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Review

The role of extracellular ATP-mediated purinergic signaling in bone, cartilage, and tooth tissue

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ABSTRACT

Background: Adenosine 5′-triphosphate (ATP) is a nucleotide that is known to play a multitude of important roles in intracellular energy metabolism in eukaryotic cells. It has also been reported that ATP acts as an extracellular autocrine and/or paracrine signaling molecule upon being secreted from a cell, affecting numerous downstream factors and signaling cascades involved in both normal cellular physiology and disease development.
Highlight: Signaling that involves a purine nucleotide or nucleoside, such as ATP or other adenosine containing molecules (e.g., ADP, AMP, and adenosine), is called purinergic signaling. ATP-sensitive purinergic receptors include the P2Y family of G protein-coupled receptors and the P2X family of ligand-gated cation channels. These receptors have been characterized in almost all cell types. The vast amount of literature concerning these receptors has provided evidence that connects purinergic signaling with a variety of cellular functions. In this review, we summarize previous reports focused on extracellular ATP-mediated purinergic signaling observed in cells found in bone, cartilage, and teeth.
Conclusion: Purinergic signaling is involved in osteogenesis, chondrogenesis, and dental sensory perception, indicating that ATP is an essential signaling molecule in bone, cartilage, and teeth. The downstream effects of ATP-mediated signaling are largely dependent on the receptors expressed in the tissue as well as the stage of cellular differentiation. While the current literature has greatly advanced our understanding of purinergic signaling, additional research is necessary to fully elucidate the function of ATP-mediated pathways.

Contents

1. Introduction

The importance of purine nucleotides and nucleosides in the human body is widely known. Investigations into the role of adenosine 5′-triphosphate (ATP) started in the 1920s, when important

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articles detailing the discovery of ATP were published simultaneously by independent groups. The potent actions of numerous purine nucleotides and nucleosides, including ATP and adenosine, on the heart, blood vessels, and muscles were first reported in 1929 [1–3]. Since these early publications, the continuing study of ATP has provided further insights into its structure and function, highlighting the importance of this molecule in a multitude of processes and tissues.

ATP consists of an adenosine nucleoside, which contains an adenine ring structure covalently linked to a ribose sugar molecule, and three phosphate groups (Fig. 1). This molecular structure was first proposed by Katashi Makino at the Dailen Hospital in 1935 [4]. In 1954, it was determined that ATP is released from sensory nerve endings during antidromic stimulation of the great auricular nerve, and induces arterial vasodilatation in the rabbit ear [5]; this was the first report indicating that ATP might act as a neurotransmitter. However, only adrenergic and cholinergic signaling had been identified in the autonomic nervous system at this time, neither of which appeared to involve ATP. Subsequently, in 1972, Burnstock [6] proposed a role for ATP as a novel nerve signaling component involved in a third signaling pathway, termed the purinergic pathway, which is neither adrenergic nor cholinergic. Recent studies have demonstrated that purinergic receptors are also expressed in many non-neuronal cell types and participate in various biological processes, such as, cell proliferation, survival, migration, and differentiation [7,8]. Furthermore, extracellular ATP has been shown to play a major role in purinergic signaling, modulating diverse cellular functions in an autocrine or paracrine fashion.

There are two types of purinergic receptors: the P2Y family of G protein-coupled receptors and the P2X family of ligand-gated cation channels [9,10]. To date, eight subtypes of P2Y ($P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$, and $P2Y_{11-14}$) and seven subtypes of P2X ($P2X_{1-7}$) have been identified [11] (Fig. 2). Among these, $P2Y_2$, $P2Y_4$, $P2Y_{11}$, $P2Y_{13}$, and all P2X receptors interact with ATP and activate intracellular signaling pathways [12]. The P2Y receptors $P2Y_3$, $P2Y_5$, and $P2Y_{7-10}$ have also been cloned, but are not included in the P2Y family because they do not respond to purinergic ligands [11]. Most of the ATP-bound P2Y receptors activate $G_{q/11}$-mediated signaling pathways to stimulate phospholipase C beta, and also inhibit production of cyclic adenosine 5′-monophosphate (cAMP) [9]. In relation to P2X receptors, ATP binds to the extracellular portions of the receptors and regulates the pore, thus allowing small cations, including Ca^{2+}, to permeate the channel [10].

