Endocrinol Diabetes Nutr. 2017;64(6):317–327

Endocrinología, Diabetes y Nutrición

www.elsevier.es/endo

REVIEW ARTICLE

Role of adenosine receptors in the adipocyte–macrophage interaction during obesity☆

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Received 4 January 2017; accepted 29 March 2017
Available online 24 August 2017

KEYWORDS
Obesity;
Adenosine;
Adenosine receptors;
Lipoinflammation

Abstract Lipoinflamation is the inflammation generated in the adipose tissue. It can contribute to the development of insulin resistance. The lipoinflammation-associated mechanisms are related to the function of adipocytes and macrophages present in the adipose tissue. In this regard, the level of nucleoside adenosine is increased in individuals with obesity. Causes or consequences of this increase are unknown. Although, adenosine activating its receptors (A_1, A_{2A}, A_{2B} and A_3) is able to differentially modulate the function of adipocytes and macrophages, in order to avoid the reduction of insulin sensitivity and generate an anti-inflammatory state in subject with obesity. In this review we propose that adenosine could be a key element in the development of new strategies for limit lipoinflammation and regulate metabolic homeostasis through modulation of adipocyte-macrophage dialog.

PALABRAS CLAVE
Obesidad;
Adenosina;
Receptores de adenosina;
Lipoinflamación

Rol de los receptores de adenosina en la interacción adipocito-macrófago durante la obesidad

Resumen La inflamación generada en el tejido adiposo o lipoinflamación, puede contribuir al desarrollo de la resistencia a la insulina. Los mecanismos asociados a la lipoinflamación están relacionados con la función de los adipocitos y los macrófagos presentes en el tejido adiposo. En este contexto, el nivel del nucleósido adenosina está aumentado en individuos con obesidad.

☆ Please cite this article as: Meriño M, Briones L, Palma V, Herlitz K, Escudero C. Rol de los receptores de adenosina en la interacción adipocito-macrófago durante la obesidad. Endocrinol Diabetes Nutr. 2017;64:317–327.

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http://dx.doi.org/10.1016/j.endien.2017.08.001

Las causas o consecuencias de este aumento no se conocen. Aunque, adenosina al activar a sus receptores (A_1, A_{2A}, A_{2B} y A_3) es capaz de modular diferencialmente la función de adipocitos y macrófagos, con el fin de evitar la reducción de la sensibilidad a la insulina y generar un estado antiinflamatorio en el individuo con obesidad. En esta revisión proponemos que adenosina podría ser un elemento clave en el desarrollo de nuevas estrategias para el control de la lipoinflamación y homeostasis metabólica a través de la regulación del diálogo adipocito-macrófago.

Introduction

Obesity, regarded as an abnormal or excessive accumulation of body fat which has a harmful effect upon the health of the individual, is defined by the World Health Organization (WHO) as a body mass index (BMI) of $\geq 30\,kg/m^2$.[1] The prevalence of obesity has increased rapidly throughout the world, becoming an epidemic.[2,3]

Much research has focused on clarifying the physiopathology of obesity.[4] In this context, adipocytes are specialized cells with functions that extend beyond simple lipid uptake and accumulation. Indeed, they are currently regarded as endocrine cells. In turn, adipose tissue macrophages constitute a complex family of cells that recognize the metabolic signals released from the adipose tissue as an activation signal, resulting in the generation of a chronic inflammatory state. Lipoinflammation is therefore a result of an interaction between adipocytes and macrophages. The mechanisms of communication between these two cell types are not fully known.

Adenosine (ADO) is a nucleoside derived from the metabolism of adenosine triphosphate (ATP), which is very widely produced within the body. It exerts a series of homeostatic effects through the activation of four receptors coupled to protein G: A_1, A_{2A}, A_{2B} and A_3.[5,6] The functions of ADO include an increase or decrease in blood flow, the inhibition of the aggregation of platelets and macrophages, the reduction of inflammatory states (to the point of causing immune deficiency situations in extreme cases), the reduction of lipid metabolism, and the facilitation of insulin sensitivity and its consequent metabolic effects, among other functions.[7] Despite the available information on ADO and its relation to adipose tissue, the role of this molecule in communication between adipocytes and macrophages has not been fully clarified.

The present review postulates that ADO could constitute a key element in the development of new strategies for the control of lipoinflammation and metabolic homeostasis through regulation of the communication between adipocytes and macrophages.

Adipose tissue and lipoinflammation

Adipose tissue is more than simply a fat storing tissue; it has a number of physiological functions, depending on the histological type of the tissue. Thus, white adipose tissue is mainly in charge of storing excess energy, while brown adipose tissue specializes in dissipating energy in the form of heat, in response to situations of hypothermia or excess energy. Beige adipose tissue, which is mainly found in the subcutaneous tissue derived from white adipose tissue, possesses functions similar to those of brown adipose tissue.[8]

Adipose tissue in general is composed of adipocytes, preadipocytes, endothelial cells, fibroblasts and immune cells–fundamentally macrophages and T lymphocytes. Adipocytes are able to exert their influence upon the rest of the tissues by releasing interleukins, chemokines, growth factors and hormones.[9] In fact, white adipose tissue is currently recognized as a secretory organ with an effect upon the physiology of the entire body, since it is able to regulate systemic functions such as insulin sensitivity, immune response, cardiovascular function and autocrine and paracrine processes. This tissue therefore not only plays a passive role as an energy store but also acts as a modulator in metabolic homeostasis, thermoregulation, hormone regulation, blood pressure and coagulation.[8]

However, in the context of an excessive energy intake through the diet, together with a deficit in accumulated energy expenditure, body fat is susceptible to adipose tissue remodeling.[10] In effect, 70–80% of all obese individuals suffer from such remodeling, which affects both the structure and normal function of the tissue, generating a subclinical and chronic inflammatory process. The mechanisms underlying the lipoinflammatory state associated with obesity are still the subject of research. However, animal and human models have shown that hypoxic zones are generated in the early stages of adipose tissue hypertrophy, i.e., areas of adipose tissue with low oxygen exposure, which in turn exhibit an increased secretion of proinflammatory interleukins, growth factors (see Table S1 of the supplementary material in the annex)[10–12] and inflammatory modulators such as leptin, adiponectin and resistin.[13]

Furthermore, it has been seen that hypoxia in adipose tissue reduces the expression of two proteins that are crucial for tissue recovery, namely peroxisome proliferator-activated receptor-gamma (PPARy) and adiponectin, which is in charge of reducing the inflammatory state in this tissue.[11] Thus, while such inflammation is initially of an acute nature, it becomes chronic, systemic and of low grade when not correctly resolved: a situation known as lipoinflammation.[14,15]

Proinflammatory interleukins derived from adipose tissue macrophages

Macrophages form part of the immune system and are derived from monocytes generated in the bone marrow. In turn, there are two macrophage activation pathways.