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Short communication

INVOLVEMENT OF SEROTONERGIC, NORADRENERGIC AND GABAERGIC SYSTEMS IN THE ANTINOCICEPTIVE EFFECT OF A KETAMINE-MAGNESIUM SULFATE COMBINATION IN ACUTE PAIN

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Ketamine and magnesium can interact in additive, supra-additive and antagonistic manners in analgesia or anesthesia. Ketamine is a non-competitive NMDA receptor antagonist. Magnesium is an endogenous non-competitive NMDA antagonist that causes anion channel blockade in a dose-dependent manner. It has been established that ketamine and magnesium interact synergistically in the tail-immersion test in rats.

To determine the role of serotonergic, GABAergic and noradrenergic systems in analgesia induced by the ketamine-magnesium sulfate combination.

Experiments were performed on male Wistar albino rats (200-250 g). Antinociception was evaluated by the tail-immersion test.

Methysergide (0.5 and 1 mg/kg, sc) administered alone did not affect nociception in rats. Methysergide (0.5 and 1 mg/kg, sc) antagonized the antinociceptive effect of the ketamine (5 mg/kg)-magnesium sulfate (5mg/kg) combination. Bicuculline (0.5 and 1 mg/kg, sc) given alone did not change the threshold to thermal stimuli in rats. Bicuculline (0.5 and 1 mg/kg, sc) antagonized the antinociceptive effect of the ketamine (5 mg/kg)-magnesium sulfate (5 mg/kg) combination. Yohimbine (0.5, 1 and 3 mg/kg, sc) applied alone did not change nociception. Yohimbine at a dose of 0.5 mg/kg did not influence the effect of ketamine (5 mg/kg)-magnesium sulfate (5 mg/kg), while yohimbine at doses of 1 and 3 mg/kg antagonized the antinociceptive effect of this combination.

Serotonergic, noradrenergic and GABAergic systems participate, at least in part, in the antinociceptive effect of the ketamine-magnesium sulfate combination in acute pain in rats.

Key words: analgesia, bicuculline, ketamine, magnesium, methysergide, yohimbine

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INTRODUCTION

Ionotropic receptors have an important role in the pathogenesis of pain. N-methyl-D-aspartate (NMDA) receptors are present in the dorsal root ganglia of the spinal cord and in certain pre- and postsynaptic parts of the spinal cord and brain. These receptors in the ascendant and descendent pathways modulate the transmission of nociceptive stimuli from the periphery [1]. The nociceptive impulses which are transmitted in the spinal cord by unmyelinated C fibers and myelinated Aδ fibers, lead to glutamate release in the spinal cord and to the sensation of pain. Pain modulation refers to the process by which the body alters a pain signal. Descending pathways project to the dorsal horn and inhibit pain transmission. Descending inhibition of pain is mostly accomplished by enkephalins, 5-hydroxy tryptamine (5-HT, serotonin) and noradrenaline (NA). Serotonin receptors can be pro- (5-HT_3) and antinociceptive (5-HT_1) [2], whereas all central noradrenergic receptors are antinociceptive [3].

The balance between the activity of inhibitory and excitatory amino acids, gamma-aminobutyric acid (GABA) and glutamate determines the level of pain transmission [4]. The role of GABA transmission in the spinal cord can vary in different pain states. Opioids enhance the descending inhibitory pain pathway by suppressing the inhibitory influence of GABA on neurons that form this antinociceptive pathway [5].

Ketamine is an NMDA receptor antagonist with a clinical application. It is a dissociative anesthetic with an analgesic effect at subanesthetic doses [6]. The mechanisms of ketamine anti-nociceptive actions include activation of descending inhibitory monoaminergic pain pathways and antagonism of NMDA receptors [7]. Ketamine has little risk of cardiorespiratory depression and is an excellent drug for the treatment of pain in trauma [8]. The adverse effects of ketamine are produced at therapeutic doses and include sedation, motor coordination, confusion, hallucinations.

Magnesium is physiologically a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist that blocks the ion channel in a dose-dependent manner [9]. Magnesium blocks calcium channels associated with NMDA receptors, which is considered as the main mechanism through which it achieves its central effects [10,11]. Alternatively, there is evidence suggesting that its antinociceptive mechanism can arise through blockade of other ion channels and modulation of neurotransmitter release [12-16].

