Magnesium involvement in pain

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The very interesting paper of Pickering *et al.* [1] raises the issue of the involvement of this cation in different types of pain. Pain is very important as a marker of the existence of pathological processes. There are two different and important types of pain: inflammatory pain and neuropathic pain. Neuropathic pain is defined according to The International Association for the Study of Pain (IASP), as a pain resulting from diseases of or damage to the peripheral or central nervous system, and dysfunctioning of the nervous system.

Many factors are involved in the mechanism of pain production. Magnesium ions can influence both types of pain, but existing data concerning the effects of magnesium administration on pain are discordant. Some authors have reported the lack of any effect of magnesium in pain; however, many authors have shown that magnesium can influence pain intensity and consequently the requirement for analgesics or anaesthetic drugs.

The mechanisms by which magnesium might reduce pain include the following:

**A. Central nervous system action:**

1. In the spinal dorsal horn:
   a. A decrease in N-methyl-D-aspartic acid (NMDA) receptor activity:
      i. by blocking the receptor-coupled calcium channel
      ii. by an allosteric antagonist action on the receptor
      iii. by reducing spinal cord receptor phosphorylation
   b. The reduction of substance P synthesis and action in the dorsal horn.
   c. The potentiation of the action of morphine in the presynaptic area of dorsal horn.
   d. The reduction in activity of other presynaptic or postsynaptic calcium channels.

2. Supraspinal action.

**B. Peripheral (outside the CNS) mechanism of action:**

1. Reduction in thromboxan A2 (and probably of other proinflammatory eicosanoids).
2. Reduction in the synthesis of certain cytokines (TNFα and others).

Different types of *NMDA receptors* are expressed in synaptic and extrasynaptic regions in the spinal dorsal horn [2] and may have different roles in nociception. The NMDA receptors have an essential role in the mechanism of central sensitization [3]. The stimulation of C-nociceptor fibers induce glutamate release in presynaptic terminals from the spinal horn. This glutamate release produces NMDA and causes 3-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor stimulation. This is a key point in pain production. μ morphine receptor stimulation decreases glutamate release.

The interaction between magnesium and NMDA receptors is complex. In the central nervous system, Mg²⁺ is a voltage-dependent blocker of NMDA-coupled channels, but this action also reduces NMDA-receptor phosphorylation in the spinal dorsal horn [4]. The level of hyperphosphorylation of these receptors was higher in diabetic rats and was involved in the development of diabetic neuropathy and pain hypersensitivity. Magnesium deficiency is involved in diabetic neuropathy facilitating the NMDA receptor hyperstimulation. Evidence that magnesium acts by reducing NMDA receptor activity is provided.
by the similar effects of magnesium and MK-801 (an antagonist of NMDA receptors) [5].

Combined administration of morphine and magnesium in neuropathic rats attenuated pain-related behavior [6]. The stimulation of NMDA receptors by glutamate is very important, not only for acute pain but also for chronic pain. The release of glutamate, substance P and CGRP in the spinal cord after nociceptive peripheral stimulation is essential in nociception. Magnesium modulates the release and action of all three neuromediators [7-9].

There is evidence for the interaction of magnesium with the next groups of drugs used for pain suppression or reduction: narcotic analgesics, local anesthetics, intravenous general anesthetics, and antidepressants.

The treatment of neuropathic pain is difficult because the efficacy of narcotic analgesics (morphine, fentanyl, alfentanil, petidine, buprenorphine and others) is reduced in this type of pain.

Pickering et al. [1] showed that magnesium alone did not improve the pain indicators compared to the placebo group in neuropathic patients. This result and those of others studies pose an important question: does magnesium itself play an analgesic role or does this cation modulate the analgesic action of others substances? Magnesium administration in an experimental model of vincristine-induced neuropathy in rats significantly increased the analgesia produced by morphine and other narcotic analgesics [10]. In patients with osteoarthritis, intra-articular magnesium administration for pain control before knee arthroplasty diminished morphine consumption during the 24-48h post-operative period [11, 12]. Fentanyl-induced anti-nociception was also increased by magnesium [13]. Magnesium sulphate has also been shown to decrease intravenous general anesthetic (propofol) requirements [14].

The addition of magnesium to a local anesthetic (ropivacaine) in caudal anaesthesia did not affect the postoperative pain scale score (POPS) [15].

Antidepressant drugs are an effective way of reducing pain intensity in some pathological situations. We believe that magnesium plays an important role in this situation because our studies have shown that antidepressant drugs increase intracellular magnesium concentrations and that this effect correlates positively with the antidepressant action [16].

There are important disagreements regarding the clinical effect of magnesium on pain. Felsby et al. [17] failed to demonstrate any reduction in pain following i.v. magnesium administration in patients with chronic neuropathic pain. Mikkelsen et al. [18] tested the effect of i.v. magnesium sulphate administration on hyperalgesia following heat/capsaicin stimulation in healthy volunteers: no anti-hyperalgesic effect could be demonstrated during the magnesium infusion. On the other hand, some studies have shown that i.v. magnesium sulphate infusion during spinal anaesthesia improved postoperative analgesia [19]. Magnesium administration, as a continuous perfusion during surgical interventions in children, significantly reduced the cumulative analgesic consumption following the operation at 48h [20]. The association of morphine and magnesium sulphate administration in surgical patients decreased post-operative morphine requirements. This fact suggests a potentiating effect of magnesium on the analgesic action of morphine because magnesium alone is unlikely to provide analgesia [21]. It seems highly probable that magnesium potentiates the action of various drugs, which, in turn, reduces the pain even more. Unfortunately, those studies evaluating the effect of magnesium alone are lacking the determination of intracellular magnesium concentrations. An important aspect of the research by Pickering et al. [1] is the observation that magnesium diminished the frequency of pain paroxysms and improved the emotional component of behavior in patients suffering from neuropathic pain. The antidepressive action of magnesium might be involved in this effect.

References


3. Woolf CJ, Thompson SW. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation:


