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Narrative Review

The Fundamental Role of ATP: The Universal Energy Currency of the Cell

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Abstract

ATP is synthesized by harnessing the energy derived from nutrient metabolism, serving as the fundamental intermediary in bioenergetic processes. Beyond its role in energy transfer, ATP also functions as a signaling molecule, triggering cellular responses to metabolic demands and stress conditions. Additionally, both *in vitro* and *in vivo* studies have demonstrated that intracellular ATP levels are intricately involved in fundamental cellular processes, including proliferation, differentiation, and programmed cell death.

All living organisms engage in the continuous acquisition of nutrients to extract the energy required for cellular and systemic functions. This notion underscores the pivotal role of adenosine triphosphate (ATP), the primary molecular currency through which biochemical energy is stored and utilized in higher organisms. ATP rightly deserves its designation as the "universal energy currency of the cell".

Let's carefully analyze the role of ATP in different organisms and systems, emphasizing its primary role in the functioning of biological structures.

Keywords: *ATP; Immune-Regulation; Energy; Cellular Patterns; Biological System*

Introduction

When we observe the space surrounding us or contemplate the origins of the universe, we seldom consider that, in its initial state, it consisted solely of energy-energy existing in the form of extremely rarefied radiation, insufficient to give rise to matter. As the universe underwent gradual expansion and cooling, matter began to emerge. This transition occurred when the energy density of matter exceeded that of radiation, effectively confining and masking radiation in various forms, from the largest celestial bodies to the most fundamental atomic constituents. Protons, neutrons, and quarks, all manifestations of energy, serve as the building blocks of atoms and molecules, which in turn constitute the human body. From this perspective, one could infer that the human organism itself is energy materialized in the form of matter. While this hypothesis may appear speculative, it is substantiated by the fundamental biological principle that all living organisms engage in the continuous acquisition of nutrients to extract the energy required for cellular and systemic functions. This notion underscores the pivotal role of adenosine triphosphate (ATP), the primary molecular currency through which biochemical

energy is stored and utilized in higher organisms. ATP is synthesized by harnessing the energy derived from nutrient metabolism, serving as the fundamental intermediary in bioenergetic processes. ATP is universally recognized as the essential mediator linking anabolic and catabolic pathways. Beyond its role in energy transfer, ATP also functions as a signaling molecule, triggering cellular responses to metabolic demands and stress conditions. Additionally, both *in vitro* and *in vivo* studies have demonstrated that intracellular ATP levels are intricately involved in fundamental cellular processes, including proliferation, differentiation, and programmed cell death (apoptosis) [1]. Given its indispensable role in cellular physiology and the survival of living organisms, ATP rightly deserves its designation as the "universal energy currency of the cell".

Materials and Methods

Objective

The objective of this review is not to provide a biochemical-metabolic analysis of cellular activities but rather to underscore the pivotal role of ATP in regulating the physiology of multiple organs and systems. ATP, synthesized within mitochondria, not only serves as a key energy currency linking anabolic and catabolic cellular processes, nor is it solely responsible for supplying the energy required for muscle contraction and phosphorylation processes. ATP also plays a crucial role in neuro-signaling and functions as an extracellular messenger.

It is well established that all cells, including those of the immune and nervous systems, respond to stress or injury by mobilizing all available resources to restore homeostasis. This process necessitates energy expenditure, prompting the rapid release of ATP as part of the cellular defense response [2]. This universal characteristic highlights at least one fundamental role of ATP. However, the primary objective of this review is to elucidate which organs are influenced by ATP and the mechanisms underlying its autocrine and paracrine effects.

ATP as a signaling molecule

The first indication of ATP as a signaling molecule dates back to Burnstock (1972) [3], who proposed that nucleotides function as neurotransmitters. He identified extracellular ATP and its receptors as key effectors in the pathophysiological mechanisms underlying various disorders, including chronic pain [4]. More recently, extensive research has demonstrated the involvement of purinergic receptors, particularly P2X receptors (P2X-Rs), in multiple pathological conditions [5]. The physiological activity of ATP is further modulated by its degradation products, such as ADP and adenosine, which act via P2Y receptors (P2Y-Rs).

