Magnesium and Zinc Involvement in Tobacco Addiction

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Abstract
This paper is a review regarding magnesium and zinc influence on smoking and tobacco addiction. Magnesium and zinc are two very important bivalent cations involved in different functions of central nervous system. There are different mechanisms by which magnesium can decrease the nicotine addiction. Magnesium decreases the dopamine release and the NMDA receptor stimulation by glutamate (two essential steps in the development of nicotine addiction). This cation also inhibits the synthesis of substance P and nitric oxide, others important neurotransmitters involved in addiction. Magnesium may decrease the nicotine effect on GABA synthesis and could reduce also NPY involvement in nicotine addiction. Zinc also reduces the glutamatergic brain systems activity and modulates the nicotinic receptors activity from brain. The hypomagnesemia favours the development of tobacco addiction. The magnesium treatment can be beneficial for reducing the smoking and nicotine addiction in heavy smokers. By increasing the magnesium concentration we can moderately improve the stimulation of the reward system and can reduce the needs of stimulation by nicotine or by others addictive substances. The treatment of intracellular and plasma magnesium deficit could be way to minimize the development of tobacco smoking and nicotine addiction.

Keywords: Nicotine addiction; Magnesium; Zinc; Tobacco smoking

Introduction
Tobacco is addictive drug and use enhances the mortality. There are a lot of smoking-related diseases. Cigarette smoking is a prevalent addiction and probably the most preventable cause of death. The key substance for tobacco dependence is the nicotine. Nicotine acts as an agonist of nicotinic receptors. Withdrawal syndrome is developed after smoking cessation and is evident by physical dependence [1]. Nicotine acts as an agonist at nicotinic receptors. Withdrawal syndrome is developed after smoking cessation and is evident by physical dependence [1].

There are very few studies about the divalent cations influence on nicotine action and on tobacco smoking. From about 24000 articles and reviews indexed in data bases on smoking cessation only less than 10 are focused on magnesium, zinc, copper and other bivalent cations influence on nicotine addiction or tobacco smoking. Magnesium and zinc are two important bivalent cations from human body. Magnesium is the second most abundant intracellular bivalent cation. This cation plays an important role in central nervous system. The magnesium disbalances are involved in various pathological states such as attention deficit hyperactivity disorders [2], ischemic brain injury [3], seizures [4] and others. There are about 300 zinc dependent enzymes and also a lot of magnesium dependent enzymes. Zinc ions have been found in neurons, in neuroglia. The highest zinc concentrations in CNS are in the limbic system and in the cerebral cortex [5]. In some synapses, zinc is localized in synaptic vesicles. This cation provides an important antioxidant activity [6]. Both magnesium and zinc modulate the presynaptic release, the agonist induced response at the level of some receptors (human glycine receptor, P2X receptor) [7,8] and also several ion-gated ion channels [9]. Zinc-containing neurons are mainly located in the cerebral cortex and in the amygdala [10]. Zinc-containing fibers connect these regions to brain areas involved in addiction (limbic system, striatum and others) [1]. This cation is involved in cognition [11] appetite regulation [12] cortical plasticity [13] and other functions. Both cations have selective transporters in brain [14,15]. Both magnesium and zinc modulate the presynaptic transmitters release, the agonist induced response at the level of some receptors [16] and also several ion-gated ion channels [10]. Magnesium is used in the treatment of neurosis, in eclamptic and pre-eclamptic states, and also in traumatic and ischemic brain injury. This cation is recommended to be associated to antidepressant drugs in the treatment of major depression.

Magnesium
The key point for addiction is the increase of dopaminergic and glutamatergic activity in the reward system. Drug self-administration is regulated by nucleus accumbens dopamine levels [17]. The serotonin, opioids, GABA system. Nitric oxide substance P is also involved. The brain area involved in addiction (locus coeruleus, nucleus accumbens, ventral striatum) have nicotinic receptors [18]. The transporters of neurotransmitters are also involved in addiction. The inhibition of dopamine transporter decreases in cocaine self-administration [19].

