Bridging the translational gap

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Arendt-Nielsen, Lars; Klitgaard, Henrik; Hansen, Stine N.

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Topical Review

Lars Arendt-Nielsen*, Henrik Klitgaard and Stine N. Hansen

Bridging the translational gap: adenosine as a modulator of neuropathic pain in preclinical models and humans

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Abstract

Objectives: This review aims to analyse the published data on preclinical and human experimental and clinical adenosine modulation for pain management. We summarise the translatability of the adenosine pathway for further drug development and aim to reveal subgroups of pain patients that could benefit from targeting the pathway.

Content: Chronic pain patients suffer from inadequate treatment options and drug development is generally impaired by the low translatability of preclinical pain models. Therefore, validating the predictability of drug targets is of high importance. Modulation of the endogenous neurotransmitter adenosine gained significant traction in the early 2000s but the drug development efforts were later abandoned. With the emergence of new drug modalities, there is a renewed interest in adenosine modulation in pain management. In both preclinical, human experimental and clinical research, enhancing adenosine signalling through the adenosine receptors, has shown therapeutic promise. A special focus has been on the A_1 and A_3 receptors both of which have shown great promise and predictive validity in neuropathic pain conditions.

Summary: Adenosine modulation shows predictive validity across preclinical, human experimental and clinical investigations. The most compelling evidence is in the field of neuropathic pain, where adenosine has been found to alleviate hyperexcitability and has the potential to be disease-modifying.

Outlook: Adenosine modulation show therapeutic potential in neuropathic pain if selective and safe drugs can be developed. New drug modalities such as RNA therapeutics and cell therapies may provide new options.

Keywords: adenosine; neuropathic pain; translation; animal models; human studies

Introduction

Pain conditions are complex, multifactorial disorders associated with several severe comorbidities such as depression, anxiety, sensitisation, and sleep disorders significantly impacting patient life-quality and increasing healthcare costs for societies [1]. Development of new drugs for pain has been impaired by the low translatability of animal pain models to humans and the patients are often left with insufficient or addictive treatment options. Therefore, there is a large unmet need for new drug candidates with minimal adverse effects for treatment of specific subcategories of pain preferable with a personalised medicine approach considering the individual patient needs. This is evident after the opioid crisis and the concerns with alternative approaches such as the long-term benefits of cannabis and cannabidiol [2]. Translation from bench to bedside is associated with a high attrition rate and only one in 10 pain drug candidates entering phase I clinical studies ends up becoming an approved drug [3].

Adenosine is a ubiquitous, endogenous neurotransmitter that exerts its function through four distinct G-protein coupled receptors (AR), A_1R, $A_{2A}R$, $A_{2B}R$ and A_3R. The receptors are widely distributed through the body including in central nervous system (CNS) areas known to be involved in spinal and supraspinal pain modulation [4]. This distribution equates adenosine modulation with the antinociceptive properties but also several other pharmacological effects through presence of AR in e.g. the cardiovascular system.

***Corresponding author: Prof., Dr. Med. Lars Arendt-Nielsen, PhD**, Department of Health Science and Technology, Center for Neuroplasticity and Pain, CNAP, School of Medicine, Aalborg University, Selma Lagerløfs Vej 249, 12.02.024, 9260 Gistrup, Denmark; Department of Gastroenterology & Hepatology, Mech-Sense, Clinical Institute, Aalborg University Hospital, DK-9000 Aalborg, Denmark; and Steno Diabetes Center North Denmark, Clinical Institute, Aalborg University Hospital, DK-9000 Aalborg, Denmark, Phone: +4520940764, E-mail: LAN@hst.aau.dk

Henrik Klitgaard and Stine N. Hansen, NEUmiRNA Therapeutics, Copenhagen, Denmark, E-mail: hk@neumirna.com (H. Klitgaard), snh@neumirna.com (S.N. Hansen)