Mechanisms of ATP transport

Recent advances have provided deeper insights into ATP transport mechanisms, which regulate its intracellular trafficking through vesicle-mediated pathways. In 2008, a landmark study identified a membrane protein involved in vesicular ATP transport, designated as the vesicular nucleotide transporter (VNUT), encoded by the SLC17A9 gene. VNUT is broadly expressed in various tissues and organs where ATP is actively released, reinforcing its critical role in extracellular nucleotide signaling [6,7].

ATP and pain transmission: A purinergic mechanism in nociception

The role of ATP in nociceptive pain is well established, even at the cutaneous level. When cutaneous nociceptors of Aδ, Aβ, and C fibers are stimulated by excitatory neurotransmitters-including substance P (SP), prostaglandins (PGs), bradykinin (BK), and hydrogen ions (H^+)-released by injured cells in response to external mechanical, thermal, or chemical stimuli, pain impulses propagate along nociceptive afferent fibers to the dorsal horns of the spinal cord. Concurrently, stimulated keratinocytes release ATP, which, beyond serving as an intracellular energy source, is encapsulated in vesicles and subsequently secreted into the extracellular space. Here, ATP and its metabolites interact with purinergic P2X and P2Y receptors, triggering intracellular signaling cascades that regulate the expression of factors involved in the activation of immune cells and neurons via paracrine mechanisms [8]. Peripheral nociceptive fibers activated by external stimuli release not only various neuropeptides, neuromodulators, and glutamate but also ATP. At the spinal level, ATP modulates

nociceptive transmission by interacting with purinergic receptors at the synapses between primary and secondary afferent neurons, thereby facilitating pain signal propagation.

In addition to neurons, microglial cells play a pivotal role in pain modulation by releasing ATP at millimolar concentrations [9]. ATP secreted within the dorsal horn interacts with purinergic receptors on microglial membranes, promoting their polarization into a pro-inflammatory phenotype. This activation results in the release of brain-derived neurotrophic factor (BDNF) and several cytokines, which contribute to neuroinflammation and enhance central sensitization in conjunction with ATP and glutamate. Therefore, ATP is not only a key player in peripheral pain signal transmission but also a crucial mediator in central pain sensitization mechanisms [10,11]. Notably, ATP also functions as a co-transmitter alongside norepinephrine and catecholamines, further underscoring its multifaceted role in nociceptive processing.

ATP as a damage-associated molecular pattern in immune regulation

In 2014, Tanaka., *et al*. [12] identified adenosine triphosphate (ATP) as a potential damage-associated molecular pattern (DAMP), a molecule capable of activating the innate immune system. Beyond its role as a danger signal, ATP is actively synthesized and released by immune cells in response to pathogenic stimuli or other activating factors. Intracellular ATP is transported into vesicles via the SLC17A9 channel, also known as the vesicular nucleotide transporter (VNUT), and released into the extracellular space through exocytosis, where it stimulates purinergic receptors. This signaling cascade plays a pivotal role in macrophage polarization and the regulation of cytokine expression [13,14]. Additionally, specific membrane channels, including pannexins and connexins, facilitate the direct efflux of ATP into the extracellular milieu, enabling its paracrine action on neighboring immune cells.

Neutrophil functions, including chemotaxis, are similarly modulated by ATP, which is secreted by neutrophils themselves and acts in an autocrine fashion via P2Y2 receptors on the cell membrane [15,16]. In a comparable manner, ATP signaling influences the activity of lymphocytes, further underscoring its role as a key mediator of immune responses.

Skin

The skin is another structure that provides numerous examples of ATP's role in conveying signals that activate the immune system in response to external damage. One example is the reaction occurring during infections by *Candida albicans*, an invasive and opportunistic fungus that can infect various parts of the body, inducing allodynia and pruritus [17].

