The role of the purinergic system in the acupuncture-induced analgesia

O papel do sistema purinérgico na analgesia induzida pela acupuntura

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ABSTRACT

BACKGROUND AND OBJECTIVES: Musculoskeletal disorders and acute and chronic pain are the main causes of disability. Acupuncture is a safe and well-tolerated treatment, and the understanding of the physiological basis of its effectiveness in the management of acute and chronic painful conditions is growing. The objective of this study was to describe the main components of the purinergic system involved in the acupuncture-mediated analgesia.

CONTENTS: Review the literature relevant to the terms "acupuncture", "purinergic system", "purines", "pain" and "analgesia" found on the Pubmed platform.

CONCLUSION: Several previous studies have shown relevant roles of purines and their derivatives on acupuncture-mediated analgesia, displaying promising results in the knowledge of the potential biological benefits of acupuncture. New experimental and clinical studies are warranted to further investigate the purinergic mechanisms involved in the acupuncture-mediated analgesia, addressing potential therapeutic benefits of acupuncture in different clinical settings.

Keyword: Intractable pain, Pain, Purines.

RESUMO

JUSTIFICATIVA E OBJETIVOS: Os distúrbios musculoesqueléticos e a dor aguda e crônica são as principais causas de incapacidade. A acupuntura é um tratamento seguro e bem tolerado, e o entendimento sobre a base fisiológica de sua eficácia para o tratamento de quadros dolorosos agudos e crônicos está crescendo. O objetivo deste estudo foi descrever os principais componentes do sistema purinérgico envolvidos na analgesia mediada pela acupuntura.

CONTEÚDO: Revisar a literatura pertinente aos temas "acupuntura", "sistema purinérgico", "purinas", "dor" e "analgesia" encontrados na plataforma Pubmed.

CONCLUSÃO: Diversos estudos prévios têm evidenciado efeitos relevantes das purinas e seus derivados na analgesia mediada pela acupuntura, demonstrando resultados promissores no conhecimento dos potenciais benefícios biológicos da acupuntura. A ampliação da investigação dos mecanismos purinérgicos envolvidos na acupuntura deverá ser garantida por meio de novos estudos experimentais e clínicos, abordando potenciais benefícios terapêuticos da acupuntura em diversos cenários clínicos.

Descritores: Dor, Dor intratável, Purinas.

INTRODUCTION

Acupuncture is a form of treatment coming from Traditional Chinese Medicine (TCM) and has gained a lot of popularity in the western world[1,2]. Today, acupuncture refers to a family of procedures involving physical or chemical stimulation at specific body points, using a variety of techniques with the objective of healing a medical condition or promoting health. Are present in this overview several types or subtypes of techniques, such as manual acupuncture by inserting needles into the cutis/subcutis and moving/twisting them at regular intervals, electroacupuncture by stimulating these needles through different frequencies of electric current, and moxibustion, the method of burning cone-shaped preparations, the moxa, positioned above the acupuncture points[1,2].

Acupuncture has been used in the treatment of a wide variety of diseases, with particularly high efficiency for relieving conditions of pain[3-6]. An estimated 3 million American adults receive acupuncture treatment each year, and chronic pain is the most common presentation. Although there are multiple previous studies indicating the potential benefit of acupuncture treatment for pain, there is still a lot of debate over its clinical efficacy for the treatment of painful syndromes, thus, it's specially important to produce and study new clinical and experimental evidence on the subject. Acupuncture is known to have relevant analgesic effects, but there is no definitive evidence on the mechanism by which it could have persistent effects in treatment of acute and chronic pain. Although initially developed as part of TCM, some contemporary acupuncturists, particularly those with medical qualifications, acupuncturists, seek to understand acupuncture in physiological terms, without reference to premodern concepts. The purinergic system is composed of purine bases, such as adenine and guanine, and their nucleotides and nucleosides deriva-

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tives, which are molecules widely distributed inside and outside the cells of living organisms. These molecules are responsible for acting in several biological functions, such as in the construction of DNA and RNA (adenine and guanine), in the biochemical pathways involved in cellular energy metabolism (ATP), and in the intracellular signal transduction mechanisms as secondary messengers (cAMP and cGMP)[7-9]. However, in the last 20 years, several works have showed the fundamental role of these molecules in the extracelular space on homeostasis[8-10]. In the transmission of pain, various studies have showed that the purines, specially adenosine and ATP, exert multiple influences in central and peripheral locations[11,12]. Within that context the present study aimed to describe the main available evidence on the role of purines in the acupuncture's mechanism of action, as well as to list potential acupuncture-focused strategies capable of modulating components of the purinergic system in the treatment of acute and chronic pain syndromes.

