Magnesium in drug abuse and addiction

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Abstract

Addiction to different substances is considered to be a psychiatric disorder. Magnesium reduces the intensity of addiction to opiates and psychostimulants (cocaine, amphetamine, nicotine, cocaine and others). It also decreases the auto-administration of cocaine and the relapse into cocaine and amphetamine intake, as well as reducing the experimental addiction to morphine, cocaine and other substances in animals. In heroin addicts, alcohol consumers and other drug abusers, the plasma and intracellular magnesium concentration is lower compared to healthy subjects. We consider that one of the mechanisms by which magnesium reduces the consumption of some highly addictive substances is its moderate effect of stimulating the reward system. However, other main mechanisms involved in magnesium's action are the reduction of dopamine and glutamate release at presynaptic terminals in the brain, the decrease of NO synthase activity, the stimulation of GABAergic system activity, the reduction of postsynaptic NMDA receptor activity, and the reduction of some neuromediators released by Ca^{2+} and acting at calcium channels. Apart from the action of magnesium ions during emerging addiction, administration of this cation after the appearance of withdrawal syndrome reduces the intensity of the clinical symptoms. There are data that show that stress increases the vulnerability of people to develop addiction to different substances, and also reduces drug-free time and increases the incidence of relapse in heroin addicts. Stress increases catecholamine release and stimulates magnesium release from the body. This decrease in magnesium concentration is one of the important factors that hastens relapse.

Introduction

Drug dependence is today considered a chronic medical illness (Kosten, 1998) producing significant changes in the biochemistry and function of the brain (McLellan *et al,* 2000). Koob and Le Moal (2001) presented the neurobiology of addiction from the perspective of allostasis, whereby addiction is considered a cycle of progressively increasing dysregulation of reward systems, producing compulsive use of drugs with the loss of control over drug-taking.

There is a large group of substances that result in more or less intense addiction, which is characterized by three major features: compulsive use (intake), craving, and withdrawal syndrome (when the administration is stopped). The number of substances for which a more or less intense dependence was signaled is relatively high and is growing continuously. These include the opiates (morphine, heroin, etc.), the psychodysleptics (LSD), alcohol, cannabinoids and psycho-stimulants.

The main brain structures involved in development of drug dependence are the nucleus accumbens, ventral tegmentum, the periductal grey substance, the mesolimbic system, and the nucleus coeruleus. Dysfunction in the mesolimbic system, nucleus accumbens, prefrontal cortex, and ventral tegmental area are considered involved in the mechanism of drug abuse disorders (Miguel- Hidalgo, 2009).

The molecular mechanisms involved in addiction are complicated but the main chemical neuro-mediators involved are dopamine, glutamate, serotonin, endogenous opioid peptides, nitric oxide (NO) and others. The glutamatergic, dopaminergic and opioid mechanisms are considered the most involved (Grass and Olive, 2007). These mechanisms involve not only the neurons but also the neuroglia. There are many factors that can influence the intensity of addiction or withdrawal syndrome symptoms. Amongst them are magnesium and other bivalent cations (Ruiz Martinez *et al*, 1990).

Opiates

Opiates are the cause of one of the most powerful and frequent addictions, with heroin intake especially resulting in unique medical and social problems. There are data that show that magnesium decreases the intensity of opioid addiction, with administration of Mg acetate (0.5mEq/Kg/day) reducing the experimental physical dependence (Nechifor *et al,* 2004b). The intensity of symptoms in naloxone-induced withdrawal syndrome reduced, even when magnesium administration was stopped during the period of withdrawal syndrome. Administration of Mg aspartate (732 mg mg/day) for 12 weeks in heroin-addictive patients was also beneficial (Daini *et al*, 2006; Karakiewicz *et al,* 2007). Magnesium can potentially reduce the intensity of addiction through a number of mechanisms (Figure 1), including:

- decreasing dopamine synthesis and pre-synaptic release in brain;
- decreasing the activity of glutamate NMDA receptors;
- decreasing the activity of brain NOS and NO synthesis;
- modulating the opioid coupling at brain μ receptors;
- increasing glutamate metabolism (as the main excitatory amino acid involved in addiction) by enhancing glutamate decarboxylase activity;
- increasing GABAergic activity in some brain areas by increasing the vesicular GABA transporter synthesis (Gerstein *et al*, 2005).

Magnesium also potentiates the function of $GABA_A$ receptors suggesting a putative Mg^{2+} binding site on the $GABA_A$ receptor protein (Möykkynen *et al*, 2001).