The early findings of antinociceptive effects of adenosine modulation triggered the design of adenosine analogues, positive allosteric modulators, and agonists – particularly for the inhibitory A_1R and A_3R receptors. However, no adenosine drugs for pain indications have reached the market. Increased levels of adenosine shows rapid and potent effects on the cardiovascular system where A_1R activation of the heart leads to bradycardia and suppression of the sinus node, atrioventricular node and His bundle potentially leading to complete atrioventricular block [5]. Concurrently, the effects on A_2R in the blood vessels are responsible for vasodilation leading to hypotension [5]. Due to these cardiovascular effects, adenosine is currently only approved for myocardial perfusion scintigraphy and treating supraventricular tachycardia [6, 7].

Another promising therapeutic approach has been to activate adenosine receptors through design of specific inhibitors for the enzyme responsible for adenosine breakdown; adenosine kinase (ADK) [8]. The two isoforms of this enzyme serve distinct physiological functions with the short isoform ADK-S being responsible for regulation of extracellular adenosine levels and the long isoform ADK-L being a nuclear epigenetic regulator [8]. Modulation of the adenosine system has seen a revival of interest as a novel pain target as new drug development options (e.g. RNA therapeutics and cell therapies) have appeared in recent years and may pave the way for interaction with the adenosine pathways in new ways [9].

This review aims to analyse published data on preclinical and human (both experimental and clinical) evaluations of adenosine approaches for pain management with the perspective to investigate translatability of adenosine regulation and to reveal subgroups of patients that could benefit the most from treatment. A brief bibliometric analysis on papers focusing on adenosine in selected pain relevant journals (Pain, European Journal of Pain, Clinical Journal of Pain, Anesthesia and Analgesia, Scandinavian Journal of Pain, Acta Anaesthesiologica Scandinavica) show a peak interest in the beginning of this millennium (Figure 1) and a decline thereafter.

The mechanism-based analgesic effect of adenosine in preclinical pain studies

Drug discovery for pain indications has generally been marred by the low translatability of preclinical pain models into the clinic and novel approaches emphasizing the need for novel approaches [10, 11]. In the field of adenosine modulation in pain, preclinical research has elucidated the contributions of agonism and antagonism of the four ARs in animal models of nociceptive and neuropathic pain [4, 12]. Activation of the adenosine pathway has been found in few studies to alleviate inflammatory and postoperative pain primarily through the A_1R in animal models [13–15] but the most compelling evidence for adenosine's anti-hyperexcitability properties is in neuropathic pain [16–29]. Experimental research has primarily focused on activation of A_1R and A_3R as underlying the analgesic properties of adenosine in preclinical neuropathic pain but the $A_{2A}R$ has also been implicated [25, 26]. The A_1R is expressed pre- and postsynaptically and is found in brain areas associated with supraspinal pain perception, on neuronal cell bodies in the dorsal spinal horn, and on the endings of peripheral sensory nerves [4]. A_1R knockout mice exhibit increased neuropathic pain-like behaviours after partial nerve injury [30] and A_1R modulation has been found to decrease allodynia and hyperalgesia in models of nerve injury [18, 24, 30, 31] indicating the potential role of adenosine in neuropathic pain conditions.

In relation to certain chemotherapies, neuropathic-like conditions associated with hyperalgesia and allodynia is often a side effect as the medications have become increasingly neurotoxic. In a rat model of chemotherapy-induced peripheral neuropathy, intrathecal administration of an A_1R agonist alleviated the neuropathic symptoms [22], a finding which has been reproduced by others [21]. Another study showed a chemotherapy-induced increase in spinal ADK implying that imbalances in the adenosine pathway in itself can be an underlying cause of neuropathic pain conditions in the animal models [29]. Additionally, A_1R activation has been found to alleviate mechanical allodynia in models of diabetic neuropathy [16, 23]. Thus, increased A_1R activation has been found to counteract hyperalgesia and allodynia in preclinical neuropathic pain models of different aetiologies. Other studies have shown that the A_3R may also be involved in neuropathic pain as activation of this receptor can reduce the allodynic and hyperalgesic reactions [4]. The A_3R is expressed on immune and glial cells and activation has been found to counteract the pro-inflammatory and – algesia factors released by these cells in pathological conditions [32]. A_3R activation has likewise been found to alleviate chemotherapy-induced peripheral neuropathy by decreasing astrocyte activation and cytokine release [19, 20] and to decrease neuronal hyperexcitability [33, 34].

