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THE IMMUNOMODULATORY EFFECT OF KETAMINE IN DEPRESSION

Łukasz P. Szałach[1,2], Katarzyna A. Lisowska[1], Jakub Słupski[2], Adam Włodarczyk[2], Natalia Górska[2], Joanna Szarmach[2], Katarzyna Jakuszkowiak-Wojten[2], Maria Gałuszko-Węgielnik[2], Mariusz Stanisław Wiglusz[2], Alina Wilkowska[2] & Wiesław J. Cubała[2]

[1]Department of Physiopathology, Faculty of Medicine, Medical University of Gdańsk, Poland
[2]Department of Psychiatry, Faculty of Medicine, Medical University of Gdańsk, Poland

SUMMARY

Major depression is one of the most frequent psychiatric conditions. Despite many available treatment methods, more than 30% of patients do not achieve remission, even after trying several antidepressants and augmentation strategies. S-enantiomer of ketamine, well-known anesthetic and analgesic, has been recently approved by Food and Drug Administration in the intranasal form as a new generation antidepressant. However, the mechanism in which ketamine reduces depressive symptoms in treatment-resistant depression patients is still not completely understood. There are several theories explaining how ketamine might reduce depressive symptoms, which have been described in detail; one of them is immunomodulatory effect of ketamine, according to the inflammatory theory of depression. In the review authors present and summarize studies showing ketamine effect on human immune system ex vivo and in vitro, including changes in cytokine levels, number, ratio and activity of various immune cell population and the correlation with clinical improvement in depressive symptoms. Most of the results confirm the anti-inflammatory effect of ketamine. There are only a few studies in the population of patients suffering from depression receiving ketamine, focused on correlation between immunological changes and clinical outcome of the therapy; further studies of that area are neccesary for understanding the immunomodulatory effect of ketamine in depression.

Key words: *ketamine - depression - inflammation - cytokines - lymphocytes*

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INTRODUCTION

Major depression is one of the most occurring psychiatric condition. Despite many available treatment methods, more than 30% of patients do not achieve remission, even after trying several antidepressants and augmentation strategies. Therefore, seeking for other antidepressive agents with different mechanism of actions is necessary to help patients suffering from treatment-resistant depression.

Ketamine is a well-known, widely used anesthetic and analgesic drug. Its S(+) enantiomer esketamine in the intranasal form has been recently approved by Food and Drug Administration (FDA) as a new generation antidepressant (Walsch 2019). Its rapid antidepressive activity has been proven in numbers of studies (Berman et al. 2000, Zarate et al. 2006, Daly et al. 2019). Newport's meta-analysis shows that a single intravenous infusion of ketamine at a dose of 0.5 mg/kg produces robust and rapid antidepressant response within 24 hours after administration that declined steadily, but remained statistically significant up to 2 weeks (Newport et al. 2015). However, the mechanism in which ketamine reduces depressive symptoms in treatment-resistant depression (TRD) patients is still not completely understood.

KETAMINE MECHANISM OF ACTION IN DEPRESSION

There are several theories explaining how ketamine might reduce depressive symptoms (Figure 1). The most known mechanism of ketamine is its effect on glutaminergic system. Ketamine directly blocks N-methyl-D-aspartate (NMDA) receptors in the brain, which reduces neuronal excitotoxicity caused by glutamate. On the other hand, blockade of NMDAR on γ-aminobutyric acid (GABA) neurons leads to disinhibition of pyramidal cells in prefrontal cortex causing locally increased glutamate release (Abdallah et al. 2016). It results in activation of the α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors, glycogen synthase kinase 3 (GSK-3) phosphorylation, mammalian target of rapamycin (mTOR) signaling activation, inhibition of eukaryotic elongation factor 2 (eEF2) kinase and increased production of brain-derived neurotrophic factor (BDNF), which overall increase synaptogenesis, dendrite spine density and neuroplasticity, resulting in antidepressive effect (Pesic et al. 2016, Miller et al. 2014, Li et al. 2010).

Ketamine binds to both σ(1) and σ(2) receptors and thus reduces the depressive symptoms in rats (Robson et al. 2012). Even though function of this receptors is still poorly understood, it seems that ketamine's antidepressive effect might be associated with stimulation of BDNF release caused by increased activity of cAMP response element-binding protein (CREB) (Zhang et al. 2017). Antidepressive properties of ketamine may result from modulation of other neurotransmitter systems. It has been shown that ketamine increases dopamine levels (Kokkinou et al. 2018), reverses deficit in dopamine-dependent synaptic plasticity (Belujon & Grace 2014),