Once ATP is released into the extracellular space, it is rapidly degraded to adenosine 5′-diphosphate (ADP), AMP, and adenosine by ectonucleotidases [13,14]. However, these other purine

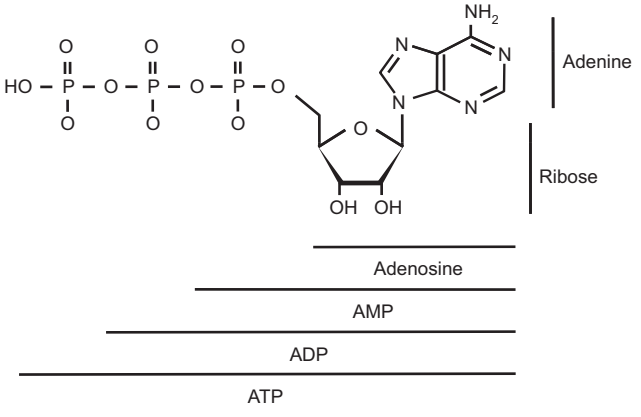

Fig. 1. Chemical structure of adenosine 5′-triphosphate (ATP). ATP consists of an adenosine ring and a ribose sugar molecule linked to three phosphate groups.

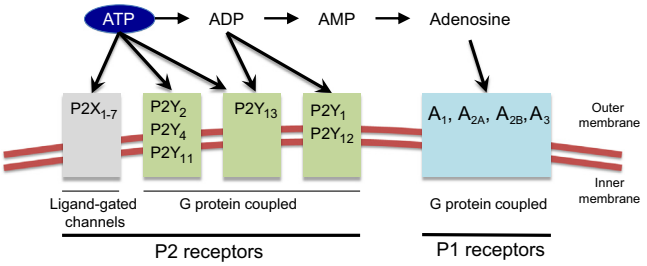

Fig. 2. Breakdown of the purinergic receptors for extracellular nucleotides. Extracellular ATP is converted to adenosine 5′-diphosphate (ADP), adenosine 5′-monophosphate (AMP), and adenosine by ectonucleotidases that are expressed on the plasma membrane. The purinergic receptors can be divided into two major families, the P1 receptors for adenosine and the P2 receptors for ATP and ADP.

nucleotides and nucleosides have additional functions compared to ATP. For example, ADP has a crucial role in regulating platelet function by activating two types of P2Y receptors, $P2Y_1$ and $P2Y_{12}$ [15]. The adenosine generated from the breakdown of ATP can activate the four known P1 adenosine G protein-coupled receptors, A_1, A_{2A}, A_{2B}, and A_3 [16,17] (Fig. 2).

The vast number of tissue-specific functions of ATP-mediated purinergic signaling have been widely investigated and reviewed. The focus of this review is on the function of purinergic signaling in three specific tissues: bone, cartilage, and teeth.

2. Purinergic signaling in bone

The importance of purinergic signaling in bone was first identified in the 1990s. These first reports focused on the extracellular ATP-mediated increase in intracellular calcium concentration ($[Ca^{2+}]_i$) in both normal human osteoblasts and two osteoblastic cell lines, SaOS-2 and UMR-106, which suggested that ATP released from cells damaged by structural or local pressure could be important in the formation and remodeling of bone [18,19]. Following these initial reports, a number of additional studies have demonstrated that ATP-mediated purinergic signaling plays a pivotal role in osteoblast function. For example, in the human osteosarcoma cell line, MG-63, the presence of extracellular ATP increases cell proliferation by inducing insulin-like growth factor 1 or platelet-derived growth factor via a mitogen-activated protein kinase (MAPK)-dependent pathway [20]. In rat calvarial osteoblasts, ATP was shown to enhance the expression of genes encoding alkaline phosphatase, bone morphogenetic protein (BMP)-2, BMP-4, BMP-5, and bone sialoprotein, as well as enhancing nodule mineralization [21]. On the other hand, a recent study has demonstrated that apyrase, which sequentially hydrolyzes ATP to ADP and ADP to AMP and pyrophosphate, increased mineralization of bone nodules in rat primary osteoblasts [22]. All of these studies indicate a prominent role of ATP-mediated purinergic signaling in bone.

Importantly, osteoblasts have the potential to express all of the P2Y and P2X receptors [20,23–25]. The expression of these receptors, in some cases, appears to be context- and/or species-dependent. For example, mRNA for $P2Y_4$ was detected in the human osteosarcoma cell lines OHS-4 and MG-63 by reverse transcription PCR (RT-PCR) [24]; conversely, mRNA for this receptor was not detected in rat osteoblastic cells by *in situ* hybridization or RT-PCR [26], which suggests that the expression of $P2Y_4$ may change depending on the stage of cellular differentiation and the species. Orriss et al. [27] reported that there is a shift from P2X to P2Y expression during differentiation of rat primary osteoblasts. In this study, $P2X_2$, $P2X_5$, and $P2Y_1$ were expressed in the early stage, but their expression declined in the terminal differentiation stage, while $P2X_7$ was detected in all stages of differentiation. In contrast, $P2Y_2$ expression progressively increased during differentiation, reaching a maximum at the terminal