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MAGNESIUM AND KETAMINE IN THE TREATMENT OF DEPRESSION

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SUMMARY

Depression affects over 121 million people annually worldwide. Relatively low remission rates among depressive patients enforce the search for new therapeutic solutions and an urgent need to develop faster-acting antidepressants with a different mechanism of action occurs. The pathomechanism of depression postulated by the monoamine hypothesis is limited. The results of abnormalities in glutamate and γ-aminobutyric acid (GABA) systems in the brains of people with mood disorders allowed to develop new theories regarding pathophysiology of these disorders. Glutamatergic transmission is influenced by magnesium and ketamine through glutamatergic N-methyl-D-aspartate receptor (NMDAR) antagonistic effects.

Magnesium and ketamine have a common mechanism of action in the treatment of depression: an increase in GluN2B (NMDAR subunit) expression is related to the administration of both of the agents, as well as inhibition of phosphorylation of eEF2 (eukaryotic elongation factor 2) in cell culture and increase of the expression of BDNF in the hippocampus. Combination of ketamine and magnesium in a normal magnesium level presents a superadditive effect in depression treatment. Analysed substances affect the GABAergic system and have anti-inflammatory effects, which is correlated with their antidepressant effect.

The synergistic interaction between the pharmacodynamic activity of magnesium and ketamine may be of particular importance for patients with mood disorders. Further research is needed to determine the relationship between magnesium levels and ketamine treatment response mainly in the attempt to establish if the magnesium supplementation can change ketamine treatment response time or present superadditive effect.

Key words: *magnesium - ketamine - depression*

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INTRODUCTION

Depression affects over 121 million people annually worldwide, being a common cause of disability, social disfunctions, family life disruptions and work environment problems (Gelenberg 2010, Tizabi et al. 2012). Current pharmacological treatment for depression includes a wide range of drugs, unfortunately with a homogeneous mechanism of action mainly related to the regulation of the monoamine system. Relatively low remission rates (approximately one third of patients do not achieve remission due to this treatment) among depressive patients, numerous side effects and delayed onset of action enforce the search for new therapeutic solutions, there is an urgent need to develop faster-acting antidepressants with a different mechanism of action (Gaynes et al. 2009, McIntyre et al. 2014). The last two decades of research on the neurobiological foundations of depression have been dominated by the study focused on the glutamatergic system (Sanacora et al. 2008). Glutamatergic transmission is influenced by magnesium and ketamine through glutamatergic N-methyl-D-aspartate receptor (NMDAR) antagonistic effects (Berman et al. 2000, Murck 2013, Zarate et al. 2006). The synergistic interaction between the pharmacodynamic activity of magnesium and ketamine may be of particular importance for patients with mood disorders.

DEPRESSION - A NEW POINT OF VIEW

The pathomechanism of depression postulated by the monoamine hypothesis is limited. It was reported that monoamine deficiency did not reliably indicate depression in healthy people and did not significantly increase the symptoms of depression in untreated patients (Duman et al. 2016). The results of abnormalities in glutamate and γ-aminobutyric acid (GABA) systems in the brains of people with mood disorders allowed to develop new theories regarding pathophysiology and treatment of these disorders. It was observed that GABA levels in the cortical areas of patients with depression are reduced (Godfrey et al. 2018, Price et al. 2009). Reduction in the level of glutamate metabolites in the central frontal cortex in MDD was observed as well (Moriguchi et al. 2018). In contrast, acute stress increases extracellular glutamate amount in the medial prefrontal cortex and hippocampus indicating that excitotoxicity of glutamate acting on NMDAR is responsible for neuronal damage (Popoli et al. 2011).

MAGNESIUM DEPENDENCY IN DEPRESSION

The importance of magnesium ions for the biochemical processes of an organism cannot be overestimated. This element is indispensable for the catalytic

activity of about 300 enzyme proteins as well as being a micronutrient of considerable importance for the proper functioning of the central nervous system, therefore its fluctuations can be a risk factor leading to mental disorders (Schwalfenberg et al. 2017). Low levels of magnesium with high levels of calcium and glutamate in the hippocampus may cause changes in the functioning of synapses which may lead to the development of depression (Serefko et al. 2016).

Magnesium blocks NMDAR in a voltage-dependent manner; when its concentration is too low there is an abnormal influx of calcium into the cells resulting in the release of intracellular glutamate that causes depolarization and can lead to neuronal dysfunction (Murck 2013, Sowa-Kućma et al. 2013). However, it is worth noticing the effect of magnesium is not only related to NMDAR antagonism. Magnesium indirectly increases α-Amino-3-hydroxy-5-methyl-4 isoxazolepropionic acid- ergic (AMPAergic) activity, increases the expression of brain derived neurotropic factor (BDNF), suppresses hippocampal kindling, modulates protein kinase C (PKC), affects P-glycoprotein which alters the hypothalamic-pituitary-adrenal axis (Murck 2013). Magnesium is also important for the functioning of serotonergic, noradrenergic, dopaminergic, and γ-aminobutyric acid-ergic (GABAergic) systems and has anti-inflammatory activity. All the above-mentioned mechanisms are associated with its antidepressant effect (Cubała et al. 2016, Sanacora et al. 2008, Singewald et al. 2004).