CONTENTS

An unsystematized, narrative literature review addressing the literature pertinent to the topics "acupuncture," "purinergic system," "purines," "pain," and "analgesia." Databases searched included Pubmed, Medline (Ovid), and Cochrane Central Register of Clinical Trials (Central) platforms.

Biological mechanisms of acupuncture

Acupuncture for pain treatment is essentially a procedure in which fine needles are inserted into specific points of the body and then manipulated with the intention of relieving pain. Several techniques have been described, including manual acupuncture, electroacupuncture, moxibustion, laser acupuncture through acupoints irradiation, and auricular acupuncture[1-4]. Since its development, acupuncture has become a worldwide practice[2]. Western medicine has looked at acupuncture rather skeptically[4], but it has great acceptance worldwide, including from several health institutions. The World Health Organization has endorsed acupuncture for multiple clinical conditions, for example[13].

An acupuncture session usually lasts approximately 30 minutes, during which needles are inserted and rotated intermittently or electrically stimulated. The insertion of acupuncture needles alone is not enough to relieve pain[14]. The pain threshold is modulated gradually, showing a longer effect than the time in which the treatment is instituted[14]. There has been a large number of randomized clinical trials conducted on acupuncture for acute or chronic pain[1-6]. Moreover, several systematic reviews on the application of acupuncture in pain management have also been performed, producing consistent but still limited evidence due to variability in outcomes, heterogeneity, and low quality of some clinical trials[1,3,4,6,15-19]. Although the analgesic effect of acupuncture is well documented, there is still much controversy about its biological basis and the multiple mechanisms that seem to be involved with it[14,20-24].

The main mechanism implicated in the antinociceptive effect of acupuncture involves the release of endogenous opioid peptides (β-endorphins, enkephalins, and dynorphins) in the central nervous system (CNS) in response to long-term activation of the ascending sensory pathways during stimulation[14]. Experiments in rodents and humans have demonstrated that administration of the opioid antagonist naloxone antagonized the analgesic effects of acupuncture[14]. Analgesia caused by electroacupuncture with low frequency stimulation was mediated by μ and δ opioid receptors (β-endorphin and enkephalins), while the one caused by high frequency stimulation was mediated by κ opioid receptors (dynorphins)[20]. An additional study demonstrated that electroacupuncture is associated with the release of endogenous opioids by lymphocytes and other immune system cells in response to tissue inflammation, leading to antinociception through the activation of specific receptors on peripheral nerve terminals[21].

However, this mechanism alone does not seem to explain several clinical phenomena conventionally related to acupuncture therapy and additional mechanisms must be related, constituting a multifactorial biological basis for the phenomenon[22]. Acupuncture stimulates cutaneous, subcutaneous, and muscular sensory nerve terminals, causing the release of a variety of neurotransmitters such as noradrenaline, serotonin, acetylcholine, glutamate, GABA, opioid neuropeptides, cholecystokinin, substance P, and somatostatin in the periphery, spinal cord, and encephalus[23]. Studies have shown that descending noradrenergic and serotonergic inhibitory pathways originating in the *locus coeruleus* and the raphe nuclei, respectively, and ending in encephalinergic interneurons of the dorsal horn of the spinal cord execute the acupuncture-induced analgesia[24]. More recently, new experimental and clinical studies have proposed additional mechanisms related to the antinociceptive effects of acupuncture, including the potential role of the purinergic system[25-29].

The role of the purinergic system in pain transmission

Purines can be classified into adenine derivatives (ATP, ADP, AMP, adenosine, adenine) and guanine derivatives (GTP, GDP, GMP, guanosine, guanine), as well as direct metabolites of these derivatives, such as inosine, xanthine, hypoxanthine, and uric acid (Figure 1). The adenine derivatives, especially the ATP nucleotide and the nucleoside adenosine, are considered the main effectors of the purinergic system at the extracellular level[7,8]. The role of ATP as a neurotransmitter, at central and peripheral levels, is widely established; it's stored and released from presynaptic terminals and acts on P_2-type receptors[7,8]. Adenosine also has widely recognized and characterized neuromodulatory effects, as do its substrates[30]. In addition, purines, especially adenosine, are important modulators of synaptic activity in the CNS, interacting with various systems, such as glutamatergic, dopaminergic, serotoninergic and cholinergic[8,12].