A study by Maruyama K., *et al*. demonstrates that certain components of the *Candida* cell wall act as stimuli for keratinocytes, triggering the production of ATP that is subsequently transported within the same keratinocyte to activate purinergic receptors. The keratinocyte response to external stimuli is also well documented following skin damage caused by various types of injuries, such as those occurring in prosthetic surgery or in complex regional pain syndrome, where the keratinocyte response and the release of ATP represent the initial reaction that activates the immune system and promotes the expression of various pro-inflammatory cytokines [18].

Bone

Similarly, bone trauma is perceived by bone cells, which send appropriate signals to stimulate intracellular ATP formation. The ATP, once transported extracellularly, activates membrane-bound purinergic receptors and, in a paracrine manner, also stimulates nearby immunocompetent cells, which produce cytokines, nitric oxide (NO), and reactive oxygen species (ROS). These, together with other factors such as TNF-α, IL-1β, and matrix metalloproteinases (MMPs), amplify the inflammatory process leading to bone resorption.

Bone trauma also activates nociceptive peripheral nerve sensors (Aδ and C fibers), which are widely distributed in the periosteum and bone marrow. These fibers conduct signals to the dorsal horn of the spinal cord, where postsynaptic receptors of afferent fibers leading to higher centers (hypothalamus, cortex, etc.) are activated, enhancing the perception of pain [19].

Pancreas

The pancreas is another organ containing large ATP reserves and purinergic receptors involved in insulin secretion. As early as 1975, it was demonstrated that ATP is released by exocytosis from pancreatic secretory granules together with insulin, similar to how norepinephrine is released from adrenal chromaffin granules [20]. In addition to insulin, ATP also stimulates glucagon secretion.

Liver

Several experimental data confirm the influence of ATP, ADP, and adenosine on hepatic metabolism, where they act as danger signals and mediate a broad spectrum of liver pathologies [21]. Hepatocytes parenchyma, vascular smooth muscle cells, stellate cells, myofibroblasts, bile canaliculi and immune cells all express purinergic receptors and are activated by ATP and its degradation products. Under normal physiological conditions, extracellular nucleotides modulate various hepatic metabolic processes, including gluconeogenesis, insulin sensitivity, bile secretion and blood flow regulation. However, ATP also activates purinergic receptors involved in pathological processes. Experimental data suggest that ATP release mediated by transport vesicles (VNUT) regulates triglyceride secretion and induces chronic inflammation in hepatocytes; VNUT-mediated vesicular ATP release regulates triglyceride secretion and involves in chronic inflammation in hepatocytes. Since blockade of vesicular ATP release protects against progression of steatohepatitis, VNUT may be a pharmacological target for NASH [22]. Due to its physiological role, the liver is exposed to a wide range of toxic substances and pathogens, all of which induce adaptive changes and lead to the release of high concentrations of ATP.

Urinary bladder

It is well known that ATP release from parasympathetic neuronal vesicles contributes to bladder contraction, and it has been established that ATP is also released from the urothelium during bladder filling and stress, leading to mechanotransducer activation. In the bladder, ATP presence is due not only to exocytosis from transport vesicles but also to certain efflux channels (pannexin, connexin). Once released, ATP interacts with P2X3 and P2X2/3 receptors on suburothelial nerves, initiating the voiding reflex and the sensation of urgency [23]. However, some data suggest that excessive ATP release from the urothelium is responsible for bladder disorders [24]. Under pathological conditions, it appears likely that increased uroepithelial ATP release mediates bladder hyperactivity. The release mechanisms and ATP-activated receptors may serve as targets for future drugs for the treatment of lower urinary tract disorders.

