doi: http://dx.doi.org/10.11606/issn.1679-9836.v100i5p460-471 Rev Med (São Paulo). 2021 Sept-Oct;100(5):460-71.

Brown adipose tissue in adults as a study target in the development of new therapies for the management and treatment of obesity: an integrative review

Tecido adiposo marrom em adultos como alvo de estudo no desenvolvimento de novas terapias para o manejo e tratamento da obesidade: uma revisão integrativa

Juliana Moreira Schnaider[1], Beatriz Essenfelder Borges[2]

Schnaider JM, Borges BE. Brown adipose tissue in adults as a study target in the development of new therapies for the management and treatment of obesity: an integrative review / *Tecido adiposo marrom em adultos como alvo de estudo no desenvolvimento de novas terapias para o manejo e tratamento da obesidade: uma revisão integrativa*. Rev Med (São Paulo). 2021 2021 Sept-Oct;100(5):460-71.

ABSTRACT*:* Introduction: The brown adipose tissue was first evidenced in animals and later in humans being its main function the thermoregulation process. From this, possibilities of this auxiliary tissue in the control of body mass are investigated, in order to reach new perspectives in the treatment of obesity, a pandemic of today. Objective: To understand brown adipose tissue and address hypotheses that characterize its contribution to the treatment of obesity and its comorbidities. Materials and Methods: An integrative review was performed in which the keywords brown adipose tissue, obesity, thermogenesis, uncoupling protein 1, UCP were used in the PubMed® and Google Scholar databases. In all, 19 articles and 4 books referring to the histology, cell biology and physiology sciences support the review. Discussion: Adipose tissue is present throughout the human body and causes significant effects on the body's physiology and pathophysiology. The adipocytes that compose it present histological, biocellular and distribution differences and are subdivided into unilocular and multilocular. Multilocular cells form brown fat that is able to regulate energy expenditure through adaptive thermogenesis via an uncoupling protein (UCP). With this knowledge, we look for relationships between adipose tissue composed of unilocular cells, which is responsible for the development of obesity, and brown adipose tissue. In this context, among the study possibilities there are the factors that influence the tissue expression of the uncoupling protein and increase the chemical thermogenesis, there is the control of the energy balance, also, the capacity of brown adipocytes to sequester the succinate (flavoprotein that has acute control over thermogenesis) of the circulation. Conclusion: It was possible to understand the multifunctionality and the physical and chemical characteristics of the brown adipose tissue, and this tissue was recognized as one of the potential study targets given the epidemiological singularity of obesity and its treatment history.

Keywords: Brown adipose tissue; Adipocytes; Thermogenesis; Obesity.

RESUMO: Introdução: O tecido adiposo marrom foi inicialmente evidenciado em animais e posteriormente em humanos tendo sua função principal a termorregulação. A partir disso, pesquisam-se possibilidades desse tecido auxiliar no controle de massa corporal, a fim de alcançar novas perspectivas no tratamento da obesidade, uma pandemia da atualidade. Objetivo: Compreender o tecido adiposo marrom e abordar hipóteses que caracterizam a contribuição deste no tratamento da obesidade e de suas comorbidades. Materiais e Métodos: Realizou-se uma revisão integrativa na qual foram usados os descritores brown adipose tissue, obesity, thermogenesis, uncoupling protein 1, UCP nas bases de dados PubMed® e Google Acadêmico. Ao todo, 19 artigos e 4 livros referentes às ciências Histologia, Biologia Celular e Fisiologia embasam a revisão. Discussão: O tecido adiposo está presente por todo corpo humano e ocasiona efeitos significantes na fisiologia e patologia do organismo. Os adipócitos que o compõem apresentam diferenças histológicas, biocelulares e de distribuição e subdividem-se em uniloculares e multiloculares. As células multiloculares formam a gordura marrom que é capaz de regular o gasto energético por meio da termogênese adaptativa via proteína desacopladora (UCP). Com esses conhecimentos, buscam-se relações entre o tecido adiposo composto pelas células unicelulares, o qual é o responsável pelo desenvolvimento da obesidade, e o tecido adiposo marrom. Nesse âmbito, dentre as possibilidades de estudo há fatores que influenciam a expressão tecidual da proteína desacopladora e aumentam a termogênese química, há o controle do balanço energético e, ainda, a capacidade de adipócitos marrons de sequestrarem o succinato (flavoproteína que exerce controle agudo sobre a termogênese) da circulação. Conclusão: Foi possível compreender a multifuncionalidade e as características físicas e químicas do tecido adiposo marrom e reconheceu-se esse tecido como um dos potenciais alvos de estudo dada a singularidade epidemiológica da obesidade e seu histórico de tratamentos.

Palavras-chave: Tecido adiposo marrom; Adipócitos; Termogênese; Obesidade.

1. Faculdades Pequeno Príncipe. https://orcid.org/0000-0002-5968-1862. E-mail: schnaiderjuliana@gmail.com.
2. Faculdades Pequeno Príncipe. https://orcid.org/0000-0001-9750-5635. E-mail: biaessenfelder@gmail.com
Correspondence: Avenida Sete de Setembro, nº 3000 – Centro. Curitiba, PR. CEP: 80230-010.

INTRODUCTION

According to the Obesity and Comorbidities Research Center (2018)[1], brown adipose tissue (BAT) was initially evidenced in hibernating animals and rodents and, later, in human newborns. Its function would be to produce heat, using the energy released by the oxidation of metabolites, especially fatty acids - uncoupling capacity - during a period of partial inactivity and extreme metabolic reduction in order to avoid hypothermia, mainly in animals[2]. From this capacity to generate heat that BAT presents, it is understood a large part of the importance of brown adipose tissue in thermoregulation of all living beings that have it, and the relevance of further studies is evaluated, since its thermogenic activity can contribute for the control of body mass in mammals[2, 3].

In this context, the identification of brown adipose tissue in adults with 18-fluorodeoxyglucose-labeled positron emission tomography (PET-FDG) was characterized as an incentive for further research and discoveries in this area of knowledge[4]. Thus, since BAT can oxidize fatty acids up to twenty times faster than white adipose tissue (TAB) and, consequently, can increase heat production in cold environments, the relevance of exploring further evidence of the presence of brown adipose tissue in adults is understood[5]. Thus, research on this physiological process of brown adipose tissue becomes essential, as they can result in solid scientific advances when it comes to obesity, which is a severe threat to global public health[6,7].

Obesity has taken on epidemic proportions worldwide, for example, Brazilian data presented in 2018 by the Ministry of Health via Surveillance Survey of Risk and Protection Factors for Chronic Diseases by Telephone Survey (Vigitel) show that 19, 8% of the Brazilian population is obese, a problem whose prevention and control should provide for a wide range of actions that support individuals[8].