In the transmission of pain, adenosine and ATP perform multiple influences in peripheral and central locations (Table 1)[11]. The antinociceptive effects of adenosine are related to the intrinsic inhibition of neurons by increasing conductance to K^+ and presynaptic inhibition of sensory nerve terminals, decreasing the release of substance P and glutamate[11]. Adenosine, through its agonist action on P_1 receptors (especially the A_1

subtype), attenuates nitric oxide production mediated by the glutamatergic NMDA receptor and is directly related to opioid analgesia (Figure 2)[11].

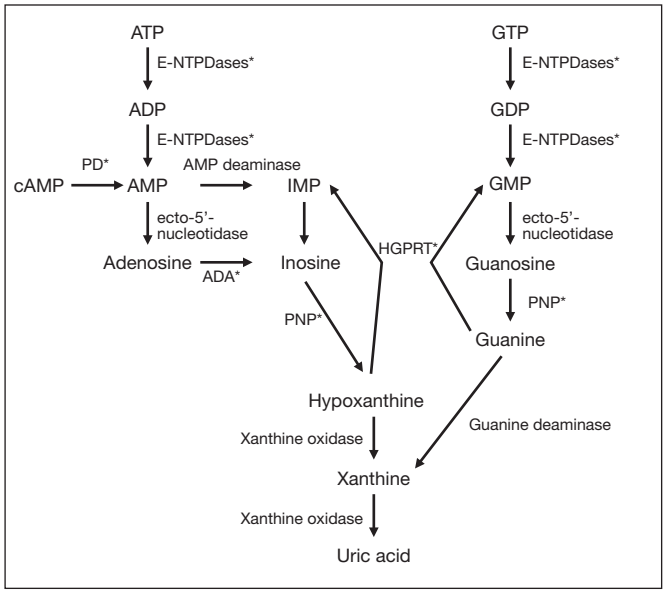

Figure 1. Schematic model of the enzymatic pathways of extracellular purine degradation to adenine and guanine bases
E-NTPDases* = ecto-nucleoside triphosphate diphosphohydrolase; ADA* = adenosine deaminase; PD* = ecto-phosphodiesterase; PNP* = purine nucleoside nucleoside phosphorylase, HGPRT* = hypoxanthine-guanine-guanine-phosphoribosyltransferase

Table 1. Main purinergic receptors involved in acupuncture-mediated analgesia

- P_2X_3
- P_2X_4
- P_2X_7
- P_2Y_1
- A_1

ATP is a classical neurotransmitter, but it's also released by non-neuronal cells and injured tissue. It acts on specific purinergic receptors (P_2), which can be subdivided into P_2X and P_2Y that are coupled, respectively, to G protein and ion channels (Figure 2)[8]. In experimental models of neuropathic pain, there is a reduction (after axotomy or partial nerve ligation) or increase (chronic constrictive lesion) of P_2X_3 receptors; however, even in the reduction, the sensitivity of these receptors increases[31]. Blockade of P_2X_3 receptors attenuates thermal and mechanical allodynia in rats[31]. P_2X_4 receptors also increase their expression in microglia after nerve injury and pharmacologic blockade of P_2X_4 reverses allodynia[32]. P_2X_7 receptors are present on T cells and macrophages. Rats that do not express this receptor are resistant to the development of neuropathic pain[33]. On the other hand, P_2Y_1 receptors increase by 70% after sciatic nerve injury in rats and may also be related to the development of conditions of pain[34]. The evaluation of the potential of the purinergic system in pain modulation is of great importance and in recent years has received signi-