In addition to the evidence of adenosine modulation of hyperexcitability in neuropathic pain conditions. In a model of diabetic neuropathy adenosine administration reversed diabetic hyperalgesia in thermal and chemical stimuli tests

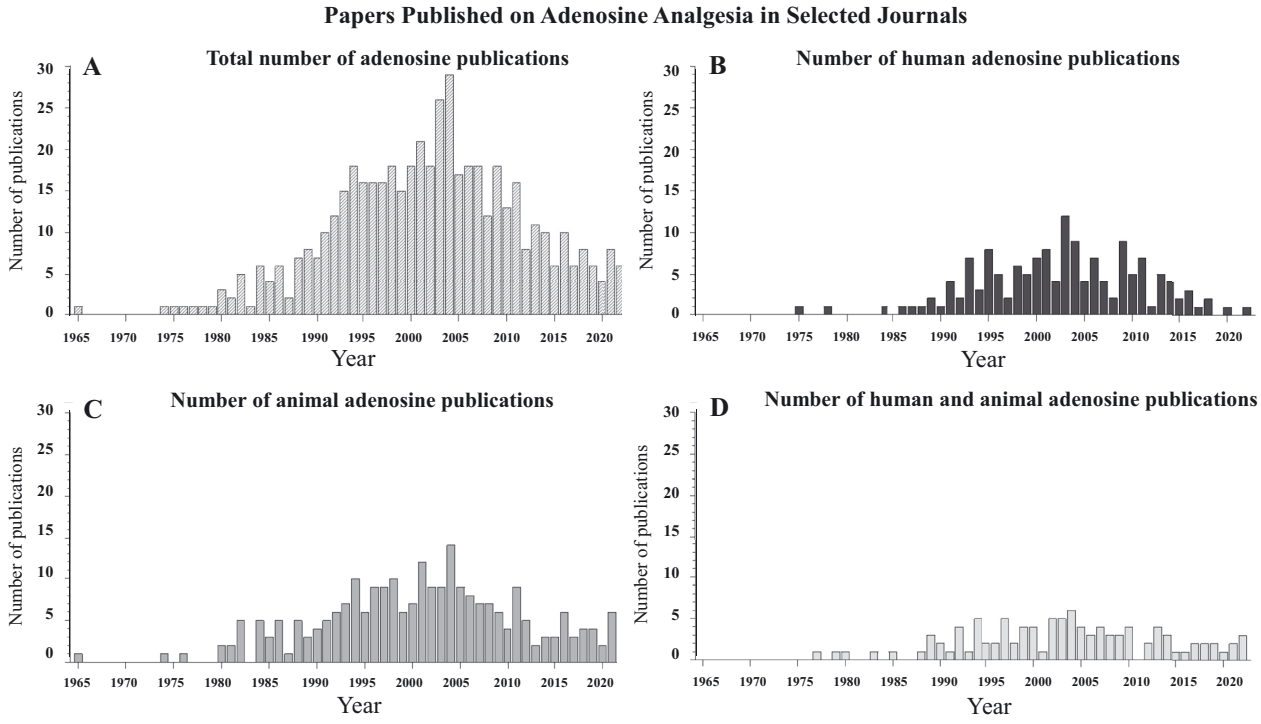

Figure 1: The total number of papers published in selected pain/analgesia journals (Pain, European Journal of Pain, Clinical Journal of Pain, Anesthesia and Analgesia, Scandinavian Journal of Pain, Acta Anaesthesiologica Scandinavica) (A). The separation of these publications into human studies; both experimental and clinical (B), preclinical (C) and combined preclinical and human (experimental and clinical studies) and the combined preclinical and human studies (D).

