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Is beige adipose tissue induced by physical exercise?

O tecido adiposo bege é induzido pelo exercício físico?

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ABSTRACT

Introduction: Adipose tissue is divided into yellow, brown and beige. Beige has a thermogenic function in newborns and recent research has shown its potential for improving metabolic health in adults; its synthesis is associated with practice of physical exercise and related to the potential treatment of obesity.

Objective: To present the histology of adipose tissue, its general characteristics, formation, biochemical and physiological mechanisms, as well as the relationship between beige adipose tissue, physical exercise, and obesity.

Method: Narrative review, comprising 27 articles, available in PubMed and Scielo databases and technical scientific books. The descriptors used were "beige adipose tissue", "exercise", "adipose tissue".

Result: Yellow adipose tissue is related to the storage of triglycerides and energy maintenance. Brown is primarily thermogenic, its adipocytes using the energy contained in triacylglycerols to release heat. Beige consists of a combination of unilocular and multilocular adipocytes and can imitate the metabolic function of brown adipose tissue when stimulated. The hormone irisin, stimulated by physical exercise, induces the mRNA of uncoupling protein 1 which promotes the darkening of yellow adipose tissue, forming beige adipose tissue. Regular physical activity increases mitochondrial biosynthesis, increasing the oxidative and thermogenic capacity of beige adipose tissue. This effect may be beneficial against obesity.

Conclusion: Regular physical exercise has a great impact on the modulation of beige adipose tissue, promoting the conversion of yellow adipose tissue into beige, favoring energy expenditure and the secretion of metabolic regulation molecules. Thus, physical exercise is powerful ally in the treatment of obesity, as it stimulates the formation of beige adipose tissue.

KEYWORDS: Beige adipose tissue, exercise, adipose tissue

Mensagem Central

Beige adipose tissue plays a relevant thermogenic and metabolic role and can be induced from white adipose tissue through physical exercise. The activation of hormonal pathways, particularly mediated by irisin and uncoupling protein 1, is associated with increased energy expenditure and improved metabolic profile, representing a potential adjuvant strategy in the treatment of obesity.

Perspectiva

Evidence that physical exercise positively modulates beige adipose tissue reinforces its indication as a non-pharmacological intervention in obesity management. The clinical application of this knowledge may contribute to more effective, safe, and sustainable therapeutic approaches for the control of metabolic diseases.

RESUMO

Introdução: O tecido adiposo é dividido em amarelo, marrom e bege. O bege tem função termogênica em recém-nascidos e pesquisas recentes mostram seu potencial na melhoria da saúde metabólica em adultos, sendo sua síntese associada à prática de exercícios físicos e relacionada ao potencial tratamento da obesidade.

Objetivo: Apresentar a histologia do tecido adiposo, suas características gerais, formação, mecanismos bioquímicos e fisiológicos, bem como, a relação entre tecido adiposo bege, exercícios físicos e o tratamento da obesidade.

Método: Revisão bibliográfica narrativa composta por 27 artigos, disponíveis nas bases de dados PubMed e Scielo e livros técnicos científicos. Os descritores utilizados foram "beige adipose tissue", "exercise", e "adipose tissue".

Resultado: O tecido adiposo amarelo está relacionado com o armazenamento de triglicerídeos e manutenção energética; o marrom é primordialmente termogênico, seus adipócitos utilizam a energia contida nos triacilgliceróis para liberar calor; o bege é constituído pela junção dos adipócitos uniloculares e multiloculares, podendo imitar a função metabólica do tecido adiposo marrom quando estimulado. O hormônio irisina, estimulado pelo exercício físico, induz o mRNA da proteína desacopladora 1 que promove o escurecimento do tecido adiposo amarelo formando o bege. A atividade física regular aumenta a biossíntese mitocondrial elevando a capacidade oxidativa e termogênica do tecido adiposo bege; esse efeito pode ser benéfico contra a obesidade.

Conclusão: Exercícios regulares têm grande impacto na modulação do tecido adiposo bege, promovendo a conversão do amarelo em bege; também favorece o gasto energético e a secreção de moléculas de regulação metabólica. Assim, o exercício físico é grande aliado para tratar a obesidade, uma vez que estimula a formação do tecido adiposo bege.