All addictive drugs increase the dopamine level in nucleus accumbens. This is an essential step in development of addiction [20]. The presynaptic nicotinic receptors stimulation increases the neurotransmitters release [21]. After brain presynaptic nicotinic receptors activation, nicotine increases the dopamine release and the dopamine concentration. The mesocorticolimbic and nigrostriatal dopamine is involved in the reward. Some nACh receptor antagonists blocked the reward stimulating effect of nicotine [22]. The chronic nicotine administration in mice induces changes in dopaminergic brain systems and is thought to lead to compulsive nicotine use. The nicotine increases the firing rate and the phasic burst of midbrain dopaminergic neurons [23]. Increased extracellular striatal dopamine levels have been observed after nicotine administration [24]. The NMDA receptors and nicotinic cholinergic receptors have a cooperative of contribution in the control of presynaptic dopamine release [25]. An evidence of major dopamine involvement in the tobacco addiction is the effect.

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Magnesium reduces the NMDA receptors activity by blocking for the antiaddictive action. Mg\(^{2+}\) exhibits anxiolytic-like activity like to the tobacco use. The anxiolytic effect of a substance could be important reduction of the development of nicotine addiction and for diminishing in activity of NMDA receptors. Consequently the reward system is linked with NMDA receptors. In this way, it appears as an increase the blocking effect of endogenous magnesium on calcium channels inhibition depends to magnesium concentration. Stimulation of N\(^3\) channels coupled to NMDA receptor is voltage dependent [30]. This effect on the NMDA receptors response to agonist stimulation. dopamine release induces an increase in the calcium entry into neurons and also increases glutamate release [29]. The NMDA receptors stimulation increases the dopamine release. The activation of nACh receptors has a permissive effect on the NMDA receptors response to agonist stimulation.

**Experimental evidences**

Magnesium is a potent inhibitor of the NMDA receptor complex. The magnesium reduces the NMDA receptors activity by blocking NMDA receptor coupled calcium channel. Mg\(^{2+}\) blocking action of ion channels coupled to NMDA receptor is voltage dependent [30]. This inhibition depends to magnesium concentration. Stimulation of N\(^3\) pre-synaptic nicotine receptors by nicotine may decrease or suppress the blocking effect of endogenous magnesium on calcium channels linked with NMDA receptors. In this way, it appears as an increase in activity of NMDA receptors. Consequently the reward system is stimulated. We consider that the reduction of dopamine release and glutamate NMDA receptors activity is the main way for magnesium reduction of the development of nicotine addiction and for diminishing the tobacco use. The anxiolytic effect of a substance could be important for the antiaddictive action. Mg\(^{2+}\) exhibits anxiolytic-like activity like to antagonists of NMDA receptors [31].

The GABA-ergic system activity and the ration between glutamate and GABA at the level of reward system is important in nicotine addiction. Activation of NMDA receptors blocks GABA-ergic inhibition [32]. Nicotine diminishes GABA synthesis and release in some brain areas by stimulation of nicotine presynaptic receptors. Magnesium may decrease the nicotine effect on GABA synthesis. By reducing the NMDA receptors activation, magnesium can enhance the gabaergic system activity and can reduce the nicotine dependence. Mg\(^{2+}\) may enhance some of the GABA effects and diminishes some effects of the excitatory aminoacids in drug dependences [33,34]. Magnesium decrease the substance P synthesis in by this way can reduce the nicotine addiction [35]. Another way by which magnesium can impair the nicotine addiction is the inhibition of nitric oxide synthesis. NO is involved in the mechanism of nicotine addiction. The mechanism of reinforcing properties of addictive substances (including nicotine) involves brain nitric oxide [36,37]. The experimental pretreatment with inhibitors of NO synthase blocked the nicotine induced increase of dopamine synthesis and dopamine neurons activity [37]. Magnesium inhibits the synthesis of nitric oxide [38,39] and by this way can reduce the nicotine dependence and the tobacco use. In magnesium deficient animals the nitric oxide synthesis is increased [40].