[16]. Interestingly, increased levels of adenosine have been found to be disease-modifying in epilepsy where mice with forebrain specific ADK reduction show reduced epileptogenesis and ADK-deficient ES cell – derived brain implants suppressed spontaneous seizures in mice even when implanted after the induction of epileptogenesis [35]. The nuclear long isoform of ADK responsible for modulating intranuclear adenosine levels has also been found to have epigenetics modulatory effects implying that the disease-modifying effects of the adenosine pathway may be AR-independent [8].

In summary, adenosine modulation shows therapeutic properties in neuropathic animal models with manifestations of allodynia and hyperalgesia.

Mechanism-based analgesic effect of adenosine in human experimental pain studies

Between 1990 and 2004, there was a significant interest in proof-of-concept studies evaluating adenosine in human experimental pain. Most of those studies used quantitative, mechanistic pain biomarkers in healthy volunteers to study the analgesic action of adenosine administered via various routes. In particular three groups have been involved in this work: the Karolinska Hospital, Stockholm, Sweden Group (Sollevi and Segerdahl), the Wake Forest School of Medicine, Winston-Salem, NC, USA Group, US (Eisenach) and the Aalborg University Group, Aalborg, Denmark (Arendt-Nielsen).

Initial research focused on the hypothesis that adenosine functioned as a mediator of pain sensation. In 1989, Jonzon et al. studied adenosine in ischaemic pain sensation by using the A_1R and A_2R blocker theophylline [36]. In healthy volunteers, muscle ischaemia was induced, and the pain sensation was continuously reported. A small, significant inhibitory effect on the ischaemic pain sensation was detected and found to be compatible with a hyperalgesic effect of endogenous adenosine. The background for this study was the finding that adenosine caused ischemic angina-like pain due to the AR in the heart muscles [37] and the role of adenosine as a stimulator of angina-like pain.

Fifteen years later, the theophylline study was followed up by the same group later using a sub-maximum effort forearm tourniquet ischemic test [38]. It was shown that the peak Visual Analog Scale (VAS) pain score was lowered by the theophylline treatment. Theophylline therefor seemed to

both have the potential to both inhibit and facilitate pain caused by ischaemia.

The view on adenosine as a possible algesic substance was later replaced by the view that adenosine has analgesic properties. The analgesic effects were supported by Rae et al. who concluded that continuous intravenous (IV) adenosine infusion inhibited ischaemic pain, though efficacy was not sustained after discontinuation of the infusion [39]. A series of human experimental pain studies expanded on the ischemic muscle pain model and found that IV adenosine alleviated experimentally-induced ischemic muscle pain in healthy volunteers [40]. The study suggested an additive effect on pain reduction when adenosine was combined with morphine or ketamine suggesting that adenosine may function as an opioid sparing drug.

The next steps involved other human experimental pain tests such as the heat pain stimulus. IV adenosine revealed a significantly increase in cutaneous heat pain threshold without effecting ketamine or morphine (as known from other studies). This highlighted the interesting aspect that adenosine in combination with morphine and ketamine may provide synergistic effects on different pain modalities [41].

In 1998, the first clinical trial of experimental pain investigating the effect of intrathecal adenosine was conducted and explored the effects on cold-pain rating of the foot (submersion in ice water for 1 min), the forearm ischemic pain rating during a 30 min tourniquet test, and the thermal and tactile pain thresholds on healthy and inflamed skin after 4 min application of mustard oil to the calf [42]. Adenosine treatment reduced the areas of secondary allodynia after mustard oil-induced skin inflammation and reduced the pain intensity scores from pain induced by ischaemia. This was the first experimental study to show the effects of adenosine on the central sensitization phenomena as a manifestation in neuropathic pain.

The findings were followed up by additional studies investigating the effect of adenosine on other central pain manifestations such as hyperexcitability (hyperalgesia and allodynia).