Cardiac physiology

Under both physiological and pathological conditions, the heart releases adenosine triphosphate (ATP), which, along with adenosine diphosphate (ADP) and adenosine, exerts significant biological effects. Studies conducted *in vitro* and *in vivo* have demonstrated that ATP plays a crucial role in coronary vasodilation, an effect mediated via purinergic receptors [25]. Moreover, myocardial ATP concentration has been implicated in cardiac contractility. A reduction in ATP levels has been correlated with impaired myocardial contraction and diminished cardiac pump function [26] highlighting its essential role in maintaining cardiac homeostasis. The reduced ATP levels found in heart failure have led to the failing heart being regarded as an 'engine out of fuel'.

Neurophysiology

The expression of ionotropic (P2X) and metabotropic (P2Y) purinergic receptors in neuronal and glial cells underscores ATP's functional relevance in the central nervous system. ATP is released by neural cells via exocytosis and hemichannel-mediated pathways (pannexins), regulating a variety of neurophysiological processes. Astrocytes, in particular, play a pivotal role in synaptic modulation by releasing ATP in conjunction with neurotransmitters such as glutamate, γ-aminobutyric acid (GABA), and D-serine [27]. Astrocytic ATP influences nearly all neuronal and glial activities by modulating synaptic transmission and signal propagation. Furthermore, microglial cells express P2Y12 receptors and are subject to adenosine-mediated signaling, reinforcing the purinergic system's integral role in neuroimmune

interactions. ATP and adenosine signaling at synapses are essential for the fine-tuning of neural communication, particularly in axonal signal modulation [28].

ATP in spermatogenesis

ATP is also critically involved in spermiogenesis, where it regulates cellular differentiation and function through the activation of P2X and P2Y receptors in nearly all cell types of the seminiferous tubules. Sertoli and germ cells have been identified as the primary ATP-secreting cells within the testes [29]. Additionally, experimental models in mice have revealed that smooth muscle cells within the seminiferous tubule walls generate contractile waves that facilitate sperm transport. ATP orchestrates a cascade of molecular events that promote these contractions, underscoring its role in reproductive physiology [30,31].

Conclusion

Since its discovery in 1929 as a fundamental energy carrier involved in muscle contraction, ATP has been increasingly recognized as a critical mediator at the interface between cellular anabolism and catabolism. Beyond its well-established intracellular functions, ATP also acts as an extracellular signaling molecule, transported in vesicles to exert autocrine and paracrine effects via purinergic receptors alongside ADP and adenosine. In addition to its central metabolic role, ATP functions as a key signaling molecule, modulating cellular responses to external stimuli. This dual function highlights ATP's universal significance in biological systems, making it a fundamental regulator of homeostasis across multiple physiological domains.

Bibliography

1. Bonora M., *et al*. "ATP synthesis and storage". *Purinergic Signal* 8.3 (2012): 343-357.
2. Naviaux RK. "Metabolic features of the cell danger response". *Mitochondrion* 16 (2014): 7-17.
3. Burnstock G. "Introduction to purinergic signaling". *Methods in Molecular Biology* 2041 (2020): 1-15.
4. Abbracchio MP., *et al*. "Purinergic signalling in the nervous system: an overview". *Trends in Neurosciences* 32.1 (2009): 19-29.
5. Kazuhide Inoue and Makoto Tsuda. "Nociceptive signaling mediated by P2X3, P2X4 and P2X7 receptors". *Biochemical Pharmacology* 187 (2021): 114309.
6. Keisuke Sawada., *et al*. "Identification of a vesicular nucleotide transporter". *Proceedings of the National Academy of Sciences of the United States of America* 105.15 (2008): 5683-5686.
7. Yoshinori Moriyama., *et al*. "Vesicular nucleotide transporter (VNUT): appearance of an actress on the stage of purinergic signaling". *Purinergic Signal* 13.3 (2017): 387-404.
8. Burnstock G. "Purinergic signalling past, present and future". *Brazilian Journal of Medical and Biological Research* 42.1 (2009): 3-8.
9. Xu X., *et al*. "Emerging roles of keratinocytes in nociceptive transduction and regulation". *Frontiers in Molecular Neuroscience* 15 (2022): 982202.
10. Salter MW and Stevens B. "Microglia emerge as central players in brain disease". *Nature Medicine* 23.9 (2017): 1018-1027.
11. McMahon SB and Malcangio M. "Current challenges in glia-pain biology". *Neuron* 64.1 (2009): 46-54.
12. Tanaka K., *et al*. "Extracellular ATP acts as a damage-associated molecular pattern (DAMP) signal in plants". *Frontiers in Plant Science* 5 (2014): 446.

