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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 decrease the dopamine release and the NMDA receptor stimulation by glutamate (two essential steps in the devolopment of nicotine addiction). This cation also inhibits the synthesis of substance P and nitric oxide, others important neurotransmiters 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 favorises 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 deaths. 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 abundent 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 defficit 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 has 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 transmitters 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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of L-745870 a competitive antagonist of D4 dopamine receptors. This antagonist significantly attenuated the reinstatement of nicotine-seeking induced by nicotine priming [26]. The presynaptic nicotinic receptors stimulation increases the release of dopamine and norepinephrine. An increasing magnesium concentration reduces the nicotine stimulated norepinephrine release [27].

The glutamate, on of the most important neurotransmitters involved in all dependences including nicotine dependence stimulate different receptors in the brain. There are data which showed a different involvement of these receptors in nicotine addiction The AMPA receptors did not appear to be involved in the reinforcing effect of nicotine but they may be involved in the development of nicotine dependence [28]. NMDA receptors play the most important role in nicotine dependence.

The stimulation of pre-synaptic nicotine receptors into the brain 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 N3 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 anxyolitic 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 oxid 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 synthetised in nucleus accumbens and has receptors in this brain area. The NPY administration increased the extacellular 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 Y5 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_6 (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 neuroiritability 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 via a transient receptor potential melastatin 7 (TRPM7) channel into the intracellular space of rat hippocampal neurons [56]. By this mechanism is regulated the intraneuronal magnesium concentration. Hypomagnesaemia with secondary hypocalcaemia is due to disturbed renal and intestinal magnesium Mg^{2+} (re)absorption. The defect is a mutation in the TRPM6, a Mg (2+)-permeable ion channel expressed in the kidney and intestine [57]. There are 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 verancline. 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 nicotinic 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]. Mg^{2+} (a partial antagonist of Ca^{2+} 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. $MgCl_2$ decreased the aversive effect of naloxone 2 mg/kg [68]. In cocaine-dependent rats, $MgCl_2$ 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 the intensity of tobacco addiction. The treatment of hypomagnesaemia in young people could reduce initiation of smoking.

References

1. Zhang L, Dong Y, Doyon WM, Dani JA (2012) Withdrawal from chronic nicotine exposure alters dopamine signaling dynamics in the nucleus accumbens. Biol Psychiatry 71: 184-191.
2. Oner O, Oner P, Bozkurt OH, Odabas E, Keser N, et al. (2010) Effects of zinc and ferritin levels on parent and teacher reported symptom scores in attention deficit hyperactivity disorder. Child Psychiatry Hum Dev 41: 441-447.
3. Abumaria N, Yin B, Zhang L, Li XY, Chen T, et al. (2011) Effects of elevation of brain magnesium on fear conditioning, fear extinction, and synaptic plasticity in the infralimbic prefrontal cortex and lateral amygdala. J Neurosci 31: 14871-14881.
4. Kang SW, Choi SK, Park E, Chae SJ, Choi S, et al. (2011) Neuroprotective effects of magnesium-sulfate on ischemic injury mediated by modulating the release of glutamate and reduced of hyperreperfusion. Brain Res 1371: 121-128.
5. Voss LJ, Melin S, Jacobson G, Sleigh JW (2010) GABAergic compensation in connexin36 knock-out mice evident during low-magnesium seizure-like event activity. Brain Res 1360: 49-55.
6. Frederickson CJ, Suh SW, Silva D, Frederickson CJ, Thompson RB (2000) Importance of zinc in the central nervous system: the zinc-containing neuron. J Nutr 130: 1471S-1483S.
7. Powell SR (2000) The antioxidant properties of zinc. J Nutr 130: 1447S–1454S.
8. Harvey RJ, Thomas P, James CH, Wilderspin A, Smart TG (1999) Identification of an inhibitory Zn2+ binding site on the human glycine receptor alpha1 subunit. J Physiol 520: 53-64.
9. Huang EP (1997) Metal ions and synaptic transmission: think zinc. Proc Natl Acad Sci U S A 94: 13386-13387.
10. Casanovas-Aguilar C, Reblet C, Perez-Clausell J, Bueno-Lopez JL (1998) Zinc-rich afferents to the rat neocortex: projections to the visual cortex traced with intracerebral selenite injections. J Chem Neuroanat 15: 97-109.
11. Brewer GJ (2012) Copper excess, zinc deficiency, and cognition loss in Alzheimer's disease. Biofactors 38 107-113.
12. Suzuki H, Asakawa A, Li JB, Tsai M, Amitani H, et al. (2011) Zinc as an appetite stimulator - the possible role of zinc in the progression of diseases such as cachexia and sarcopenia. Recent Pat Food Nutr Agric 3: 226-231.
13. Nakashima AS, Dyck RH (2009) Zinc and cortical plasticity. Brain Res Rev 59: 347-373.
14. Colvin RA, Davis N, Nipper RW, Carter PA (2000) Zinc transport in the brain: routes of zinc influx and efflux in neurons. J Nutr 130: 1484S-1487S.