In preclinical studies it was observed that feeding mice on a low magnesium diet is associated with an increase of depressive-like behavior in the forced swim test (FST), similar behavior was observed in rats (Singewald et al. 2004, Spasov et al. 2008). Cotreatment with magnesium and some antidepressants, such as imipramine, fluoxetine, citalopram, tianeptine, and bupropion, results in a synergistic antidepressant effect similar to FST (Szewczyk et al. 2018, Poleszak et al. 2005). Antidepressant activity of magnesium in combination with glutamatergic N-methyl-D-aspartate (NMDA) antagonists was observed in mice, therefore magnesium supplementation may be an effective method of reducing the NMDA antagonist dose (Poleszak et al. 2007). One animal study hypothesized about magnesium potentially being a cofactor which would increase the effect of ketamine. The results of this study did not confirm the usefulness of magnesium as a supportive treatment for ketamine in depression in mice (Razmjou et al. 2016). The issue calls for further investigation.

The concentration of magnesium in serum may be a potential marker in patients with depression as multiple studies have observed a relationship between depression and magnesium levels, but obtained results are not homogeneous. Most studies exhibit low magnesium levels in the course of depression (Cheungpasitporn et al. 2015, Frizel et al. 1969, Islam et al. 2018), however, there are also studies presenting high magnesium concentration in patients' blood (Cubała et al. 2013, Styczeń et al. 2013).

Studies indicate the antidepressant properties of magnesium and/or potential usage of magnesium as an additive to antidepressant treatment (Cardoso et al. 2009, Poleszak et al. 2005). Response to antidepressant treatment in patients with higher levels of magnesium was observed (Camardese et al. 2012). Another study showed an increase in intracellular magnesium concentration after treatment with amitriptyline or sertraline (Nechifor 2009). Tarleton et al. (2017) demonstrated a decrease in depression symptoms after just a two-week period of magnesium supplementation, also relationship between low magnesium intake and depression was observed (Tarleton & Littenberg 2015). Rapid (in the duration of less than 7 days) antidepressant effect associated with the response to magnesium treatment was shown (Eby & Eby 2006). Magnesium treatment was as effective as imipramine in two-week randomized study in a group of elderly patients with hypomagnesemia/ type 2 diabetes (Barragan-Rodriguez et al. 2006). In the contrast to aforementioned research, in the Mehdi et al. (2017) study no improvement in the symptoms of depression after magnesium supplementation was observed, lack of antidepressant effect was also reported in a randomized clinical trial in a group of patients with postpartum depression (Fer et al. 2017).

KETAMINE AND ITS ANTIDEPRESSANT PROPERTIES

Ketamine is an intravenous anesthetic presenting a wide spectrum of pharmacological effects, including sedation, catalepsy, analgesia, and sympathetic stimulation (Kishimoto et al. 2016, Kurdi et al. 2014). Recently, it is increasingly used in psychiatry due to the fact that a single injection of ketamine shows a rapid antidepressant effect (Berman et al. 2000, Kishimoto et al. 2016, Zarate et al. 2006). Ketamine is an NMDAR antagonist, but it shows different mechanism of antidepressant action as well. The immediate effect of ketamine is the blockade of the postsynaptic GluN2B NMDA receptors (glutamate ionotropic receptors NMDA type subunit 2B)- these receptors activate the eukaryotic extension factor-2 (eEF2) which decrease BDNF levels. By blocking NMDA receptors containing GluN2B, ketamine can prevent phosphorylation of eEF2, increase BDNF levels and promote AMPA receptors in the synapses, increasing synaptic connectivity. Preclinical studies show that ketamine causes a glutamate burst by blocking NMDAR on GABA interneurons, which results in its indirect action. GABA interneurons are more sensitive to ketamine because their tonic activity removes magnesium ions from channel, allowing ketamine to block NMDAR. Ketamine reduces the inhibition of glutamate release and results in increased stimulation of AMPA glutamate receptors which activates a signaling cascade that raises BDNF levels. Local release of BDNF stimulates tropomyosin kinase B receptor (TrkB), resulting in the activation of mammalian target of

rapamycin complex 1 (mTORC1) which increases synaptic plasticity (Murck 2013, Duman et al. 2019, Krystal et al. 2019). Ketamine also presents an effect on the normalization of proinflammatory cytokines in mice, in particular interleukin 1 beta (IL-1β), tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6) (Tan et al. 2017). Human studies confirm the reduction of proinflammatory cytokines (TNF-α) after infusion of ketamine, which was associated with the reduction of depressive symptoms in treatment-resistance depression (Chen et al. 2018, Szałach et al. 2019).

