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The Involvement of Purinergic System in Pain: Adenosine Receptors and Inosine as Pharmacological Tools in Future Treatments

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1. Introduction

During the recent years, the interest in the purinergic system has been gaining importance, and this interest is not accidental. The purinergic system is so far known to be involved in several physiological conditions in mammals, becoming a potential therapeutic target for the treatment of many pathologies and disorders. One of the physiological roles is the control of pain. This chapter will emphasize adenosine receptors (P1) and its activation and inhibition by adenosine and by specific agonists or antagonists in the treatment of pain. Although most of the studies quoted in this chapter were performed in animals, in this chapter we will use the expression *analgesia* instead of *antinociception* (term used to report pain in animals) to simplify our communication. Some drugs that act on adenosine receptors have presented interesting results in clinical studies of pain and other drugs are under investigation. Of note, it has recently been shown that inosine, a metabolite of adenosine, has significant analgesic effects in several pre-clinical models of pain. Thus, the inosine can be an important tool in this area of study or even a molecule of interest for future pharmacological approaches, knowing that such as adenosine, it is produced endogenously and devoid of side effects in normal doses. In addition, new approaches using enzyme inhibitors of the purinergic system or supplies of adenosine suggest alternatives to potentiate and lasting analgesic effects of adenosine or analogs. Moreover, the release of purines and the adenosine A₁ receptor activation are essential to analgesia by acupuncture in mice. Thus, purinergic system will be the target of many future pain-treatment researches. After all, it is indispensable to students and biomedical professionals to know and understand basic concepts about this endogenous system.

2. Involvement of purinergic system in pain

2.1 Purinergic receptors: History and involvement in pain

Purinergic receptors history began when Drury and Szent-Györgi described the potent actions of purines adenine and adenosine on the heart and blood vessels (Drury & Szent-

Györgi, 1929). Later, in 1970 Burnstock presented evidence that ATP acted as a neurotransmitter in nonadrenergic noncholinergic (NANC) nerves supplying the gut, and finally, in 1972, the purinergic neurotransmission hypothesis was proposed (Burnstock, 1972). With these discoveries, the number of publications involving ATP and its metabolites grew quickly and continues to do so (Figure 1).

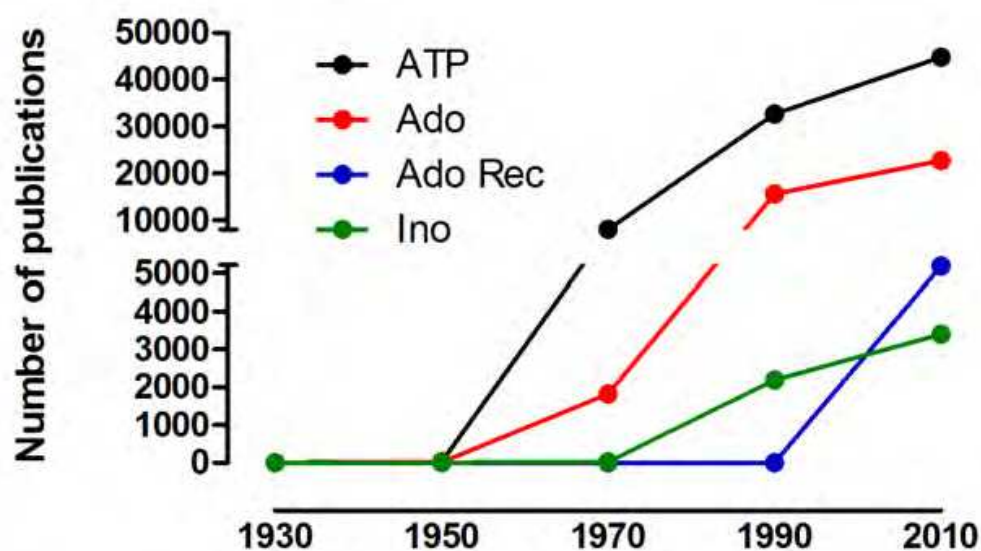


Fig. 1. Total of publications with keywords ATP, Adenosine (Ado), Adenosine Receptors (Ado Rec) and Inosine (Ino) from 1930 until 2010. Source: Pubmed

Afterwards, it was established that the ATP acted as a cotransmitter with classical transmitters in both the peripheral nervous system and in the central and that purines are also powerful extracellular messengers to non-neuronal cells (Burnstock & Knight, 2004). Burnstock, in 1978, provided the basis for the distinction of two classes of purinergic receptors; adenosine-sensitive P1 and ATP-sensitive P2 receptor classes. In 1985, Burnstock and Kennedy proposed a basis for distinguishing two types of P2 purinoceptors, namely, P2X and P2Y. Afterwards, in 1994 Abbracchio and Burnstock through studies of transduction mechanisms and cloning of both P2X and P2Y receptors put forward a new nomenclature system, naming them, P2X ionotropic ligand-gated ion channel receptors and P2Y metabotropic G protein-coupled receptors, respectively. Currently, seven subtypes of P2X receptors (P2X₁, P2X₂, P2X₃, P2X₄, P2X₅, P2X₆, P2X₇) and eight subtypes of P2Y receptors (P2Y₁, P2Y₂, P2Y₄, P2Y₆, P2Y₁₁, P2Y₁₂, P2Y₁₃, P2Y₁₄) are clearly established. P2X and P2Y receptor activation by ATP stimulates cellular excitability, augments the release of excitatory amino acids, and consequently initiates pain responses (Burnstock, 2007; Burnstock & Williams, 2000). In the context of pain neurotransmission, preclinical studies show us that activation of P1 receptors by adenosine decreases pain, inflammation, and cellular excitability (McGaraughty & Jarvis, 2006). During the 80's and 90's research evaluating purinergic system in pain rocketed (Figure 2).

