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Glutamatergic hyperfunctioning during alcohol withdrawal syndrome: Therapeutic perspective with zinc and magnesium

Pedro Luis Prior [a], José Carlos Fernandes Galduróz [b,*]

[a] Department of Medicine, Federal University of São Paulo, Brazil
[b] Department of Psychobiology, Federal University of São Paulo (Universidade Federal de São Paulo), R. Napoleão de Barros, 925, Vila Clementino 04024-002, São Paulo, SP, Brazil

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ABSTRACT

It is known that the glutamatergic pathways are hyperfunctioning during alcohol withdrawal syndrome. It has been demonstrated that hyperfunctioning of this system causes a great damage to the superior cortical activity, the ability to concentrate and the control of impulses. Recent studies show that the cations zinc and magnesium modulate the glutamatergic function, reducing it to non-toxic levels, yet not reducing it to the point of depriving this neurotransmitter of its normal activity. New perspectives of treatment focus on the modulation of this system, having, as a result, reestablishment of impulse control abilities, damage prevention to the hippocampus and the amygdala and prevention of future relapses.

Introduction

The cognitive impairments observed in alcohol dependence syndrome are well documented in several studies [1–4]. Some functions, such as verbal fluency, working memory and frontal functions are so severely impaired that they can be compared with the cognitive impairment caused by Alzheimer's disease [1]. Several relapses and the consequent withdrawal syndromes might cause more intense cognitive impairment. The reason why it happens has not been clearly established.

On the other hand, it is known that glutamatergic pathways are hyperfunctioning during alcohol withdrawal syndrome, especially through NMDA receptors, which are responsible for maintaining, in normal conditions, individual ability of performing complex planning, task-resolution performance and behavior restraint. This hyperactivity stemming from NMDA receptors causes great calcium influx, increasing the activity of nitrous oxide synthase (one of the main enzymes activated by transduction), which in turn increases the excitotoxic activity and accelerates the production of free radicals of oxygen, and the resulting in irreversible neural death [5–7]. It has been proved that the hyperfunctioning of the glutamatergic system causes great damage to the superior cortical activity, the ability to concentrate and the control of impulses [6–8].

Recent studies show that low doses of zinc and magnesium cations modulate the glutamatergic function, reducing it to non-toxic levels, yet not reducing it to the point of depriving this neurotransmitter of its normal function [9,10].

Zinc

Zinc (Zn) is an important body element which, in the central nervous system (CNS), is concentrated mainly in the hippocampus, in the subiculum of the dentate gyrus and in the accessory olfactory bulb [11]. It is found mainly in glutamatergic neurons, in specific pathways whose nuclei are in the putamen, caudatum and amygdala, with efferences to the cortex, striatum and hippocampus [12].

Fig. 1 shows its main metabolic functions: (1) blockage of glutamate on the synaptic cleft, (2) storage of glutamate in the presynaptic neuron, so as to regulate its distribution, and (3) action on several pre- and post-synaptic intracellular proteins, such as enzymes, second messengers and transcription factors which favor the synthesis of glutamatergic receptors (NMDA and KA), growth factors and mitosis inducers (neurogenesis) [12–14]. Fig. 2 shows possible roles of zinc in reducing symptoms in withdrawal.

Magnesium

Magnesium is the fourth most abundant ion in human metabolism, and has particular importance in the central nervous system as a cofactor in many enzymes, in the DNA synthesis, as inhibitor of voltage-dependent calcium channels and the release of neurotransmitters [6,15]. Its role is as a negative modulator of the NMDA receptors, competing with glutamate in its binding site and inhibiting the nitrous oxide synthase enzyme, important in the neural transmission in glutamatergic pathways [16,17].

Magnesium can provoke a modest stimulation for the gabaergic system and is capable of reducing the oxidative stress in the brain, lowering the concentration of neurotoxic substances stimulating

* Corresponding author.
E-mail addresses: pedrolsprior@uol.com.br (P.L. Prior), galduroz@psicobio.epm.br (J.C.F. Galduróz).

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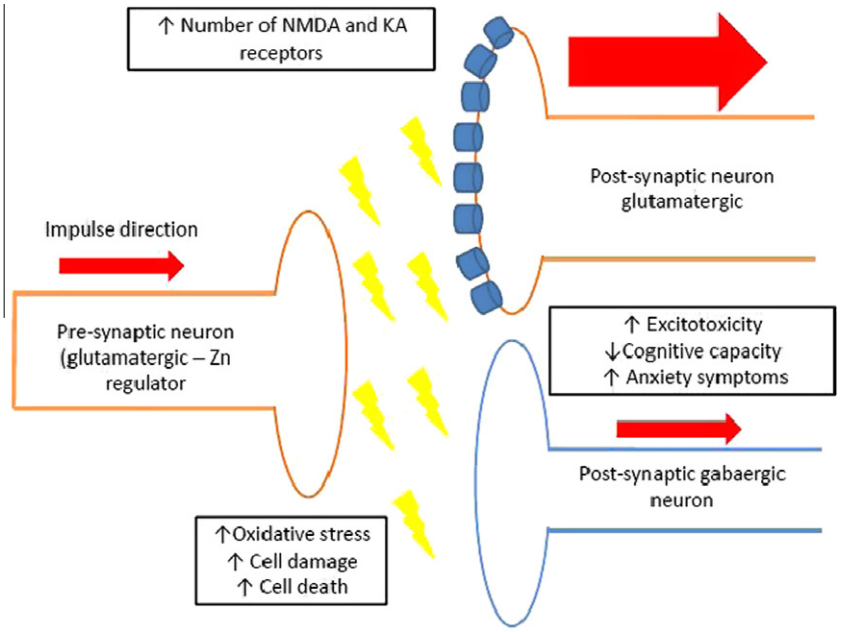

Fig. 1. Neurochemical effects of the lack of zinc in the central nervous system, mimicking the abstinence-like syndrome effects on neural function. As described, lack of zinc may cause increase and lack of control in cellular oxidative activity, increase in glutamatergic activity, through NMDA receptors [12,14].

