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Role of copper in depression. Relationship with ketamine treatment

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ABSTRACT

Depression is one of the most common psychiatric issues with a proportion of adults with major depressive disorder who fail to achieve remission with index pharmacological treatment. There are unmet needs in ADT focus on non-monoaminergic agents. Accumulating evidence suggests that the N-Methyl-D-aspartate receptor (NMDAR) plays an important role in the neurobiology and treatment of major depressive disorder. The role of copper ions in pathogenesis and treatment of depression is not fully clarified, however interaction between copper and NMDAR is of prime importance. Release of copper ions inhibits NMDAR and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor function thus protects neurons from glutamatergic excitotoxity. Abnormalities in glutamatergic transmission are the key of glutamate hypothesis of depression. Some authors revealed that NMDARs are also regulated by cellular prion protein (PrP^C) and indicated that interactions of copper, glycine and NMDARs subunits are vital for the regulation of the receptor. As NMDAR antagonist ketamine is known to produce rapid antidepressive effect, observation of copper serum levels in patients treated with ketamine may provide important information about connections between NMDAR antagonistic agents and trace elements antagonistic to that receptor. It is necessary to carry out further studies related to copper and ketamine in depression treatment.

Hypothesis

Depression is one of the most common psychiatric issues with a proportion of adults with major depressive disorder (MDD) who fail to achieve remission with index pharmacological treatment [1,2]. Trace elements such as copper are involved in the function and homeostasis of serotonergic, noradrenergic, dopaminergic, glutamatergic and GABAergic systems, which are closely connected to depression. There are unmet needs in contemporary antidepressant treatment and the focus on non-monoaminergic agents is of major concern. Numerous studies demonstrated ketamine use in short- and long-term MDD treatment. However, only a proportion of subjects respond to ketamine treatment and the factors determining the response are to be established [3].

The role of copper ions in pathogenesis and treatment of depression with ketamine is not fully clarified. However, interaction between copper and N-Methyl-D-aspartate receptors (NMDAR) is of prime importance [4].

Copper

Copper is an essential trace metal in human body, as it is a cofactor for numerous enzymes of biochemical processes, such as: erythropoiesis, metabolism of cholesterol, glucose and iron, cellular respiration or hormone synthesis [5]. Main exogenous source of copper in human is diet. Copper consumption is provided by legumes, potato and potato products, beef, nuts and seeds, chocolate and shellfish [6]. Daily intake is roughly 1.5 mg and depends on dietary copper content and regional location [7]. Bioavailability varies from 60 to 70% and is inversely correlated with intake. The highest tolerable limit is reported to be up to 10 mg per day – with no liver impairment present [8]. Absorption is dependent on chemical form of copper, competitive antagonism by other metals (zinc, iron, selenium, cadmium), and malabsorption syndromes [9]. In healthy human ceruloplasmin (serum enzyme) bounds 96% of the total serum copper, the rest is associated to albumin, transcuprein, and copper–amino acid complexes [10]. Liver, brain, kidney, and heart contain the highest copper concentrations which vary with gender and age [11].

Copper is transported from the blood circulation into the brain via the blood-brain barrier (BBB) and blood-CSF barrier (BCB) [12]. BBB acts as the major transporting route for the copper into the brain parenchyma, while the BCB mainly maintains the Cu homeostasis in the brain by exporting excess copper from the CSF to the blood. The uptake

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of copper into the cells is mediated by two transporter proteins: Cu transporter 1 (Ctr1) and divalent metal transporter 1 (DMT1) [13]. Copper content and spatial distribution in the brain are uneven [14] and change during the development, with age and in neurodegenerative conditions [15]. Copper can be found throughout the brain, mostly in the cerebellum, hippocampus, basal ganglia, numerous synaptic membranes, cell bodies of cortical pyramidal and cerebellar granular neurons [16]. Copper deficiency as well as excess of copper can seriously affect brain functions. Accordingly, this organ possesses adequate mechanisms to regulate its copper metabolism, in which astrocytes are considered as important regulators [17].

Also, central nervous system development and functioning is strongly copper-dependant [17]. Processes in which copper plays important role are, among others: signal neurotransmission, cognitive, learning and memory processes, neurogenesis, synaptogenesis, neuron growth [18,19], functioning of the NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), gamma-aminobutyric acid (GABA), kainate, and glycine receptors [20], catecholamine metabolism, antioxidant processes and regulation of immunological system [21].

Taking monoaminergic approach on depression, copper must be mentioned for its role in conversion of dopamine to norepinephrine [22]. Dopamine to norepinephrine conversion is copper dependent as copper ions interact with dopamine β-hydroxylase [23].

