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REVIEW

ADENOSINE RECEPTOR TARGETS FOR PAIN☆

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Abstract—The main focus for the development of adenosine targets as analgesics to date has been A_1Rs due to its antinociceptive profile in various preclinical pain models. The usefulness of systemic A_1R agonists may be limited by other effects (cardiovascular, motor), but enhanced selectivity for pain might occur with partial agonists, potent and highly selective agonists, or allosteric modulators. A_{2A}R agonists exhibit some peripheral pronociceptive effects, but also act on immune cells to suppress inflammation and on spinal glia to suppress pain signaling and may be useful for inflammatory and neuropathic pain. A_{2B}R agonists exhibit peripheral proinflammatory effects on immune cells, but also spinal antinociceptive effects similar to A_{2A}R agonists. A_3Rs are now demonstrated to produce antinociception in several preclinical neuropathic pain models, with mechanistic actions on glial cells, and may be useful for neuropathic pain. Endogenous adenosine levels can be augmented by inhibition of metabolism (via adenosine kinase) or increased generation (via nucleotidases), and these approaches have implications for pain. Endogenous adenosine contributes to antinociception by several pharmacological agents, herbal remedies, acupuncture, transcutaneous electrical nerve stimulation, exercise, joint mobilization, and water immersion via spinal and/or peripheral effects, such that this system appears to constitute a major pain regulatory system. Finally, caffeine inhibits A_1-, A_{2A}- and A_3Rs with similar potency, and dietary caffeine intake will need attention in trials of: (a) agonists and/or modulators acting at these receptors, (b) some pharmacological and herbal analgesics, and (c) manipulations that enhance endogenous adenosine levels, all of which are inhibited by caffeine and/or A_1R antagonists in preclinical studies. All adenosine receptors have effects on spinal glial cells in regulating nociception, and gender differences in the involvement of such cells in chronic neuropathic pain indicate gender may also need attention in preclinical and human trials evaluating the efficacy of adenosine-based analgesics.

This article is part of a Special Issue entitled: Pain.

Key words: adenosine, antinociception, inflammatory pain, neuropathic pain, acupuncture, caffeine.

Contents

☆ Note: Abbreviations for specific compounds are in original studies.

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Abbreviations: AMP, adenosine 5′-monophosphate; ASIC, acid-sensitive ion channel; ATP, adenosine 5′-triphosphate; CNS, central nervous system; CREB, cyclic AMP responsive element binding protein; DAG, diacylglycerol; ERK, extracellular signal-regulated protein kinase; GABA, γ-aminobutyric acid; 5-HT, 5-hydroxytryptamine; IL-4, interleukin-4; IL-10, interleukin-10; IL-1β, interleukin-1β; IP_3, inositol trisphosphate; i.pl., intraplantar; i.t., intrathecal; i.v., intravenous; NFκB, nuclear factor κB; NMDA, N-methyl-D-aspartate; PAG, periaqueductal gray; PAP, prostatic acid phosphatase; PI3K, phosphatidylinositol 3-kinase; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; RVM, rostroventral medulla; SAH, S-adenosylhomocysteine; TENS, transcutaneous electrical nerve stimulation; TNFα, tumor necrosis factor-α; TRPV1, transient receptor potential vanillioid 1; TRPV4, transient receptor potential vanilloid 4.

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INTRODUCTION

Adenosine acts at four distinct extracellular G-protein-coupled receptors (A_1R, $A_{2A}R$, $A_{2B}R$, A_3R) as an endogenous signaling agent, and participates in physiological, non-physiological (perturbed) and pathological (diseased, dysfunctional) states. It can regulate diverse functions such as cardiovascular, respiratory and renal function, inflammatory and immune events, and CNS events, and there has been considerable interest in developing adenosine-based therapeutics for conditions involving these systems (Jacobson and Gao, 2006; Schenone et al., 2010; Gessi et al., 2011; Chen et al., 2013). A role for adenosine in antinociception was first identified in the 1970s and then elaborated in the 1980s with systemic and spinal (intrathecal, or i.t.) administration of selective agonists. These studies emphasized the role of adenosine A_1Rs in producing antinociception, with some effects due to adenosine A_{2A}Rs (the only other subtype known at the time) also identified. In the 1990s, adenosine receptor actions at peripheral sites were identified, and actions in nerve injury models for neuropathic pain elaborated. These observations were the subject of several earlier reviews on nociception (Sawynok, 1998; Dickenson et al., 2000; Sawynok and Liu, 2003). During this time period, clinical studies examined effects of intravenous (i.v.) infusions of adenosine and of ATP (which is rapidly metabolized to adenosine in blood) for chronic pain and in a perioperative setting, and these studies have been reviewed specifically (Segerdahl and Sollevi, 1998; Hayashida et al., 2005; Gan and Habib, 2007). Importantly, during the 1990s, A_{2B}- and A_3Rs were cloned and adenosine receptor nomenclature was refined to include the four distinct receptors that are currently known (Fredholm et al., 2001, 2011). Adenosine has a higher affinity for A_1-, A_{2A}- and A_3Rs than for A_{2B}Rs (Fredholm et al., 2011), but its affinity can vary according to the assay and, in some cases, it has a similar affinity for all four subtypes (Fredholm, 2014).

