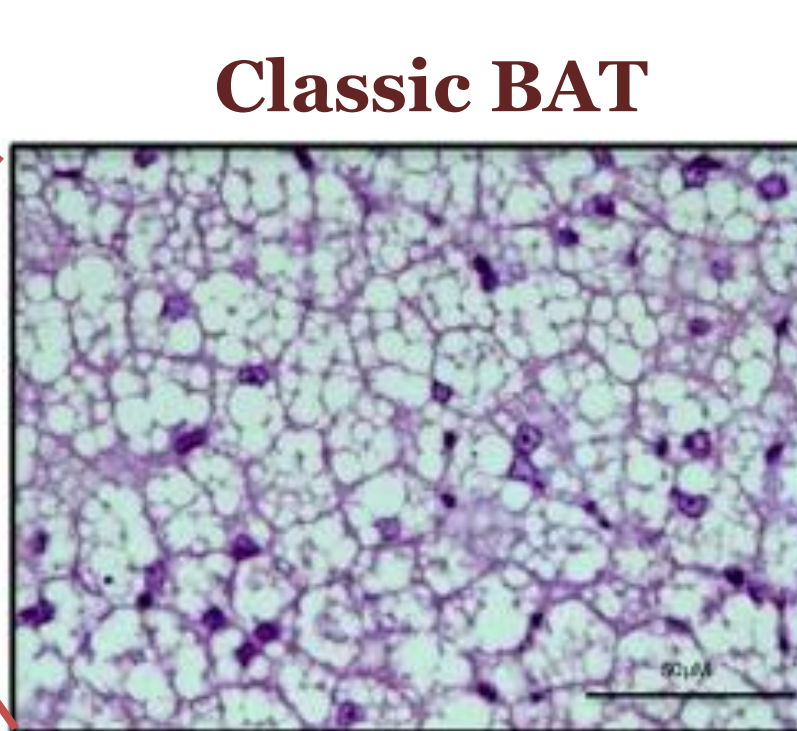


- **Activated states:** similar to classic BAT, increases number of mitochondria and expression of **UCP1 protein**

Heat production

- **Basal states:** similar to WAT

Storage of energy



- Polygonal shape and smaller size
- Numerous small lipid droplets
- Central nucleus
- High number of mitochondria, which contain **UCP1 protein**
- Brownish colouring
- Highly vascularized tissue, innervated by SNS

Heat production

Fig.2 Morphology of the 3 different types of adipocytes. Hematoxylin and eosin staining. [3]

BAT

This tissue is highly abundant in infants. Although it was believed that it gradually disappeared with age, in 2009 studies utilizing detection of ¹⁸F-FDG uptake using PET-CT confirmed its persistence in adults. Some depots are found in cervical and supraclavicular regions. [4]

BAT is the only tissue that expresses:

UCP1 protein

This protein is located in the inner mitochondrial membrane and UCP1 acts as a H⁺ channel, **uncoupling the respiratory chain**.

HEAT

Regulation of BAT

The SNS is the principal pathway of BAT regulation. However, there is a large number of endogenous molecules which regulate and activate it too.

1. Sympathetic nervous system

In response to **cold exposure** or an **excessive intake of food**, the sympathetic tone, which releases **noradrenaline (NE)**, is increased by central mechanisms. Then, NE binds to **β3 receptors** present in the adipose tissue, promoting an intracellular response with the activation of PKA. This activation causes: (Fig.3) [2]

- In BAT → Lipolysis and increase in thermogenic activity.
- In WAT → Lipolysis and browning.

