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This section, edited by Michael C. Rowbotham, MD, and Annika Malmberg, PhD, presents timely topics in pain research and treatment.

Adenosine—A New Analgesic for the Treatment of Neuropathic Pain?

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The available pharmacological treatments for patients with neuropathic pain are not very effective or often carry severe or disturbing side effects. This is true for tricyclic antidepressants (TCA), anticonvulsants, tramadol, or drugs with local anesthetic properties. Although treatments have incorporated several new pharmacological principles in recent years, neuropathic pain still remains a challenge for the clinician and a burden for the patient (Karlsten and Gordh 1997). Experimental and clinical data are pointing at the adenosine system as an interesting target in relation to hypersensitivity states, a feature often seen in neuropathic pain.

Purinergetic Receptors

The endogenous compound adenosine is present in all cells. Adenosine may be released from cells directly or via degradation of ATP and is involved in many regulatory mechanisms both in physiological and pathophysiological conditions (for review see Pelleg and Porter 1990; Abbracchio and Burnstock 1998). Purines (adenosine, AMP, ADP, ATP) mediate their effect by acting on a novel type of receptor classified into two main subgroups of purine receptors, P1 and P2 receptors. The endogenous compound adenosine is pharmacologically active on extracellular P1 receptors (Burnstock 1972).

The P1 receptors can be further divided into A1, A2a, A2b, and A3 receptors (Fredholm et al. 1994). Activation of A1 receptors inhibits adenylate cyclase activity and thereby decreases the intracellular levels of cAMP, while activation of the A2 receptor stimulates adenylate cyclase and increases the intracellular level of cAMP (Van Calker et al. 1979). A1 and A2 receptors have been found in the brain (Goodman and Snyder 1982) and in the spinal cord, where A1 receptors occur predominantly in the substantia gelatinosa (Choca et al. 1988). An A3 receptor recently was classified based on the the inhibition constant of antagonist binding. A3 receptors have not yet been found in the nervous system, but peripheral effects have been documented. Activation of A3 receptors on mast

cells mediates a release of histamine and 5-hydroxytryptamine (Sawynok et al. 1997), which in turn act on histamine H1 and 5-HT₂ receptors on the sensory nerve terminal to induce a pronociceptive action (Sawynok 1998).

Adenosine and Pain

Biochemical markers for adenosine activity in the spinal cord, such as enzymes for synthesis of adenosine, adenosine immunoactivity, receptors, uptake sites, and catabolic enzymes, show poor anatomical correlation in the CNS (Fastbom 1988). This is not the case within the substantia gelatinosa, which has a concentration of biochemical markers. In addition adenosine, perhaps originating from ATP, is released from spinal synaptosomes (Sawynok and Sweeney 1989). These findings indicate that adenosine may play a role in the modulation of nociceptive transmission at the spinal level.

Early animal studies in mice and rats that used escape reactions as endpoints for measuring nociceptive threshold suggested that adenosine and adenosine analogues had antinociceptive properties after systemic or intrathecal (i.t.) administration (Post 1984; Ahlijanian and Takemori 1985; Holmgren et al. 1986). Later studies, using adenosine analogues with different efficacy for the A₁ and A₂ adenosine receptors, have indicated that spinal adenosine A₁ receptors are involved in inducing the antinociceptive effects (Karlsten et al. 1990; Sawynok 1991; Lee and Yaksh 1996). The role of the A₁ adenosine receptor in inhibiting spinal sensory transmission has been confirmed by the inhibitory effect of A₁ analogues on the C-fiber-evoked responses of wind-up and post-discharge of dorsal horn neurons (Reeve and Dickenson 1995). Recordings of evoked potentials from the spinal cord in rats support the findings by Reeve and Dickenson (Nakamura et al. 1997). Adenosine agonists dose dependently inhibited the slow ventral root potential, which is the C-fiber-evoked excitatory response associated with nociceptive information. The rank order of agonist potency indicated that adenosine agonists inhibit spinal sensory transmission by acting on A₁ receptors (Nakamura et al. 1997). It seems that adenosine modulates spinal nociceptive transmission by inhibition of intrinsic neurons through an increase in K⁺ conductance and presynaptic inhibition of sensory nerve terminals to inhibit the release of substance P and perhaps glutamate (Sawynok 1998).