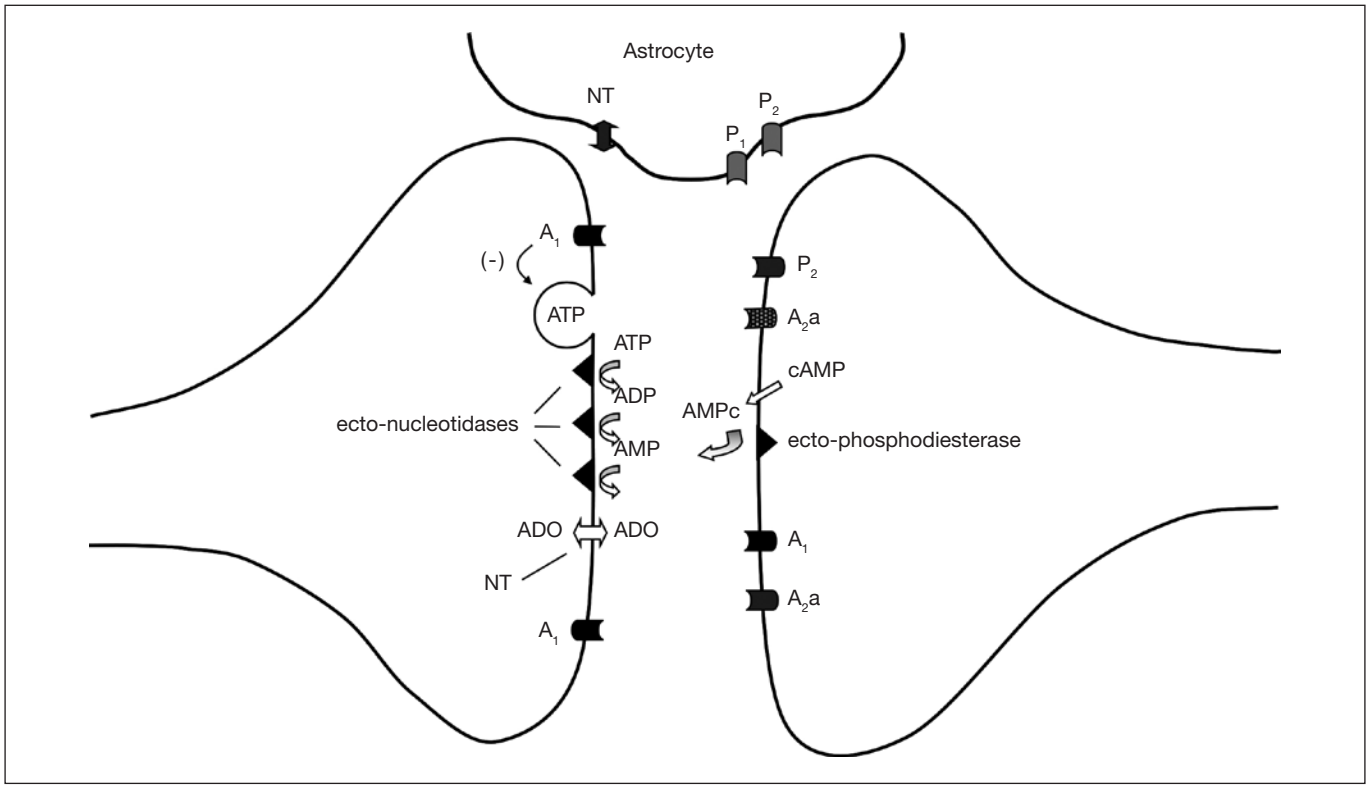

Figure 2. Schematic model of a purinergic synapse
NT = nucleoside transporter; ADO = adenosine; AMP = adenosine monophosphate; cAMP= cyclic adenosine monophosphate; ADP = adenosine diphosphate; ATP = adenosine triphosphate.

ficant attention in the literature, especially considering that several drugs capable of modulating directly or indirectly the activity of purinergic receptors, such as adenosine, allopurinol, and caffeine, among others, are available for clinical and experimental use[12,35-39].

Local release of ATP and adenosine induced by acupuncture

The skin and subcutaneous tissues contain immune cells, mainly mast cells, which play a relevant role in anti-inflammatory responses, angiogenesis, immune tolerance and defense against exogenous pathogens. Due to their location, these cells are highly sensitive to mechanical stimulation. Mast cells contain ATP in significant quantities, and is released as a result of acupuncture[40,41]. Some recent evidence support the following hypothesis: i. cell-deficient (c-kit gene mutation) mice exhibit less analgesia to mechanical stimuli than wild animals[41]; ii. mechanical stimuli lead to an increase in the intracellular Ca^{+2} level of mast cells and ATP release dependently from Ca^{+2};[42] iii. non-specific (P_2) or specific antagonists (P_2X_7 or P_2Y_{13}) attenuate ATP release from mast cells; iv. the release of ATP and its various metabolites (ADP, AMP and adenosine) is increased in the interstitium after acupuncture stimulation of the Zusanli point (E36) in mice[43].