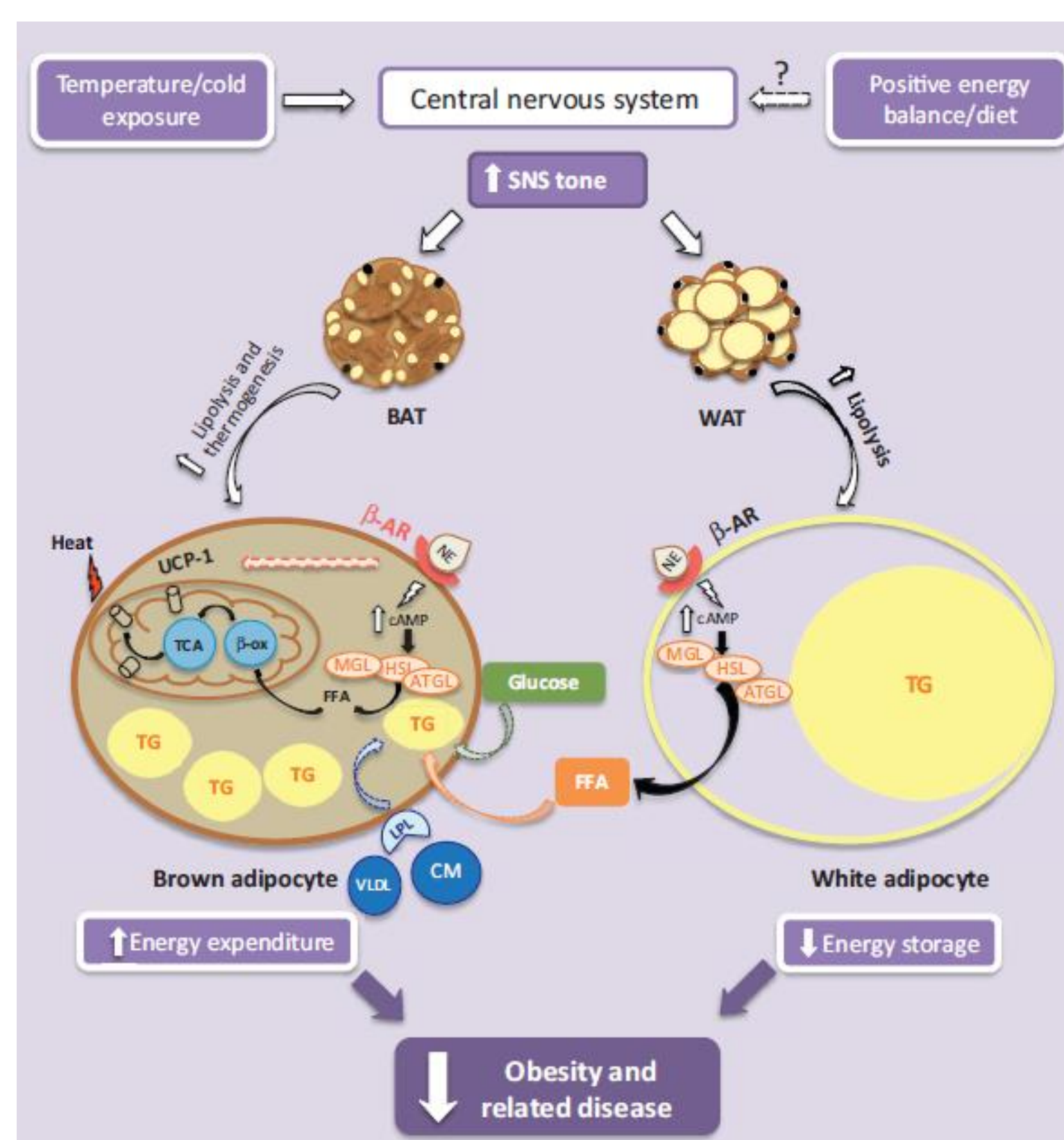


Fig.3 SNS activates BAT and WAT. The increased in the sympathetic tone is a thermogenic stimulus that causes an increase in energy expenditure by activating BAT. [4]

➤ **Lipolysis:** The hydrolysis of triglycerides (TG) generates and releases free fatty acids (FFA). FFA are the substrates of β-oxidation and activate the UCP1 present in BAT.

➤ **Thermogenic activity:** Transcriptional induction of **PGC-1α** which enhances the expression of thermogenic genes such as **UCP1**. There is an increase in energy expenditure.

➤ **Browning:** The expression of thermogenic genes in WAT and energy expenditure are increased.

2. Endogenous molecules that stimulate BAT

All these molecules are proposed as potential therapeutic targets to combat obesity. [5]

Irisin [6,7]

- Myokine identified in 2012 by Boström *et al.*
- Irisin is secreted into the bloodstream by skeletal muscles after doing exercise or shivering in response to cold.
- It acts on CD137+ precursors within sWAT and promotes **WAT browning**, increasing both the expression of thermogenic genes (UCP1) and the thermogenic activity in beige, and energy expenditure.
- Despite having clear therapeutic potential in mice, it is doubtful in humans. Contradictory results were obtained in studies which used different methods for the measurement of irisin after physical exercise.
- It derives from the cleavage of FNDC5, which is expressed in muscle and in WAT. In humans, there is a mutation in the FNDC5 start codon, which could explain why the increase in irisin levels are not detected.
- Mice treated with recombinant irisin showed weight loss.

FGF21

- It is expressed in the liver and in BAT, and regulates glucose and lipid metabolism, and also thermogenesis. Upon cold exposure, its secretion rises in BAT.[7]
- FGF21 acts by **increasing thermogenic activity in BAT** and enhancing **browning in WAT**.
- The administration of FGF21 in animal models with metabolic syndrome causes an increase in energy expenditure and weight loss, and improves insulin sensitivity and lipid parameters. Bone loss was observed as an adverse effect in these mice.
- Obese subjects with Type 2 Diabetes treated with an FGF21 analog showed similar results in animal models.