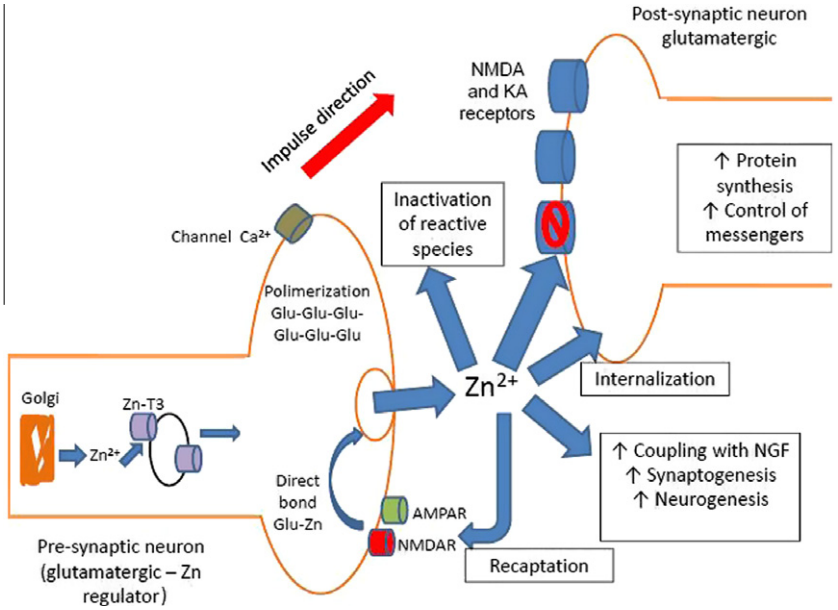

Fig. 2. Possible effects of zinc supplementation, according to evidence.

both synaptogenesis and neurogenesis in the limbic cortex, acting as an ameliorator in mid-crisis alcohol abstinence [5–7].

The role of magnesium would stand out not only in the NMDA receptor, but also in the inhibition of the NO-synthase and calcium dependent channels, lowering effects for action potential firing, also mitigating certain symptoms (as seen in Fig. 3).

Hypothesis

Although the relapse during the treatment of alcoholism is seen as inevitable by some authors [18], the damage caused to neurons by excessive stimulation by glutamate and lack of inhibition of the NMDA receptors may be decisive factors for the maintenance of dependence in the long term. Therefore, the use of zinc and magnesium to treat abstinence syndrome is a hypothesis worth considering.

New perspectives

The unstable mechanisms of action of pure NMDA receptors' agonists and antagonists have shown irregular and conflicting results in literature, which shows, as a consensus, that antagonists are effective in rats and humans in relation to alcohol and nicotine dependence [19,20], and agonists mainly in cocaine dependence. Neither has apparent effect in opioid dependence.

Even though many different symptoms are involved in each substance's pathway targets, we believe that the NMDA receptors' effects are a common factor in developing tolerance, dependence

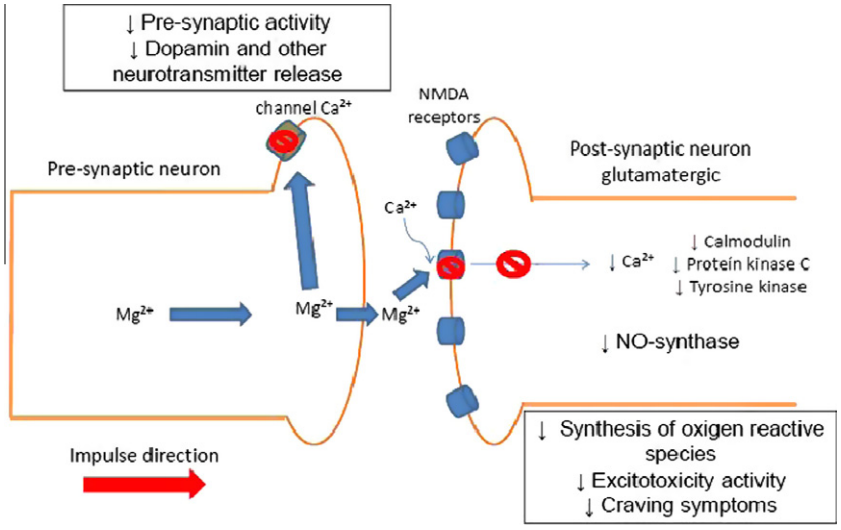

Fig. 3. Possible effects in magnesium supplementation (Mg) [9,10].

and craving symptoms, and the effects of rapid inhibition and slow potentiation of the glutamatergic system by zinc and magnesium synthesize the beneficial effects of the chemical compounds described above, without their side effects and downsides

Both ions (magnesium and zinc) have the great advantage of inhibiting immediate excitotoxic activity of glutamate in its ionotropic receptor, and, at the same time, stimulating metabolic changes in protein synthesis and second messengers, which will stabilize and adapt glutamatergic activity to its normal and necessary rate. This shows their regulatory nature in the central nervous system.

It is suspected that, since both compounds act in different sites inside and outside neurons, and by different mechanisms in the same pathways, one can potentialize and increase the other's effect, with very few registered side effects (mainly diarrhea) and low costs.

Conflict of interest

We declare we have no conflict of interest.

Acknowledgments

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