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Mini Review

Extracellular ATP and Adenosine: A Dynamic Danger-to-Resolution Switch in Purinergic Signaling

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Abstract

Adenosine triphosphate (ATP) is traditionally recognized as the primary intracellular energy currency. However, over the past decades, accumulating evidence has established ATP as a key extracellular signaling molecule involved in the regulation of immune, inflammatory, and neuronal responses. This narrative mini-review examines the dual biological nature of ATP, highlighting how its functions depend on cellular compartmentalization, local concentration, signal duration, and the pattern of purinergic receptor expression.

Beyond its canonical role in cellular bioenergetics, intracellular ATP contributes to protein homeostasis by acting as a biological hydrotrope that maintains protein solubility and limits pathological aggregation. Following tissue injury or cellular stress, ATP is released into the extracellular space, where it functions as a damage-associated molecular pattern (DAMP), activating P2 purinergic receptors and promoting nociception, inflammation, and immune cell recruitment. Its rapid enzymatic degradation into ADP, AMP, and ultimately adenosine progressively shifts extracellular signaling toward predominantly anti-inflammatory and analgesic responses mediated by adenosine receptors. Within this framework, the dynamic ATP-to-adenosine transition may represent a functional indicator of the extracellular microenvironment, acting as a genuine danger-to-resolution switch that orchestrates the progression from tissue alarm to restoration of homeostasis. Rather than representing independent signaling pathways, extracellular ATP and its enzymatic conversion into adenosine should be viewed as sequential phases of a single adaptive biological program linking tissue injury, immune activation, and resolution.

Although the direct therapeutic administration of ATP or adenosine has thus far yielded limited clinical benefit, selective modulation of purinergic receptors and extracellular nucleotide metabolism represents a promising strategy for the treatment of chronic pain and inflammatory disorders.

Keywords: *Adenosine Triphosphate (ATP); Damage-Associated Molecular Pattern (DAMP); Purinergic Signaling; Vesicular Nucleotide Transporter (VNUT)*

Introduction

The aim of this narrative mini-review is to illustrate how a single molecule can exert profoundly different, and sometimes seemingly opposite, biological effects depending on its cellular compartment, local concentration, duration of signaling, and the repertoire of purinergic receptors expressed by target cells.

The molecule under consideration is adenosine triphosphate (ATP), which is synthesized predominantly within mitochondria through oxidative phosphorylation and, to a variable extent depending on cell type and metabolic conditions, through glycolysis. While ATP has long been regarded as the universal intracellular energy currency, increasing evidence indicates that it also functions as a pivotal extracellular signaling molecule coordinating immune, neuronal, inflammatory, and tissue repair responses [1].

We propose that extracellular ATP and its enzymatic conversion into adenosine should not be regarded as two independent signaling pathways but rather as sequential phases of a single adaptive response. From this perspective, the ATP-to-adenosine transition represents a dynamic regulatory axis linking tissue injury, immune activation, and pain resolution, with potential implications for future therapeutic strategies.

Whenever tissues experience injury, infection, or metabolic stress, resident cells—including immune cells, glial cells, and neurons—activate a coordinated adaptive response aimed at restoring homeostasis. This process requires a substantial increase in energy expenditure, which is sustained by accelerated ATP turnover through enhanced oxidative phosphorylation and glycolysis.

Although most newly synthesized ATP is consumed to meet intracellular metabolic demands, a fraction is released into the extracellular space through several mechanisms, including pannexin and connexin hemichannels, vesicular exocytosis mediated by the vesicular nucleotide transporter (VNUT), and, in severely injured tissues, passive leakage resulting from loss of plasma membrane integrity. Similar to classical neurotransmitters, ATP may reach the extracellular environment either through conductive membrane pathways or via secretory vesicles loaded by the vesicular nucleotide transporter (VNUT), encoded by the *SLC17A9* gene, which is responsible for ATP accumulation within secretory vesicles [2].

The biological significance of extracellular ATP therefore extends far beyond its intracellular metabolic role, positioning ATP as a versatile signaling molecule capable of integrating tissue injury, immune activation, and intercellular communication.

