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Review

Magnesium enhances opioid-induced analgesia – What we have learnt in the past decades?

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ABSTRACT

Opioids are increasingly used in alleviating pain, including cancer-related pain and postoperative pain. Unfortunately, the development of tolerance, the resistance of neuropathic pain on opioid analgesia or other undesirable effects may limit their utility. In order to reduce opioid doses, and thereby to avoid the risk of side effects and sudden deaths due to overdosing, attempts have been made to introduce co-analgesics. Due to an increasing amount of data concerning a potential enhance of opioid analgesia by the physiological antagonist of *N*-methyl-D-aspartate receptors, magnesium ions (Mg^{2+}), a concomitant use of such a combination seems to be interesting from a clinical point of view. Therefore, the aim of this review is to provide an analysis of existing preclinical and clinical studies in the context of the benefits of using this combination in clinical practice. A potential mechanism of magnesium - opioid interaction is also suggested. The potential influence of Mg on opioid adverse/side effects as well as conclusions on the safety of combined administration of magnesium and opioid drugs were also summarized. Data from animal studies indicate that magnesium increases opioid analgesia in chronic (e.g., neuropathic, inflammatory) as well as acute pain. In clinical trials, most authors confirmed that magnesium reduces opioid consumption and alleviates postoperative pain scores while not increasing the risk of side effects after opioids. However, more clinical studies are needed concerning an influence of Mg on opioid activity in other difficult to treat types of pain, especially neuropathic and inflammatory.

Contents

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1. Introduction

The treatment of pain still remains an unsatisfactorily resolved problem in medicine. The algorithm of pain treatment is based on the rule that the stronger the pain, the more effective and stronger the analgesic needed. This schematic is also known under the common name of the analgesic ladder, which individual rungs are occupied by non-steroidal analgesics, then by weak opioids, and finally potent opioid analgesics (Vargas-Schaffer, 2010; Vargas-Schaffer and Cogan, 2014). In the absence of other, equally effective analgesic drugs, opioids are often used in the treatment of not only cancer but also other types of pain (e.g., acute, postoperative, inflammatory or osteoarthritic pain). Opioids (morphine, heroin, oxycodone, methadone, fentanyl, tramadol, pethidine, dextropropoxyphene, etc.) in humans induce a pain relief, while their long-term repeated use leads to addiction and tolerance. Opiate intake is potentially linked with a strong withdrawal symptom including both somatic and affective components. Opioid drugs reduce the intensity of pain signals acting mainly on G protein-coupled mu opioid receptors localized both in the central as well as peripheral nervous system (Chen et al., 2005; Dietis et al., 2011; Dualé et al., 2007; Gutstein and Akil, 2006; Jongeling et al., 2009; Loyd and Murphy, 2009; Narita et al., 2008; Stein et al., 2003; Zhang et al., 2009). Pharmacological actions of opioids in animals and humans and their adverse effects are widely discussed in literature (Ahmedzai and Boland, 2007; Drewes et al., 2013; Gutstein and Akil, 2006; Inturrisi, 2002; Sauriyal et al., 2011).

Unfortunately there are many problems related to pain treatment. The development of tolerance, the resistance of neuropathic pain to opioid analgesia, or the so-called "paradoxical pain" following opioid use, all limit opiod analgesic effectiveness. Other undesirable effects of opioids also limit their utility. These are, among others, chronic constipation, dizziness, disturbances of central nervous system, such as consciousness disorders, cognitive impairment or respiratory depression (particularly in the case of an overdose).

In clinical practice, in order to reduce opioid doses, and thereby to avoid the risk of deleterious side effects, attempts have been made to introduce co-analgesics, which enhance the analgesic activity of opioids. The representative of such co-analgesics are *N*-methyl-D-aspartate (NMDA) receptor blockers.

NMDA receptor (NMDAR) is key ionotropic glutamatergic receptor, activated by excitatory amino acids - glutamate and aspartate, and is widely distributed in the nervous system (Oliet and Mothet, 2009). This receptor consists of two glycine-binding NR1 subunits and two glutamate-binding NR2 subunits. It contains also a non-specific cation channel allowing the influx of calcium (Ca^{2+}) and sodium (Na^{+}) ions into and efflux of potassium ions (K^{+}) out of the cell (Paoletti and Neyton, 2007). One of the physiologic antagonists of NMDA receptors are magnesium ions (Mg^{2+}) (Nechifor, 2011). They produce a voltage-dependent block of NMDA receptor channel that prevents ligand gating of channel conductance (Augustine, 2008a, b; Vargas-Caballero and Robinson, 2004).