The first study in a series investigated the effects of IV adenosine on a superficial cutaneous burn injury by 4 min topical application of mustard oil or by heat injury (47 °C for 7 min). Adenosine significantly reduced the area of secondary hyperalgesia in both models with no other differences in sensory functions [43]. These findings underlined the selective effect on the peripheral and central sensitization phenomena supporting the previous finding by Rane et al. [42]. However, conflicting evidence exist. Dirks et al. found no effects on acute nociceptive pain induced by heat stimulation or on secondary hyperalgesia induced by heat/capsaicin sensitization in healthy volunteers [44]. This suggests that adenosine modulation may show different efficacy based on the pain aetiology.

Central sensitization was further studied in two studies by Eisenach et al. investigating the effects of intrathecal adenosine on intradermal capsaicin injection in humans. No decreases in acute pain evoked by thermal or chemical stimulation was found but a reduction in mechanical hyperalgesia and allodynia after intradermal capsaicin injection was shown, further substantiating the possible central actions of adenosine on sensitisation [45]. The follow-up dose-response study in the same experimental models showed no difference in adenosine efficacy against experimental hypersensitivity between the largest experimental dose of intrathecal adenosine and a 75 % lower dose, but side effects are more common with the larger dose [46]. The controversies between studies can be related to different methods used, different dosing regimens or sample size differences resulting in possible false positive or false negative studies.

This role of adenosine as particularly a modulator of sensitization was further consolidated in an IV adenosine study by Chizh et al. [47] where electrically evoked hyperalgesia was tested. The area of pinprick hyperalgesia was reduced during the adenosine infusion compared with placebo but there was no significant effect on tactile allodynia or evoked pain ratings. In addition, adenosine did not have long-term analgesic effects as efficacy were only seen during the infusion. In a study by Morélot-Panzini et al. [48], healthy volunteers received an IV administration of adenosine or placebo and the nociceptive withdrawal RIII reflex was assessed. Adenosine induced dyspnea, tachycardia, and significant RIII reflex inhibition suggesting a role of adenosine on the central descending pain modulatory pathways [48]. Another study investigated trigeminal nociception using the nociceptive blink reflex as read out. The experimental A_1R agonist GR79236 inhibited trigeminal nociception in humans which could hint a possible therapeutic role for A_1R agonists in headache disorders [49] suggesting direct acute, anti-nociceptive effect.

In summary, different routes of exogenous adenosine are consistently showing efficacy on pain sensitisation phenomena such as experimentally induced hyperalgesia, allodynia, and descending pain modulation which can be via a modulation of the afferent drive or a direct effect on the central mechanisms. The next important question is if this translates into a beneficial effect on neuropathic pain.

The mechanism-based analgesic effects of adenosine in neuropathic pain

The effect of exogeneous adenosine on clinical pain conditions have a long track record expanding almost 40 years (Figure 1).

The Swedish group headed by Alf Sollevi pioneered the evaluation of adenosine in clinical pain conditions. In 1995, the group published a study where two patients with peripheral neuropathic pain received IV adenosine which showed that particularly hyperalgesia and allodynia was attenuated by treatment [50]. This critical study paved the way for the experimental pain studies investigation the effect of adenosine on neuropathic pain.

The study was followed by a larger IV adenosine study in neuropathic pain patients where perception thresholds for touch, touch-evoked pain, cold, warmth, painful heat, and cold were assessed. In the neuropathic area, VAS ratings to pin prick stimulation and perception threshold for touch-evoked pain using von Frey filaments were assessed [51]. The study demonstrated that adenosine infusion alleviated spontaneous neuropathic pain, tactile allodynia, and pinprick hyperalgesia in patients with peripheral neuropathic pain [47].