This scenario, therefore, justifies the relevance of understanding the activity of the adipose tissue, essentially the BAT, given that it is a topic that is currently little discussed in terms of the topic of obesity related to public health. Thus, the authors seek to contextualize hypotheses about this tissue as possible new clinical approaches in the management and treatment of obesity and its comorbidities.

OBJECTIVE

The objective of this review is to understand and describe brown adipose tissue in adults, as a study target in the development of new therapies for the management and treatment of obesity.

METHOD

For this study, an integrative review (IR) was carried out, which followed the six steps proposed by Mendes et al.[9].

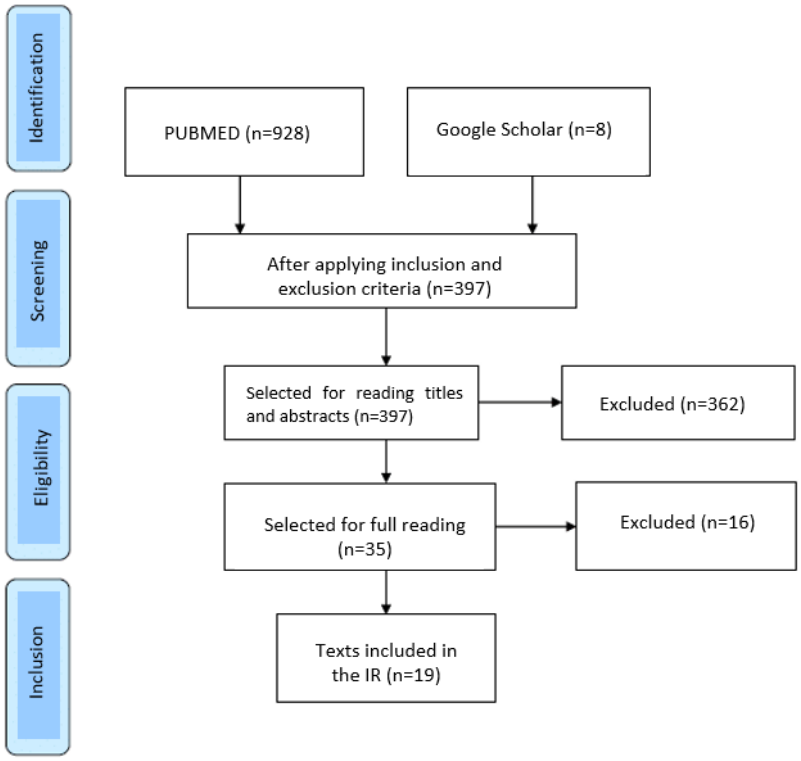
In the first stage, the study theme "Brown Adipose Tissue in Adults and Obesity" was defined, with the guiding question: "How could brown adipose tissue act for the possible treatment of obesity?". The following descriptors were used: brown adipose tissue, obesity, thermogenesis, uncoupling protein 1, UCP and the Boolean operator "and". The search strategy used consisted of dividing the descriptors, so that each search had at least one combination of descriptors. on the theme "adipose tissue" addressing its morphofunctional characteristics, along with the evolution of research in the health area focused on the relationship between obesity and brown fat, as well as the importance of current hypotheses for the development of an effective treatment for obesity, both in books and in the PubMed® and Google Scholar databases.

In the second stage, the criteria for inclusion and exclusion of articles were established. For inclusion, articles published from 2010 to 2020 were selected, in Portuguese and English, complete, free to read, and referring to the tissue in focus of this work and that addressed methods for validating the hypotheses about the presence of this adipose tissue in adult human beings. Articles that were in another language, duplicated articles and that did not focus on the functioning, activation or characterization of adipose tissue, as well as articles that did not address a plausible theoretical correlation between the treatment of obesity and brown adipose tissue, were excluded.

In the third stage (Flowchart 1), in PubMed®, 928 articles were found with two searches. After applying a filter for the period 2010-2020, 636 articles were found. After the selection of free-read texts, 390 articles remained and, using the Portuguese and English language filter, 389 remained. In the reading of the abstracts and titles, articles that did not address the theme of this review were excluded, that is, they did not include the brown adipose tissue or its correlation with obesity and associated comorbidities. Thus, 27 were selected for full reading, among which 11 were chosen that fit the objectives of this review.

In the isolated search in the Google Academic database, we chose to search for free terms related to the central theme of this review and, with this strategy, there was a comprehensive retrieval of references, ensuring the selection of 4 papers published between 2010 and 2020, and with essential relevance, from 4 articles that had dates between 1994 and 2008. With this, 8 articles were chosen, which are compatible with both the pre-established language and thematic criteria.

In all, therefore, 19 articles were used in this study, written in English and Portuguese, the descriptors adopted for the search were selected through the Descriptors in Health Sciences (DeCS). Furthermore, books referring to the sciences Histology, Cell Biology and Physiology were resources used for the technical-theoretical basis.



Source: author, 2021

Flowchart 1. Articles Selection

For the fourth stage, the studies were separated according to the points addressed in the article: definition of adipose tissue and its general characteristics, its identification through tests, as well as its cellular and physiological characterization, the problematization of obesity in the current scenario and the description of scientific hypotheses that address how the activation of brown adipose tissue could be an option for the treatment of obesity.

The fifth step consisted of reflecting on the analyzed texts and compiling the articles to formulate the results of this IR regarding brown fat associated with the treatment of obesity. Finally, the sixth stage aimed to present the synthesis of knowledge evidenced in the articles analyzed, as well as the knowledge produced.

RESULTS

After the selection of articles, a categorization table of selected materials was built, ordered by publication date, to assist in the discussion of the work (Table 1). The table shows the distribution of works according to the first author, year of publication, type of study, sampling, objective and its respective category in this article.

Table 1. Distribution of researched works according to the first author, year of publication, type of study, sampling, objective and its respective category regarding the topic addressed

Articles	Year	First Author	Abstract	Category
1	1994	Kozak	It investigates the UCP1 mini gene region in detail in brown adipocyte tumor cells grown in mice. Deletion analysis of two types of chloramphenicol acetyltransferase genes under control of the UCP promoter defined the mini gene as an enhancer in an essential fragment for the specificity of BAT and the inducibility of noradrenaline	Mitochondria and UCP
2	2004	Cannon	It presents functions of the brown adipose tissue, as well as its importance for classical thermogenesis without tremors, with specifications on the UCP1 protein. In addition, it deals with activation mechanisms of this tissue and, based on that, it justifies, for example, how large amounts of lipid and glucose are used by the tissue	The cells and the tissue Mitochondria and UCP Obesity and Hypotheses

Table 1. Distribution of researched works according to the first author, year of publication, type of study, sampling, objective and its respective category regarding the topic addressed