Literature data indicate that magnesium and ketamine can interact in additive, antagonistic and supraadditive manners [17-23]. Previously we demonstrated that ketamine and magnesium individually had no effects on the tail immersion test in rats, but in combination they can interact synergically [24]. The aim of the present study was to investigate the role of serotonergic, noradrenergic and GABAergic systems in ketamine-magnesium sulfate-induced analgesia.

MATERIALS AND METHODS

Ethical approval

The experimental animals were handled as prescribed by the Ethics Committee for Animal Research and Welfare of the Faculty of Medicine, University of Belgrade (Permit N° 3416/2). All experiments were approved by the Ethical Council for the Protection of Experimental Animals of the Ministry of Agriculture, Forestry and Water Management of the Republic of Serbia, which operates in accordance with the Animal Welfare Law of the Republic of Serbia and the International Association for the Study of Pain (IASP) Guidelines for the Use of Animals in Research.

Animals

The study was performed using 120 male Wistar rats (Military Farm, Belgrade, Serbia) weighing 200-250 g. The animals were housed in groups of three in Plexiglass cages (42.5×27×19 cm) under standard conditions of temperature (22±1°C), relative humidity (60%) and a 12 h light/dark cycle, with lights on at 08:00. Food and water were freely available, except during the experimental procedures. The animals were fed standard rat pellets obtained from the Veterinary Institute Subotica, Serbia. The experiments were conducted by the same experimenter on consecutive days, always at the same time of the day, between 08:00 and 14:00, to avoid diurnal variation in the behavioral tests. The animals were unrestrained throughout, except during testing. Each animal was used only once and was killed at the end of the experiments by an intraperitoneal (ip) injection of sodium thiopental (200 mg/kg).

Administration of drugs

Ketamine (InresaArzneimittel GmbH, Freiburg, Germany) and magnesium sulfate (Zorka, Šabac, Serbia) were dissolved in 0.9% NaCl and injected intraperitoneally (ip) and subcutaneously (sc) respectively, in a final volume of 2 ml/kg. Magnesium sulfate was administered 5 min after ketamine injection. Antagonists (methysergide maleate, yohimbine hydrochloride and bicuculline (Sigma-Aldrich Chemical Co., St Louis, Mo., SAD), were administered sc 5 min before ketamine [24]. To test whether the 0.9% NaCl injection had any effect on the antinociception, the same volume of 0.9% NaCl was administered to a control group of rats.

Tail-immersion test

In the first set of experiments, the analgesic activity was determined using a tail-immersion test. The rat was placed in a hemicylindrical Plexiglass cage with its tail hanging freely outside the cage. The distal 5 cm of the tail was immersed in a warm water bath (55 ± 0.5°C), and the time for tail-withdrawal was measured to the nearest 0.1 s. Animals that had a tail-withdrawal response within 1-2 s were selected for the study. To minimize tissue damage by repeated testing, a cut-off time of 10 s was

adopted. The pre-medication latency was determined from an average of two pre-medication determinations obtained with a 30 min interval. There was no difference in basal tail-withdrawal latency between the tested groups ($p>0.05$). Post-medication latency was measured after the ip and/or sc administrations of the test compounds (or 0.9% NaCl in the control group) at 30, 60, 90, 120, 150 and 180 min.

Statistical Analysis

The differences between the corresponding means in tail-withdrawal latency were verified using one-way analysis of variance (ANOVA), followed by Tukey's HSD post hoc test [25]. A $p<0.05$ was considered to be statistically significant.

RESULTS AND DISCUSSION

Previously we showed by the (rat) tail-immersion test that ketamine at a dose of 5 mg/kg and magnesium sulfate at a dose of 5 mg/kg did not produce an antinociceptive effect, however, ketamine (5 mg/kg) in combination with magnesium sulfate (5 mg/kg) had an antinociceptive effect [24,26]. The mechanism of the antinocicetive effect of this combination remained unknown. The present study explores the influence of serotonergic, noradrenergic and GABAergic systems in the antinociceptive effect of the ketamine-magnesium sulfate combination.

Serotonin has a complex role (it can inhibit and facilitate) in the process of transmission and perception of pain impulses. Different 5-HT receptors are distributed throughout the central and peripheral nervous systems and mediate these effects [27]. Electrophysiological studies have shown that 5-HT1 receptors are mainly responsible for antinociception, and that the activation of 5-HT2 receptors underlies pronociceptive effects [28,29].