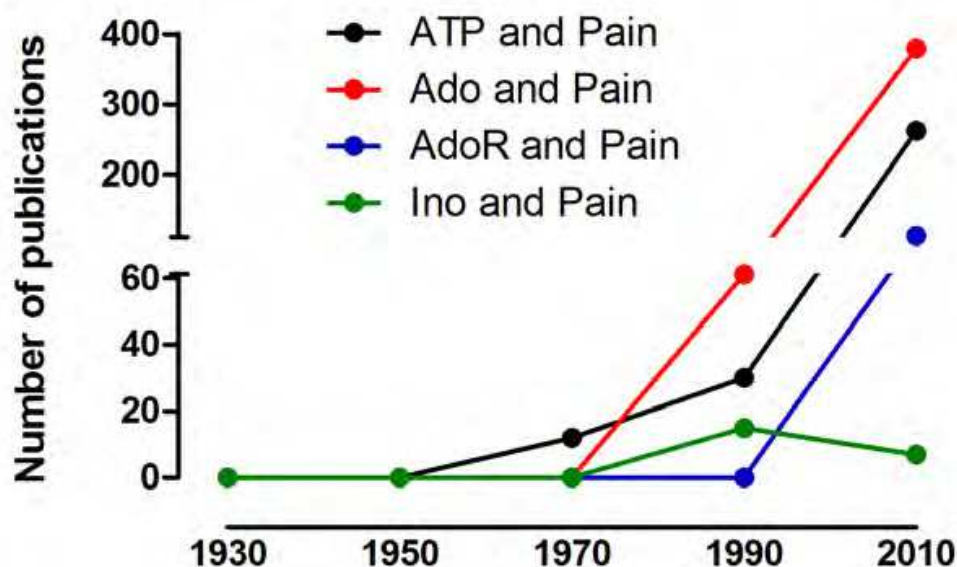


Fig. 2. Total of publications with keywords ATP, Adenosine (Ado), Adenosine Receptors (AdoR) and Inosine (Ino) plus Pain from 1930 until 2010. Source: Pubmed

3. Adenosine receptors and pain

3.1 Adenosine receptors

Adenosine is the natural ligand of P1 receptors, also called adenosine receptors. All these receptors are G-protein coupled and are divided according to pharmacological, biochemical and molecular properties into four subtypes: A_{1R} , A_{2AR} , A_{2BR} and A_3 . Each receptor has a distinct distribution and due to its special features, has distinct roles as well (Burnstock et al., 2011; Fredholm et al., 2011; Ralevic & Burnstock, 1998; Ribeiro et al., 2002; Sawynok & Liu, 2003). Adenosine receptors were cloned and characterized in several mammal species (Burnstock, 2008).

3.2 Distribution of adenosine receptors

Adenosine receptors are present in several species and in distinct tissues. However, their distribution is quite irregular and different among species and mainly among tissues (Fredholm et al., 2011). A_1 receptor (A_{1R}) is a ubiquitous receptor. In the central nervous system, it is distributed in the cerebellum, cerebral cortex, hippocampus, thalamus, spinal cord (substantia gelatinosa), brain stem, olfactory bulb and other central sites. Peripherally A_{1R} distribution is less wide than centrally, but there is a considerable density of A_{1R} in sensory afferent fibers, mainly on C-fibers which are responsible for receiving and conducting the painful stimuli (Dixon et al., 1996; Sawynok, 2009). A_{2A} receptor (A_{2AR}) has an even distribution between central and peripheral nervous system, but mainly in central structures as nucleus accumbens, putamen, caudate and in immune tissues, vascular smooth muscle, endothelium, platelets and sensory neurons (Dixon et al., 1996; Fredholm, 1995; Ralevic & Burnstock, 1998; Sawynok, 2009). A_{2B} receptor (A_{2BR}) is also a ubiquitous receptor and it has been found either in many central or peripheral tissues. However, A_{2BR} density is

very low and it has been found in great density only in bowel and bladder. A_3 receptors (A_{3R}) are widely distributed in several mammals, however, few studies have indicated specific roles for this receptor (Dixon et al., 1996; Ralevic & Burnstock, 1998; Salvatore et al., 1993).

3.3 General adenosine receptor signaling

All adenosine receptors are coupled to G-protein. Nevertheless there are many kinds of G-protein and each one may activate a distinct pathway. Thus, the four adenosine receptors can stimulate or inhibit several pathways and consequently exert many physiological actions (Jacobson & Gao, 2006; Ralevic & Burnstock, 1998). We show below the main signaling characteristics of each adenosine receptor.

3.3.1 A_1 receptor signaling

A_{1R} is coupled to $G_i/0$ protein family which is pertussis toxin-sensitive. Most of the biological effects induced by A_{1R} activation are due to inhibition of cAMP second messenger (Burnstock, 2007; Jacobson & Gao, 2006; Ralevic & Burnstock, 1998; Sawynok, 1998) (Figure 3 and Table 1).