ATP: Energy and hydrotropy

Beyond its well-established role in cellular energy metabolism and in mediating cellular responses to external stimuli [3], ATP, at its high intracellular concentrations (millimolar range), also exerts biochemical functions that are independent of energy transfer. In particular, ATP acts as a biological hydrotrope, promoting the solubility of numerous proteins and preventing their aggregation. This property has attracted considerable interest because protein aggregation is a hallmark of several neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS) [4]. Thus, ATP-mediated hydrotropy suggests that ATP contributes to the maintenance of cellular homeostasis independently of its canonical function as the universal energy currency of the cell.

One of the most intriguing aspects of purinergic biology is that the same ATP molecule, immediately after its release into the extracellular space, functions as a damage-associated molecular pattern (DAMP), promoting nociception, inflammation, and immune activation. However, extracellular ATP is rapidly hydrolyzed by ectonucleotidases into ADP, AMP, and ultimately adenosine, a molecule that, in many physiological and pathological settings, exerts largely opposite effects by limiting inflammation and promoting the resolution of pain.

An emerging concept is that ATP should be regarded not only as the principal intracellular energy carrier but also as a multifunctional signaling molecule whose apparently contrasting biological activities are determined by the specific context in which it operates.

ATP and purinergic signaling

The best-characterized extracellular function of ATP is its role as a signaling molecule. Following its release from damaged or stressed cells, extracellular ATP activates multiple purinergic receptors. In particular, activation of P2X3 and P2X2/3 receptors contributes to nociceptive transmission and hyperalgesia, whereas stimulation of the P2X7 receptor promotes inflammatory responses through the release of IL-1β [5-7].

Extracellular ATP, however, has an extremely short half-life and is rapidly degraded by ectonucleotidases to ADP, AMP, and ultimately adenosine. The sequential generation of these metabolites progressively reshapes the biological signal, reflecting both their distinct kinetic properties and the activation of different receptor populations.

Collectively, these observations support the view that ATP should not be considered a molecule with a single biological function, but rather a mediator whose physiological significance is determined by its spatiotemporal context. Within the cell, ATP sustains energy metabolism and contributes to protein homeostasis through its hydrotropic activity. Immediately after extracellular release, it serves as a danger signal by activating P2 purinergic receptors. As it is enzymatically converted into adenosine, the signaling profile shifts toward the limitation of inflammation and nociception.

Adenosine and resolution

Unlike ATP, adenosine predominantly exerts analgesic and cytoprotective actions. These effects are mediated primarily through activation of A1 receptors, leading to reduced release of glutamate and substance P, decreased excitability of primary sensory neurons, and subsequent inhibition of nociceptive transmission within the spinal cord.

Taken together, these findings suggest that the analgesic response traditionally attributed to the disappearance of extracellular ATP is, to a large extent, mediated by its rapid conversion into adenosine. Rather than representing an inactive metabolic end product, adenosine constitutes a distinct functional phase of purinergic signaling, during which the initial pro-inflammatory signal is progressively transformed into one that promotes modulation, tissue protection, and resolution.

Nevertheless, this paradigm is not absolute. ATP itself may also exert antinociceptive effects through activation of specific P2Y receptor subtypes, which negatively modulate pain transmission, probably by recruiting inhibitory interneurons within the spinal cord. Accordingly, purinergic signaling should be viewed as an integrated regulatory network rather than as a simple functional opposition between ATP and adenosine.

Although more stable than extracellular ATP, adenosine also displays a relatively short extracellular half-life. It is removed primarily through cellular uptake mediated by equilibrative nucleoside transporters (ENT1 and ENT2) or metabolized by adenosine deaminase to inosine. Depending on the characteristics of the local microenvironment, extracellular adenosine persists from a few seconds to several minutes, remaining sufficiently long-lived to prolong and reshape the biological response initiated by ATP [8,9].

Overall, the purinergic system appears to operate as a dynamic signaling cascade organized into sequential phases. ATP functions as an immediate alarm signal that alerts surrounding tissues to cellular injury, whereas adenosine mediates the subsequent phase of containment, tissue protection, and resolution. Rather than acting as opposing mediators, ATP and adenosine represent two temporally linked stages of the same purinergic signaling program, whose dynamic balance reflects the functional state of the tissue microenvironment.