15. Zhang J, Zhao F, Zhao Y, Wang J, Pei L, et al. (2011) Hypoxia induces an increase in intracellular magnesium via transient receptor potential melastatin 7 (TRPM7) channels in rat hippocampal neurons in vitro. J Biol Chem 286: 20194-20207.

16. Harvey RJ, Thomas P, James CH, Wilderspin A, Smart TG (1999) Identification of an inhibitory Zn2+ binding site on the human glycine receptor alpha1 subunit. J Physiol 520: 53-64.

17. Veeneman MM, Broekhoven MH, Damsteegt R, Vanderschuren LJ (2012) Distinct contributions of dopamine in the dorsolateral striatum and nucleus accumbens shell to the reinforcing properties of cocaine. Neuropsychopharmacology 37: 487-498.

18. Egan TM, North RA (1986) Actions of acetylcholine and nicotine on rat locus coeruleus neurons in vitro. Neuroscience 19: 565-571.

19. Hiranita T, Soto PL, Kohut SJ, Kopajtic T, Cao J, et al. (2011) Decreases in cocaine self-administration with dual inhibition of the dopamine transporter and σ receptors. J Pharmacol Exp Ther 339: 662-677.

20. Di Chiara G, Bassareo V (2007) Reward system and addiction: what dopamine does and doesn't do. Curr Opin Pharmacol 7: 69-76.

21. Dani JA, De Biasi M (2001) Cellular mechanisms of nicotine addiction. Pharmacol Biochem Behav 70: 439-446.

22. Dwoskin LP, Smith AM, Wooters TE, Zhang Z, Crooks PA, et al. (2009) Nicotinic receptor-based therapeutics and candidates for smoking cessation. Biochem Pharmacol 78: 732-743.

23. De Biasi M, Dani JA (2011) Reward, addiction, withdrawal to nicotine. Annu Rev Neurosci 34: 105-130.

24. Janson A M, Fuxe K (1997) Chronic nicotine treatment differentialy regulates substance P and tyrosine hydroxylase immunoreactivity in substantia nigra ipsilataral to unilateral lesions. Exp Neurol 147: 575-586.

25. Cheramy A, Godeheu G, L'Hirondel M, Glowinski J (1996) Cooperative contributions of cholinergic and NMDA receptors in the presynaptic control of dopamine release from synaptosomes of the rat striatum. J Pharmacol Exp Ther 276: 616-625.

26. Yan Y, Pushparaj A, Le Strat Y, Gamaleddin I, Barnes C, et al. (2012) Blockade of dopamine d4 receptors attenuates reinstatement of extinguished nicotine-seeking behavior in rats. Neuropsychopharmacology 37: 685-696.

27. Jayasundar S, Vohra MM (1977) The calcium-magnesium interaction in the process of release of noradrenaline by nicotine. Can J Physiol Pharmacol 55: 1383-1386.

28. Liechti ME, Markou A (2008) Role of the glutamatergic system in nicotine dependence: implications for the discovery and development of new pharmacological smoking cessation therapies. CNS Drugs 22: 705-724.

29. Lena C, Changeux JP (1997) Pathological mutations of nicotinic receptors and nicotine-based therapies for brain disorders. Curr Opin Neurobio l 7: 674-682.

30. Sobolewski AI, Khodorov BI (2002) Blocker studies of thefunctional architecture of the NMDA receptor channel. Neurosci Behav Physiol 32: 157-171.

31. Poleszak E, Szewczyk B, Kedzierska E, Wla Y P, Pilc A, et al. (2004) Antidepressant- and anxiolytic-like activity of magnesium in mice. Pharmacol Biochem Behav 78: 7-12.

32. Stelzer A, Slater NT, ten Bruggencate G (1987) Activation of NMDA receptors blocks GABAergic inhibition in an invivo model of epilepsy. Nature 326: 698-701.

33. Prior PL, Galduróz JC (2011) Glutamatergic hyperfunctioning during alcohol withdrawal syndrome: therapeutic perspective with zinc and magnesium. Med Hypotheses 77: 368-370.