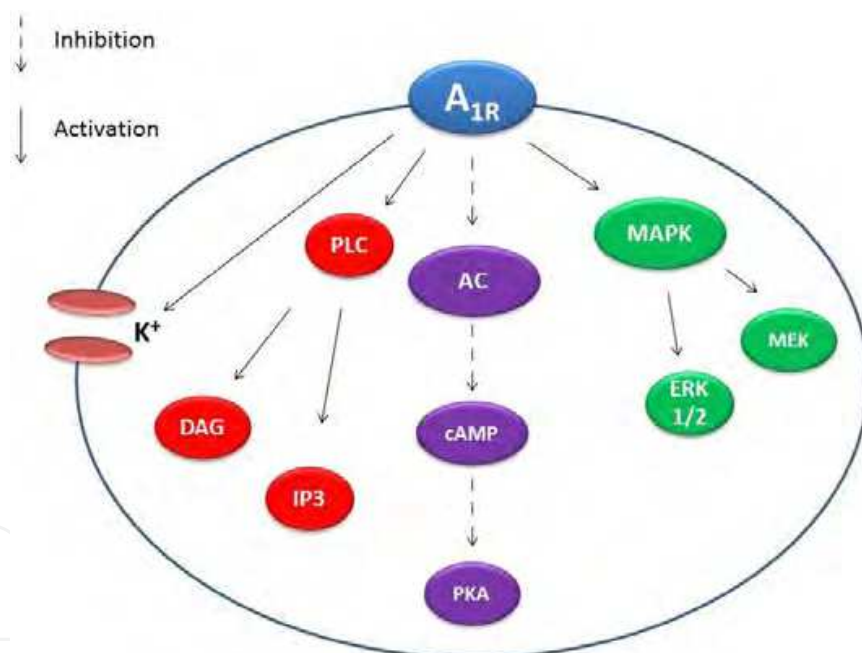


Fig. 3. Adenosine A_1 receptors and its main pathways. A_{1R} , adenosine A_1 receptor; AC, adenylate cyclase; cAMP, cyclic adenosine monophosphate; DAG, diacylglycerol; ERK1/2, extracellular signal-regulated kinases 1 and 2; IP_3 , inositol triphosphate; K^+ , potassium channels; MAPK, mitogen-activated protein kinase; MEK, MAPK and ERK kinase; PKA, protein kinase; PLC, phospholipase C.

Beta and gamma subunits of A_{1R} , when activated stimulate phospholipase C (PLC). Activation of PLC cleaves phosphatidylinositol 4,5-bisphosphate (PIP_2) into diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP_3) leading to increased levels Ca^{+2} . Moreover, the enhancement of intracellular calcium can induce some enzymes such as protein kinase C

(PKC), phospholipase D (PLD), phospholipase A₂ (PLA₂) and others. Furthermore, adenosine or adenosine agonists can activate K⁺ channels (Jacobson & Gao, 2006; Megson et al., 1995; Ralevic & Burnstock, 1998). A_{1R} activation can also activate PI3K and MAPK pathways, more specifically ERK1/2 and MEK inducing gene expression changes and glial cell protection (Boison et al., 2010; Shulte & Fredholm, 2003).

3.3.2 A_{2A} receptor signaling

A_{2AR} is coupled to G_s (the most part) and Golf protein (mainly in striatum). The main intracellular event after activation of these proteins is adenylate cyclase activation followed by cAMP production enhancement (Table 1).

Receptor	Adenosine affinity (EC50;nm)	G-protein	cAMP	PKA	PLC	Ca ²⁺ channels	K ⁺ channels
A ₁	~ 70	Gi/Go	Decrease	Inhibits	Activates	Inhibits	Activates
A _{2A}	~ 150	Gs/Golf	Increase	Activates		Inhibits or Activates	Activates
A _{2B}	~ 5100	Gs/Gq	Decrease	Activates	Activates		
A ₃	~ 6500	Gi/Go	Increase	Inhibits	Activates		

Table 1. Adenosine receptors signaling. Adapted from Ralevic and Burnstock, 1998; Sawynok and Liu, 2003; Jacobson and Guao, 2006.

The increasing of cAMP stimulates cAMP-dependent kinase (PKA). Thus, PKA becomes able to activate several pathways through PKC, calcium channels, potassium channels, cAMP responsive element-binding (CREB), MAPK, PLC activation (Burnstock, 2007; Cunha et al., 2008; Fredholm et al., 2003, 2007; Jacobson & Gao, 2006; Ralevic & Burnstock, 1998).

3.3.3 A_{2B} receptor signaling

Through G_s and G_q activation A_{2BR} receptor induces adenylate cyclase and PLC. In humans, A_{2BR} can increase intracellular calcium by IP₃ activation. Moreover, the arachidonic acid pathway is also involved in A_{2BR} signaling (Feoktistov & Biaggioni, 2011; Jacobson & Gao, 2006; Peakman and Hill, 1994).

3.3.4 A₃ receptor signaling

A_{3R} like A_{1R} is coupled to Gi/0 and also to Gq/11 protein. Its main signaling transduction is the inhibition of adenylate cyclase and stimulation of PLC, IP₃, DAG, PKC and PLD. Also, like other adenosine receptors, A_{3R} activates MAPK pathway, mainly ERK1/2 (Abbracchio et al., 1995; Armstrong & Ganote, 1994; Palmer et al., 1995; Shneyvays et al., 2004).

3.4 A₁ receptors and pain

A_{1R} is the main responsible for inducing analgesia among the adenosine receptors (Burnstock et al., 2011; Sawynok, 1998; Sawynok & Liu, 2003). It has been shown that A_{1R} is widely distributed in the dorsal spinal cord, mainly in lamina II (substantia gelatinosa) (Choca et al., 1988; Horiuchi et al., 2010; Sawynok, 1998). In this site, many afferent sensory nerve have connections with post-synaptic neurons. Also, A_{1R} are localized in the descending projection within dorsal horn (Choca et al., 1988).

3.4.1 Effects of A₁ receptor activation in acute pain

There are several published data showing the important effect of A_{1R} in controlling acute pain (review see Jacobson & Gao, 2006; Sawynok, 1998). Moreover, it has been shown that systemic administration of various A_{1R} agonists can produce analgesic effect in several models of acute pain in animals (Gong et al., 2010; Sawynok, 1998). Probably, these effects are caused by peripheral, supraspinal and mostly by spinal A_{1R}. In mice lacking A_{1R} (knockout animals) a lower pain threshold was observed in hyperalgesia tests (Wu et al., 2005). Further, analgesic effect induced by intrathecal adenosine was abolished as well as the increase of thermal hyperalgesia in A_{1R} knockout mice (Johansson et al., 2001).

Several studies published show that intrathecal injection of A_{1R} agonists cause analgesia in various animal models of acute pain, including tail flick, tail immersion, hot-plate, formalin, acetic acid, capsaicin models and others (Nascimento et al., 2010; Song et al., 2011; Zahn et al., 2007).