Articles	Year	First Author	Abstract	Category
3	2006	Alaniz	This review addresses functional aspects of adipocytes, such as metabolism, participation in energy homeostasis, their endocrine ability and adipogenesis, understood as the capacity of pre-adipocytes to differentiate into new adipocytes and reconstitute tissue. In addition, studies on the relationship between adipose tissue and the pineal gland, a little-known but promising aspect of adipocyte physiology with possible favorable repercussions for the treatment of obesity	Cells and tissue Mitochondria and UCP Thermogenesis
4	2008	Murano	Taken together, the data suggest that cold acclimation induces noradrenergic fiber branching in the adipose organ of adult mice, and that these changes may be a precondition for their plastic transformation into a brown phenotype.	Mitochondria and CPU Thermogenesis Obesity and Hypotheses
5	2012	Broetto	This review sought to describe the functioning of brown adipose tissue in normal individuals and the mechanisms by which its deficiency could contribute to the onset of obesity, as well as the possible mechanisms by which its activation could minimize it	Obesity and Hypotheses
6	2012	Cassolla	Work with the main objective of investigating the importance of the thermogenic activity of interscapular brown adipose tissue in the effects induced by the administration of C75 in rats with 24-hour food deprivation	Mitochondria and UCP Obesity and Hypotheses
7	2012	Vicente	He comments on fat metabolism, the causes of brown fat uptake with F18FDG and some protocols adopted to prevent this uptake	Cells and Tissue Identification Obesity and Hypotheses
8	2014	Crane	It addresses recent findings suggesting that increased peripheral serotonin and TPH1 polymorphisms are associated with obesity. It notes that Tph1 deficient mice fed a high-fat diet (HFD) are protected against obesity, insulin resistance and non-alcoholic fatty liver disease (NAFLD), while exhibiting increased energy expenditure by BAT	Obesity and Hypotheses
9	2014	Halpern	This review discusses how old and new concepts, some marginalized for decades, can help to understand diet-induced thermogenesis in brown adipose tissue.	Obesity and Hypotheses
10	2015	Vieira	Study that evaluated the impact of weight reduction after bariatric surgery on brown adipose tissue activity and its connection with the hypothalamus in humans	Cells and Tissue Identification Thermogenesis Obesity and Hypotheses
11	2015	Rachid	An article that evaluated 12 obese, non-diabetic individuals undergoing gastric bypass and 12 lean, for hypothalamic activity in response to cold by magnetic resonance, while the BAT activity was assessed by positron emulsion tomography by fluorodoxyglucose and PCR in real time	Obesity and Hypotheses
12	2015	Wang	This review discusses the evidence that supports BAT an independent role in brown fat thermogenesis, primarily through the release of secreted factors and its implications for physiology and therapeutic development.	Mitochondria and UCP Thermogenesis
13	2017	Emmett	It shows that histone deacetylase 3 (HDAC3) is required to activate brown adipose tissue enhancers to ensure thermogenic suitability. Furthermore, it shows that uncoupling protein 1 (UCP1) is almost absent in brown adipose tissue without HDAC3, and BAT is also markedly down-regulated by mitochondrial oxidative phosphorylation genes, resulting in decreased mitochondrial respiration.	Thermogenesis

Table 1. Distribution of researched works according to the first author, year of publication, type of study, sampling, objective and its respective category regarding the topic addressed

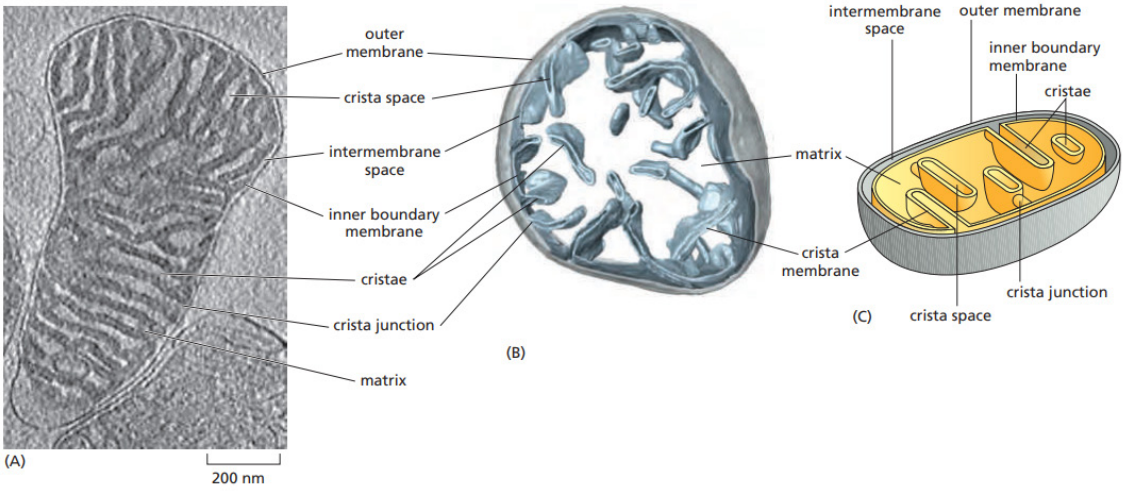
Articles	Year	First Author	Abstract	Category
14	2017	Marzetti	This review provides an overview of current knowledge on the regulation of brown adipose tissue function and discusses the possibility of stimulating it to treat obesity and other metabolic disorders.	Cells and Tissues Thermogenesis
15	2017	Marlatt	Assesses the potential role in stimulating energy expenditure of the activation of brown adipose tissue that has become a trending topic as an anti-obesity treatment	Obesity and Hypotheses
16	2017	Ricquier	The text summarizes the efficiency of uncoupling protein 1 (UCP1), the mitochondrial uncoupler of brown adipocytes. The research aimed to identify the mechanisms of heat production by brown adipocytes that occur in mammals at birth or during exposure to cold.	Mitochondria and UCP
17	2018	Chouchani	Reviews the evidence for regulators of heat production in thermogenic adipocytes in the context of thermodynamic and kinetic principles that have therapeutic utility	Mitochondria and UCP Cells and the Tissue
18	2018	Mills	Identifies a mechanism by which succinate oxidation leads to thermogenic respiration, while succinate dehydrogenase inhibition suppresses thermogenesis	Obesity and Hypotheses
19	2019	Symonds	It reviews the potential mechanisms by which glucose might be utilized by BAT in adult humans and the extent to which they are sensitive to temperature and diet. Including the proportion of glucose oxidation that may be independent of UCP1	Identification Mitochondria and UCP Thermogenesis