34. Burnashev N, Schoepfer R, Monyer H, Ruppersberg JP, Günther W, et al. (1992) Control by asparagine residues of calcium permeability and magnesium blockade in the NMDA receptor Science 257: 1415-1419.

35. Vink R, Donkin JJ, Cruz MI, Nimmo AJ, Cernak I (2004) A substance P antagonist increases brain intracellular free magnesium concentration after diffuse traumatic brain injury in rats. J Am Coll Nutr 23: 538S-540S.

36. Vleeming W, Rambali B, Opperhuizen A (2002) The role of nitric oxide in cigarette smoking and nicotine addiction. Nicotine Tob Res 4: 341-348.

37. Di Matteo V, Pierucci M, Benigno A, Esposito E, Crescimanno G, et al. (2010) Critical role of nitric oxide on nicotine-induced hyperactivation of dopaminergic nigrostriatal system: Electrophysiological and neurochemical evidence in rats. CNS Neurosci Ther 16: 127-136.

38. Sun X, Mei Y, Tong E (2000) Effect of magnesium on nitric oxide synthase of neurons in cortex during early period of cerebral ischemia. J Tongji Med Univ 20: 13-15.

39. Jandova K, Langmeier M, Maresova D, Pokorny J, Trojan S (2006) Effect of magnesium pre-treatment on the hippocampal NOS activity during long-lasting intermittent hypoxia. Prague Med Rep 107: 108-116.

40. Miyamoto A, Moriki H, Ishiguro S, Nishio A (2005) In vitro application of endotoxin enhances nitric oxide production in thoracic aortas from Mg-deficient rats. Magnes Res 18: 155-162.

41. Bruijnzeel AW (2012) Tobacco addiction and the dysregulation of brain stress systems. Neurosci Biobehav Rev 36: 1418-1441.

42. Sorensen G, Wegener G, Hasselstrøm J, Hansen TV, Wortwein G, et al. (2009) Neuropeptide Y infusion into the shell region of the rat nucleus accumbens increases extracellular levels of dopamine. Neuroreport 20: 1023-1026.

43. Huang H, Xu Y, van den Pol AN (2011) Nicotine excites hypothalamic arcuate anorexigenic proopiomelanocortin neurons and orexigenic neuropeptide Y neurons: similarities and differences. J Neurophysiol 106: 1191-1202.

44. Sorensen G, Jensen M, Weikop P, Dencker D, Christiansen SH, et al. (2012) Neuropeptide Y Y5 receptor antagonism attenuates cocaine-induced effects in mice. Psychopharmacology (Berl) 25.

45. Corr L, Burnstock G, Poole-Wilson P (1991) Magnesium inhibits the responses to neuropeptide Y in the rabbit coronary artery. J Mol Cell Cardiol 23: 231-235.

46. Nechifor M, Chelarescu D, Mandreci I, Cartas N (2004) Magnesium influence on nicotine pharmacodependence and smoking. Magnes Res 17: 176-181.

47. Dalack GW, Healy DJ, Meador-Woodruff JH (1998) Nicotine dependence in schizophrenia: clinical phenomena and laboratory findings. Am J Psychiatry 155: 1490-1501.

48. Heffner JL, Strawn JR, DelBello MP, Strakowski SM, Anthenelli RM (2011) The co-occurrence of cigarette smoking and bipolar disorder: phenomenology and treatment considerations. Bipolar Disord 13: 439-453.

49. Prochaska JJ, Reyes RS, Schroeder SA, Daniels AS, Doederlein A, et al. (2011) An online survey of tobacco use, intentions to quit, and cessation strategies among people living with bipolar disorder. Bipolar Disord 13: 466-473.

50. Nechifor M, Vaideanu C, Mandreci I, Palamaru I, Boisteanu P (2006) The influence of bipolar disorders treatment on plasmatic and erythrocyte levels of some catios: Metal ions in biology and Medicine. Philippe Collery 9: 556-560.

51. Parrott AC, Murphy RS (2012) Explaining the stress-inducing effects of nicotine to cigarette smokers. Hum Psychopharmacol 27: 150-155.

52. Eby GA, Eby KL (2010) Rapid recovery from major depression using magnesium treatment. Med Hypotheses 74: 649-660.

53. Nechifor M (2009) Magnesium in major depression. Magnes Res 22: 163S-166S.

54. Gardner EL (2011) Addiction and brain reward and antireward pathways. Adv Psychosom Med 30: 22-60.

55. Forcen FE, Martinez FL, Moya AM (2012) Varenicline precipitating psychosis in a patient with no previous psychiatric history: a case report of a Spanish patient who was later diagnosed with paranoid personality disorder. Clin Schizophr Relat Psychoses 5: 221-223.