It has been reported that the administration of ketamine provides antidepressant effects in rodents, i.e. multiple infusions of ketamine in rats exposed to the forced swim test reverted chronic stress-induced depressive behavior (Parise et al. 2013).

The effectiveness of ketamine in the treatment of depression has been confirmed in meta-analyses and systematic reviews (Coyle & Laws 2013, Serafini et al. 2014). The antidepressant efficacy was demonstrated within a few hours after administration of ketamine in randomized, placebo-controlled, double-blind studies for unipolar and bipolar depression (Berman et al. 2000, Kishimoto et al. 2016, Zarate et al. 2006, Diazgranados et al. 2010). Significantly higher rate of relapse in patients randomized to the placebo, compared with patients randomized to esketamine nasal spray was observed (Daly et al. 2018). Single intravenous infusion of ketamine led to a rapid (80 min) and sustained (up to 7 days) antidepressant response (Berman et al. 2000, Zarate et al. 2006). An open study showed that six intravenous infusions of ketamine over 12 days were safe and effective for ten patients with drug-resistant depression, with an average relapse time of 19 days (Aan het Rot et al. 2010). In the study of 24 patients with treatment-resistant depression (TRD), the mean time to relapse was 18 days (Murrough et al. 2013).

KETAMINE AND MAGNESIUM RELATIONS IN DEPRESSION TREATMENT

Magnesium and ketamine have a common mechanism of action in the treatment of depression. An increase in GluN2B expression is related to the administration of both ketamine and magnesium (Chatterjee et al. 2012). Magnesium and ketamine inhibit phosphorylation of eEF2 (eukaryotic elongation factor 2) in cell culture and increase the expression of BDNF in the hippocampus, which increases synaptogenesis (Slutsky et al. 2010). Administration of magnesium and ketamine leads to synaptic strengthening, measured by the increase in slow wave sleep in humans (Murck 2013). It was observed that sensitivity of ketamine increases in the state of magnesium depletion (Begon et al. 2001). Combination of ketamine and magnesium in a normal magnesium level has a superadditive effect in depression treatment (Orser et al. 1997). Ketamine directly or indirectly increases magnesium levels in the brain by activating a non-NMDA glutamate receptors (Murck 2013). Ketamine and magnesium also affect the GABAergic system and have anti-inflammatory effects, which is associated with their antidepressant effect (Chen et al. 2018, Cubała et al. 2016, Sanacora et al. 2008, Szałach et al. 2018).

CONCLUSIONS:

Decreased levels of magnesium are reported to cause changes in the functioning of synapses which may lead to the development of depression, therefore concentration of magnesium may be treated as a potential marker in patients with depression (Cheungpasitporn et al. 2015, Frizel et al. 1969, Islam et al. 2018). Studies indicate the antidepressant properties of magnesium and/or its potential usage as an additive to antidepressant treatment (Barragan-Rodriguez et al. 2008, Eby & Eby 2006, Tarleton et al. 2017). Ketamine presents a rapid antidepressant effect due to which it is increasingly used in psychiatry (Coyle & Laws 2015, Serafini et al. 2015). Its rapid action and effectiveness in depression makes it promising for patients who are refractory to treatment (Aan het Rot et al. 2010, Daly et al. 2018, Murrough et al. 2013). Studies on the complexity of antidepressant action of ketamine contribute to the development of knowledge about the pathogenesis of depression (Duman et al. 2019, Krystal et al. 2019, Murck 2013).

In summary, magnesium and ketamine are involved in many key mechanisms of the pathophysiology of depression. The presented data may indicate a synergistic effect between the pharmacodynamic activity of magnesium and ketamine in the treatment of depression. Further research is needed to determine the relationship between magnesium levels and ketamine treatment response mainly in the attempt to establish if the magnesium supplementation can change ketamine treatment response time or present superadditive effect.

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Contribution of individual authors:

Natalia Górska: design of the study, literature research and analysis, manuscript writing.

Jakub Słupski & Katarzyna Jakuszkowiak-Wojten: literature research.

Łukasz P. Szałach: literature research and analysis.

Adam Włodarczyk & Mariusz Stanisław Wiglusz: manuscript redaction.

Joanna Szarmach & Maria Gałuszko-Węgielnik: literature analysis.

Alina Wilkowska: literature research and analysis.

Wiesław Jerzy Cubała design of the study.

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