Source: author, 2021

DISCUSSION

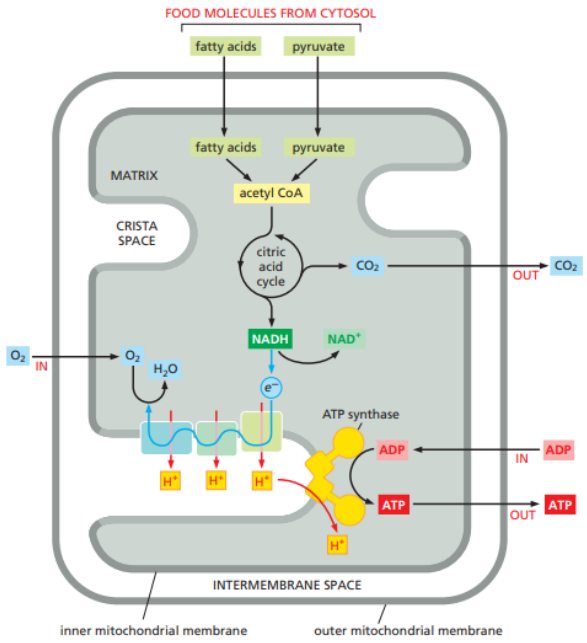
Mitochondria and UCP

Mitochondria are substantial organelles to adipose tissue, so it is important to understand their molecular and functional characteristics. Mitochondria, in general, carry out most of the cellular oxidation and produce energy, adenosine triphosphate (ATP) from animal cells, in addition to having their own genome, ribosomes and exclusive carrier RNA (ribonucleic acid)[10,11]. Given the above, to perform their main function, cell respiration, mitochondria have two membranes, one external and one internal (Figure 1). The internal one projects ridges into the mitochondrial matrix, which have BAT enzymes that participate in oxidation reactions to produce molecules that transfer high-energy electrons to the respiratory chain[10,12].



Source: AlbertsB, et al.[10]
Figure 1. Structure of the mitochondria. Electron microscopy image of a mitochondria (A) and illustrative image (B, C), containing the identification and location of the main structures of the organelle.

The respiratory chain (Figure 2) then uses energy derived from electron transport to produce an electrochemical proton gradient across the inner mitochondrial membrane[13]. Thus, the large amount of free energy released when protons flow back into the matrix provides the basis for ATP production by ATP-synthase[10].



Source: Alberts B, et al.[10]

Figure 2. Mitochondrial energy production. Pyruvate and fatty acids enter the mitochondria (top of figure) and are converted to acetyl-CoA which is metabolized by the citric acid cycle, which reduces NAD+ to NADH, which then transfers its high-energy electrons to the first complex in the chain. electron carrier. In the process of oxidative phosphorylation, these electrons are transferred along the electron transport chain in the ridges of the inner membrane to oxygen (O2). Process that generates a proton gradient, which is used to direct the production of ATP by ATP-synthase. Electrons from an oxidation process follow a separate path to the electron transport chain

After this overview of the functioning of mitochondria in cells, attention is turned to specialized brown adipose cells, in which mitochondrial respiration is uncoupled from ATP synthesis by specific proteins. In these fat cells, most of the oxidation energy is preferentially dissipated in the form of heat and not by conversion to ATP[14,15]. In the inner membranes of multilocular cell mitochondria, uncoupling proteins allow protons to move against the electrochemical gradient without passing through ATP-synthase14. Thus, brown fat serves as a "heating block", capable of resuscitating hibernating animals and protecting newborn humans from the cold10. Thus, the entire process is activated when heat generation is necessary, causing cells to rapidly oxidize their lipid reserves[13,14]. Therefore, it is considered that uncoupled breathing and thermogenesis are responsible for the metabolic benefits of brown adipose tissue to mammals[15].

In this way, known since 1982 when it was identified in the brown adipose tissue of rodents, the uncoupling protein (thermogenin or UCP) is the main source of cellular heat generation[13]. UCP is located in the inner mitochondrial membrane and its mechanism of action is to uncouple the oxidative phosphorylation of the adenosine diphosphate (ADP) molecule[12,16]. Given the findings, the first UCP that was identified in brown adipose tissue was renamed UCP1. Then, in 1997, two new isoforms of this protein were identified: UCP2, which due to its wide distribution in tissues, including white adipose tissue, can act in determining the basal metabolic rate; and UCP3 which is found only in skeletal muscles[10]. Due to the fact that the UCP works by consuming energy stores and releasing heat, its presence in a wide variety of tissues has brought new perspectives regarding its possible role in the clinic of obesity and related pathologies[17].

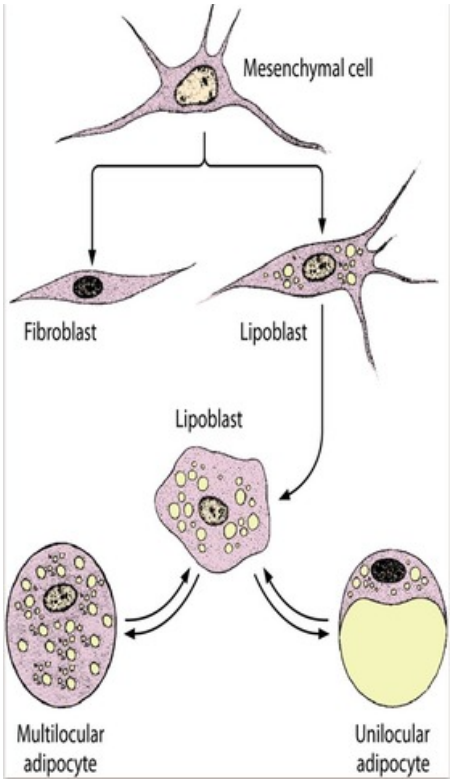
As already mentioned, in the ATP synthesis process, electrons pass through the transport chain, which then return to the mitochondrial matrix passing through ATP-synthetase proteins that use energy for ATP synthesis from ADP and phosphate[10,16,17]. Thus, when UCP1 is stimulated in this process, it serves as an alternative channel for electrons to cross back to the matrix[12]. This protein is responsible for uncoupling oxidative phosphorylation from electron transport, thus, part of the oxidation energy is dissipated in the form of heat and not by conversion into adenosine triphosphate[10,18]. In this sense, this uncoupling protein is essential for the heat production process, that is, the facultative thermogenesis independent of tremor5. Thus, from the exclusive expression of the gene that encodes the UCP protein, an induction of temperature response is noted[19].

In rodents, it has been shown that UCP is stimulated in two situations that activate the sympathetic nervous system: when they are exposed to low temperatures, in which the extra heat generation maintains body temperature, and when they consume a caloric amount above the needs, being a way of expending excess energy to maintain energy balance. Thus, it is understood that in these animals the thermogenesis of brown adipose tissue plays a role both in thermoregulation and maintenance of body mass[18]. Analysis of UCP expression in transgenic mice provided the information that the gene contained regulatory information for specific brown fat expression and cold induction. In this context, the induction of this protein gene is centrally controlled from the hypothalamus through the sympathetic nervous system, with evidence suggesting that noradrenaline, an adrenergic neurotransmitter, binds to beta receptors to initiate an adenosine signal 3 ',5'-cyclic

monophosphate (cyclic AMP)[19].