NMDA receptor complex has been implicated in the mechanisms underlying chronic pain. The activation of NMDA receptors causes removing of Mg^{2+} block in channel and calcium entry into the cell that triggers neuronal sensitization (McCartney et al., 2004; Tramèr et al., 1996; Woolf and Chong, 1993; Woolf and Thompson, 1991). On the other hand, the blockade of NMDA receptor channel by administration of Mg is responsible for its analgesic properties in different kinds of pain both in preclinical (animal) (Begon et al., 2000, 2001, 2002; Cavalcante et al., 2013; DeRossi et al., 2012; Ditor et al., 2007; Farsi et al., 2015; Gupta et al., 2011; Hasanein et al., 2007; Ishizaki et al., 1999; Jahangiri et al., 2013; Lee et al., 2009; Prado and Machado Filho, 2002; Rondón et al., 2010; Srebro et al., 2014; Takano et al., 2000; Tamba et al., 2013; Tsai et al., 2001; Ulugol et al., 2002; Xiao and Bennett, 1994; Zochodne et al., 1994) and clinical (Bigal et al., 2002; Bondok and Abd El-Hady, 2006; Brill et al., 2002; Crosby et al., 2000; Demirkaya et al., 2001; Elsharnouby et al., 2008; Felsby et al., 1996; Fischer et al., 2013; Fontana-Klaiber and Hogg, 1990; Ginder et al., 2000; Kahraman and Eroglu, 2014; Kocman et al., 2013; Mauskop et al., 1996; Opavský, 1991; Ryu et al., 2009; Seifert et al., 1989; Shahrami et al., 2015; Shechter et al., 2003; Sun et al., 2015; Teragawa et al., 2000; Turan et al., 2003; Yousef and Al-deeb, 2013) studies. The exact mechanism of magnesium analgesia is not well understood. However, it was demonstrated that the activation of NMDA receptors during neuropathic pain leads to excitation of protein kinase C (PKC), which in turn phosphorylates serine residue 896 of the NMDA receptor NR1 subunit (Gao et al., 2005, 2007; Roh et al., 2008; Tingley et al., 1997; Ultenius et al., 2006). This allows for transfer of NMDA receptors from the cell interior to the cell membrane (Scott et al., 2003; Xia et al., 2001), induces membrane insertion (Scott et al., 2003), and leads to central sensitization. It was reported that oral administration of magnesium sulfate ($MgSO_4$) prevents spinal cord NMDA receptor NR1 subunit phosphorylation, as well as alleviates hyperalgesia and allodynia in a streptozotocin-induced diabetic neuropathy in rats (Rondón et al., 2010). Moreover, an intra-articular administration of $MgSO_4$ attenuated phosphorylation of the NMDA receptor NR1 subunit in rats (Lee et al., 2009).

It should be noted that magnesium is relatively safe at therapeutic doses. The most undesirable effects of this ion occur at high doses, and include - among others - cardiovascular (Albrecht et al., 2013a, b; Bourgeois et al., 1986; Drugdex Drug Evaluations, 2007; Fassler et al., 1985; Ferasatkish et al., 2008; Hwang et al., 2010; Jaoua et al., 2010; Kaya et al., 2009; Levaux et al., 2003; McLaughlin and McKinney, 1998; Richards et al., 1985; Tramèr et al., 1996; Tramèr and Glynn, 2007; Zarauza et al., 2000), metabolic/endocrine (Bradford and McElduff, 2006; Cardosi and Chez, 1998; Drugdex Drug Evaluations, 2007; Faraj, 1989; Garcia-Webb et al., 1984; Hung et al., 2005; Levav et al., 1998; Nassar et al., 2007; Rodis et al., 1987; Spital and Greenwell, 1991), renal (Razavi and Somers, 2000; Wilson et al., 1986), respiratory (Drugdex Drug Evaluations, 2007; Fassler et al., 1985; Jenny et al., 1978), hematologic (Kynczl-Leisure and Cibils, 1996; Ravn et al., 1996; Sacha and Skotnicki, 1997), ophthalmic (Digre et al., 1990) and peripheral (Albrecht et al., 2014; Bashuk and Krendel, 1990; Castelbaum et al., 1989; Drugdex Drug Evaluations, 2007; Durlach, 1984; Fawcett et al., 1999; Klair et al., 2014; Nethravathi et al., 2007; Zwanger, 1986) as well central nervous (Albrecht et al., 2013a; Drugdex Drug Evaluations, 2007; Ghia et al., 2000; Kaya et al., 2009; Kiran et al., 2011) effects.

Due to an increasing amount of data concerning a potential augmentation of opioid analgesia by magnesium ions, a concomitant use of such a combination seems to be interesting from the clinical point of view. Therefore, the aim of this review is to provide an analysis of existing