13. Sperlagh B., *et al*. "ATP released by LPS increases nitric oxide production in raw 264.7 macrophage cell line via P2Z/P2X7 receptors". *Neurochemistry International* 33.3 (1998): 209-215.

14. Sakaki H., *et al*. "Autocrine regulation of macrophage activation via exocytosis of ATP and activation of P2Y11 receptor". *PLoS One* 8.4 (2013): e59778.

15. Yuika Harada., *et al*. "Vesicular nucleotide transporter mediates ATP release and migration in neutrophils". *Journal of Biological Chemistry* 293.10 (2018): 3770-3779.

16. Hasuzawa N., *et al*. "Physiopathological roles of vesicular nucleotide transporter (VNUT), an essential component for vesicular ATP release". *Biochimica et Biophysica Acta - Biomembranes* 1862.12 (2020): 183408.

17. Farmer MA., *et al*. "Repeated vulvovaginal fungal infections cause persistent pain in a mouse model of vulvodynia". *Science Translational Medicine* 3.101 (2011): 101ra91.

18. Maruyama K., *et al*. "The ATP Transporter VNUT Mediates Induction of Dectin-1-Triggered Candida Nociception". *I Science* 6 (2018): 306-318.

19. Burnstock G. "Purinergic mechanisms and pain". *Advances in Pharmacology* 75 (2016): 91-137.

20. Burnstock G and Novak I. "Purinergic signalling in the pancreas in health and disease". *Journal of Endocrinology* 213.2 (2012): 123-141.

21. Vaughn BP., *et al*. "Pathological roles of purinergic signaling in the liver". *Journal of Hepatology* 57.4 (2012): 916-920.

22. Tatsushima K., *et al*. "Vesicular ATP release from hepatocytes plays a role in the progression of nonalcoholic steatohepatitis". *Biochimica et Biophysica Acta - Molecular Basis of Disease* 1867.3 (2021): 166013.

23. Andersson KE. "Purinergic signalling in the urinary bladder". *Autonomic Neuroscience* 191 (2015): 78-81.

24. Takezawa K., *et al*. "Urothelial ATP signaling: what is its role in bladder sensation?" *Neurourology and Urodynamics* 36.4 (2017): 966-972.

25. Korchazhkina O., *et al*. "Intravascular ATP and coronary vasodilation in the isolated working rat heart". *British Journal of Pharmacology* 127.3 (1999): 701-708.

26. Beard DA., *et al*. "Reduced cardiac muscle power with low ATP simulating heart failure". *Biophysical Journal* 121.17 (2022): 3213-3223.

27. Cisneros-Mejorado A., *et al*. "ATP signaling in brain: release, excitotoxicity and potential therapeutic targets". *Cellular and Molecular Neurobiology* 35.1 (2015): 1-6.

28. Lezmy J. "How astrocytic ATP shapes neuronal activity and brain circuits". *Current Opinion in Neurobiology* 79 (2023): 102685.

29. Mundt N., *et al*. "Purinergic signaling in spermatogenesis". *Frontiers in Endocrinology (Lausanne)* 13 (2022): 867011.

30. Gelain DP., *et al*. "Extracellular purines from cells of seminiferous tubules". *Molecular and Cellular Biochemistry* 245.1-2 (2003): 1-9.

31. David Fleck., *et al*. "ATP activation of peritubular cells drives testicular sperm transport". *eLife* 10 (2021): e62885.

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