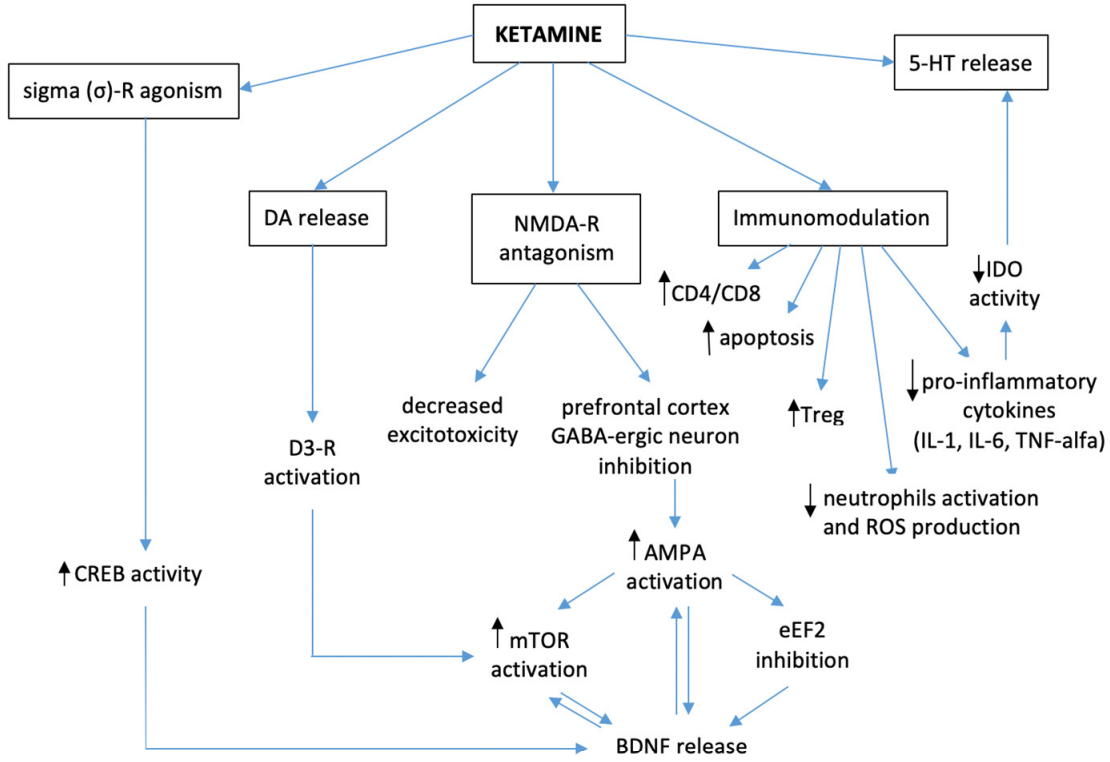

Figure 1. Ketamine's mechanisms of action in depression

and modulates mTOR signaling in rodent limbic system due to activation of dopamine D3 receptors (Chiamulera et al. 2018). Serotonin activity in the brain is also modulated by ketamine. Studies have shown that ketamine enhances serotonin release in medial prefrontal cortex by cholinergic neurons projecting from pedunculopontine tegmental nucleus to dorsal raphe nucleus (Kinoshita et al. 2018).

Modulation of serotoninergic system is connected to the kynurenine pathway. Studies show that in patients suffering from depression there is a shift in tryptophan metabolism towards neurotoxic metabolite of kynurenine pathway − quinolinic acid, a NMDA-R agonist, instead of serotonin or neuroprotective kynurenic acid (KYNA) (Zou et al. 2015). Intravenous administration of ketamine seems to be reversing these changes causing significant increase in KYNA serum level after 24 hours, which is associated with clinical antidepressive effect (Zhou et al. 2018).

The changes in kynurenine pathway described above are strongly connected to the hypothesis that ketamine might have antidepressant properties due to its anti-inflammatory effect. Pro-inflammatory cytokines, such as IFN-γ, IL-1 or IL-6 produced excessively by activated immune cells in depressed patients are responsible for triggering pro-depressive effects through the induction of indolamine 2,3-dioxygenase (IDO), an enzyme involved in the shift of tryptophan to kynurenine and consequently to quinolinic acid (Dantzer et al. 2016). There are several other mechanism in which ketamine modulates immune system, and thus contribute to the antidepressive effect.

IMMUNOMODULATORY EFFECT OF KETAMINE

Regulation of immune system activity and chronic inflammation seems to play an important role in the pathogenesis of depression, as we reported recently (Szałach et al. 2019). The inflammatory hypothesis of depression has been described in a number of studies. It has been demonstrated that concentrations of pro-inflammatory cytokines, mainly IL-1, IL-6, IFN-γ and TNF-α, are elevated in the serum of patients suffering from depressive disorders, which has been confirmed in several meta-analyzes (Dowlati et al. 2010, Haapakoski et al. 2015, Schmidt et al. 2014). Also, the increase in the level of pro-inflammatory cytokines is accompanied by an increased plasma concentrations of granulocyte-macrophage colony-stimulating factor (GM-CSF) (Schmidt et al. 2014) and monocyte chemoattractant protein 1 (MCP-1) (Kiraly et al. 2017).