A_{1R} is also found in primary afferent neurons and in the cell body and the dorsal root ganglia (Lima et al., 2010; Sawynok, 2009), then it has an important role in modulation of peripheral pain. Many studies have shown that administration of A_{1R} agonists into the paw of animals causes an analgesic effect in several animal models of pain. It has been shown that A_{1R} activation in the periphery inhibits formalin-induced pain and reduces hyperalgesia induced by PGE₂ (Karlsten et al., 1992; Taiwo & Levine, 1990). Further, when the peripheral adenosine A_{1R} is activated, it triggers the NO/cGMP/PKG/K_{ATP} intracellular signaling pathway and then inhibits pain (Lima et al., 2010). Moreover, A_{1R} agonists reduce the thermal hyperalgesia, but not mechanical allodynia, caused by sciatic nerve injury. The thermal hyperalgesia is mediated by C fibers and mechanical allodynia, in turn, is mediated by A fibers, which demonstrates the presence of A_{1R} in C but not in A fibers (Sawynok, 2009).

3.4.2 A₁ receptor and chronic pain

Several authors have shown that different agonists of A_{1R} are able to reduce distinct kinds of chronic pain. The agonist R-PIA inhibits mechanical allodynia induced by spinal nerve ligation in rats (Hwang et al., 2005; Song et al., 2011). In addition, R-PIA also reduces thermal pain threshold in rats that underwent an injury in the spinal cord (Horiuchi et al., 2010). Moreover, other mechanisms are generally involved in analgesic effect in chronic pain induced by A_{1R} activation, such as inhibition of glutamate release. Another A_{1R} agonist, CPA, when given to rats, inhibits pain induced by arthritis and pain induced by neuropathy (Curros-Criado & Herrero, 2005). Also, in experiments with A_{1R} knockout mice it has been observed that these animals present a lower pain threshold than wild-type animals in inflammatory and neuropathic pain models (Wu et al., 2005).

3.4.3 Interactions between A₁ receptor and opioid system

There is a strong relationship between opioidergic and adenosinergic systems in pain modulation. Morphine and other opioids are able to release adenosine (Sawynok et al., 1989; Sweeney et al., 1987a,b; Sweeney et al., 1989). Adenosine or analog administration combined with opioids enhances the analgesic effect of the latter (DeLander & Hopkins, 1986). However, administration of methylxanthines, adenosine receptor antagonists, can augment, decrease or have no effect on analgesic activity of opioids (Sawynok, 2011). In addition, A_{1R} can undergo dimerization with μ receptor in afferents neurons and induce the decrease of cAMP production (Sawynok, 1998).

3.4.4 Interactions among A₁ receptor and other receptors in pain mechanisms

A_{1R} is able to dimerize with alpha-2-adrenergic receptor. Also, it has been shown that serotonin releases adenosine from primary afferents and that A_{1R} receptor antagonist blocks serotonin analgesic actions, suggesting a close involvement between adenosinergic and serotonergic systems in pain modulation (Sawynok, 1998).

3.4.5 A₁ agonists/antagonists

Methylxanthines (caffeine included) are natural antagonists of adenosine A_{1R} and A_{2AR}. However, the main selective agonists/antagonists to A_{1R} are synthetics. Some of them are listed in Table 2.

Role of drugs	Drug	Chemical name
Agonists A _{1R}	R-PIA	(-)-N ⁶ -(2-Phenylisopropyl)adenosine
	CHA	N ⁶ -ciclohexyladenosine
	CPA	N ⁶ -cyclopentyladenosine
	CCPA	2-chloro-N ⁶ -cyclopentyladenosine
	CPT	8-cyclopentyl-1,3-dimethylxanthine
Antagonists A _{1R}	DPCPX	8-Cyclopentyl-1,3-dipropylxanthine
	8-PT	8-phenyltheophylline

Table 2. Principal adenosine A₁ receptor agonists and antagonists.

3.5 A_{2A} receptors and pain

Taiwo & Levine (1990) demonstrated clear distinct effects of A_{1R} and A_{2AR} activation in peripheral pain. They showed that, in peripheral sites, A_{1R} mediates analgesia while A_{2AR} facilitates painful perception. In addition, other studies also showed that peripheral A_{2AR} activation induced pain (Doak & Sawynok, 1995; Li et al., 2010; Taiwo & Levine, 1990). However, systemically and spinally, the role of A_{2AR} is not entirely clear. Some publications have demonstrated that A_{2AR} activation induces pain (Bastia et al., 2002; Hussey et al., 2007). On the other hand, other authors have showed a reduction of pain when A_{2AR} is activated (By et al., 2011; Borghi et al., 2002; Yoon et al., 2005). These controversial results might be associated with A_{2AR} intracellular signaling. A_{2AR} activation induces cAMP increased

production (it can cause pain) and also K^+ channels opening (it can inhibit pain) (Jacobson & Gao, 2006; Regaya et al., 2004; Sawynok, 1998).

A_{2AR} knockout animals are less sensitive to pain, suggesting that A_{2AR} is a pain facilitator in acute (Hussey et al., 2007) and chronic pain (Bura et al., 2008). Bura and coworkers (2008) also demonstrated that microglia and astrocytes expression was higher in wild-type A_{2AR} animals than in A_{2AR} knockout animals. Also, A_{2AR} located in glial cells is responsible for the release of inflammatory mediators that induce and maintain chronic pain (Boison et al., 2010). Thus, A_{2AR} blockade might be an interesting approach for future treatments of neuropathic and chronic pain. Meantime, also in chronic pain exists distinct results about A_{2AR} . A report showed that only one spinal injection of A_{2AR} agonist was able to induce analgesia during several days in rats undergoing neuropathic pain (Loram et al., 2009). After all, it is clear that A_{2AR} is involved in pain modulation. However, more studies are necessary to precisely explain how this receptor works in distinct situations, only then it will be possible to make clinical approaches.

3.6 A_{2B} receptors and pain

Few studies have been evaluating the A_{2BR} role in pain. Most part of these studies showed that A_{2BR} facilitates pain transmission, because A_{2BR} antagonists have reduced pain (Abo-Salem et al., 2004; Bilkei-Gorzo et al., 2008; Godfrey et al., 2006). A_{2BR} antagonist reduced thermal hyperalgesia and was able to potentiate the analgesic effect caused by morphine and acetaminophen (Abo-Salem et al., 2004; Godfrey et al., 2006). Also, the blockade of A_{2BR} presented an analgesic effect in inflammatory pain (Bilkei-Gorzo et al., 2008).