In 1989 Sosnowski and Yaksh demonstrated that the adenosine agonists R-phenyl-isopropyl adenosine (R-PIA, with high affinity for the A₁ receptor) and N-ethyl-carboxamide adenosine (NECA, with equal affinity for the A₁ and A₂ receptor) induced a dose-dependent inhibition of the hypersensitivity evoked by intrathecal strychnine in rats. The response was seen in doses between 0.3–1 nmol, doses that have only mild antinociceptive effects on thermal stimulation and withdrawal tests (hot-plate, tail-flick, tail immersion) (Sosnowski and Yaksh 1989). The study by Sosnowski and Yaksh was the first to suggest that adenosine might have a role in the modulation of pathological pain as seen in many patients with neuropathic pain. A later study revealed that R-PIA inhibits the spontaneous and touch-evoked agitation seen after administration of i.t. prostaglandin F₂ in mice (Minami et al. 1992).

In new experimental methods for rodents, induced nerve injuries produce a state that mimicks clinical findings often seen in neuropathic pain in humans, with hypersensitive reactions to low-threshold mechanical stimulation and heat. Bennett and Xie (1988) introduced a technique involving four loose ligatures around the sciatic nerve, called the chronic constriction injury (CCI) model. Use of CCI showed that the adenosine agonist NECA reduced the hypersensitive reaction to heat stimuli in doses that did not affect the normal paw latencies in rats (Yamamoto and Yaksh 1991). Sjölund et al. (1996) demonstrated that R-PIA reduces the scratch behavior induced by CCI in the rat, after both intravenous (i.v.) administration (30 nmol) and i.t. injection (3 nmol). In rats subjected to CCI, Cui et al. (1998) demonstrated a dose-dependent reduction of hypersensitivity to tactile stimulation after i.t. R-PIA (1–10 nmol). The effect was abolished by i.t. injection of the A1 receptor antagonist cyclopentylxanthine. Cui et al. also observed a potentiation of the effect of spinal cord stimulation after concomitant i.t. injection of a submaximal dose of R-PIA (3 nmol).

Lee and Yaksh (1996) used the animal model developed by Kim and Chung (Lee and Chung 1991), which involves a tight ligation of the L4–S1 spinal nerves to produce a state of tactile hypersensitivity, adenosine analogues dose-dependently diminished the hypersensitivity reaction to mechanical stimulation with von Frey filaments. Comparison of the effects of A1 and A2 adenosine receptor agonists and antagonists suggested that activation of the A1 receptor mediates the "antiallodynic" effect of adenosine and that activation of the A2 receptor mediates motor dysfunction effects (Lee and Yaksh 1996).

In a recently published study Lavand'homme and Eisenach (1999) demonstrated that adenosine given i.t. induced a dose-dependent reduction of tactile hypersensitivity in rats following spinal nerve ligation. Interestingly, a single i.t. injection of 30 mg of adenosine reduced hypersensitivity for more than 24 hours. They also observed a delay in onset of drug effect, with a maximal effect after 1–2 hours.

In a new model of photochemically induced ischemic spinal cord injury in rats, which induces hypersensitivity to cold and mechanical stimuli, 3 and 10 nmol of R-PIA reduced the hypersensitivity to both mechanical and cold stimulation (Sjölund et al. 1998). Another study, using the same model, showed that R-PIA injected twice daily maintained the effect on hypersensitivity for 5–7 days (von Heijne et al. 1998).

The above indications that spinal administration of adenosine or adenosine agonists with selectivity for the A1 receptor, might be of potential analgesic use in humans have prompted neurotoxicological studies. It is important to investigate potential noxious effects on the spinal cord are investigated in animals before performing studies in humans. Studies have used laser Doppler flowmetry (Karlsten et al. 1992) and the iodo-antipurine (Kristensen et al. 1993) to test the adenosine analogue R-PIA, selective for the A1 receptor, for effects on spinal cord blood flow in rats. In both studies, R-PIA induced a slight but significant increase in spinal cord blood flow. A neurotoxicological evaluation with morphologic and morphometric methods (Karlsten et al. 1993) showed that chronic i.t. administration of R-PIA once daily (5 and 25 nmol in two groups) for 14 days induced no changes in rats. In a recent similar study using the same methods, 100 m

g i.t. adenosine administered to rats twice daily for 14 days showed no neurotoxic effects (Rane et al. 1999).

Preclinical Versus Clinical Studies

Animal studies have shown that adenosine or adenosine analogues may have a potential role in treatment of pain in humans. Most interesting is the potential to modulate the pathological pain states, such as hyperexcitability associated with injuries to the peripheral and central nervous systems. Several obvious difficulties prompt caution in transferring animal data to humans. In humans a nerve lesion may result in hypo- or hypersensitive reactions, and sometimes both phenomena can be found in the same patient upon neurological examination. Most patients with injuries to the nervous system do not develop pain, which seems counter to the findings in the Bennett and Chung models, where the rats as a rule seem to develop a hypersensitive reaction to mechanical stimulation. In humans neuropathic pain often presents as a longstanding chronic pain, while the hyperphenomena seen in rodents after nerve ligation sometimes subside within weeks. Of course, it is not possible to know if the reaction the rats show after nerve ligation is truly painful because by definition, pain, hyperalgesia, and allodynia are human reactions. Furthermore, the pharmacological properties of the various adenosine receptors differ between species (Kennedy and Ijzerman 1994), so it might be difficult to draw conclusions from animal experiments when considering potential effects of adenosine and its analogues in humans. We should interpret animal data carefully and try to avoid using terms and phrases unique for humans.