It's important to highlight that ATP is degraded by ectonucleotidases to AMP, which is subsequently dephosphorylated into adenosine by 5'-nucleotidase[44]. Finally, adenosine is broken down by adenosine deaminase (ADA) to inosine, which has relatively minor effects on adenosinergic receptors. More recently, some studies have shown that 5'-nucleotidase is widely distributed in the body, being an enzyme closely related to the production of adenosine from AMP[45].

Quantification of extracellular purines in samples collected through microdialysis in the vicinity of acupuncture points revealed that the extracellular concentration of adenosine increases after the release of ATP in the periphery, this nucleotide being dephosphorylated to ADP, AMP, and adenosine by potent ectonucleotidases (Figure 3). As with most other neurotransmitters, adenosine has a short half-life in the extracellular space as a result of uptake facilitated by nucleoside transporters (NT) and concurrent degradation to inosine[46]. After its reuptake, adenosine is rapidly converted to AMP by cytosolic adenosine kinase, facilitating the rapid clearance of adenosine present in the extracellular space and shortening the antinociceptive effects of acupuncture[47].

A previous study showed that the activity of AMP deaminase is high in muscle and subcutaneous tissues, and that only a fraction of AMP is dephosphorylated to adenosine[48]. Thus, it can be stated that AMP deaminase creates a primary enzymatic pathway for the elimination of extracellular AMP without degradation to adenosine. Consequently, acupuncture associated with pharmacological suppression of AMP deaminase activity increases adenosine availability, increasing the clinical benefits of acupuncture. This same study showed that administering deoxyformycin, an AMP deaminase inhibitor, resulted in increased concentration of adenosine in the extracellular space and caused longer-lasting suppression of chronic pain after acupuncture. Considering these results, it can be strongly inferred that the antinociceptive action of acupuncture is related to the increase in extracellular adenosine concentration and the activation of A_1-type adenosinergic receptors located on nerve terminals. Therefore, drugs that can interact with purinergic receptors (especially A_1 subtype) or that modulate adenosine metabolism can enhance the clinical benefit of acupuncture[48].

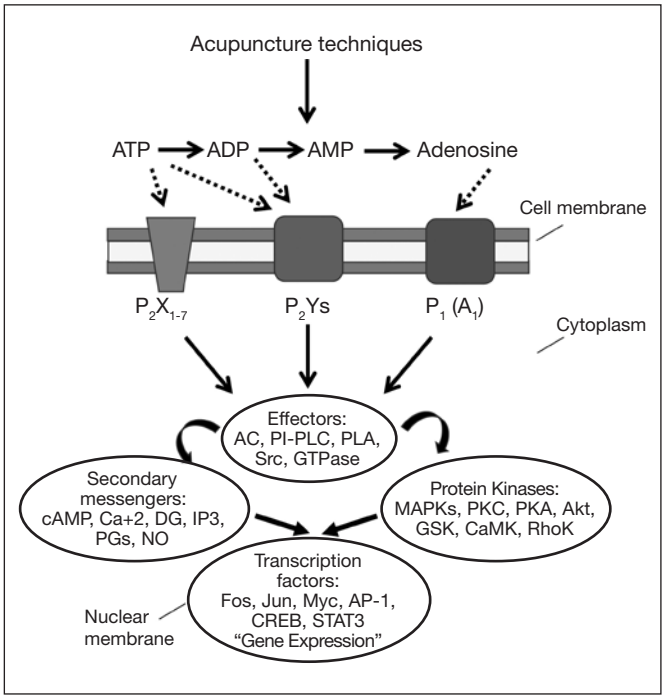

Figure 3. Purinergic mechanisms related to the acupuncture techniques for pain treatment[27,28]

AC = adenylyl cyclase; PI-PLC = phosphatidylinositol-bisphosphate phosphodiesterase; PLA = phospholipase A; Src = Src tyrosine kinase; cAMP = cyclic adenosine monophosphate; DG = diacylglycerol; IP3 = inositol-trisphosphate; PGs = prostaglandins; MAPKs = mitogen-activated protein kinase; PKC = protein kinase C; PKA = protein kinase A; Akt = protein kinase B; GSK = GS protein kinase; CaMK = Ca^{+2}/calmodulin-dependent protein kinase; RhoK = Rho-associated protein kinase; CREB = cAMP response element binding protein; STAT3 = signal transducer and activator of type 3 transcription.