3.7 A_3 receptors and pain

Similar to A_{2BR} , adenosine A_{3R} is not an interesting target to pain relief. However, A_{3R} is implicated in pathological conditions such as ischemic diseases and in inflammation (for review see Borea et al., 2009). Regarding pain, there are few studies evaluating A_{3R} role. Sawynok and colleagues (1997) showed that A_{3R} activation causes pain and paw oedema through release of histamine and serotonin. A_{3R} knockout animals presented an increased pain threshold in some models of pain but not difference in others (Fedorova et al., 2003; Wu et al., 2002). A_{3R} might be an interesting target to inflammatory and autoimmune diseases, but not to pain states.

3.8 Novel approaches in pain management involving adenosine receptors

3.8.1 Management of adenosine receptors by metabolism modulation

The first report showing that adenosine kinase (AK) inhibition reduces behaviour associated to pain was published by Keil and DeLander, 1992. AK inhibitors are able to decrease pain levels when given peripherally or sistemically (Kowaluk et al., 1999; Lynch et al., 1999; Sawynok, 1998). Moreover, these inhibitors are efficacious against acute and chronic pain (Kowaluk et al., 2000; Lynch et al., 1999; McGaraughty et al., 2005; Poon & Sawynok, 1998, 1999; Suzuki et al., 2001). Another enzyme that regulates adenosine level is adenosine deaminase (ADA), that converts adenosine to inosine (Sawynok, 1998). However, the analgesic effect caused by ADA inhibition is not so clear yet. It has been showed that

inhibitors of ADA itself are able to cause analgesia in determined animal models (Poon & Sawynok, 1999), but not in others (Keil & DeLander, 1992, 1994).

Coadministration of AK and ADA inhibitors potentiates the analgesic effect of the former (Poon & Sawynok, 1999). Also, adenosine effect is synergically augmented by coadministration of ADA inhibitor (Keil & DeLander, 1994). Distinct effects between AK inhibitors and ADA inhibitors might be because adenosine has a higher affinity by AK than ADA (Arch & Newsholme, 1978). In this point of view, AK seems to be the most important enzyme to regulate adenosine endogenous levels.

3.8.2 Analgesic effect by supply of purinergic substrates

Ecto-5'-nucleotidase (NT5E) is an enzyme located in the cell membrane that catalyzes the extracellular conversion of adenosine monophosphate (AMP) into adenosine in several tissues, included dorsal root ganglia (DRG) and substantia gelatinosa (Zylka, 2011). Recent studies have demonstrated that the analgesic effect of AMP combined with an AK inhibitor halved in NT5E knockout animals and is totally reversed in A_{1R} knockout animals (Sowa et al., 2010a). These results inspired another study that evaluated whether exogenous supply of NT5E (increases supply of adenosine) could induce a long lasting analgesic effect. NT5E presented effects that lasted for 2 days in models of inflammatory and chronic pain. Both effects were dependent on A_{1R} (Sowa, 2010b). Hence, the supply of enzymes that generate adenosine is a new interesting approach that may be used in studies to treat chronic pain.

3.8.3 Involvement of adenosine receptors in acupuncture pain relief

In an elegant study published in 2010, Goldman and colleagues showed that analgesia induced by acupuncture depends on purine release, such as ATP, ADP, AMP and adenosine. In addition, it has been showed that A_{1R} agonist replicates the acupuncture effect. Also, in A_{1R} knockout animals, acupuncture did not present analgesia. Moreover, inhibition of adenosine deaminase prolonged the analgesic effect of acupuncture in mice (Goldman et al., 2010). It is interesting to mention that caffeine, the most widely used drug across the world in beverages such as teas, coffee, *mate*, soft drinks, energy drinks and others is an antagonist of adenosine receptors. Therefore, patients in treatment with acupuncture should not drink these caffeine beverages, because caffeine might reduce the acupuncture analgesic effect (for review see Zylka, 2010).

4. Inosine and pain

4.1 Inosine within of purinergic system

ATP is the main molecule of purinergic system. Inside the cell, ATP may be bi-directionally converted into AMP. AMP is broken down into adenosine. Adenosine may be converted back into AMP through phosphorylation by AK. Moreover, adenosine might leave the cell by nucleoside transporter (NT). Inside the cell, adenosine deaminase is responsible for the conversion from adenosine to inosine. Outside the cell, this conversion is performed by ecto-adenosine kinase or even adenosine deaminase. Inosine is a substrate to purine nucleoside phosphorylase (PNP), leading to hypoxanthines as its products. Hypoxanthines are converted into xanthines and afterwards to uric acid by xanthine oxidase (Figure 4) (See review Sawynok & Liu, 2003).