In the present study, at doses of 0.5 and 1 mg/kg, methysergide antagonized the antinociceptive effect of ketamine-magnesium sulfate combination ($p<0.05$) (Figure 1A). The effect of both doses was significant at 60 min after ketamine administration. There was no statistical significance between the effects produced by different doses of methysergide when used in combination with the ketamine-magnesium sulfate combination ($p>0.05$) (Figure 1A). Methysergide (0.5 and 1 mg/kg, sc) administered alone did not have an antinociceptive effect in comparison to 0.9% NaCl ($p>0.05$) (Figure 1B).

The finding that methysergide as a non-selective antagonist of 5-HT receptors antagonized the antinociceptive effects of the ketamine-magnesium sulfate combination suggests that serotonergic receptors are involved directly or indirectly in the antinociceptive effect of this combination. It has been previously shown that (S)-ketamine can act as an antagonist of 5-HT(3) receptors [30]. Since neither ketamine, nor magnesium possesses direct agonist activity at 5-HT receptors and literature data indicate that ketamine augments endogenous anti-nociceptive and antidepressant

systems via its serotonergic activation and inhibition of re-uptake [31-33], it would seem that the descending serotonergic inhibitory pathway is implicated in the mechanism of the action of ketamine-magnesium sulfate combination. In addition, magnesium is well known for its NMDA receptor ion channel blocking effect, modulatory action on different ion channels and neurotransmitters release [12-16]. Moreover, the finding that ketamine interacts synergically with magnesium sulfate suggests the activation of different and complementary mechanisms, since the activation only of common mechanism would presumably produce an additive interaction [34].

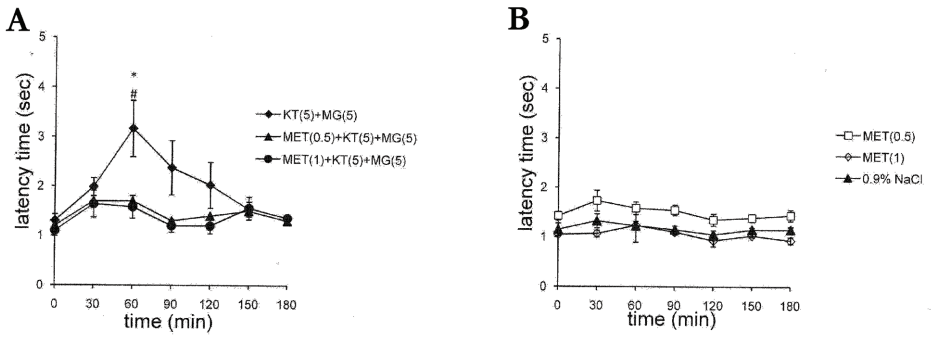

Figure 1. Antinociceptive effects of: **A)** combination of ketamine (KT, 5 mg/kg, ip), magnesium sulfate (5 mg/kg) and methysergide (MET, 0.5 and 1 mg/kg, sc) and **B)** methysergide (MET, 0.5 and 1 mg/kg, sc). Each point is the mean±SEM of the antinociceptive latency time in seconds (s) obtained in 6-8 rats. The latency time is the reaction time (in s) of a rat tail exposed to hot water. Statistical significance exists between KT(5)-MG(5) and MET(0.5)-KT(5)-MG(5) (*$p<0.05$); KT(5)-MG(5) and MET(1)-KT(5)-MG(5) (#$p<0.05$) (One-Way ANOVA, Tukey's HSD test).

GABA modulates spinal and supraspinal levels of analgesia as well as peripheral pain signaling [35,36]. Endogenous peripheral GABA could arise from primary afferent fibers and act at $GABA_A$ receptors present on some unmyelinated afferent axons [35]. Both directly and indirectly acting GABA-mimetic agents, including antiepileptic drugs, produce analgesia in a variety of animal test systems.

In the present study, bicucculine (0.5 and 1 mg/kg, sc) administered alone had no influence on antinociception in rats ($p>0.05$) (Figure 2B). At doses of 0.5 mg/kg and 1 mg/kg bicucculine antagonized the antinociceptive effect of the ketamine-magnesium sulfate combination ($p<0.05$) (Figure 2A). The effect of bicuccline appeared at 30 min and lasted 90 min ($p<0.05$) (Figure 2A). The maximum effect was achieved at the 60 min time point. There was no statistical difference between the effects of the different doses of bicucculine (1 and 2 mg/kg) and the ketamine (5 mg/kg)-magnesium sulfate combination (5 mg/kg) ($p>0.05$) (Figure 2A).