Alternatively, $TRPV_2$ channels may also be, at least partially, related to the antinociceptive effects of acupuncture, since they respond to mechanical stimulation and noxious heat (>52°C) by triggering a nonselective cation current[49]. Apparently, activation of $TRPV_2$ receptors allows extracellular Ca^{+2} to cross the mast cell membrane and cause the degranulation of stored constituents, such as histamine and ATP itself, later degraded into adenosine. Consequently, these mast cell products can cause analgesia, with histamine acting via release of β-endorphin in the cerebrospinal fluid[50] and adenosine acting on its own, activating inhibitory A_1 receptors located in the peripheral terminals of the dorsal horn neurons of the spinal cord. Finally, the recently discovered $Piezo_1$ receptors may also be the immediate sensors to the mechanical stimulus resulting from acupuncture, promoting direct stimulation of the mast cell membrane with similar consequences to the stimuli caused by the previously mentioned vanilloid receptors[51].

Modulation of adenosinergic receptors (A_1) in acupuncture-induced analgesia

A recent study demonstrated that gentle manual rotation of an acupuncture needle inserted at E36 acupuncture point in animals caused increased release of adenosine in the anterior tibial muscle and adjacent subcutaneous territory, an event demonstrated by microdialysis and high-performance liquid chromatography (HPLC) techniques[29]. The concentration of adenosine increased approximately 24 times and slowly returned to baseline levels. Interestingly, local application of an A_1 adenosinergic receptor agonist (2-chloro-N6-cyclopentyl-adenosine; CCPA) directly at E36 acupuncture point caused inhibition of mechanical and thermal allodynia induced by injection of Freund's complete adjuvant (CFA) into the right paw of rodents[52].

The relatively high extracellular concentrations of ATP metabolites after acupuncture in experimental models probably represent the rapid enzymatic degradation of ATP promoted by ectonucleotidases. Several evidence have indicated that blocking the ADA enzyme by increasing the concentration of adenosine after acupuncture increased the analgesic effect in both inflammatory and neuropathic pain models[27].

Prostatic acid phosphatase (PAP) causes the degradation of AMP to adenosine and its administration at the B40 acupuncture point (Weizhong) in the popliteal fossa, located close to the E36 point, resulted in long-term analgesia against noxious mechanical and thermal stimuli after CFA injection into the hind paw of mice. The analgesic effect seems to be related to an increase in the local concentration of adenosine and the subsequent stimulation of neuronal A_1-type adenosinergic receptors located near the acupuncture point. Antinociception through PAP can be potentiated transiently with additional substrate (e.g. AMP) or blocked temporarily by specific A_1 receptor antagonists such as 8-cyclopentyl-1,3-dipropylxanthine (CPX). The strong analgesic effect of PAP has been previously documented in mouse models of inflammatory and neuropathic pain after its subarachnoid injection[53].

Modulation of P_2X and P_2Y purinergic receptors in acupuncture-induced analgesia

Considering the studies previously cited in this review, evidences indicate that the acupuncture-related effect of adenosine is likely due to local stimulation of A_1 receptors located on peripheral nerve terminals and in neurons of the dorsal root ganglion of the medulla. In contrast, ATP is released through multiple noxious stimuli and is expected to cause pain by occupying P_2X-type receptors on the same sensory neurons (P_2X_3)[54] or on neighboring macrophages (P_2X_4; P_2X_7)[55]. In case of significant tissue damage, ATP is released from the intracellular space through the cell membrane through leakage or active ATP transporters into the cell interstitium. Consequently, this ATP activates, at lower concentrations, the P_2X_3 and/or P_2X_4 receptors and, at higher concentrations, the P_2X_7 receptors[55].

