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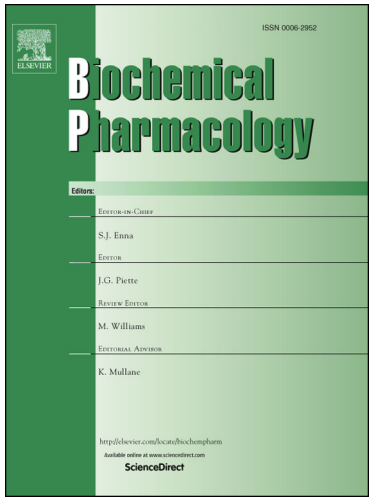

Review

Adenosine Metabolism, Immunity and Joint Health

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Adenosine Metabolism, Immunity and Joint Health

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Abstract

The purine nucleoside adenosine is a present in most body fluids where it regulates a wide variety of physiologic and pharmacologic processes. Adenosine mediates its effects through activating 4 G protein-coupled receptors expressed on the cell membrane: A1, A2A, A2B, and A3. The adenosine receptors are widely distributed in the body, and tissues with high expression include immune tissues, cartilage, bone, heart, and brain. Here we review the source and metabolism of adenosine and the role of adenosine in regulating immunity and cartilage biology.

Introduction

Adenosine is an endogenous purine nucleoside, a catabolite of ATP, that binds and activates one or more of four transmembrane G-protein-coupled cell surface adenosine receptors (R)s, which are A1R, A2AR, A2BR and A3R (1). Extracellular adenosine can accumulate during inflammation, hypoxia, and associated cellular damage and stress and several studies indicate that it may contribute to innate inflammation (2-4). The accumulation of extracellular adenosine is the result of a multistep process, where ATP is first released from its intracellular pool to the pericellular space, and is then degraded to adenosine by a cascade of cell surface ectonucleotidases, including CD39 (ectonucleoside triphosphate diphosphohydrolase 1 (E-NTPDase1)) and CD73 (5'-ectonucleotidase or Ecto5'NTase) (4-9). Adenosine, the pharmacologic effects of which were first described by Drury and Szent-Gyorgy (10), regulates every organ system in the body, most notably the cardiovascular, nervous, gastrointestinal and immune systems. Indeed, all four of the adenosine receptors are widely expressed throughout the body and different cell types express different combinations of adenosine receptors. In this review we will discuss two newly described regulatory functions of adenosine and adenosine receptors in regulation of Type 2 immunity and chondrocyte homeostasis.

Sources of adenosine

In a cell type and context-dependent manner, several mechanisms for ATP liberation have been proposed, including channel-dependent, cell death, and vesicular release mechanisms (11). ATP release in response to immune activation occurs mostly through Connexin (Cx) and Pannexin (Panx) channels. Cx channels were first described in the 1970s as the principal proteins comprising intercellular gap junctions (12-14). Cx channels are half channels or hemichannels that can readily dock unapposed hemichannels on adjacent cells to form gap junctions. However, they can also remain unapposed and serve as conduits for extracellular ATP liberation. Of the ~25 Cx