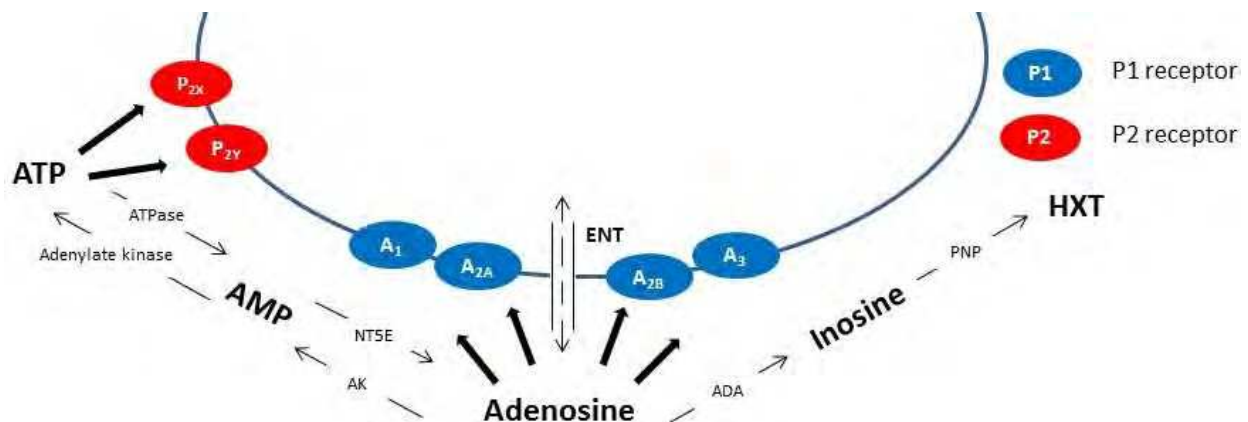


Fig. 4. Purinergic metabolism and its main molecules and enzymes. A₁, adenosine A₁ receptor; A_{2A}, adenosine A_{2A} receptor; A_{2B}, adenosine A_{2B} receptor; A₃, adenosine A₃ receptor ADA, adenosine deaminase; AK, adenosine kinase; AMP, adenosine monophosphate; ATP, adenosine triphosphate; ENT, equilibrative nucleoside transporter; HXT, hypoxanthines; NT5E, *ecto-5' nucleotidase*; P_{2X}, purine P_{2X} receptor; P_{2Y}, purine P_{2Y} receptor; PNP, purine nucleoside phosphorilase.

Thus, inosine is one among many molecules in purinergic system. However, inosine has specific roles in several physiological states, we will show some functions and discuss the role of inosine in pain control in next sections.

4.2 Inosine physiological roles

In recent decades, many physiological roles for inosine have been shown. During the 70's, Aviado demonstrated that inosine exerts cardiotoxic actions, such as preventing negative inotropic effect and increasing coronary vasodilatation (Aviado, 1978). Also, inosine presents several effects on axonal growth, such as axon growth induction and damaged neurons stimulation (Benowitz et al., 1999, 2002; Chen et al., 2002). Inosine also induces a regrowth in axotomized retinal ganglion cells in rats (Wu et al., 2003). These data indicate that inosine may constitute a new approach to treat the injured or degenerated nerves in central or peripheral nervous system. Despite of cardiovascular and axonal growth effects, the inflammatory effects of inosine are the most studied. Inosine has significant anti-inflammatory effects in several *in vivo* and *in vitro* models of inflammation (Gomez & Sitkovsky, 2003; Haskó et al., 2000; Marton et al., 2001; Schneider et al., 2006). These effects seem to be mediated by A_{1R}, A_{2R} and A_{3R} (Gomez & Sitkovsky, 2003; Haskó et al., 2000, 2004).

4.3 Inosine effect on acute pain

Inosine has analgesic action when administered by different routes (i.e. intraperitoneal, oral, intrathecal or intracerebroventricular) against pain induced by acetic acid (Nascimento et al., 2010). Of note, inosine also inhibits pain induced by formalin. Formalin test induces 2 distinct types of pain, neurogenic phase (acute pain) and inflammatory phase (inflammatory pain). Inosine is not able to relieve pain in neurogenic phase. However, inosine reduces nearly totally the inflammatory pain in formalin test (Nascimento et al., 2010). The effects of inosine in this model of pain extended the acetic acid data because formalin is a more

specific model. Therefore, these results indicate that inosine is able to prevent and reduce pain induced by inflammatory mediators. In this way, inosine may be inhibiting the synthesis or release of several neurotransmitters and mediators involved in pain conditions (Nascimento et al., 2010). We can also conclude that inosine is able to inhibit pain induced by central facilitation. Therefore, inosine increases pain threshold and it may be useful to treat some kinds of pain injury that result from a central sensitization. Adenosine receptors distribution on substantia gelatinosa, mainly A_{1R} and A_{2AR} could explain how inosine acts in this case (Sawynok, 1998; Sawynok & Liu, 2003). Inosine also presents a significant and dose-related inhibition of pain induced by glutamate (acute pain model) injection into the paw of mice (Nascimento et al., 2010).

4.4 Inosine effects on chronic pain

The data described in literature strongly suggests that inosine may have an important effect in controlling chronic pain, since it has anti-inflammatory effect and can reduce acute pain. In fact, Nascimento and colleagues (2010) demonstrated that acute administration of inosine, intraperitoneally, was able to inhibit chronic inflammatory pain induced by CFA in mice, being effective up to 4 hours after administration. The CFA is responsible for inducing chronic inflammation by stimulating the body's immune response, this response is mediated by the synthesis and release of cytokines and inflammatory mediators (Zhang et al., 2011).

In the study published by Nascimento and colleagues (2010), inosine was effective against mechanical and thermal allodynia induced by partial sciatic nerve ligation (PSNL) up to 4 hours after treatment by intraperitoneal route. Further, in another experiment, inosine was given daily for until 22 days and it also presented significant analgesic effect. Pain induced by PSNL is very strong and may last for weeks (Ueda, 2006). Animal models of neuropathic pain induce many functional and biochemical changes in local injury site. After the surgery there is the release of multiple inflammatory and pain mediators which in turn, may also be present in other areas involved and affected by sciatic nerve, as spinal cord and brain (Bridges et al., 2001; Ji & Woolf, 2001; Inoue et al., 2004; Ueda, 2006). Inosine activity in this kind of pain may indicate a promising molecule to new studies, because inosine might have a longer half-life than adenosine and admittedly does not have toxic or side effects.

4.5 Adenosine receptors involved in analgesic effects of inosine

A_{1R} has been considered the main receptor responsible for analgesic effect among adenosine receptors (Burnstock, 2007; Sawynok, 1998). A_{1R} is also the main receptor involved in inosine analgesic effect. Both A_{1R} antagonists DPCPX and 8-PT were able to reverse the inosine action. Inosine in a direct or indirect way activates A_{1R} to induce analgesia (Nascimento et al., 2010). Other studies have showed that adenosine receptor antagonists block *in vivo* and *in vitro* inosine effects (Haskó et al., 2000) and adenosine receptor knockout animals do not present immunoprotective effects of inosine (Gomez & Sitkovsky, 2003). Thus, it is clear that the A_{1R} activation is essential for inosine to exert its effect (Figure 5).