Neuropeptide Y also plays a role in nicotine addiction [41]. The increase of extracellular dopamine concentration in nucleus accumbens is involved in mediating of addictive drugs action. The NPY is synthesised in nucleus accumbens and has receptors in this brain area. The NPY administration increased the extracellular level of nucleus accumbens dopamine [42]. Nicotine at concentrations similar to those determined in heavy smokers blood plasma stimulates some NPY neurons [43]. Substances which reduced the NPY brain action diminished the dependence to other addictive compounds. The antagonists of Y\(^5\) NPY receptors (like L-152804) attenuated cocaine self administration in mice [44]. Magnesium inhibits the responses to NPY in different tissues [45] and could reduce also NPY involvement in addiction.

**Human and epidemiological evidences**

The intensity of nicotine addiction in adult heavy smokers (i.e. the number of daily smoked cigarettes) was significantly decreased after Mg\(^{2+}\) administration for 4 weeks [46]. In our study, the daily administration of Magne B\(_3\) (186 mg magnesium lactat+936 mg magnesium pidolate/day p.o. 4 weeks) clearly reduced the number of smoked cigarettes and the Fagerstrom score. This study was not a randomized controlled study.

The nicotine addiction and the tobacco smoking have an high prevalence in schizophrenia and bipolar disorders [47,48]. In the bipolar disorder peoples, tobacco smoking is prevalent [49]. In the both psychiatric disorders the patients have a lower intracellular magnesium and plasma zinc concentrations [50]. The incidence of major depression the neuroses and the neuroirritability are higher in adult smokers than in non-smokers [51]. In patients with major depression the plasma level of magnesium is decreased compared to normal adults [52,53]. The anxiety, major depression and panic disorders are associated with tobacco use. The vulnerability to addiction is increased by stress. The tobacco smoking is higher in stressed adults. The stress favors the loss of magnesium and a low magnesium concentration. A magnesium deficit is involved in some clinical symptoms of drug dependencies. This fact could be involved in the development of tobacco addiction.

There are genetic and non-genetic factors involved in the vulnerability to addiction. The genetic vulnerability to addiction appears to be correlated to a hypodopaminergic dysfunctional state of reward system [54]. We think that between the non-genetic factors the magnesium deficit and low magnesium concentration plays an important role. Now the varenicline is the most used drug for the treatment of nicotine addiction but behavioral changes were reported after this drug [55]. Magnesium association could by a good way for increasing the efficacy of this treatment. This cation do not induces psychiatric disorders. There are evidences that magnesium level is partially controlled by transporters. Magnesium was transported from the cation diffusion facilitator (CDF) family are a role in zinc efflux or intracellular sequestration and were cloned as a result of conferring intrinsic protein 2, glutamine synthetase and others) [58]. Most genes from the cation diffusion facilitator (CDF) family are a role in zinc efflux or intracellular sequestration and were cloned as a result of conferring resistance to transition metal toxicity [59]. The genetic differences in trace elements regulation and trace elements influences on genes. Several genes have been reported to be up-regulated by Cu, (e.g., plasma intrinsic protein 2, glutamine synthetase and others) [58]. Most genes from the cation diffusion facilitator (CDF) family are a role in zinc efflux or intracellular sequestration and were cloned as a result of conferring resistance to transition metal toxicity [59]. The genetic differences in trace elements regulation could be involved in the differences in the vulnerability to addictions.
There are many proposed means for reduction of tobacco dependence and smoking. The therapeutic means can be divided in two groups:

1. Substances which act at the dopamine receptors level
2. Drugs which act before the dopamine stimulation of dopamine receptors

Magnesium is a substance which acts surely before the dopamine receptors stimulation but not only. Different authors consider that the reduction of dopamine receptors function (antagonism or desensitization) is crucial to reduce or to abolish nicotine dependence [60]. In this direction are the action of bupropion and veranclire. Bupropion treatment diminished the dependence producing effects of nicotine and also the cognitive effects related to nicotine addiction [61]. Magnesium decreased the nicotine addiction and the tobacco smoking [46] but unlike bupropion magnesium increases the memory [62]. The major target for magnesium administration is the reduction of nicotine dependence.