In recent years, there have been further significant developments that enhance an understanding of the role of adenosine in nociception. Thus, novel methods of recruiting adenosine A_1Rs have been developed, and the role of adenosine A_{2A}- and A_3Rs in nociception has been further elaborated. Furthermore, a contribution of endogenous adenosine to the actions of several pharmacological agents, as well as non-pharmacological procedures, used to manage pain has been described. The focus of the present review is a current view relating to potential development of adenosine-based therapeutics as analgesics, and to contributions of endogenous adenosine systems to the efficacy of drugs and procedures used to manage chronic pain. Furthermore, pragmatic issues relating to the influence of caffeine on this therapeutic development are considered.

ADENOSINE A_1RS AND PAIN

Preclinical studies

Since initial observations in the 1970s, numerous studies have demonstrated that systemic administration of adenosine A_1R agonists produces pain-alleviating actions in preclinical models including inflammatory and neuropathic models that exhibit hyper-responsiveness (allodynia, hyperalgesia), and the potential of A_1R agonists to represent a class of therapeutics for pain was considered in earlier reviews (Sawynok, 1998; Dickenson et al., 2000). Subsequent preclinical studies further illustrate the diversity of pain models that exhibit antinociceptive and/or antihyperalgesic properties of adenosine A_1R agonists and continue to consider this potential. These include studies using the formalin model of inflammation (Yoon et al., 2005, 2006; Maione et al., 2007), the carrageenan model of arthritis (Ramos-Zepeda et al., 2004; Curros-Criado and Herrero, 2005; Ramos-Zepeda, 2013), hyperalgesia following surgical incision (Zahn et al., 2007; Yamaoka et al., 2013), the spinal nerve ligation model of neuropathic pain (Gong et al., 2010), the chronic constriction injury model of neuropathic pain (Yamaoka et al., 2013), pain following spinal cord injury (Horiuchi et al., 2010; Yamaoka et al., 2013), and the streptozotocin model of diabetic neuropathy (Katz et al., 2015). More recent reviews on the analgesic potential of A_1R agents are available (Zylka, 2011; Sawynok, 2013).

Adenosine A_1Rs are located on peripheral sensory nerve endings (Lima et al., 2010), within the superficial layers of the dorsal horn of the spinal cord (Ackley et al., 2003; Schulte et al., 2003), and at specific supraspinal sites (Maione et al., 2007) within the pain signaling neuraxis. In addition to their neuronal localization, A_1Rs are now identified on microglia (Boison et al., 2010; Magni and Ceruti, 2014), and inhibitory actions on this cellular target also contributes to antinociception in instances where the pain state involves glial activation and hypertrophy (Luongo et al., 2012, 2014). Mechanisms implicated in antinociceptive actions of A_1Rs at peripheral, spinal, and supraspinal sites are summarized in Box 1. Several of these mechanisms are consistent with general A_1R signaling pathways elaborated at the cellular level. Thus, A_1R signaling can involve inhibition of cyclic AMP/PKA and interactions with Ca^{2+} and K^+ channels via $G\alpha i$, interactions with the PLC/IP_3/DAG pathway via $G\alpha$ or $\beta\gamma$ subunits, and β-arrestin mediating receptor uncoupling and downregulation (Chen et al., 2014). Additional potential clinical applications for A_1R agents in cardiovascular, respiratory, neuroprotective and metabolic conditions are being explored (Schenone et al., 2010; Gessi et al., 2011).

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