Cells and the tissue

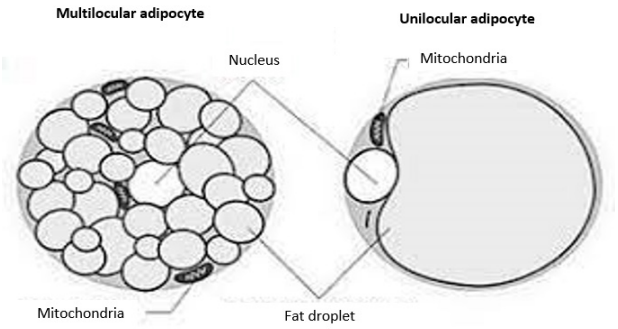
Adipocytes are the cells that form adipose tissue and can be found throughout the human body, whether isolated, such as in loose connective tissue, or even grouped, forming adipose tissue[10,16]. Adipocytes originate from undifferentiated mesenchymal cells (Figure 3), that is, undifferentiated embryonic stem cells that later configure into pre-adipocytes that, under the influence of several activating factors, completely differentiate into adipocytes[10,16, 20]. Therefore, the cells of the classic brown adipose tissue are specified, which have their origin in a cell line that expresses the surface antigen Myf-5, which also gives rise to myocytes, for example[21].



Source: Junqueira LCU, et al.[12]

Figure 3. Origin and development of adipose cells. The uppermost cell is an undifferentiated mensenchymal cell that gives rise to fibroblasts (left) and lipoblasts (right). Lipoblasts differentiate into fat cells.

Given the above, adipocytes are classified into two groups (Figure 4), unilocular and multilocular[22]. In unilocular adipose cells, only a single large droplet of lipid is seen, characterizing white fat. It can be noted that white adipose tissue adipocytes are large, spherical cells that continuously store fat, which can make their cytoplasm and nucleus peripheral[16]. In cells called multilocular, there are multiple small lipid droplets, which belong to the brown adipose tissue. Multilocular adipocytes differ from those mentioned above in that they are more polygonal and, as they store fat in several spherical droplets, the nucleus becomes spherical and more centralized[10,16].



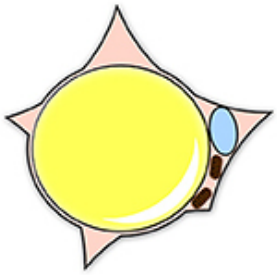
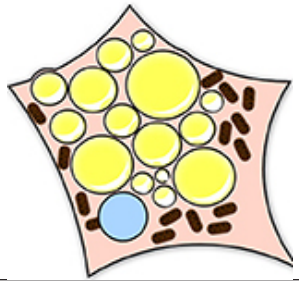
Source: Neves, N.[23]

Figure 4. Representation of multilocular adipocyte and unilocular adipocyte.

In addition, brown adipose tissue cells contain fewer free ribosomes than white fat cells and much more mitochondria, which exclusively express uncoupling protein 1 (UCP1), responsible for uncoupling oxidative phosphorylation from electron transport[10,18, 21].

Given the above, the primary formation of fat in the developing fetus is also analyzed, in which adipocytes are distributed and lipid droplets begin to accumulate in the form of brown adipose tissue[12,16]. Thus, towards the end of fetal life, spindle-shaped precursor cells differentiate into many areas of connective tissue within the fetus and begin to accumulate lipids that coalesce to form the unilocular fat cells found in the adult (secondary fat formation). Therefore, it is understood that brown adipose tissue is present in the embryo and that white appears after birth[11]. With its formation, adipose tissue causes significant effects on the physiology and pathophysiology of the human body, since it conducts one third of the heat conducted by other tissues[3,20]. The two types of adipose tissue, brown and white, differ histophysiologically in terms of vascularization and innervation - these two characteristics are in greater quantity in BAT - but the literature does not address the difference between the distribution of these vessels (Chart I). BAT and TAB also differ in the distribution pattern, as white is much more abundant than BAT[21,22].

Chart 1. Comparison between unilocular and multilocular cells

CELL TYPE	Unilocular	Multilocular
TISSUE	TAB	BAT
REPRESENTATION		
Lipid Content	Larger amount, one drop	Smaller amount, multiple drops
Number of Mitochondria	Few	Many
Expression of UCP1	Many	Few
Vascularization	Adequate, committed to obesity	Very vacularized
Location	Subcutaneous or intra-abdominal	Mainly interscapular and subscapular
Function	Lipid reserve and endocrine function	Thermogenesis

Source: Adapted from Hildebrand S, et al.[24]

Therefore, first, the white adipose tissue (unilocular) that is present in the subcutaneous layer and accumulates in characteristic places, such as the abdominal cavity, neck, shoulders, around the hips, breasts and sides of the skin, is addressed. thighs, being irrigated by blood vessels that contemplate the nerve endings of the tissue and that form networks of capillaries, having their access through the connective tissue septa[12,16]. Secondly, the brown adipose tissue (multilocular) is described, which is found in the neck and interscapular regions, which presents its color and may vary due to its extensive vascularization and also by the cytochromes of the mitochondria[25]. In addition, the nerve fibers penetrate the brown adipose tissue and the axons end with the vessels and also along with the adipose cells[12].

Identification

Adipose tissue is the body's main energy reservoir and the identification of the brown phenotype in adults, with the development and use of 18-fluorodeoxyglucose-labeled positron emission tomography (PET-FDG), showed how important this tissue is in human metabolism[21 ,25]. PET-FDG is a test that has the ability to detect metabolically active areas that absorb FDG, a glucose radioisotope[14]. This PET-FDG test began to be used in oncology in the 1990s to detect tumors and metastases, which generally have a high metabolic rate and, therefore, high glucose uptake[14].

Then, in 2009, with the publication of articles[26,27,28] in the same issue of the *New England Journal of Medicine*, the scientific community realized that a fraction of human adults has brown adipose tissue and it has again attracted attention in the scientific community. In these studies, published in *The New England Journal of Medicine*, five healthy adult subjects underwent PET-CT during cold exposure. All had increased FDG uptake in the supraclavicular region and three of these individuals underwent tissue biopsy from this region, which revealed the presence of brown adipose tissue markers, such as UCP-1 (Uncoupling protein 1), DIO2 (type II iodothyronine deiodinase), PGC1α (Peroxisome proliferator-activated receptor-γ coactivator 1-α), PRDM16 (PR/SET domain 16) and ADRB3 (Adrenoceptor Beta 3)[26,27,28].

