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ROLE OF COPPER AND KETAMINE IN MAJOR DEPRESSIVE DISORDER - AN UPDATE

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SUMMARY

Major depressive disorder is one of the most important psychiatric issues worldwide, with important prevalence of treatment-resistant depression (TRD). Non-monoaminergic agents are currently in the spotlight. Objective was to explore for information about mechanisms of action of ketamine, its connections with copper and possible importance for TRD treatment. There are at least few possible pathways for ketamine action in depression in which copper and other divalent ions may show a vital role. There is urgent need for more studies to gather information about correlation between ketamine, copper and antidepressive features of these agents.

Key words: *ketamine - copper - major depressive disorder - NMDA*

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INTRODUCTION

Major depressive disorder (MDD) is one of the key public health problems worldwide. It has a negative influence of personal life, work life, education also sleeping, eating habits, and general health (Hasin et al. 2005). About one third of depressed patients experience treatment-resistant depression (TRD) despite broad use of monoaminergic antidepressants (Ionescu et al. 2015). The definition of TRD varies worldwide – some authors define TRD as failure in achieving remission with two or more adequate antidepressant trials (McIntyre et al. 2014). The number of patients not able to have good response to conventional treatment makes need of non-monoaminergic antidepressive agents of prime importance.

KETAMINE

Ketamine, which is commonly used to induce anesthesia, is a dissociative agent used in psychiatry to trigger a fast antidepressive and antisuicidal effects (Larkin et al. 2011). What is more, ketamine shows a rapid antidepressant effect in patients with TRD (Diamond et al. 2014). In view of increased response compared to traditional antidepressant treatment, ketamine seems to be an auspicious drug in TRD with prevalent pharmacodynamic effect of the N-methyl-D-aspartate receptor (NMDAR) antagonism. Ketamine promotes fast antidepressant effect - it starts within hours of administration and is mediated by alteration in glutamate transmission (Berman et al. 2000). However, there are more suggested mechanisms of action highlighted later in this paper. (S) – ketamine has a much greater affinity for the NMDAR, and (R) – ketamine has a greater opioid receptors affinity (Morgan et al. 2012). One of the first clinical studies on ketamine's potential antidepressant effects was conducted over a decade ago. The study was double blinded, performed on eight patients during the depressive episode (seven suffering from MDD, one bipolar), randomized to receive either a subanesthetic dose of ketamine (0.5 mg/kg) or saline placebo. Four patients reported an antidepressant response to ketamine, evaluated a reduction of at least 50% on the Hamilton Depression Rating Scale (HAM-D) (Berman et al. 2000). Other researches iterated this ketamine-associated antidepressant reaction in clinical trials with single and repeated administrations under open-label, double-blind, placebo-controlled, and double-blind active comparator conditions via parallel arm or crossover treatment paradigms, but notably in treatment-resistant depression (Newport et al. 2015). Ketamine could be taken into consideration as the model glutamatergic agent, in particular because it is the best known and - to date - the most effective of the glutamatergic agents (Kishimoto et al. 2016). The molecular mechanisms underlying ketamine's antidepressant effects is being revealed by recent studies concerning the properties of ketamine and its metabolites (Lener et al. 2017).

COPPER

Copper (Cu) has been linked to mental disorders as for example autism and epilepsy. So far, researches measuring copper levels in patients' blood or hair with depressive disorder showed contrary results. To obtain a versatile approximation of the correspondence between body burden of copper and depressive disorder and examine the possible role of copper in mental health, there was a systematic review and meta-analysis performed. Gathered studies found that patients suffering from depression had higher blood levels of copper than the control group without depression (Ni et al. 2018).

NMDAR AND DIVALENT IONS

One of the most opulent ionotropic glutamate receptors in the human brain are the NMDARs (McBain et al. 1994). Binding the synthetic agonist NMDA, for instance glutamate, with the co-agonist glycine (Shleper et al. 2005) opens cation channel, which causes entry of calcium and sodium ions into the intracellular space. An excitatory postsynaptic potential could be induced by the activation of NMDAR by glutamate. Assembling evidence implies that the NMDAR has an important role in the treatment and neurobiology of major depressive disorder (Dang et al. 2014). Extracellular magnesium ions inhibit NMDARs, when negative membrane potential is attendant (Nowak et al. 1984). There are many elements such as magnesium and zinc ions, which are involved in the etiology of depression due to effect on biological pathways by modulating the NMDAR activity (Sowa-Kućma et al. 2013, Peters et al. 1987). Copper is another divalent ion having a major influence on NMDA receptor. It is reported to inhibiting NMDAR channels with the half maximal inhibitory concentration close to 20 mM. Although, the significance of values presented in the varied researches was rather wide and the molecular mechanism underlying inhibition of NMDAR activity is largely unclear (Trombley et al. 1996). Copper at doses >30mM prevalently blocks the NMDAR, however there are some studied that notifies that copper can facilitate this receptor at lower concentrations (Marchetti et al. 2014). This aspect may concern metal activity in synaptic and non-synaptic sites. The NMDARs undergo desensitization (Mayer et al. 1989) which leads to deplete toxic calcium overextension of cells during intervals of prolonged glutamate raisings. High glycine concentration is neurotoxic as it essentially slows desensitization kinetics, namely blocking glycine reuptake increases NMDAR mediated neuronal excitability (Chen et al. 2003). Some authors divulged that NMDARs are likewise adjusted by cellular prion protein (PrP^C) (Khosravani et al. 2008, You et al. 2012).