PALAVRAS-CHAVE: Tecido adiposo bege, exercício, tecido adiposo

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INTRODUCTION

Adipose tissue (AT) participates in the formation of body mass in individuals and represents 20% to 28% of the body mass of healthy individuals, and can reach up to 80% in obese people.[1,2] Primarily, AT is formed by adipocytes, which are specialized and responsible for accumulating triglycerides in order to store energy that will later be metabolized to other cells in the body.[1] The storage of energy in the form of triglycerides is exerted by yellow adipose tissue (AAT) and its main deposits are in the dermis and subcutaneous tissue, that is, in the adipose panniculus.[1] Brown adipose tissue (TAM) is responsible for dissipating energy in the form of heat.[1] AT has several functions, such as thermogenic, physiological and endocrine.[1]

Recently, beige adipose tissue (BAD) was discovered, which is made up of unilocular and multilocular adipocytes, it is commonly located in the subcutaneous tissue and its origin may be associated with the practice of physical exercise.[2]

Thus, the objective of this review was to present, in addition to the histology of adipose tissue, its general characteristics, formation, biochemical and physiological mechanisms, as well as the relationship between beige adipose tissue, physical exercise, and the treatment of obesity.

METHOD

Narrative review of the literature composed of articles available in the PubMed and Google Scholar databases carried out in April 2024. The keywords used were "beige adipose tissue", "exercise", and "adipose tissue". The final sample consisted of 23 articles.

DISCUSSION

Adipose tissue is formed by adipocytes, which are responsible for the accumulation of triacylglycerols (TAGs) in droplets, which are lodged in their cytoplasm. GADs originate from ingested lipids that are absorbed by the epithelial cells of the small intestine, from lipids originating from the liver and transported by the bloodstream, from lipids synthesized in fat cells, liver cells, muscle cells, and other cells from glucose.[3] They are deposited in the lipid vacuola (lipid storage vacuole), which contains enough energy to meet the energy needs of a healthy adult for at least 2 months.[1,2]

In addition, it is vascularized tissue whose function is to provide support for organs, energy regulation and physiological processes, such as maintaining body temperature, angiogenesis, adipogenesis and restructuring of the extracellular matrix.[1,2] Cells constitute 30% of the volume of tissue, due to their size, and the other 70% are represented by endothelial cells of blood capillaries, fibroblasts, among other cells.[1] There are 3 types of adipose tissue: yellow, brown, and beige.[2]

Yellow adipose tissue

Yellow adipose tissue (AAT) or unilocular adipose tissue is composed of unilocular adipocytes, which are responsible for accumulating TAGs in the form of lipid droplets and have little mitochondrial content.[4] Histologically, the single lipid drop fills almost the entire cytoplasm, as they are large and lack of membrane, displacing the flattened nucleus to the periphery of the cell.[2] When organic solvents are used during the preparation of the slides of the histological sections, they remove the contents of the droplet; for this reason, the adipocyte alone shows under the optical microscope only a thin layer of cytoplasm in the periphery of the cell around the space left by the removed lipid droplet.[2]

TAA corresponds to most adipose tissue in adult humans and its name corresponds to its color, which can vary between white and dark yellow depending on the diet ingested, and the yellowish color comes mainly from carotenes dissolved in the fat droplet that is vascularized in smaller quantities compared to brown adipose tissue (TAM).[1,2]

Its performance is related to energy storage and maintenance, it also promotes thermal insulation in the skin and subcutaneous tissue, as fat is not a good conductor of heat.[2] In addition, the TAA is responsible for absorbing mechanical shocks, keeping some organs in their proper positions, and filling spaces between tissues.[2] TAA is also an endocrine gland, in which it releases its contents directly into the bloodstream, which synthesizes molecules such as adiponectin, resistin and leptin, a protein hormone that acts mainly in the hypothalamus, reducing food intake and increasing energy expenditure.[2]