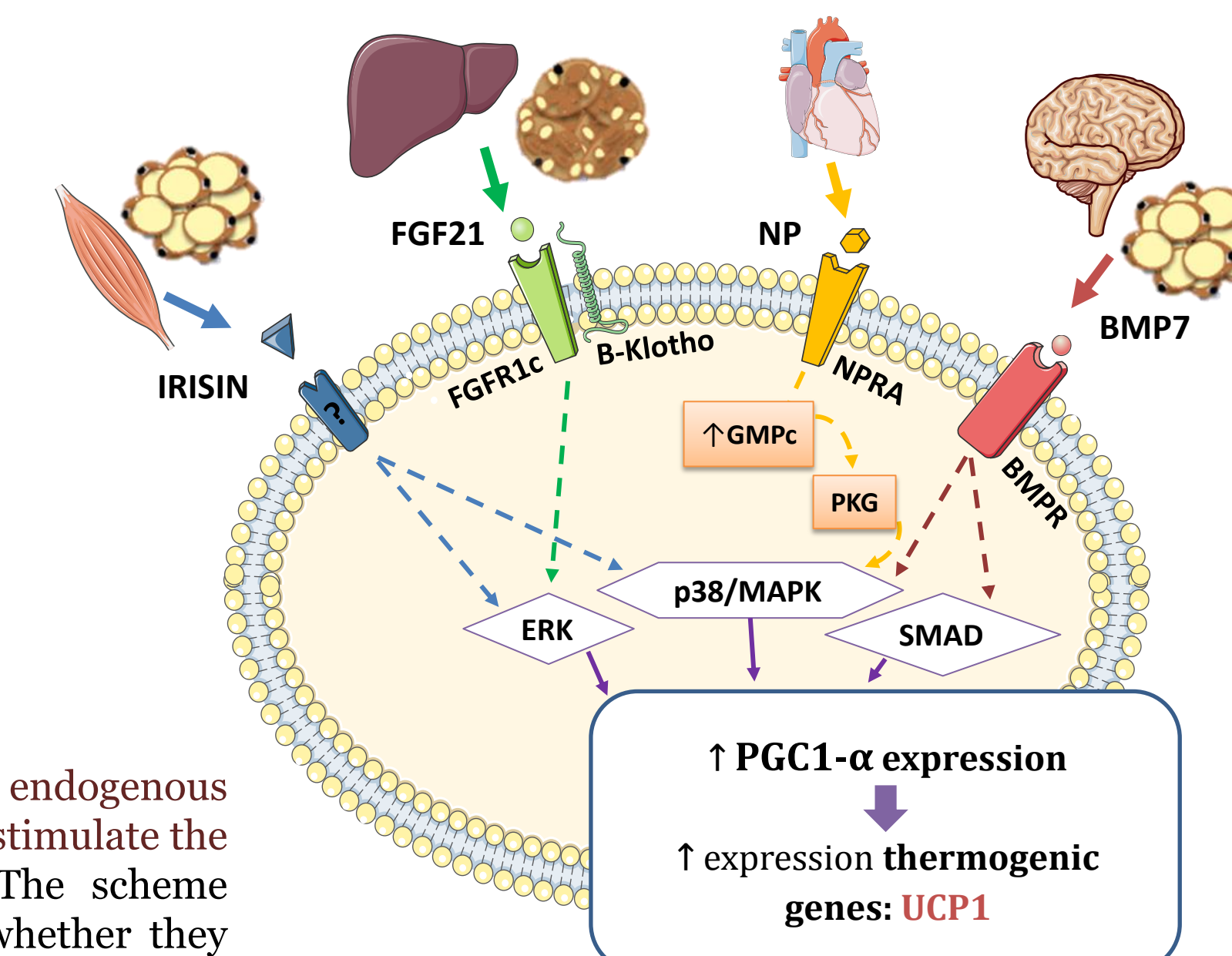


Fig.4 Various endogenous ways which can stimulate the adipose tissue. The scheme does not differ whether they act on WAT or BAT.

Cardiac natriuretic peptides (NP) [2]

- In 2012 Bordicchia *et al.* determined that an increase in circulating NP promotes **browning in sWAT** and **boosts thermogenic activity in BAT**.
- After cold exposure NP levels rise, the expression of NPR1 receptor is augmented and NPR2 expression decreases. So, lipolysis and thermogenic activity are improved.
- An inverse relationship between NP levels and BMI is established.
- Limitation: high NP systemic levels might cause undesirable effects, such as excessive vasodilatation.

BMP7 [8]

- BMP7 is primordial for the development of BAT and promotes **increased thermogenesis in BAT** and **browning in WAT**.
- There is BMP7 expression in the hypothalamus too. This secretion stimulates BAT by a central mechanism and also **decreases appetite** by leptin-independent mTOR pathway.

References

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Conclusions

- There are different endogenous molecules which have thermogenic properties because they could activate BAT and/or promote WAT browning. All these factors are potential therapeutic strategies to combat obesity by increasing energy expenditure and therefore, enhancing weight loss. BMP7 has possibly the greatest therapeutic potential because it acts on BAT and also on the hypothalamus by decreasing appetite.
- Further studies are needed in this area, both regarding the origin of beige or BAT regulation. These studies should be performed mainly on humans, because the regulation may vary from animal models to people.
- Gene therapy could be used to increase PGC-1α expression in WAT or to induce BAT browning, in order to increase adaptive thermogenesis and energy expenditure.