Our experiments revealed that, bicuculline, a selective, competitive antagonist of $GABA_A$ receptors, inhibited the systemic antinociceptive effect of the ketamine-

magnesium sulfate combination. This data indicates that $GABA_A$ receptors, at least in part, are involved in the antinociceptive effect of the ketamine-magnesium sulfate combination. This interaction can be interpreted as that ketamine or magnesium sulfate interact with $GABA_A$ receptors either directly or indirectly, thereby potentiating GABAergic inhibitory neurotransmission. In agreement with this, some preclinical data and one human single-photon emission computerized tomography (SPECT) study suggested that ketamine modulates $GABA_A$ activity [37,38].

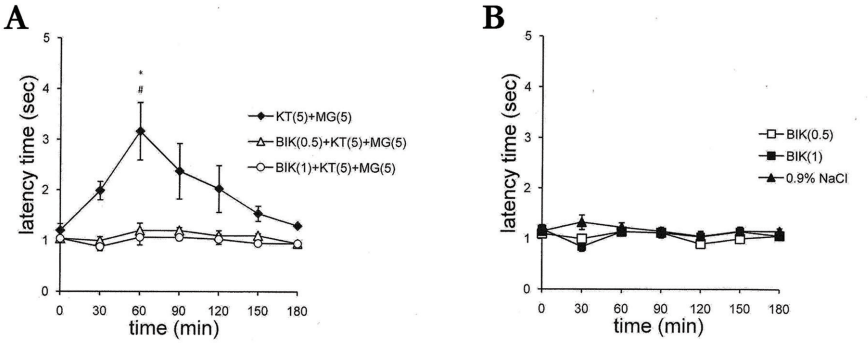

Figure 2. Antinociceptive effects of **A)** combination of ketamine (KT, 5 mg/kg, ip), magnesium sulfate (5 mg/kg) and bicucculine (BIK, 0.5 and 1 mg/kg, sc), and **B)** bicucculine (BIK, 0.5 and 1 mg/kg, sc). Each point is the mean±SEM of the antinociceptive latency time in seconds (s) obtained in 6-8 rats. The latency time is the reaction time (in s) of a rat tail exposed to hot water. Statistical significance exists between KT(5)-MG(5) and BIK(0.5)-KT(5)-MG(5) (*$p<0.05$); KT(5)-MG(5) and BIK(1)-KT(5)-MG(5) (#$p<0.05$) (One-Way ANOVA, Tukey's HSD test).

Our data also indicate that α_2-adrenergic receptors are involved in the antinociceptive effect of the ketamine-magnesium sulfate combination. At a dose of 0.5 mg/kg, yohimbine did not affect the antinociceptive effect of the ketamine-magnesium sulfate combination, however, at doses of 1 and 3 mg/kg, yohimbine abolished the effect of this combination (Figure 3A). The maximum effect was achieved at the 60 min time point. Yohimbine (0.5, 1 and 3 mg/kg) did not produce anantinociceptive effect in rats ($p>0.05$) (Figure 3B).

The ketamine-magnesium sulfate combination could interact directly (binding to receptors) and/or indirectly (potentiation of noradrenergic neurotransmission) with receptors. It has been established that the noradrenergic system is often involved in the analgesic effect of different substances [39,40]. Activation of α_2-adrenergic receptors has been shown to inhibit nociceptive transmission at the level of the spinal cord through presynaptic activity, inhibiting the release of excitatory neurotransmitters from primary afferent terminals, as well as through postsynaptic sites [41]. Recordings performed on spinal cord slices revealed that activation of α_2-adrenergic receptors hyperpolarized neurons and was thus inhibitory. There is no data about the binding of ketamine or magnesium sulfate to α_2-adrenergic receptors nor about the possible impact of this combination on endogenous norepinephrine levels. However, it has been previously reported that ketamine activates the descending noradrenergic

pathway [7,31]. It was shown that ketamine increased NA release from the medial prefrontal cortex [42].