Brown adipose tissue

Brown adipose tissue (TAM) or multilocular tissue is composed of several lipid droplets in smaller size in its cytoplasm, which is why it is also called TAM.[4] Its characteristic color is the result of the large amount of cytochromes present in the mitochondria of its cells and its abundant vascularization by blood capillaries.[2] It exists in small quantities and with limited location in the body, being in the human species more abundant in newborns than in adults, due to the deficient thermoregulation of newborns, it collaborates to maintain body temperature.[2]

TAM is primarily thermogenic, playing an important role in thermoregulation, in which its adipocytes use energy contained in TAGs to release heat.[2] They do this through a protein called thermogenin or UCP1 (uncoupling protein 1), which uncouples oxidative phosphorylation and ATP synthesis, so that the energy generated by the flow of protons in the mitochondria is dissipated as heat.[2] This heat emitted warms the blood that is distributed throughout the body, warming it.[2]

Beige adipose tissue

Beige adipose tissue (BAD) is made up of unilocular adipocytes of yellow adipose tissue (TAM) and multilocular adipose adipocytes of brown adipose tissue (TAM); however, it is still doubtful whether it is a third type of adipose tissue. It is commonly located in the subcutaneous tissue, but its adipocytes seem to originate from different precursors of the other 2 types of tissue.[2] Its multilocular adipocytes are thermogenic, featuring uncoupling protein 1 (UCP 1), just as TAM in your mitochondria results in the release of heat to your blood capillaries.[2]

The origin of its cells are from mesenchymal cells.[2] However, there are disagreements about the precursors of BAD, and some authors suggest that it is likely that transformation of yellow adipocytes into beige adipocytes is likely.[2] Beige have several lipid droplets and are thermogenic and, like TAM, have UCP1, better known as thermogenic, effectively functioning as heat generators.[5]

Its adipogenesis

Boychenko et al.[6] point out that beige adipose tissue is influenced in transcription by industrial chemicals (pollutants), environmental disruptors and other substances from the external environment, as well as the activity of phytochemical dietary molecules, impact the transdifferentiation process connected in transcription elements. In addition, "small molecule compounds" such as fibroblasts, endothelial cells, and myoblasts function as inducers of TAA adipocytes in beige adipocytes, as well as endocrine regulation that influences the adipogenesis process, but which is more sensitive to xenobiotics.[6]

Its therapeutic potential in obesity and metabolic diseases

Activating or increasing the amount of beige adipose tissue in an individual can improve glucose, cholesterol, triglyceride levels, inflammation, weight gain and loss, insulin sensitivity, and glucose tolerance.[7] This theory was justified by Gonzalez et al.[7] which showed that microvascular fragments from humans have potential use to generate adipose microtissues that resemble the genetic and functional characteristics of BAD; as a result, the transplantation of this tissue showed improvements in glucose metabolism and insulin sensitivity, as well as reductions in body mass and decreased adiposity. It was noted that the metabolic function of beige adipose tissues was essential to obtain potential therapeutic results in the treatment of diabetes and obesity. Therefore, this physiological impact indicates that beige adipose tissues are a therapeutic option with potential application on the treatment of obesity and metabolic diseases, although the understanding of the development of beige adipose tissue in humans is still limited.[7]

Hormone production

Adipose tissue is considered the largest endocrine gland in the body because it maintains metabolic balance, through the hormonal secretions of adipocytokines (interleukin 6, angiotensinogen, adipokines, leptin, adiponectin), peptides and bioactive proteins.[2]

Leptin and adiponectin are the main hormones secreted by this tissue.[8] The first is secreted according to the size of adipocytes and the amount of adipose tissue.[8] It acts on the central nervous system by reducing food intake, increasing energy expenditure, in addition to interfering with other tissues such as skeletal muscle, liver and pancreas.[8,9] There is also the hormone ghrelin, secreted by the stomach and stimulated during fasting, which, together with leptin, is associated with body weight, sympathetic nervous system tone, and neuroendocrine responses to coordinate homeostasis.[10]

Adipocytokine influences metabolism by promoting fatty acid oxidation and reducing lipogenesis, in addition to decreasing abnormal fat deposition in the liver and muscle.[8] It also stimulates glucose uptake by the muscle and increases fatty acid oxidation in both the muscle and liver, which causes greater insulin sensitivity.[8] The practice of physical exercise increases the production of this hormone, promoting the regulation of its receptors in skeletal muscle.[8]