56. Zhang J, Zhao F, Zhao Y, Wang J, Pei L, et al. (2011) Hypoxia induces an increase in intracellular magnesium via transient receptor potential melastatin 7 (TRPM7) channels in rat hippocampal neurons in vitro. J Biol Chem 286: 20194-20207.

57. Woudenberg-Vrenken TE, Sukinta A, van der Kemp AW, Bindels RJ, Hoenderop JG (2011)Transient receptor potential melastatin 6 knockout mice are lethal whereas heterozygous deletion results in mild hypomagnesemia. Nephron Physiol 117: 11-19.

58. Keinanen SI, Hassinen VH, Karenlampi SO, Tervahauta AI (2007) Isolation of genes up-regulated by copper in a copper-tolerant birch (Betula pendula) clone. Tree Physiol 27: 1243-1252.

59. Cragg RA, Christie GR, Phillips SR, Russi RM, Kury S, et al. (2002) A novel zinc-regulated human zinc transporter, hZTL1, is localized to the enterocyte apical membrane. J Biol Chem 277: 22789-22797.

60. Wu J (2010) Double target concept for smoking cessation. Acta Pharmacol Sin 31: 1015-1018.

61. Kruk M, Tendera K, Biala G (2011) Memory-related effects of cholinergic receptor ligands in mice as measured by the elevated plus maze test. Pharmacol Rep 63: 1372-1382.

62. Slutsky I, Abumaria N, Wu LJ, Huang C, Zhang L, et al. (2010) Enhancement of learning and memory by elevating brain magnesium. Neuron 65: 165-177.

63. Budzynska B, Polak P, Biala G (2012) Effects of calcium channel antagonists on the motivational effects of nicotine and morphine in conditioned place aversion paradigm. Behav Brain Res 228: 144-150.

64. Araki H, Kawakami KY, Jin C, Suemaru K, Kitamura Y, et al. (2004) Nicotine attenuates place aversion induced by naloxone in single-dose, morphine-treated rats. Psychopharmacology (Berl) 171: 398-404.

65. Biala G, Budzynska B (2006) Reinstatement of nicotine conditioned place preference by drug priming: effects of calcium channel antagonists. Eur J Pharmacol 537: 85-93.

66. Nechifor M, Chelarescu D, Ciubotaru D (2010) The influence of magnesium on morphine-induced stimulation of the reward system. Magnes Res 23: 41-47.

67. Lawley SI, Kantak KM (1990) Magnesium-induced conditioned place preference in mice. Pharmacol Biochem Behav 36: 539-545.

68. Kantak KM (1989) Magnesium alters the potency of cocaine and haloperidol on mouse aggression. Psychopharmacology (Berl) 99: 181-188.

69. Kantak KM, Lawley SI, Wasserman SJ, Bourg JF (1991) Magnesium-maintained self-administration responding in cocaine-trained rats. Psychopharmacology (Berl) 104: 527-535.

70. Niemela JE, Cecco SA, Rehak NN, Elin RJ (1997) The effect of smoking on the serum ionized magnesium concentration is method-dependent. Arch Pathol Lab Med 121: 1087-1092.

71. Hsiao B, Dweck D, Luetje CW (2001) Subunit-dependent modulation of neuronal nicotinic receptors by zinc. J Neurosci 21: 1848-1856.

72. Vazquez-Gomez E, Garcia-Colunga J (2009) Neuronal nicotinic acetylcholine receptors are modulated by zinc. Neuropharmacology 56: 1035-1040.

73. Szyszko M, Czarnowski W (2006) Smoking influence on cadmium, lead, selenium and zinc level in placenta, cord blood and maternal blood of women at delivery from Gdansk region. Przegl Lek 63: 993-997.

74. Dubick MA, Keen CL (1991) Influence of nicotine on tissue trace element concentrations and tissue antioxidant defense. Biol Trace Elem Res 31: 97-109.

75. Unkiewicz-Winiarczyk A, Bagniuk A, Gromysz-Kalkowska K, Szubartowska E (2009) Calcium, magnesium, iron, zinc and copper concentration in the hair of tobacco smokers. Biol Trace Elem Res 128: 152-160.

76. Iyengar V, Chou PP, Costantino AG, Cook CB (1994) Excessive urinary excretion of zinc in drug addicts: a preliminary study during methadone detoxification. J Trace Elem Electrolytes Health Dis 8: 213-215.

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