In a case story of a patient with severe erythromelalgia due to a $Na_V1.7$ mutation and presenting with ongoing burning dysesthesia and pain in the legs, sustained thermal hyperalgesia and allodynia, and intolerable pressure pain on standing and walking, symptoms were modulated by both IV and intrathecal adenosine administration [52]. In complex regional pain syndrome, another neuropathic condition, intrathecal adenosine reduced areas of hyperalgesia and allodynia and also inhibited temporal summation; another important biomarker strongly facilitated in neuropathic pain [53]. However, spontaneous pain was not dramatically reduced [53]. Lynch et al. likewise showed differentiated effects on central sensitisation mechanisms in neuropathic pain patients as IV adenosine caused significant reduction in pinprick hyperalgesia, but not in allodynia and only a few patients experienced long-term pain alleviation following IV adenosine [54]. The study further supports that IV adenosine may have long-term effects on neuropathic pain and hyperalgesia suggesting a potential disease-modifying effects of adenosine modulation.

The effect of intrathecal adenosine was further substantiated by Belfrage et al. in neuropathic pain patients with tactile hyperalgesia and/or allodynia primarily of traumatic origin finding that spontaneous and evoked pain intensity decreased in most patients with an effect lasting for a median of 24 h suggesting a possible difference in duration of action depending on IV or intrathecal administration [51]. Another neuropathic pain study by Eisenach and colleagues further investigated this and found that intrathecal adenosine reduced allodynic area and pain intensity, whereas the same dose of adenosine IV was ineffective [55] supporting that high levels of adenosine is required in the central component to inhibit the central manifestations in neuropathic pain patients. Importantly, intrathecal adenosine has in animal models been found to be safe and not elicit any histopathological or behavioural adverse effects [56, 57].

Another important question was whether adenosine could potentiate anaesthesia. It was shown that a low-dose perioperative infusion reduced the perioperative anaesthetic requirements and demand for post-operative analgesics [58] as well as the requirements for postoperative opioids [59]. However, later studies showed that intrathecal adenosine did not influence the requirement of anaesthetic drug or postoperative analgesics [60, 61]. Another study showed no effect of intrathecal adenosine on postoperative pain relief as well as no preventive effect [62]. Additional controlled studies are needed to investigate the role of adenosine in postoperative management regimes.

In summary, in neuropathic pain patients different routes of exogenous administrated adenosine show analgesic effects on central pain sensitisation mechanisms such as hyperalgesia and allodynia. In contrast, the evidence the efficacy against spontaneous pain and the role of administration route is less complete, although intrathecal administration seems favourable. Adenosine has not shown consistent results in managing post-operative pain but may have a sparing effect on other analgesics/anaesthetics. The possible synergistic action with opioids needs further investigations.

Conclusions

Adenosine effects in animal models have to a large extent replicated the anti-hyperexcitability (anti-hyperalgesia and anti-allodynia) properties in human experimental and clinical pain studies. In addition direct anti-nococeptive effects have been shown. This correlation between human and animal findings is unique and rarely seen for drugs developed in the pain space. This emphasises that drugs targeting the adenosine system screened in pre-clinical neuropathic pain models may be predictive for human neuropathic pain conditions. Early in the new millennium, the fundamental interest in adenosine and preclinical models of pain and human pain trials started to fade (Figure 1) as especially adenosine receptor activation studies in humans showed various unwanted side effects [5] and hence drug development in the field was abandoned. As the four different,

identified adenosine receptors have different physiological roles on various tissues the selectivity associated with pain processing is essential to minimise unwanted side effect and is a critical issue to pursue in the development of new adenosine-based pain therapeutics. However, the current short review indicates that adenosine may be a drug targets where the anti-hyperexcitability efficacy found in preclinical models translate into clinic and hence provide new options in management of neuropathic pain if the side effects can be minimised. New drug development options (e.g. RNA therapeutics and cell therapies) have appeared in recent years and may pave the way for interaction with selective, restricted adenosine pathways in new ways a thereby minimise unwanted side effects.

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Competing interests: Stine N. Hansen is an employee and Henrik Klitgaard is a co-founder of NEUmiRNA Therapeutics; a biotech company developing RNA drugs against neurological disorders.
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