Involvement of A_{2AR} in pain is quite controversial. Some studies show that A_{2AR} blockade leads to analgesic effect (Borghini et al., 2002; Yoon et al., 2005) while other studies demonstrate that the blockade or deletion of A_{2AR} causes pain relief (Bastia et al., 2002; Ledent et al., 1997). Inosine activates A_{2AR} to induce analgesia, at least in the acetic acid

model (Nascimento et al., 2010). However, the participation of A_{2AR} receptor in inosine analgesia in other pain animal models might be different or does not exist. Moreover, the A_{2AR} involvement on inosine effect can occur due to its anti-inflammatory profile (Milne & Palmer, 2011) and due to activation of the K^+ channels (Regaya et al., 2004).

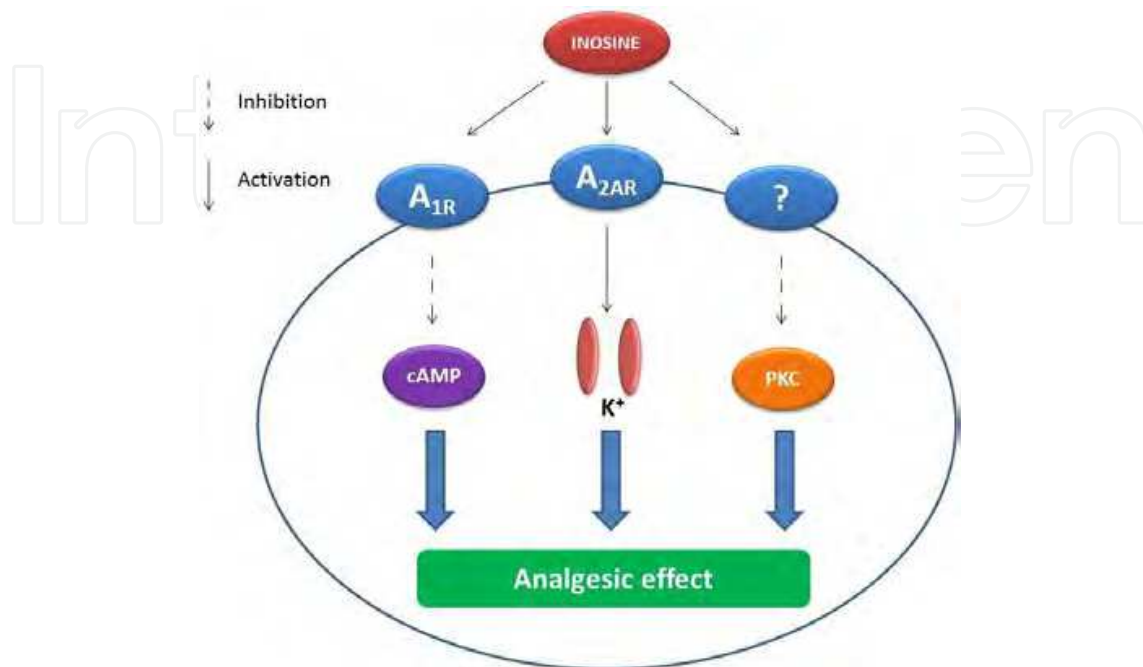


Fig. 5. Principal mechanisms of inosine antinociception. A_{1R} , adenosine A_1 receptor; A_{2AR} , adenosine A_{2A} receptor, cAMP, cyclic adenosine monophosphate; K^+ , potassium channels; PKC, protein kinase C.

A_{2BR} and A_{3R} adenosine receptors do not have significant role in pain transmission or modulation (Sawynok, 1998). Although it has been shown that inosine binds to A_{3R} , it seems that A_{2BR} and A_{3R} receptors are not involved in inosine analgesic effect (Nascimento et al., 2010).

4.5.1 Does inosine binds to adenosine receptor?

Few studies have evaluated if inosine binds to adenosine receptor. Jin and co-workers demonstrated that inosine binds to A_{3R} in mast cells, but not to A_{1R} or A_{2AR} (Jin et al., 1997). In 2001, Fredholm's group observed that inosine weakly bound to A_{1R} and A_{3R} , but not to A_{2R} (Fredholm et al., 2001). Fredholm concluded that inosine could not be considered a natural ligand of adenosine receptors. However, because of these few studies and considering *in vivo* studies where adenosine antagonists are able to block inosine effects, it is not possible to affirm whether inosine is or not a natural ligand or a partial agonist of adenosine receptors. More studies are necessary to elucidate this issue.

4.6 Intracellular signalling involved in analgesic effects of inosine

The intracellular signaling involved in analgesic action of inosine is yet not entirely elucidated. Assuming that inosine effects depend on adenosine receptors, A_{1R} and A_{2AR} , we can consider that adenosine receptors signaling pathways are the major effectors of this

effect. As fully mentioned previously, A_{1R} is coupled to $G_i/0$ protein. A_{1R} signaling causes downstream inhibition of adenylyl cyclase and induction of PLC activity. Further, when A_{1R} is activated it causes potassium channel opening, PI3K and MAPK stimulation. All these pathways might participate in the inosine analgesic effect (Ansari et al., 2009; Jacobson & Gao, 2006; Sawynok, 1998; Schulte & Fredholm, 2003). Inosine inhibits the pain caused by PKC activator. Thus, at least in part, the analgesic action of inosine depends on PKC inhibition (Nascimento et al., 2010), even though it is not clear yet how it happens (Figure 5). Costenla and coworkers showed that an adenosine analog that has preference for A_{2AR} is able to inhibit sodium current in NMDA receptors (Costenla et al., 1999). This signaling occurring *in vivo* could partially explain how A_{2AR} works in analgesia induced by inosine.

4.7 Perspectives

As previously described in this chapter, purinergic system is an important endogenous modulator of pain. Hundreds of pre-clinical studies targeting the adenosine receptors showed analgesic effect in distinct pain models. Inosine, an endogenous modulator of several physiological functions also presents a role in pain transmission. Inosine might be a natural activator of adenosine receptors. Also, it can indirectly increase the release or reduce the uptake of adenosine, potentiating the effect of its precursor. Thus, understanding how inosine acts to induce analgesia may help discover new ways to inhibit pain or new therapeutic targets. Moreover, inosine may be a potential molecule to treat pain, and it has a great advantage to be devoid of toxic or side effects because it has been used clinically for many years for other purposes. Another interesting approach would be to attempt to prolong and potentiate the effect of inosine. For this, a great understanding of purinergic metabolism is necessary in order to correctly and effectively approach this matter.