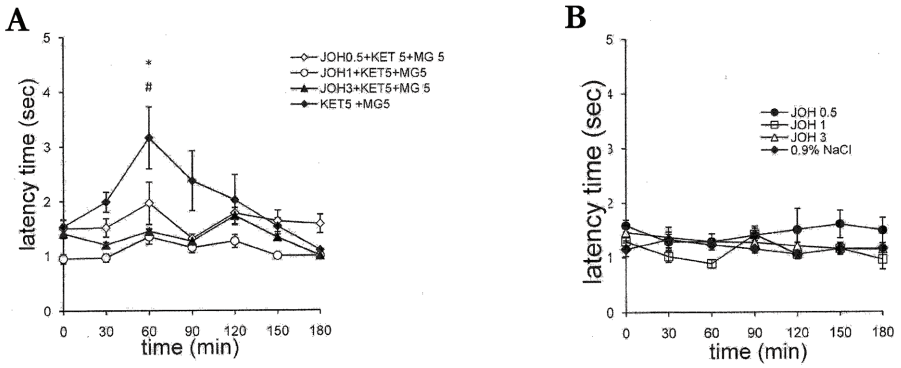

Figure 3. Antinociceptive effects of **A)** combination of ketamine (KT, 5 mg/kg, ip), magnesium sulfate (5 mg/kg) and yohimbine (JOH, 0.5,1 and 3 mg/kg, sc), and **B)** yohimbine (JOH, 0.5, 1 and 3 mg/kg, sc). Each point is the mean±SEM of the antinociceptive latency time in seconds (s) obtained in 6-8 rats. The latency time is the reaction time (in s) of a rat tail exposed to hot water. Statistical significance exists between KT(5)-MG(5) and JOH(1)-KT(5)-MG(5) (*$p<0.05$); KT(5)-MG(5) and JOH(3)-KT(5)-MG(5) (#$p<0.01$) (One-Way ANOVA, Tukey's HSD test).

CONCLUSION

The results of the present study suggest that serotonergic, noradrenergic and GABAergic systems are involved, at least in part, in the antinociceptive effect of the ketamine-magnesium sulfate combination in acute pain in rats.

Acknowledgment

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Authors' contributions

KSV and SV conceived and designed the experiments; KSV performed the experiments; KSV, SV, RS and ND analyzed the data; KSV, BM, DS and MK contributed reagents/materials/analysis tools. KSV, SV and MP wrote the paper.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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UTICAJ SEROTONERGIČKOG, NORADRENERGIČKOG I GABERGIČKOG SISTEMA U ANTINOCICEPTIVNOM EFEKTU KOMBINACIJE KETAMIN-MAGNEZIJUM SULFATA U AKUTNOM BOLU

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Ketamin i magnezijum mogu stupiti u aditivnu, supraaditivnu i antagonističku interakciju u analgeziji i anesteziji. Ketamin je nekompetitivni NMDA antagonist. Magnezijum je endogeni nekompetitivni NMDA antagonist koji blokira jonski kanal na voltažno zavistan način. U testu potapanja repa u toplu vodu, dokazano je da ketamin i magnezijum stupaju u sinergističku interakciju.

Cilj rada: utvrditi da li serotonergički, GABA-ergički i noradrenergički sistem učestvuju u analgetičkom efektu ketamin-magnezijum sulfat kombinacije.

Eksperimenti su izvođeni na mužjacima pacova Wistar soja (200-250 g). Antinocicepcija je merena pomoću testa potapanja repa u toplu vodu.

Metizergid (0.5 i 1 mg/kg, sc), primenjen sam, nije uticao na nocicepciju kod pacova. Metizergid (0.5 i 1 mg/kg, sc) je antagonizovao antinociceptivni efekt ketamin (5 mg/

kg)-magnezijum sulfat (5mg/kg) kombinacije. Bikukulin (0.5 i 1 mg/kg, sc) primenjen sam nije imao efekt u testu potapanja repa u toplu vodu, a antagonizovao je antinociceptivni efekt ketamin (5 mg/kg)-magnezijum sulfat (5 mg/kg) kombinacije. Johimbin (0.5, 1 i 3 mg/kg, sc) nije uticao na nocicepciju kod pacova kada je primenjen samostalno. U dozi od 0.5 mg/kg, johimbin nije uticao na kombinaciju ketamin (5 mg/kg)-magnezijum sulfat (5 mg/kg), dok je u dozama od of 1 i 3 mg/kg antagonizovao antinociceptivne efekte ove kombinacije.

Serotonergički, noradrenergičkii GABA-ergički sistem učestvuju bar delimično u antinocicptivnom efektu ketamin-magnezijum sulfat kombinacije kod pacova.