Copper concentration plays an important role in the oxidative stress processes, has influence on catalytic and structural properties of some antioxidant enzymes, what may be one of the main cause of depression development [24,25]. Many studies suggest that induction of oxidative stress pathways in depression is accompanied by activation of the inflammation [26]. The role of ceruloplasmin in depression has not yet been established but depression is not a prevailing presentation in diseases where ceruloplasmin levels are found to be minimal [27,28]. Elevated serum level of ceruloplasmin may be an evidence of the potential role of copper ions in mood disorders [29]. Concentration of copper ions in the extracellular space is usually low; however it can raise even dozens of times, what may have important biological significance. Release of copper ions inhibits NMDAR and AMPA receptor function thus protects neurons from glutamatergic excitotoxicity [30]. Abnormalities in glutamatergic transmission are the key of glutamate hypothesis of depression [31].

NMDA receptor

The N-methyl-D-aspartate receptors (NMDARs) are one of the most abundant ionotropic glutamate receptors in the mammalian brain [32]. Binding glutamate or the synthetic agonist NMDA with the co-agonist glycine [33] opens cation channel, which mediates entry of calcium and sodium ions into the intracellular space. The activation of NMDAR by glutamate induces an excitatory postsynaptic potential (EPSP).

Accumulating evidence suggests that the NMDAR plays an important role in the neurobiology and treatment of major depressive disorder [34]. NMDARs are inhibited by extracellular magnesium ions when negative membrane potential is present [35]. Magnesium may be involved in the etiology of depression due to its effect on biological pathways associated with the genesis of depression, including its action as an NMDA channel blocker, in which it blocks the entry of calcium in the neuron and can thus prevent cell death [36,37].

Zinc ions also bind to the NMDARs to modulate its activity [38]. The combination of NMDA subunits influences inhibition of the NMDA receptor by zinc, as the receptor subunits differ in their affinity to the metal ion. The NR2A subunit has a much higher affinity than the NR2B subunit. Receptors containing NR1/NR2A subunits can be inhibited by a high-affinity, voltage-independent mechanism as well as by a low affinity, while receptors that contain NR1/NR2B subunits are inhibited only by moderate-affinity, voltage-independent blocking [39].

Another divalent ion being the important NMDA receptor modulator is copper, which has been reported to inhibit NMDAR channels with the half maximal inhibitory concentration close to 20 mM. However, the range of values reported in the different studies was rather wide and the molecular mechanism underlying inhibition of NMDAR activity is largely unclear [40,41]. Some data indicates that copper can facilitate the NMDAR at lower concentrations than those required for blocking it, although at doses > 30 mM the blocking effect always prevails [4]. This mechanism may affect metal activity in synaptic and non-synaptic sites.

The NMDARs undergo desensitization [42] leading to diminish toxic calcium overload of cells during periods of prolonged glutamate elevations. High glycine concentration is neurotoxic as it substantially slows desensitization kinetics, namely blocking glycine reuptake increases NMDAR mediated neuronal excitability [43]. Khosravani et al. [44] and You et al. [45] revealed that NMDARs are also regulated by cellular prion protein (PrP^C).

PrP^C and copper

PrP^C is a protein which contains copper binding sites with affinities varying from the femtomolar to the micromolar range [46,47]. Conversion of PrP^C into the pathological β-sheet-rich scrapie conformation (i.e. PrP^{Sc}) has been associated with prion diseases [48–50]. Binding of copper ions induces changes in PrP^C conformation [51], what may have important implications for the regulation of NMDARs and development of depression. Lack of PrP^C in mice manifests in depressive-like behaviour [52]. This behaviour can be treated with the NMDAR antagonists, suggesting that receptor's activity may be enhanced by the absence of PrP^C.

You et al. [45] indicated that chelation of copper ions regulates native NMDARs in rat and mouse hippocampal neurons. Moreover, glycine chelates of copper ions [53], thus balance between agonist concentration and copper levels is vital. Copper-dependent interactions between PrP^C and the NMDAR subunit regulate receptor complex for glycine, leading to non-desensitizing currents irrelevant to glycine concentration. However, it is important to remember that higher levels of copper are also toxic due to the generation of free radicals [54]. Not only NMDARs are modulated by copper ions but also AMPA receptors (AMPARs), that are glutamate-gated cation channels that mediate the majority of fast central excitatory transmission [55], and calcium channels [56,57] Fig. 1.