This endocrine function of the tissue varies according to its location, since subcutaneous adipocytes have little capacity to produce adipokines; adipocytes that are located around the viscera secrete adipokines in large quantities.[2]

Histogenesis

Fat cells are derived from undifferentiated mesenchymal cells. For the formation of adipose tissue-forming adipocytes, mesenchymal cells undergo a reduction in their cytoplasmic prolongations, thus beginning to store lipid drops within the cytoplasm, forming lipoblasts or pre-adipocytes, young cells, which when they mature form adipocytes.[11] During the formation of TAA adipocytes, lipid droplets are initially small and isolated.[11] Subsequently, they come together to form a single droplet – characterizing the unilocular fat cell.[1,12] In the multilocular adipocytes of the TAM, their lipid droplets remain separate and, in addition to the different morphology, they are differentiated by receiving stimuli that also differentiate their functions.[11]

Much is discussed about the precursors of beige adipose tissue (BAD) and research shows that it is possible to transform white adipocytes into beige, which is made up of the combination of unilocular adipocytes from TAA and multilocular adipocytes from TAM – hence the name TAB.[1] It is noteworthy that this tissue is located mainly in the subcutaneous tissue and it is presumed that its multilocular cells originate from precursors distinct from TAA and TAM.[1]

Research shows that the beige cell is a type of cold-inducible adipocyte, rich in mitochondria and appears in TAA. TAM activity is significantly related to cold defiance, body mass index, and age, which are actually beige adipocytes.[3] During the beige to yellow transition, mitochondria are degraded in adipose tissue by the activation of autophagy.[3]

Relationship of beige adipose tissue with physical exercise

Physical activity has many beneficial effects on people's health, such as preventing or delaying the onset of type 2 diabetes, obesity and metabolic diseases.[13,14] Several studies suggest that both physical exercise and exposure to specific environments can stimulate beige tissue in yellow adipose tissue (BAT), due to the ability of beige cells to discard excess caloric intake in heat, this effect can be beneficial against obesity and metabolic syndrome, in addition to being stimulated by physical exercise.[15] Beige adipocytes are seen interspersed in the TAA, especially in the subcutaneous part of it, and have a morphology similar to brown adipocytes.[14,16] In addition, beiges express the distinct cell surface markers Tmem26 and Cd137, which when stimulated show increased capacity for fuel oxidation and thermogenesis.[14,16,17] Recently, studies have begun to analyze the adaptations introduced by physical exercise in adipose tissue.[14]

Physical exercise can induce the development of beige adipose tissue (BAD) in the TAA, increasing mitochondrial biosynthesis, which contributes to the improvement of oxidative and thermogenic capacity.[18,19] Irisin, a peptide hormone, stimulates this transformation. First, it is secreted by skeletal muscle and adipocytes, and activated due to the exercise of coactivator-1α (PGC-1α), in which it promotes the secretion of the fibronectin type 3 containing 5 (FNDC5) domain into skeletal muscle; then it is cleaved and then mature irisin is produced.[19]

After the end of exercise, TAB can maintain the metabolization of fuels, thus contributing to increased energy expenditure.[5] Studies in mice have shown that irisin at high levels after exercise induces UCP1 mRNA, thereby promoting the darkening of yellow adipose tissue.[19.20]

Adaptive thermogenesis, a process in which the body regulates heat production in response to changes such as temperature and caloric intake, is primarily mediated by UCP1.[15] TAM is the only one that contains UCP1 under normal conditions, allowing energy to be dissipated as heat instead of being stored as ATP.[15] Several modalities and durations of exercise (voluntary running in a wheel, forced running on a treadmill and swimming) were investigated in a study with rodents, in which they identified a significant increase in subcutaneous TAA at baseline, measured by the increase in brown and beige adipocyte markers (UCP1, Prdm16, Cidea, Elovl3, Dio2, Ppary, Pgc1α Cox8b and otopetrin), in addition to the increase in immunofluorescence of UCP1 and the presence of multilocular cells.[18,20-22] These studies indicate that the duration of exercise influences the change in UCP1 expression.[14]