ATP and adenosine: A dynamic balance

Over the past decade, this conceptual framework has evolved. Increasing emphasis has been placed not on the absolute extracellular concentrations of ATP or adenosine, but rather on their dynamic balance within the tissue microenvironment.

A high ATP-to-adenosine ratio is generally associated with acute tissue injury, immune activation, and the initiation of inflammatory responses. Conversely, when adenosine predominates, the signaling profile shifts toward the resolution of inflammation, attenuation of immune activation, analgesia, and protection of tissues from excessive excitation.

Accordingly, ATP and adenosine are increasingly viewed as components of a functional "danger-to-resolution switch."Through this mechanism, the same metabolic pathway that initially amplifies immune and inflammatory responses progressively contributes to their termination via the enzymatic degradation of extracellular ATP. This dynamic equilibrium has become a major focus of research in neuroimmunology and immunometabolism, as disturbances of the ATP-to-adenosine balance have been implicated in chronic inflammatory disorders, persistent pain, and even the ability of certain tumors to evade immune surveillance.

A substantial body of experimental evidence obtained from both *in vitro* studies and animal models indicates that adenosine is one of the major endogenous modulators of pain, acting predominantly through A1 receptors and, under specific pathological conditions, through A3 receptors [10].

Therapeutic perspectives

Despite compelling experimental evidence, translation into clinical practice has been considerably less successful. Early clinical studies reported encouraging results following intravenous adenosine infusion, including attenuation of experimentally induced pain in healthy volunteers, reduction of allodynia, and improvement of neuropathic pain in selected patients. However, as larger and more rigorous clinical trials became available, the overall therapeutic benefit proved to be modest or absent. Likewise, a meta-analysis of perioperative studies failed to demonstrate a clinically meaningful analgesic effect of systemic adenosine administration [11,12].

The limited clinical efficacy of adenosine appears to be attributable less to insufficient biological activity than to its unfavorable pharmacokinetic profile and dose-limiting cardiovascular effects [13]. Extracellular adenosine is rapidly taken up by cells and metabolized, resulting in a very short systemic half-life. Moreover, therapeutic doses may induce clinically significant cardiovascular adverse effects, including bradycardia, atrioventricular block, and hypotension.

The therapeutic use of ATP is even more challenging because systemically administered ATP is almost immediately hydrolyzed into ADP, AMP, and ultimately adenosine [14]. Consequently, distinguishing the direct pharmacological actions of ATP from those mediated by its metabolites is inherently difficult. Clinical studies, particularly in oncology and pain management, have reported reductions in pain and improvements in several symptom-related outcomes following ATP infusion. However, a substantial proportion of these effects is likely attributable to the local generation of adenosine rather than to ATP itself.

Current therapeutic strategies have therefore shifted away from the direct administration of ATP or adenosine toward selective modulation of the purinergic signaling network. These approaches include the development of selective A1 receptor agonists, A3 receptor agonists—particularly for neuropathic pain—and antagonists of P2X3 or P2X7 receptors aimed at reducing the pronociceptive and pro-inflammatory actions of extracellular ATP [15].

Compartiment	Dominant Molecule	Predominant effect
Intracellular	ATP	Energy metabolism, biological hydrotrope, protein homeostasis
Extracellular (initial phase)	ATP	Damage signal (DAMP), activation of P2 receptors, pain, inflammation
Extracellular (late phase)	Adenosine	Activation of P1 receptors, anti-nociception, immuno-modulation, resolution of inflammation

Table 1: *Dominat molecule, predominant effects in different compartiment.*

Conclusion

Collectively, the available evidence supports the view that extracellular ATP and adenosine represent sequential components of a dynamic purinergic response to tissue injury. ATP acts predominantly as an early danger signal, promoting nociception and inflammation, whereas its enzymatic conversion to adenosine progressively shifts the microenvironment toward immunomodulation, analgesia, tissue protection, and resolution. Thus, the ATP-to-adenosine axis may function as a physiological danger-to-resolution switch linking tissue damage to restoration of homeostasis. Although its therapeutic translation remains challenging, this framework provides a useful basis for understanding purinergic regulation and for developing strategies targeting extracellular nucleotide metabolism and purinergic receptors.

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