According to the *Brazilian Society of Nuclear Medicine* (2015)[29], the heart and brain are also consistently detected, given that they are organs with marked use of glucose even during fasting[29]. Thus, it is seen that, in fact, before the advent of PET/CT, brown fat uptake could be misinterpreted as muscle or tumor uptake18. With this knowledge, Vieira[21], in his investigative study on the BAT, showed that, in a fraction of the PET scans performed, bilateral areas of symmetric FDG uptake were detected in the supraclavicular, cervical and parasternal regions in adult individuals. In this context, anatomically, the highly active areas could not be easily interpreted initially due to the characteristics described, but with further analysis these areas were recognized as previously unrecognized brown adipose tissue, which proliferated under chronic noradrenergic stimuli in patients, such as exposure to cold and prolonged fasting[21].

Thermogenesis

Functionally, brown adipose tissue is able to regulate energy expenditure through a process called adaptive thermogenesis, which depends on the expression of the UCP1 protein mentioned above[3]. Thus, it is considered that

the total thermogenic capacity of the tissue is determined by the total number of brown adipocytes, that is, by the rates of proliferation and apoptosis plus the degree of tissue differentiation, including the mitochondrial density and the amount of UCP1[22].

In this sense, among the factors that most significantly influence the brown adipocyte to stimulate tissue expression of mitochondrial oxidative phosphorylation uncoupling protein and increase chemical thermogenesis or thermogenesis without chills, there are sympathetic fibers that release norepinephrine and epinephrine[14,21]. From this, the activation of brown adipose tissue leads to increased energy expenditure and reduced adiposity to lower plasma glucose and lipid levels, contributing to better homeostasis[15]. Given the above, the main signal for activation of brown adipocytes is considered to be the reduction in body temperature below the thermoneutral (23°C)[21]. In this bias, since mammals need to maintain their temperature, cold is the main physiological stimulus for this noradrenergic activation[18].

One factor that affects the intensity of chemical thermogenesis, which is not caused by chills and can serve as a tampon against obesity, is acclimatization. Whereas some animals, such as rats, exposed to the cold environment for several weeks, show a 100% to 500% increase in heat production when exposed to acute cold, in contrast to the non-acclimated animal[20]. Although brown adipose tissue is a thermogenic organ that dissipates chemical energy in the form of heat, in adult humans, it is rare for chemical thermogenesis to increase heat production by more than 10% to 15%. However, in infants, this mechanism has been proven to increase heat production up to 100%[30], since pregnant women during this period have a considerable number of brown fat cells, which is an important factor in maintaining a normal temperature in newborns[20].

In this context, it is important to remember that this elevated thermogenesis also leads to a corresponding increase in food intake and after a meal. The thermogenic effect of food corresponds to 8% of daily energy expenditure in most people[16,20]. With food, therefore, when fatty acids reach the adipocytes, through the β-oxidation mechanism, they are converted into acyl-coenzyme A and later transformed into acyl-carnitine and forwarded to the mitochondria, where they serve as a substrate for thermogenesis and regulate the function of the CPU[15].

Obesity and Hypotheses

The term obesity means depositing excessive amounts of fat in the body. It currently represents one of the biggest public health challenges in the world and is one of the most prevalent diseases on the planet, affecting 30% of the world population[20,21]. In a study published in *the International Journal of Obesity*, it was observed that there was an inverse correlation between the amount of brown adipose tissue and the body mass index, which suggested that brown adipose tissue would play a role of metabolic control, as mentioned above[31].

The behavioral approach to obese individuals, with the concomitant use of low-calorie diets and stimulation of physical activity, leads to a loss of at most 10 to 15% of the initial weight within 6 months to 1 year, however, there is often a late failure. Furthermore, with regard to drugs currently approved for use, the maximum loss in 6 months hardly exceeds 15% of the initial weight and recurrences are also recurrent21. In this context, it is known that there are still no humanly efficient therapeutic approaches to prevent or reverse obesity, thus justifying the intense search for new therapeutic targets[25].

Thus, even though it may challenge the adipostatic hypothesis of body weight control, since its activation generates an energy expenditure that is not compensated by the increase in food intake, the demonstration of the presence of brown adipose tissue in adult human beings generated theoretical expectations regarding its potential as a target for therapeutic approaches[11]. In order to understand possible treatment approaches, it is important to recognize thermogenesis as the most variable component of daily energy expenditure. Thus, the search for a safe and effective way to increase the metabolic rate has become increasingly essential, both to help with weight loss and to neutralize the metabolic adaptation that occurs with caloric restriction and weight loss[7].

Given the above, it is known that the prevalence of brown adipocytes in adipose tissue is responsible for resistance to obesity in small mammals and some recent data seem to point to a similar mechanism in humans, since the messenger RNA of UCP1 (uncoupling proteins 1) is reduced in the visceral adipose tissue of obese patients and the genes expressed in the brown phenotype are under expressed in overweight patients with insulin resistance[18].

In this way, several hypotheses are addressed in the scientific community about how brown tissue involves genetic and even thermal issues in its functioning. For example, at the *Research Center on Obesity and Comorbidities at the University of São Paulo* (USP)[1] researchers have recently discovered that brown tissue can burn even more fat through interleukin 10 (IL-10)[1]. This interleukin is produced by cells of the immune system and usually acts as an immunosuppressant, being especially useful in inflammatory situations. Although it is a controversial topic and needs further study, studies in mice showed that the inhibition of IL-10 resulted in an increase in thermogenesis, energy expenditure and darkening of white adipose tissue[32]. IL-10 binds to adipose tissue cells and reduces the expression of genes that regulate energy expenditure, promoting a metabolically harmful phenotype. For this reason, interleukin is a target of research in order

to prove whether this substance can play a role. similar in human white fat or whether the contrast with animal models will remain[32].

One possibility involved in the control of energy balance is the primordial signaling molecule, serotonin, which, in its majority, is produced by the enzyme TPH1 (tryptophan hydroxylase 1). High levels of central serotonin (5% of total serotonin) are able to reduce appetite, but studies report that peripheral serotonin (circulating part in the blood - 95%), when increased, can reduce the activity of brown adipose tissue[33]. It is known, then, that in mice, if TPH1 is genetically removed or blocked, even if they are fed a high-fat diet, they are protected from obesity and insulin resistance, since there is an improvement in the ability of the multilocular adipose tissue in burning calories. Thus, the chemical inhibition of small TPH1 molecules mimics the benefits attributed to its genetic deletion, effects dependent on UCP1[33]. Thus, since obesity increases peripheral serotonin, the inhibition of the signaling of this substance or its synthesis in the adipose tissue can be a way of treatment for obesity and its comorbidities[33].