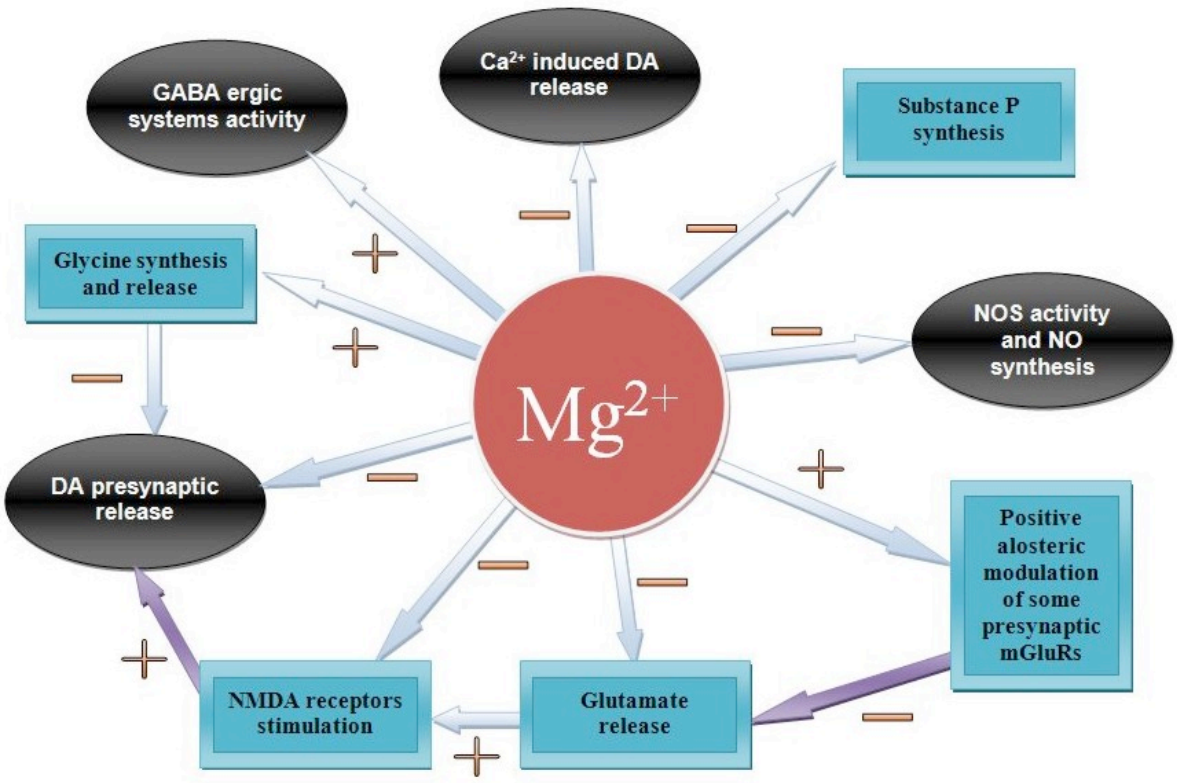

Figure 1. Mechanisms by which magnesium reduces the intensity of opiate addiction. – = inhibition; + = stimulation; DA = dopamine; NOS = nitric oxide synthase.

Dopamine is considered the most important molecule in development of pharmacodependence. Indeed, substances that result in pharmaco-dependence strongly increase the level of dopamine in midbrain. As an example, morphine produces a dose-dependent increase in dopamine-containing neurons in the substantia nigra and ventral tegmentum in rat brain (Trulson and Arasteh, 1985). Magnesium can reduce dopamine release in some brain structures through direct presynaptic action at the level of some dopaminergic synapses, by inhibiting calcium induced brain dopamine release, and by decreasing the stimulatory action of glutamate upon dopamine release. Brain dopamine level in mice is significantly increased following icv administration of $CaCl_2$. Magnesium, an antagonist to calcium, inhibits the dopamine release (Sutoo and Akiyama, 2000).

There are NMDA receptors at the level of some dopaminergic nerve endings whose stimulation also increases dopamine release. The reduction in NMDA receptor stimulation by magnesium can reduce dopamine release induced by the addictive substance (Chéramy *et al*, 1994). Extracellular Mg^{2+} blocks NMDA ion channels in a voltage dependent manner and increases the receptor affinity for glycine (Paoletti *et al*, 1995). Glycine inhibits the glutamate-evoked release of norepinephrine, and possibly other catecholamines (Johnson *et al*, 1994). In this way, the facilitating effect of magnesium on glycine linkage at its binding sites could reduce the glutamate stimulating effect of presynaptic catecholamine release (dopamine release being an essential step of addiction development). A selective inhibitor of the glycine transporter (Gly T1) significantly increased dopamine release (Bennett and Gronier, 2005). This fact indicates that glycine reduces dopamine release, in this way decreasing the intensity of addictive processes. Notably, magnesium increases both glycine synthesis and release.

Vaupel et al (1995) showed that nitric oxide synthase (NOS) inhibitors (L-nitroarginine, L-nitroarginine methyl ester) reduce several signs of opiate withdrawal (Kimes *et al,* 1993). This fact supports the involvement of nitric oxide in the pathogenic signs of the withdrawal syndrome. Mg^{2+} also inhibits NOS and we consider that in this way, it also reduces the intensity of symptoms from the withdrawal syndrome.