Multiple previous evidences have demonstrated that homomeric (P_2X_3 and P_2X_7) and heteromeric ($P_2X_{2/3}$) purinergic receptors modulate the pain response[26,56]. In general, P_2X receptors respond to noxious ATP release from the intracellular to the extracellular space, potentiating the pain response. However, during acupuncture, nociception can turn into antinociception, when, for example, P_2X_3 receptors are desensitized or the stimulation of P_2X_4 or P_2X_7 receptors causes the release of bioactive molecules from macrophages that can block the generation of action potentials in the terminals of dorsal root ganglion neurons[54]. Additionally, the reverse analgesic effect of P_2X receptors related to acupuncture could be explained by impulses evoked in nerve fibers of the skin that connect with interneurons to inhibit neural pathways directed to higher pain centers in the CNS[25].

In animal models of neuropathic pain, the use of electroacupuncture at traditional ipsi or contralateral points (E36 or VB34 - Yanglinquan) causes a gradual and moderate reversal of neuropathy symptoms. The similar sensitivity for this response to ipsi and contralateral acupuncture techniques suggests that the treatment may act at medullary and supramedullary levels, rather than only at peripheral neuron terminals of the dorsal medulla ganglion[57]. Through the induction of animal models of neuropathic pain, multiple methodologies have demonstrated that P_2X_3 receptors are present in significantly increased amounts in dorsal ganglion neurons, an effect partially reversed through the application of acupuncture techniques. Similar effects of acupuncture and electroacupuncture, inhibiting pain and proliferation of P_2X_3 receptors were observed in rodent models of diabetic neuropathy[58], in models of inflammatory pain through stimulation of acupuncture points such as E36 and Kunlun (B60)[59] and in an animal model of visceral pain[60]. These findings indicate a fundamental role of P_2X_3 purinergic receptors in pain mechanisms and the capacity of acupuncture to effectively modulate the purinergic system, promoting significant analgesia in these scenarios.

The genes responsible for the synthesis of P_2X_4 and P_2X_7 receptors in humans are closely located on chromosome 12, indicating a close relationship in their origin and functions. Overlapping expression of these receptors has been documented, especially in peripheral macrophages and in microglia[61]. The reason for this co-expression may be the involvement of both receptors in multiple inflammatory processes. Considering that P_2X_4 receptors stimulate the release of BDNF from microglia and P_2X_7 receptors modulate the secretion of inflammatory cytokines, chemokines, proteases, reactive oxygen species from activated microglia and macrophages, several evidences indicate that these receptors are closely involved in innate immunology and in several kinds of endogenous reactions to pain, mainly in situations associated with an inflammatory component[54].

Within the context of the purinergic system and ATP receptors, previous evidence indicates that electroacupuncture performed at the Huantiao point (VB30) for 14 days had analgesic effects in an animal model of neuropathic pain and inhibited the increased expression of P_2X_4 receptors in the spinal cord[62]. Another study focused on visceral hypersensitivity after colorectal distention in rats, indicating that electroacupuncture at Shangjuxu (E37) and Tianshu (E25) points not only markedly reduced abdominal withdrawal reflex scores in rats with visceral hypersensitivity, but also significantly reduced the expression of P_2X_4 receptors present in the colon and spinal cord[63]. These data suggest that

nerve injury induced in neuropathic pain models increases IFN--γ production, stimulating the synthesis and expression of P_2X_4 receptors specially in microglia, positively modulating neuronal activity in the pain pathways that ascend towards higher brain centers. Therefore, multiple pieces of evidence indicate that electroacupuncture appears to counteract this effect, and inhibition of P_2X_4 receptors appears to play a fundamental role in this process.

ATP levels and P_2X_7 receptor expression were positively regulated in the spinal cord in an animal model of pain associated with a cervical incision[64]. Additionally, subarachnoid injection of a specific P_2X_7 receptor agonist (dibenzoyl-ATP - Bz-ATP) causes pain in animals[65]. Previous evidences indicate that these events can be antagonized by acupuncture techniques, including electroacupuncture, applied to points such as Huantiao, Zusanli, Yanglinquan, and Dachangsu (B25)[64,65].

All of these results confirm that microglial P_2X_7 receptors present in the spinal cord are also involved in different pain modalities and that acupuncture and electroacupuncture may be able to relieve neuropathies, traumatic and visceral pain probably by decreasing the secretion of pro-inflammatory molecules from microglia.