The literature still brings the development of drugs that could increase the formation of brown adipose cells or even induce the differentiation of white adipose tissue into brown, increasing thermogenesis. However, development is dependent on in-depth knowledge of cellular mechanisms that control the formation and function of brown adipocytes34. Furthermore, during the development of obesity, there is a progressive deterioration of hypothalamic activity, which results in a progressive loss of response to anorectic and pro-thermogenic substances. Therefore, it is recognized that brown adipose tissue is one of the potential targets of the pro-thermogenic action of the hypothalamus through substances such as leptin, insulin, adiponectin and the neuropeptide Y[21].

Some hypotheses for the reversal of obesity are based on the activity of brown adipose tissue in response to cold, which depends on a neural signal generated in the hypothalamus, considering that this response can be modulated during weight loss[21]. In mice and rats, exposure to cold or administration of beta-adrenergic agonists induces the appearance of brown adipocytes in deposits considered specific to white fat. It is believed, then, that the activation of receptors can effect this transformation of adipocytes and that this conversion could contribute to the treatment of obesity and diabetes[18].

Therefore, it is reaffirmed that brown adipose tissue is activated mainly via beta 3 receptors, with noradrenaline being released by the sympathetic terminals, next to adipocytes, and inducing the cell machinery to produce heat, although other adrenergic receptors. can activate it[5,21]. A study in healthy humans using indirect calorimetry and stable isotopes showed that cold exposure resulted in a 14% increase in resting metabolic rate in individuals with detectable levels of brown adipose tissue and that this increase was fueled by plasma-derived glucose (30%) and free fatty acid oxidation (70%). Similarly, individuals with obesity or type 2 diabetes experienced an improvement in insulin sensitivity after a short-term 10-day cold acclimatization, which resulted in enhanced brown adipose tissue activity and whole-body insulin sensitivity (43%) in overweight men with type 2 diabetes[7].

Another study brought the newly discovered ability of brown adipocytes to sequester succinate from the circulation, since this flavoprotein exerts acute control over UCP1-dependent thermogenesis, triggering the production of reactive oxygen species (mitochondrial ROS) by oxidation. Thus, in certain physiological contexts, the accumulation of circulating succinate in the brown adipose tissue, which is further increased with exposure to 4°C, suggests that the peripheral tissues supply it to the brown adipose tissue through the circulation after exposure to cold[35]. Thus, in addition to identifying a new molecular pathway for activating adipocyte heat production, these data demonstrate that succinate acts as a systemic signal that exerts profound effects on body metabolism[35].

The correlation of brown adipose tissue with obesity, therefore, is admitted as a subject of wide possibilities and of an exploratory nature still under study, since, despite the high potential of brown adipose tissue as a target for the treatment of obesity and the role of Sympathetic nervous system as an activator of its thermogenic function, clinical studies mostly still fail in humans when trying to promote changes in the energy balance with drugs with beta-adrenergic action[2]. Given the above, therefore, given the epidemiological uniqueness of obesity, it is understood the importance of searching for new targets that provide advances in the prophylaxis and treatment of this problem and it is understood that the presented hypotheses need further investigation in order to become scientifically proven facts.

CONCLUSION

This work presented information regarding a little explored tissue in the adult human body, the brown adipose tissue. Given the above, it was possible to see that the adipose tissue in its broad approach is essential to the animal kingdom, as it is multifunctional and as a target topic for further research, since, during the performance of this IR, the lack was noticed. practical evidence regarding the theoretical hypotheses made.

Therefore, it was understood the importance of differentiating brown and white adipose tissues in terms of their anatomy and physiology, and it is also necessary to understand the events that characterize the thermogenic capacity of BAT. Given this understanding, several hypotheses were observed that correlate the importance of the physiological role of BAT as the target of studies that address the development of new therapies for the

management and treatment of obesity.

Finally, with the topics covered in this work and the construction of microscopic reasoning to the possibility of a proper clinical approach, it is stated, given the new technologies and advances in medicine, how significant is the expansion of research in this area. In addition, it is necessary to expand the search for functional correlations between brown adipose tissue and obesity in adults, since this is a worldwide problem in the context of public health.

Authors participation: Juliana Moreira Schnaider is the author who contributed to the research in the databases and informed references, conceived and wrote the integrative review. Beatriz Essenfelder Borges is the author who contributed guidance to the main author, provided scientific and methodological support, as well as corrected the integrative review.