Ketamine effect ex vivo

So far, only two articles have been published describing the immunomodulatory effect of ketamine in human participants suffering from depression. Kiraly et al. (2017) performed a study in which 33 medication-free patients suffering from treatment-resistant depression received a single dose of intravenous ketamine (0.5 mg/kg). Next, 4 and 24 hours after drug administration blood samples were taken and Montgomery-Åsberg Depression Rating Scale (MADRS) assessment was performed. Before receiving ketamine, pro-inflammatory cytokines

IL-6 and G-CSF, GM-CSF, MCP-1 as well as one of isoforms of platelet-derived growth factor (PDGF-BB) were significantly elevated in comparison to healthy volunteers. After 4 hours, levels of IL-6 and G-CSF along with IL-1α and interferon gamma-induced protein 10 (IP-10, a chemoattractant for many different immune cells) decreased. Authors haven't found any changes in BDNF levels at any point of time. Changes in cytokine levels were not correlated with MADRS score. However, it was shown that patients responding to treatment with ketamine are characterized by lower level of basic fibroblast growth factor (FGF-2) and alpha subunit of interleukin 10 receptor (IL-10RA) after 24 hours (Kiraly et al. 2017).

Another randomized, double-blind control study was performed by Chen et al. (2018). 71 patients with TRD were assigned into one of the three groups according to received treatment: 0.5 mg/kg ketamine, 0.2 mg/kg ketamine or saline infusion. Proinflammatory markers including C reactive protein (CRP), IL-6 and TNF-α were examined at baseline and at 40 min., 240 min., day 3, and day 7 after drug infusion. MADRS was used for assessment of depressive symptoms across time. Results showed that decrease in IL-6 and TNF-α levels was visible after just 40 minutes. Specifically, levels of TNF-α were significantly lower in patients who received 0.5 mg/kg of ketamine. The decrease in TNF-α between baseline and 40 min. post-infusion was positively correlated with a decrease in MADRS scores across time in these patients (Chen et al. 2018). This is the first clinical study to support a positive correlation between changes in cytokine levels after ketamine infusion and improvements in depressive symptoms in patients suffering from TRD.

The anti-inflammatory effect of ketamine also was examined in different groups of patients receiving ketamine as an anesthetic or analgesic drug. Dale et al. (2012) performed meta-analysis in which the effect of perioperative ketamine administration on postoperative inflammation was assessed. Postoperative IL-6 concentrations (up to 6 hours after surgery) was set as an outcome. The meta-analysis showed a mean preoperative-postoperative IL-6 concentration difference which supported the hypothesis that ketamine has an anti-inflammatory effect (Dale et al. 2012). Another study was conducted in group of patients undergoing orthotopic liver transplantation (Yang et al. 2006). Ten patients were given intravenous bolus injection of ketamine in a low dose of 0.25 mg/kg followed by ketamine infusion at 0.5 mg/kg/h until the end of operation except in the anhepatic phase. Arterial blood samples were obtained at the start of surgery, 5 min. before the anhepatic phase, 5 min. before recirculation, 15 and 60 min. after recirculation and 0, 4 and 24 hours after operation, and serum levels of TNF-α, IL-6 and IL-10 were measured. The cytokines levels, especially of IL-6 and IL-10, increased significantly during anhepatic phase as compared with the baseline levels. The levels of TNF-α and IL-6 in patients who received ketamine before anhepatic phase and early post-operative period were significantly lower than in the control group. Serum level of IL-10, which is an anti-inflammatory cytokine, did not show any significant difference between the two groups (Yang et al. 2006).

Ketamine effect in vitro

Immunomodulatory effect of ketamine on human immune system was widely examined *in vitro* after stimulation of human blood cells with bacterial antigens in the presence of various ketamine concentrations in the cell culture. It has been demonstrated that ketamine at concentrations exceeding 50 μM significantly suppresses staphylococcal enterotoxin B (SEB)-induced TNF-α production (Kawasaki et al. 2001). Ketamine isomers at higher concentrations (more than 100 μM) significantly suppressed IL-6 and IL-8 production as well. No significant differences between the suppressive effects of S(+)-ketamine and R(-)-ketamine on pro-inflammatory cytokine production was seen (Kawasaki et al. 2001). Similar results were observed when human blood cells were activated with lipopolysaccharide (LPS) (Kawasaki et al. 1999). Meanwhile, Larsen et al. (1998) demonstrated that ketamine inhibits LPS-induced production IL-1β.