5. Active drugs on adenosine receptors and their clinical applications

Nowadays there is increasing interest in the therapeutic potential of adenosinergic compounds (including receptor agonists and antagonists, enzyme inhibitors and others), and many adenosine compounds have been evaluated.

5.1 Adenosine receptor ligands and their potential as novel drugs

Adenosine itself, for a long time, was the only adenosine agonist used in humans. It is widely used in the treatment of paroxysmal supraventricular tachycardia (Adenocard®) due to its activation of A_{1R} , and as a diagnostic for myocardial perfusion imaging (Adenoscan®) utilizing its A_{2AR} -activating effects resulting in vasodilation (Müller & Jacobson, 2011). However, other A_{1R} -selective agonists such as Selodenoson, Capadenoson e Tecadenoson have been clinically evaluated for the treatment of paroxysmal supraventricular tachycardia, atrial fibrillation, or angina pectoris (Müller & Jacobson, 2011). Still talking about cardiovascular disorders, selective A_{2AR} agonist, Apadenoson, Binodenoson and Sonedenoson appears as candidates for clinical use (Awad et al., 2006; Desai et al., 2005; Udelson et al. 2004). These agonists are of interest as vasodilator agents in cardiac imaging (Cerqueira, 2006) and inflammation suppressors. Accordingly, Regadenoson is already approved for diagnostic imaging (Iskandrian et al., 2007). A_{3R} selective agonists are also currently in clinical trials and exhibit nanomolar affinity at the receptor, CF101 (Can-Fite Biopharma) and CI-IB-MECA (CF102) are in trials for autoimmune inflammatory disorders

and for liver cancer, respectively. Two other A_{3R} agonists CP-608,039 and its N6-(2,5-dichlorobenzyl) analogue CP-532,903 were previously under development for cardioprotection. MRS3558 (CF502) is in preclinical development for the treatment of autoimmune disease (Avni et al., 2010; Wan et al., 2008).

5.2 Adenosinergic drugs in pain clinical studies and practical

Clinical studies confirm the pre-clinical trials showing that in neuropathic pain patients, adenosine was able to alleviate spontaneous pain, tactile and thermal allodynia, as well as thermal hyperalgesia (Qu et al., 1997). In addition, intravenous infusion of adenosine during breast surgery reduced the postoperative pain (Lynch et al., 2003; Sollevi et al., 1995). Spinal administration of adenosine and adenosine analogs in humans also exhibited analgesic effect. A phase I clinical safety study in healthy volunteers demonstrated that 1000 μ g of adenosine given intrathecally lacked side effects and led to a significant decrease in mustard oil-induced inflammatory pain, in tourniquet induced ischemic pain, and decreased areas of secondary allodynia after skin inflammation (Rane et al., 1998).

In another study, a single dose of 0.1 - 0.5 mg/kg of SDZ WAG 994 (adenosine A_{1R} agonist), was evaluated in a phase I clinical study, and this compound was well tolerated. A dose of 1 mg/kg was used in a randomized double-blind clinical trial to determine its efficacy in postoperative dental pain after third molar surgery. However, SDZ WAG 994 did not show significant difference from placebo and was not effective in attenuating postoperative pain after third molar surgery. On the other hand, at higher doses, the compound showed dose-dependent adverse events (Seymour et al., 1999; Wagner et al., 1995; Yan et al., 2003).

Another full high-affinity A_{1R} agonists, GR79236X, was also evaluated in patients with dental pain after third molar extraction. Patients received a 15-min double-blind infusion containing 10 μ g/kg of GR79236X, unfortunately, no evidence of efficacy of GR79236X was observed with this compound compared with placebo (Sneyd et al., 2007). Another A_{1R} agonist GW493838 developed by GlaxoSmithKline, was evaluated in phase II clinical trials to determine its analgesic effect in patients with postherpetic neuralgia or peripheral nerve injury caused by trauma or surgery. However, further development of GW493838 has been discontinued (Nelsen et al., 2004; as cited in Elzein & Zablocki, 2008).

Allosteric modulation of A_{1R} function may also be an interesting tool. Accordingly, the A_{1R} -selective allosteric enhancer T-62, given orally was also shown to reduce hypersensitivity in carrageenan-inflamed rats, in addition, phase I clinical trials of T62 have been completed as a treatment for neuropathic pain (Childers et al., 2005). Therewithal, the A_{2AR} agonist BVT.115959 from Biovitrum completed the clinical trials for diabetic neuropathic pain and it was well tolerated but did not significantly improve pain symptoms (Biovitrum, 2005; Zylka, 2011).

6. Conclusion and future directions

This chapter presented a general and updated review about the purinergic system with emphasis in adenosine receptors (P_1) and pain. It is possible to conclude that the modulation of this system and its receptors is quite important and interesting for the control of pain. Recent studies have approached this system in new ways and contributed to the development of this research field. Some clinical studies have been carried out with

purinergic drugs (adenosine analogs) and some studies have showed quite satisfactory effects, although others haven't showed statistical difference between treated and non-treated groups. Finally, the possibility of new drugs targeting the purinergic system to treat distinct kinds of pain reaching clinical trials in the next years is clear.

7. References

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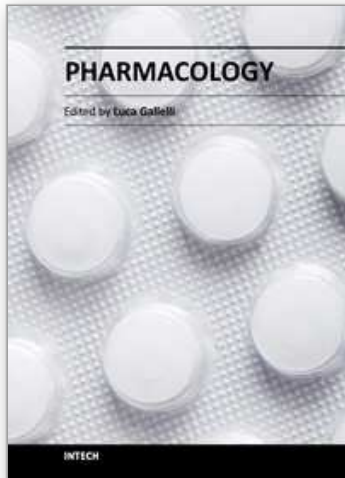
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