COPPER AND PRP^C

PrP^C is a molecule which includes copper binding sites with fluctuates varying from the femtomolar to the micromolar range (Jackson et al. 2001). Transformation of PrP^C into the abnormal β-sheet-rich scrapie conformation (i.e. PrP^{Sc}) has been affiliated with prion diseases (Kingsbury et al. 1983). Changes in PrP^C conformation is induced by binding of copper ions (Wong et al. 2003). This fact may have significant consequences for the regulation of NMDARs and progress of depression. Lack of PrP^C in mice causes depressive-like behavior (Gadotti et al. 2012). It can be cured with the NMDAR antagonists, which suggests that the absence of PrP^C may enhance the receptor's activity. You et al. (2012) suggested that chelation of copper ions adjusts native NMDARs in rat and mouse hippocampal neurons. What is more, glycine chelates of copper ions (Martin et al. 1971) by extension balance between agonist level and copper concentration is essential. Copper-dependent cooperation between the NMDAR subunit and PrP^C regulate receptor complex for glycine, conducting to non-desensitizing currents insignificant to glycine concentration (Słupski et al. 2018). Nonetheless, it is essential to remember that higher levels of copper are also toxic on account of the generation of free radicals (Simpson et al. 1988). Copper inflects also AMPA-receptors, which are glutamate-gated cation channels that intercede the majority of fast central excitatory transmission (Weiser et al. 1996) and calcium channels (Jeong et al. 2003).

FOCUS ON GLUTAMATE PATHWAY

Acute stress multiplies extracellular glutamate in the medial prefrontal cortex (mviaPFC) and hippocampus, and this has conducted to the presumption that glutamate-mediated excitotoxicity through activities at extrasynaptic N-methyl-D-aspartate receptors (NMDARs) is accountable for the atrophy of neurons in these CNS parts (Popoli et al. 2011). However, ketamine is an NMDAR channel blocker, it causes a paradoxical erupt of glutamate in the rodent PFC (Moghaddam et al. 1997). Dose-dependent increases in glutamate cycling by increased glutamate signaling is assisted by MRS studies in rodents and humans (Chowdhury et al. 2017). Essentially, these studies explain that the burst of glutamate is exponetial (within minutes) and evanescent, which is crucial to ration the excitotoxic effects of ketamine (Chowdhury et al. 2017, Moghaddam et al. 1997). The cellular trigger for this burst of glutamate is thought to involve blockade of NMDAR on tonic firing GABA interneurons, leading to disinhibition of glutamate transmission (Duman et al. 2016). Tonic activity of GABA interneurons would take into consideration removal of the Mg2+ block of the NMDAR channel, thus increasing vulnerability of these interneurons to ketamine occlusion in contrary to less active glutamate neurons. Recent slice electrophysiology studies show that ketamine incubation declines inhibitory postsynaptic currents (IPSCs) on hippocampal principle neurons, sustaining this theory (Widman and McMahon 2018). The muscarinic receptor antagonist scopolamine also causes rapid antidepressant actions in patient suffering from MDD. It is reliant on blockade of M1 receptors on GABAergic interneurons in the mPFC and disinhibition of glutamate transmission (Wohleb et al. 2016). Activity-dependent synapse formation is dependent on AMPAR activity, BDNF release, and stimulation of the mTORC1 signaling pathway, and it is caused by the ketamine-stimulated transient glutamate burst (Duman et al. 2016, Lepack et al. 2014, Li et al. 2010).

NMDA-INDEPENDENT MECHANISM OF ACTION

Another suggested pathway of ketamine action should be brought to light, as NMDA-independent action has been identified in animal study.

$G\alpha_s$ plasma membrane redistribution induced by ketamine increased pairing of $G\alpha_s$ and adenylyl cyclase and through this mechanism increased intracellular cyclic adenosine monophosphate (cAMP) (Czysz et al. 2014). Furthermore, enhanced intracellular cAMP increased phosphorylation of cAMP response element-binding protein (CREB), which respectively increased BDNF expression. Intracellular cAMP induced by ketamine remained increased even when NMDAR was not present, which indicates an NMDAR-independent effect (Wray et al. 2018). Besides, 10 μM of the ketamine metabolite (2R,6R)-hydroxynorketamine (HNK) which has no affinity to NMDAR also induced $G\alpha_s$ redistribution and increased cAMP. These results indicate a new mechanism of action in depression, mediated by acute ketamine treatment that may support ketamine's strong antidepressant effect. It seems that the translocation of $G\alpha_s$ from lipid rafts is a plausible characteristic of antidepressant action that might contribute to further diagnosing process or for drug development (Zanos et al. 2016).

DISCUSSION

Focusing on ketamine seems to be even more vital issue as ketamine may become a basis for transformative treatment with powerful impact on stigma of depression and may serve as a first agent from entirely new class of antidepressants. This approach is based on the hypothesis that both efficacy and tolerability can be better preserved with selectively targeting elements of ketamine's effects (Krystal et al. 2019). Ketamine and copper are both antagonists of NMDA receptor. Copper interacts also with PrP^C pathway (Wong et al. 2003). The evidence deliberated may testify the synergistic interaction between copper and ketamine pharmacodynamic activity being of particular importance in mood disorders. During the observation of copper serum levels in patients treated with ketamine important information about connections between NMDAR antagonistic agents and trace elements antagonistic to that receptor may be provided. It is essential to carry out further investigations referred to copper and ketamine in pharmacotherapy of depression - copper levels may be associated with the therapeutic response to ketamine in TRD and copper supplementation may increase the response rates in depressed subjects.

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Contribution of individual authors:

Jakub Słupski & Anita Słupska: manuscript writing, literature research, data analysis and interpretation.

Wiesław J. Cubała: design of the study, data analysis, manuscript redaction.

Łukasz P. Szałach, Adam Włodarczyk, Natalia Górska & Joanna Szarmach: literature research, data interpretation.

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