**Action on the Reward System**

The action on the reward system is essential for a substance which can reduce the intensity of addiction. Studies performed by conditioned place preference paradigms in rats showed that nicotine induced stimulation of the reward system. Nicotine induces the place preference and mecamylamine (a nicotinic receptor antagonist) induced a clear place aversion [63]. Nicotine 0.2 mg/kg attenuates the place aversion induced by naloxone 0.5 mg/kg s.c. in morphine treated rats [64]. This nicotic effect is inhibited by a non-selective dopamine receptor antagonist, haloperidol. The existing data involve the dopamine in the nicotine influence on place preference. Calcium channels blockers (e.g. nimodipine) attenuate the reinstatement of nicotine induced place preference [65]. Mg²⁺ (a partial antagonist of Ca²⁺ entrance through membrane channels) may decrease the nicotine can also decrease the nicotine effect on reward system. There are experimental studies in which magnesium stimulated the place preference [66, 67].

In our study, magnesium (10 mg/kg) stimulated the place preference in naïve rats but reduced the place preference increasing effect of morphine. MgCl₂ decreased the aversive effect of naloxone 2 mg/kg [68]. In cocaine-dependent rats, MgCl₂ may replace cocaine for self-administration. The rats were kept in this way for 10 days without cocaine [67, 68, 69]. Never magnesium administration regardless the dose or the duration of treatment not induced dependence.

In chronic smokers (more than 10 cigarettes/day), the plasmatic level of magnesium was significantly decreased compared with non-smoking healthy subjects [46, 70]. By increasing the magnesium concentration we can moderately improve the stimulation of the reward system and can reduce the needs of stimulation by nicotine or by others addictive substances. Other target of magnesium is the reward before the tobacco smoking start.

**Zinc**

Zinc can influence the nicotinic receptors stimulation. There are data that showed that the alpha3beta2 nicotinic receptors are inhibited by zinc and alpha4beta2, alpha2beta4 receptors exhibited a biphasic modulation by zinc [71]. The acetylcholine induced desensitization is not affected by zinc. This cation potentiating the effects of alpha4beta4nicotinic receptors stimulation in the brain. This effect is dependent to time of nicotine exposure and of the nicotine concentration [72].

The influence of the smoke on the zinc concentration in the blood is not clear. In some studies, the zinc level in smokers serum was higher than in non-smokers blood. In other clinical tests, no tobacco smoking impact on the plasma level of zinc [73]. Nicotine perfusion in rats doesn’t changes the zinc plasma level [74]. Zinc and magnesium level decreases in the hair of tobacco smokers [75]. An excessive urinary loss of zinc was observed in drugs addicts [76]. Because the copper excretion is diminished in these peoples, the ratio between zinc and copper is changed. This change could be involved in the development of addiction.

**Conclusions**

A plausible hypothesis is that the low levels of serum magnesium contribute to the emergence of nicotine addiction. We believe that an increase of intracellular and extracellular magnesium concentration can reduce the development of nicotine addiction and tobacco smoking. Some clinical data indicated that magnesium treatment is beneficial for reducing the smoking and nicotine addiction. The treatment of intracellular and plasma magnesium deficit could be way to minimize the development of tobacco smoking. Zinc may be also a modulator of the intensity of tobacco addiction. The treatment of hypomagnesemia in young people could reduce initiation of smoking.

**References**