There are few studies investigating the involvement of ATP- and ADP-sensitive P_2Y receptors in acupuncture-induced analgesia. Multiple evidences indicate that several P_2Y receptor subtypes (P_2Y_1, P_2Y_6, P_2Y_{11}, P_2Y_{12}, P_2Y_{13}) increase pain sensitivity, and their blockade by selective antagonists has analgesic effects[28,66]. Electroacupuncture appears to inhibit visceral hypersensitivity caused by intracolonic injection of acetic acid as a model of irritable bowel syndrome[67]. In that model, a selective P_2Y_1 receptor antagonist caused reduction in pain intensity. Electroacupuncture-induced analgesia simultaneously with the inhibition of astrocyte GFAP protein and P_2Y_1 receptor immunoreactivity led to the conclusion that electroacupuncture depresses visceral hypersensitivity by inhibiting P_2Y_1 receptors, an effect that appears to be mediated through the MAPK / ERK enzyme pathway in astrocytes. A strong argument for the participation of astrocytes and their P_2Y_1 receptors in acupuncture-mediated analgesia was provided by experiments that documented the blockade of their analgesic effects by subarachnoid infusion of fluorocitrate, an astrocyte-selective neurotoxin[67].

CONCLUSION

Recent experimental studies have been providing assertive evidence on the involvement of the purinergic system in the analgesia provided by acupuncture. ATP and its enzymatic degradation products such as adenosine can stimulate a variety of specific receptors, with significant findings for the purinergic P_2X_3, P_2X_4, P_2X_7 receptors and the adenosinergic A_1 receptor. It's important to note that the interactions of multiple systems in modulating the pain response make the investigation of the basic mechanisms of acupuncture extremely complex. Therefore, further experimental and clinical studies are essential for investigating the real role of the purinergic system in acupuncture-mediated analgesia.

AUTHORS' CONTRIBUTIONS

André Prato Schmidt
Data Collection, Conceptualization, Project Management, Methodology, Writing - Preparation of the original, Writing - Review and Editing, Supervision, Visualization
Sérgio Renato Guimarães Schmidt
Data Collection, Project Management, Writing - Preparation of the original, Writing - Review & Editing, Supervision

LIST OF ABBREVIATIONS

AC = adenylyl cyclase
ADA = adenosine deaminase
ADP = adenosine diphosphate
Akt = protein kinase B
AMP = adenosine monophosphate
ATP = adenosine triphosphate
B25 = Dachangsu
B40 = Weizhong
Bz-ATP = dibenzoyl-ATP
cAMP= cyclic adenosine monophosphate
CAR1-4 = G protein-linked cAMP receptors
B60 = Kunlun
BDNF = brain-derived neurotrophic factor
CaMK = Ca+2/calmodulin-dependent protein kinase
CCPA = 2-chloro-N6-cyclopentyl-adenosine
CFA = complete Freund's adjuvant
cGMP= cyclic guanosine monophosphate
CPX = 8-cyclopentyl-1,3-dipropylxanthine
CREB = cAMP response element-binding protein
DG = diacylglycerol
DNA = deoxyribonucleic acid
E25 = Tianshu
E36 = Zusanli
E37 = Shangjuxu
E-NTPDases = ecto-nucleoside triphosphate diphosphohydrolase
ERK = extracellular synthalase-regulated kinase
GABA = gamma-aminobutyric acid
GDP = guanosine diphosphate
GFAP = glial fibrillary fibrillary acidic protein
GMP = guanosine monophosphate
GSK = GS protein kinase
GTP = guanosine triphosphate
HGPRT = hypoxanthine-guanine-phosphoribosyltransferase
HPLC = high performance liquid chromatography
IFN-γ = interferon-gamma
IP3 = inositol-trisphosphate
MAPK = mitogen-activated protein kinase
NMDA = N-methyl-D-aspartate
PAP = prostatic acid phosphatase
PD = ecto-phosphodiesterase
PGs = prostaglandins
PI-PLC = phosphatidylinositol-bisphosphate phosphodiesterase
PKA = protein kinase A
PKC = protein kinase C

PLA = phospholipase A
PNP = purine nucleoside phosphorylase
RhoK = Rho-associated protein kinase
RNA = ribonucleic acid
CNS = central nervous system
Src = Src tyrosine kinase
STAT3 = signal transducer and activator of type 3 transcription
TRPV2 = transient receptor potential vanilloid receptor
VB34 = Gallbladder 34 (Yanglinquan)
VB30 = Gallbladder 30 (Huantiao)

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