Immune changes caused by ketamine are not only prominent in the pro-inflammatory cytokine levels, but also in the number, ratio and activity of various immune cell populations – alterations in that area are seen and described in patients suffering from depression (Szałach et al. 2019). An increase in the number of cells involved in the innate immune responses, i.e. monocytes, macrophages and neutrocytes (Demir et al. 2015), as well as increased production of reactive oxygen species (ROS) has been reported (Wei et al. 2015. An increase in the ratio of $CD4^+$ T (Th) cells to $CD8^+$ cytotoxic (Tc) T lymphocytes, which are responsible by adaptive immune responses, has also been described (Zorrilla et al. 2001, Di Rosso et al. 2016). Additionally, an increase in the percentage of $CD4^+CD25^+$ T cells (activated cells) (Patas et al. 2018, Müller et al. 1993) with the accompanying decrease in the total number of regulatory T lymphocytes (Treg) (Toben and Baune 2015), which are responsible for suppression of immune responses, have also been observed.

Studies show that ketamine inhibits *in vitro* induced up-regulation of (integrin beta chain-2) (CD18) and L-selectine (CD62L) on the human neutrophils surface, both of which play a significant role in cellular adhesion (Weigand et al. 2000). Ketamine also caused a significant suppression of oxygen radical generation of isolated human neutrophils regardless of whether the racemic mixture or isomers were tested (Weigand et al. 2000).

Randomized, double-blinded clinical study performed by Zilberstein et al. (2002) examined the function of neutrophils *in vitro* in patients, who received ketamine as an additional anesthetic during cardiopulmonary bypass grafting. The addition of small-dose (0.25 mg/kg) ketamine reduced increased production of the superoxide anion (O_2^-) by neutrophils compare to patients who were not given ketamine. In addition, ketamine increased the percentage of neutrophils on postoperative days 2 to 6 (Zilberstein et al. 2002).

In another study, whole blood from healthy men as well as monocyte and promyelocyte line cells were incubated in the presence of ketamine in order to examine its influence on transcription factors, such as activator protein 1 (AP-1) or nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) (Welters et al. 2010), which not only regulate the immune response but also take part in processes responsible for synaptic plasticity (Albensi & Mattson 2000, Tuvikene et al. 2016). Ketamine inhibited both transcription factors in a concentration-dependent manner; these effects did not depend on opiate or NMDA receptors. Moreover, ketamine also reduced IL-8 production in whole blood and decreased surface expression of CD11b (adhesion molecule) and CD16 (molecule that takes part of antibody-dependent cell-mediated cytotoxicity) on neutrophils (Welters et al. 2010). Another study performed on human glioma cells confirmed that endotoxin-induced NF-κB activation can be suppressed by ketamine (Sakai et al. 2000).

It seems that ketamine also can influence T cells. In a study of Hou et al. (2016), peripheral blood mononuclear cells (PBMCs) isolated from whole blood samples of patients suffering from gastric cancer were incubated for 24 hours with different concentrations of ketamine (25, 50 and 100 μM). The ratio of $CD4^+/CD8^+$ T cells as well as the percentage of Tregs were significantly increased in the presence of rising concentrations of ketamine (Hou et al. 2016). Studies in healthy people show that ketamine may inhibit the phorbol-myristate-acetate (PMA) and ionomycin induced differentiation of Th0 lymphocytes, especially towards Th2 cells, which are responsible for regulating humoral responses (Gao et al. 2011). In addition, Braun and colleagues have shown that ketamine acts pro-apoptotic on lymphocytic and neuroblastoma cell lines in a concentration-dependent manner (Braun et al. 2010). Authors observed that S(+)-ketamine was less toxic to neuroblastoma cells but this difference was minor and therefore unlikely to be mediated via the NMDA receptor. These results showed that ketamine could induce programmed cell death of lymphocytes thus reducing T cell-dependent immune responses. At the same time, it points to its potential neurotoxic properties.

CONCLUSIONS

The mechanisms of antidepressant action of ketamine are still not fully understood. It seems that this phenomenon may be partly related to its immunomodulatory effect, especially its anti-inflammatory properties. Currently, there are only a few studies in the population of patients suffering from depression, especially taking into account the effect of ketamine on immune cells, which means that there is a further need for such studies.

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Łukasz P. Szałach, Katarzyna A. Lisowska & Wiesław J. Cubała: design of the study, manuscript writing, literature research and analysis, data interpretation

Jakub Słupski, Natalia Górska & Joanna Szarmach: literature research and data interpretation

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Correspondence:

Łukasz P. Szałach, MD
Department of Physiopathology, Medical University of Gdańsk
Ul. Dębinki 7, 80-210 Gdańsk, Poland
E-mail: lukasz.szalach@gumed.edu.pl