Ketamine

Ketamine is a dissociative, anaesthetic agent used in psychiatry to promote fast-acting antidepressant and antisuicidal effects [58]. Ketamine exhibits a rapid antidepressant action in patients with treatment-resistant depression [TRD] [59,60]. Considering increased response compared to conventional antidepressant treatment, ketamine seems to be a promising drug in TRD with predominant pharmacodynamic effect of the NMDAR antagonism. Ketamine has rapid antidepressant effect, which occur within hours and is mediated by changes in glutamate transmission [61,62]. It was reported that brain-derived neurotrophic factor (BDNF) levels were reduced in major depressive disorder patients [63]. The rapid antidepressant effect of ketamine is related to the up-regulation of BDNF and the consequent potentiation of synaptic plasticity [64]. This may be related to the combination of AMPAR activation and NMDAR antagonism by ketamine [36].

Ketamine also provokes activation of dopamine release [65] and acts as a weak agonist at mu opioid receptors [66]. The neurochemical properties of ketamine depend on the isoform present in a interaction with the receptor. (S) – ketamine has a much greater affinity for the NMDA-receptor, and (R) – ketamine has a greater opioid action [67]. Animal studies indicated that copper may inhibit the binding of agonistic ligands to the opioid receptors, including mu receptor [68].

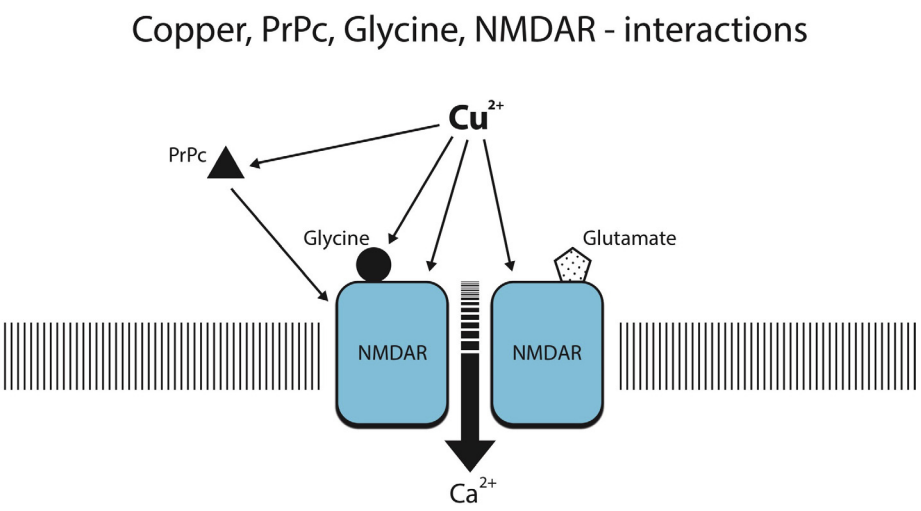

Fig. 1. Release of copper ions inhibit NMDAR and AMPA receptor function thus protect neurons from glutamatergic excitotoxity [30]. Binding of copper ions induces changes in PrP^C conformation [51]. Moreover glycine chelate copper ions and copper-dependent interactions between PrP^C and the NMDAR subunit regulate receptor complex for glycine, leading to non-desensitizing currents irrelevant to glycine concentration [53].

Discussion

Ketamine and copper directly interact with NMDAR as antagonist. Copper manifests also indirect way of interaction throughout PrP^C pathway [51]. The studies presented above concluded that the NMDA/glutamate pathway is an important mechanism in anti-depressant effects of copper and ketamine [20,30,31,59–62]. The evidence discussed may indicate the synergistic interaction between copper and ketamine pharmacodynamic activity being of particular importance in mood disorders. Observation of copper serum levels in patients treated with ketamine may provide important information about connections between NMDAR antagonistic agents and trace elements antagonistic to that receptor. It is necessary to carry out further studies related to copper and ketamine in depression treatment.

Conclusion

We hypothesize that copper levels may be associated with the therapeutic response to ketamine in TRD and copper supplementation may increase the response rates in depressed subjects. A proof of concept study of a copper supplementation in TRD subjects treated with ketamine might be performed in order to test the hypothesis.

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Conflict of interest

Dr. Cubała has received research support from Actavis, Alkermes, Allergan, Auspex, Biogen, Bristol-Myers Squibb, Cephalon, Eli Lilly, Ferrier, Forest Laboratories, Gedeon Richter, GW Pharmaceuticals, Janssen, KCR, Lundbeck, Orion, Otsuka, Sanofi, and Servier; he has served on speakers bureaus for Adamed, Angelini, AstraZeneca, Bristol-Myers Squibb, Celon, GlaxoSmithKline, Janssen, Krka, Lekam, Lundbeck, Novartis, Orion, Pfizer, Polfa Tarchomin, Sanofi, Servier, and Zentiva; and he has served as a consultant for GW Pharmaceuticals, Janssen, KCR, Quintiles, and Roche.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.mehy.2018.07.012.

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