REFERENCES

1. Jornal da EPTV destaca pesquisa do OCRC sobre tecido adiposo marrom. Obesity and Comorbidities Research Center [citado 20 jan. 2021]. Disponível em: https://www.ocrc.org.br/pesquisa-do-ocrc-e-destaque-do-jornal-da-eptv/.
2. Halpern B, Mancini MC, Halpern A. Tecido adiposo marrom: o que aprendemos desde sua recente identificação em humanos adultos. Arq Bras Endocrinol Metab. 2014;58(9):889-99. doi: 10.1590/0004-2730000003492.
3. Marzetti E, D'Angelo E, Savera G, Leeuwenburgh C, Calvani R. Integrated control of brown adipose tissue. Heart Metabol. 2016;69:9-14. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4980093/
4. Pessanha LB, Oliveira ARN, Guerra LFA, Martins DLN, Rondina RG, Mello MBN. PET/CT e gordura marrom na avaliação da resposta terapêutica no linfoma de Hodgkin. Radiol Bras. 2015;48(6):402-3. http://dx.doi.org/10.1590/0100-3984.2015.0029.
5. Cassolla P. Importância do tecido adiposo marrom na ativação da termogênese induzida pela injeção central do C75, um inibidor da ácido graxo sintase [doutorado]. Ribeirão Preto: Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo; 2012. Disponível em: https://www.teses.usp.br/teses/disponiveis/17/17134/tde-24092012-155205/publico/Tese_Pri_definitivo.pdf
6. Brasil. Ministério da Saúde. Secretaria de Atenção à Saúde. Departamento de Atenção Básica. Estratégias para o cuidado da pessoa com doença crônica: obesidade. Brasília; 2014 [citado 20 jan. 2021]. Disponível em: https://bvsms.saude.gov.br/bvs/publicacoes/estrategias_cuidado_pessoa_doenca_cronica_cab35.pdf
7. Marlatt KL, Ravussin E. Brown adipose tissue: an update on recent findings. Curr Obes Rep. 2017;6(4):389-96. doi: 10.1007/s13679-017-0283-6
8. Brasil. Ministério da Saúde. Vigitel. Ministério da Saúde alerta para doenças desencadeadas pela obesidade. Brasília; 2020 [citado 20 jan. 2021]. Disponível em: https://www.gov.br/pt-br/noticias/saude-e-vigilancia-sanitaria/2020/03/ministerio-da-saude-alerta-para-doencas-desencadeadas-pela-obesidade
9. Mendes KDS, Silveira RCCP, Galvão CM. Revisão integrativa: método de pesquisa para a incorporação de evidências na saúde e na enfermagem. Texto Contexto Enferm. 2008;17(4):758-64. https://doi.org/10.1590/S0104-07072008000400018.
10. Alberts B, Bray D, Lewis J, Raff M, Roberts, K. Biologia molecular da célula. 6a. ed. Porto Alegre: Artes Médicas; 2017.
11. Cannon B, Nedergaard J. Brown adupose tissue: function and physiological significance. Am J Physiol. 2004;277-359. doi: 10.1152/physrev.00015.2003
12. Junqueira LCU, Carneiro J. Histologia básica. 12a. ed. Rio de Janeiro: Guanabara Koogan; 2013.
13. Chouchani ET, Kazak L, Spiegelman BM. New Advances in adaptive thermogenesis: UCP1 and beyond. Cell Metab. 2018;29(1):27-37. doi: https://doi.org/10.1016/j.cmet.2018.11.002
14. Symonds ME, Farhat G, Aldiss P, Pope M, Budge H. Brown adipose tissue and glucose homeostasis - the link between climate change and the global rise in obesity and diabetes. Adipocyte. 2019;8(1):46-50. doi: 10.1080/21623945.2018.1551689
15. Wang GX, Zhao XY, Lin JD. The brown fat secretome: metabolic functions beyond thermogenesis. Trends Endocrinol Metab. 2015;26(5):231-7. doi: 10.1016/j.tem.2015.03.002
16. Gartner LP, Hiatt JL. Tratado de histologia em cores. 3a. ed. Rio de Janeiro: Elsevier; 2007.
17. Ricquier D. UCP1, the mitochondrial uncoupling protein of brown adipocyte: a personal contribution and a historical perspective. Biochimie. 2017;134:3-8. doi: 10.1016/j.biochi.2016.10.018.
18. Murano I, Barbatelli G, Giordano A, Cinti S. Noradrenergic parenchymal nerve fiber branching after cold acclimatisation correlates with brown adipocyte density in mouse adipose organ. J Anat. 2008;214(1):171-8. https://doi.org/10.1111/j.1469-7580.2008.01001.x
19. Kozak UC, Kopecky J, Teisinger J, Enerbäck S, Boyer B, Kozak LP. An upstream enhancer regulating brown-fat-specific expression of the mitochondrial uncoupling protein gene. Mol Cell Biol. 1994;14(1):59-67. doi: https://doi.org/10.1128/mcb.14.1.59-67.1994
20. Hall JE, Guyton AC. Tratado de fisiologia medica. 12a. ed. Rio de Janeiro: Elsevier; 2011.
21. Vieira BRD. O tecido adiposo marrom e o hipotálamo são regulados de forma independente em resposta ao frio em humanos obesos [doutorado]. Campinas: Universidade Estadual de Campinas; 2015 [citado 20 jan. 2021]. Disponível em: http://repositorio.unicamp.br/jspui/handle/REPOSIP/312819

22. Fonseca-Alaniz MH, Takada J, Alonso-Vale MIC, Lima FB. O tecido adiposo como centro regulador do metabolismo. Arq Bras Endocrinol Metab. 2006;50(2):216-29. https://doi.org/10.1590/S0004-27302006000200008

23. Neves NN. Indução do emagrecimento pela restrição calórica com dieta hiperlipídica e seus efeitos na inflamação do tecido adiposo de camundongos obesos [mestrado]. Diamantina: Universidade Federal dos Vales do Jequitinhonha e Mucuri; 2018. Disponível em: http://acervo.ufvjm.edu.br/jspui/handle/1/1919

24. Hildebrand S, Stumer J, Pfeifer A. PVAT and its relation to brown, beige, and white adipose tissue in development and function. Front Physiol. 2018;9:70. doi: https://doi.org/10.3389/fphys.2018.00070

25. Vicente A. Captação de gordura marrom em F18FDG PET/CT. Medicina Nuclear do Instituto Cimas de Ensino; 2012 [citado 20 jan. 2021]. Disponível em: https://docplayer.com.br/14311725-Captacao-de-gordura-marrom-em-f-18-fdg-pet-ct-uptake-brown-fat-tissue-in-f-18-fdg-pet-ct.html

26. Virtanen KA, Lidell ME, Orava J, Heglind M, Westergren R, Niemi T, et al. Functional brown adipose tissue in healthy adults. N Engl J Med. 2009;360(15):1518-25. doi: 10.1056/NEJMoa0808949

27. Cypess AM, Lehman S, Williams G, Tal I, Rodman D, Goldfine AB, et al. Identification and importance of brown adipose tissue in adult humans. New Engl J Med. 2009;360(15):1509-17. doi: 10.1056/NEJMoa0810780

28. Seale P, Kajimura S, Yang W, Chin LM, Rohas M, Uldry G, et al. Transcriptional control of brown fat determination by PRDM16. Cell Metab. 2007;6:38-54. Available from: https://www.sciencedirect.com/science/article/pii/S155041310700157X

29. Amorim BJ. Guideline para PET/CT FDG-18F. Sociedade Brasileira de Medicina Nuclear, abr; 2016. Disponível em: https://sbmn.org.br/wp-content/uploads/2016/04/Guideline-PET-CT-FDG-18F.pdf

30. Emmett M, Lim HW, Jager J, et al. Histone deacetylase 3 prepares brown adipose tissue for acute thermogenic challenge. Nature. 2017;546:544-48. doi: https://doi.org/10.1038/nature22819

31. Rachid B, Van De Sande-Lee S, Rodovalho S, Folli F, Beltramini GC, Morari J, et al. Distinct regulation of hypothalamic and brown/beige adipose tissue activities in human obesity. Int J Obes. 2015;39:1515-22. doi: 10.1038/ijo.2015.94

32. Juan RA, Tavira B, Douagi I, Kulyté A, Arner P, Rydén M, et al. Human-Specific Function of IL-10 in Adipose Tissue Linked to Insulin Tissue. J Clin Endocr Metab. 2019;104(10):4552-62. doi: https://doi.org/10.1210/jc.2019-00341

33. Crane JD, Palanivel R, Mottillo EP, Bujak AL, Wang H, Ford RJ, et al. Inhibiting peripheral serotonin synthesis reduces obesity and metabolic dysfunction by promoting brown adipose tissue thermogenesis. Nature Med. 2014;21(2):166-72. doi: https://doi.org/10.1038/nm.3766

34. Broetto FN, Brito MN. Tecido adiposo marrom e obesidade em humanos. Rev Saúde Pesq. 2012;5(1):121-35. Disponível em: https://periodicos.unicesumar.edu.br/index.php/saudpesq/article/view/2083

35. Mills EL, Pierce KA, Jedrychowski MP, Garrity R, Whinther S, Vidoni S, et al. Accumulation of succinate controls activation of adipose tissue thermogenesis. Nature. 2018;560:102. doi: https://doi.org/10.1038/s41586-018-0353-2

Submited: 2021, February 15
Accepted: 2021, September 20