AAT is induced to transform into BAD through the practice of exercises, a process that involves the mechanism of Crosstalk – mechanism that controls the contractile apparatus, blood pressure and circulating volume – between skeletal muscle and adipose tissue.[18] Therefore, regular physical activity increases mitochondrial biosynthesis, which contributes to the improvement of oxidative capacity and the increase in the number of beige adipocytes in the TAA, and also, these cells have the ability to discard excess caloric intake in heat; This effect may be beneficial against obesity and metabolic syndrome.[18,19] TAB also has UCP1 and can mimic the metabolic function of TAM when stimulated.[15] It is reported that the hormone irisin, myokine stimulated by physical exercise, acts by transforming yellow adipose tissue into beige.[15]

Beige and brown adipose tissues and their relationship to oxidative metabolism

Exercise increases the production of reactive oxygen species (ROS). While acute exercise causes increased oxidative stress in skeletal muscles, chronic exercise tends to decrease this stress.[18] Reactive oxygen species increase in obese and aging individuals. Excessive levels of ROS lead to inadequate oxidative defense, causing oxidative stress, which is related to diseases such as obesity, diabetes, cardiovascular and neurodegenerative.[18]

Free radicals, including ROS, are the main causes of aging and are produced primarily by mitochondria. However, physical exercise increases the production of beige adipose tissue (TAB) and improves the function of brown adipose tissue, which can protect the body from oxidative stress.[18] Exercise induces the appearance of BAD in yellow adipose tissue (AAT), mediated by myokines, proteins secreted by contracted muscles that transmit information from skeletal muscle.[18]

According to studies, TAA transplantation submitted to physical exercise in sedentary mice resulted in improved glucose uptake in skeletal muscles and in the metabolism of the body as a whole. This is likely due to the altered profile of adipokines – including adiponectin, leptin, interleukin 6, and tumor necrosis factor alpha, among others – in white adipose tissue after exercise.[23] It is also reported that the expression of adiponectin receptors in white adipose tissue increases significantly in humans after 4 to 12 weeks of exercise training, as does the expression of UCP1.[23]

Other exercise-induced myokines, such as fibroblast growth factor 21 (FGF21), brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), adiponectin, leptin, β-aminoisobutyric acid, follistatin, meteorin-like, interleukin-6, lactate, and succinate, have a stimulating effect on thermogenic gene expression in TAA cells, inducing the onset of BAD or promoting brown adipose tissue (TAM) function.[18] Myokines, therefore, can play a central role as mediators of the effects of physical exercise on thermogenic adipose tissues.[18]

Uncoupling in mitochondrial respiration protects against oxidative stress, as UCPs (uncoupling proteins) are involved in controlling the production of reactive oxygen species (ROS) in mitochondria.[18] Thus, it can be stated that adipose tissues adapt to physical exercise in many ways, such as releasing adipokines, producing beige fat, promoting brown fat function and, depending on the intensity and duration of exercise, increasing ROS.[18] The antioxidant effect of physical exercise is due to antioxidant enzymes that are induced by post-workout oxidative stress.[18]

CONCLUSION

Adipose tissue plays important roles in human physiology, being essential for energy regulation and thermogenesis. Yellow adipose tissue is responsible for energy storage and thermal insulation, but it also acts in the regulation of metabolism. On the other hand, brown adipose tissue is essential in thermogenesis, especially in newborns, and in the maintenance of body temperature. In addition, beige adipose tissue has intermediate characteristics between the 2 previous tissues, highlighting its therapeutic potential in obesity and metabolic diseases. In addition, the practice of regular exercise has a great impact on the modulation of adipose tissue, promoting the conversion of yellow adipose tissue into beige. Physical exercise increases the production of myokines, which induce the formation of beige adipose tissue, contributing to the improvement of metabolic health and protection against diseases associated with oxidative stress. Thus, understanding the characteristics and functions of adipose tissues, as well as the mechanisms of regulation, is essential for the development of effective therapeutic strategies for the treatment of obesity and other metabolic diseases.

Authors' contributions:
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