Clinical Studies

The effect of adenosine on pain in humans has mostly been studied through i.v. administration. The first implication that adenosine might induce pain relief in humans was the demonstration that an adenosine infusion combined with isoflurane-nitrous oxide anesthesia abolished the need for additional analgesics during surgery (Sollevi 1992). Use of a tourniquet technique in a single-blinded study, demonstrated that i.v. adenosine (70 m g/kg/min) reduces experimentally induced ischemic muscle pain in healthy volunteers (Segerdahl et al. 1994). Another single-blinded study in healthy volunteers demonstrated that i.v. infusion of adenosine 50–80 m g/kg/min increased the cutaneous heat-pain threshold but did not influence the perception thresholds for heat and cold (Ekblom et al. 1995).

Spontaneous pain was reduced and touch-evoked pain thresholds were increased, in a double-blind, placebo-controlled, crossover study in seven patients with neuropathic pain who received i.v. infusion of adenosine 50 m g/kg/min for 45–60 minutes (Belfrage et al. 1995). Two patients with peripheral neuropathic pain received adenosine 50–70 m g/kg/min; it relieved tactile allodynia and spontaneous pain in one patient and attenuated hyperalgesia to pinprick in the other (Sollevi et al. 1995). These two reports indicate that adenosine may play a role as a modulator of neuropathic pain in humans. Further support for this role was the demonstration that patients with neuropathic pain have reduced levels of adenosine in blood and cerebrospinal fluid as compared to patients with

nociceptive pain and patients with nervous system lesions without pain (Guieu et al. 1996). In a recent double-blind, placebo-controlled, multicenter study in patients with neuropathic pain, i.v. adenosine (50 mg/kg/min) significantly reduced the area of allodynia to touch (unpublished observation).

Animal studies have shown that adenosine and adenosine analogues induce antinociception predominantly by a spinal site of action, which may indicate that the i.t. route could be superior to systemic administration. Karlsten and Gordh Jr (1995) reported the case of a patient with chronic neuropathic pain in whom i.t. injection of R-PIA 50 nmol completely abolished severe allodynia to light touch and vibration and reduced the spontaneous pain. The detection thresholds for thermal stimuli and pain thresholds for heat and cold remained unchanged after i.t. R-PIA. Vital signs such as blood pressure, pulse, and respiratory status were also unaffected (Karlsten and Gordh 1995). In a study where adenosine was injected i.t. to 12 healthy volunteers (500–2000 mg), the forearm ischemic pain rating was reduced and adenosine reduced the areas of secondary allodynia after skin inflammation induced by mustard oil. One patient receiving 2000 mg i.t. experienced a transient lumbar pain following the injection; doses up to 1000 mg were tolerated without any side effects (Rane et al. 1998). In a study in 14 patients with chronic neuropathic pain of traumatic origin with tactile hyperalgesia or allodynia, i.t. adenosine (500 or 1000 mg) reduced spontaneous and evoked pain. Tactile pain thresholds also increased in the areas. In total, 12 patients experienced pain relief lasting a median 24 hours. Five patients reported a transient lumbar pain after the i.t. injection of adenosine (Belfrage et al. 1999).

Summary and Conclusions

Abundant evidence now demonstrates that adenosine has an important role in the modulation of nociception. Behavioral and neurophysiological studies in animals have indicated that A1 receptors are involved in the antinociceptive effect. In humans, almost all studies have used systemic and i.t. administration of adenosine, which is unselective for the A1 and A2 receptor. Most studies in humans confirm the results from the animal studies and indicate that adenosine and adenosine analogues may have a role in the future treatment of patients with pathological pain conditions characterized by hyperexcitability. Even though small studies on potential neurotoxicity have failed to show any signs of neuronal damage, the transient pain on i.t. injection experienced by some patients needs to be explained. We also need more controlled studies in patients with defined pain states before we can establish the role of adenosine in pain treatment. Adenosine can not yet be recommended for clinical treatment of neuropathic pain. The use of adenosine should be restricted to clinical trials performed by physicians experienced in handling the substance.

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