Chronic morphine administration decreases the NMDA receptor sensibility to Mg binding. The glutamatergic systems provide important regulation of dopamine function, while the GABA system can modulate basal levels and stimulate dopamine and glutamate release. The idea of a major role of the glutamatergic system in morphine addiction has also been proposed (Sekiya *et al*, 2004) on the basis that icv administration of DLBOA (a potent glutamate transporter inhibitor) to morphine dependent rats significantly facilitates the expression of naloxone-precipitated withdrawal. Mg^{2+} action is mainly due to its effects on neuronal activity, but also impacts upon neuroglial activity. Glial cells from CNS play an important role in regulation of glutamatergic transmission. Some substances that give rise to addiction alter the functions of astrocytes while others affect glial cell functions (Miguel-Hidalgo, 2009). Astrocyte involvement in the control of glutamate uptake and release is important for the development of addiction.

Substance P and its NK1 receptors also play a role in opiate addiction and in stress (Commons *et al,* 2010). This neuropeptide modulates NMDA receptor responses to glutamate stimulation (Parker *et al*, 1998). Magnesium reduces the synthesis and action of substance P and we believe that in this way, it can decrease the intensity of addiction. Stress induces magnesium depletion and increases the vulnerability to development of addiction or of relapse. We consider that low magnesium levels play an important role in this vulnerability.

Psychostimulants

Psychostimulants are a group of substances with various chemical structures and different mechanisms of actions, partly common, partly different, which results in a strong activation of some CNS processes. All psychostimulants induce a certain degree of addiction, but its intensity is very different. The most utilized psycho-stimulants are cocaine and its derivatives, amphetamines, caffeine and nicotine.

Cocaine

In cocaine abusers, magnesium reduced the craving for this substance (Margolin *et al*, 1992). Cocaine craving scores were 78% lower in those taking magnesium than in patients taking placebo. Mg^{2+} also reduced cocaine self-administration in patients and cocaine consumption in rats (Kantak *et al*, 1998). In cocaine addicts, the plasma level of Mg^{2+} is higher than in heroin addicts (Tonioni *et al*, 2009). NMDA receptors are essential for cocaine action in brain. NMDA antagonists and some NMDA-coupled ion channel blockers (like magnesium) may modify the cocaine effects (Kantak *et al*, 1998).

Our data shows that magnesium never determines dependence. Mg^{2+} has a moderate effect of stimulating the brain reward system. $MgC1_2$ results in an increase in time spent in the conditioning compartment in the case of conditioned place preference (CPP)(Nechifor *et al*, 2010). We consider that, apart from other mechanisms, the small stimulation on the brain reward system is important in realizing magnesium's effect of reducing cocaine consumption.

There are also data showing that genes are important for the behavior of drug abusers who have a strong genetic determination. The allelic variations related to the dopamine transporter showed a relationship with the paranoia of cocaine-dependent people (Gellertnet *et al*, 1999). We consider that genetic deficiencies in magnesium transport at the level of the neuronal membrane may be involved in the speed of addiction development and in the severity of the withdrawal syndrome.

Caffeine

Caffeine is one of the most consumed psychoactive substances, although the existence of caffeine dependence is controversial (Huges *et al*, 1992; Daly and Fredholm, 1998). There are data suggesting that caffeine results in a clinical dependence syndrome very similar to that produced by other psychoactive substances, as well as from the point of view of the caffeine-induced craving (Ogawa and Ueki, 2007). Caffeine has only week reinforcing proprieties, but the withdrawal syndrome is a reality and is similar to that produced by other drugs of abuse. Rats chronically exposed to 1 g/L caffeine a day for 20 days developed caffeine withdrawal syndrome (Dingle *et al*, 2008).

Caffeine blocks both A_1 and A_2 adenosine receptors. Chronic administration of xanthines (caffeine, theophylline) causes a significant increase in the number of adenosine, nicotine and serotoninergic receptors in the brain. It also increases the number of L-type calcium channels in the neuronal membrane. The blockade of both A_1 and A_2 receptors is necessary for the full spectrum of caffeine pharmacologic effects.

The Ca^{2+} ions from the endoplasmic reticulum are very important for normal cell function. Any change in intracellular calcium concentration can have an impact on neuronal activity. Caffeine enhances the intracellular Ca^{2+} peak. This effect is higher in young animals and is altered with aging (Alshuaib *et al*, 2006). Caffeine releasable calcium ions may stimulate glutamate synthesis and release, which increases NMDA receptor activity. Wang (2007) showed that caffeine-mediated glutamate release is produced by activation of protein-kinase C pathways and involves an interaction between caffeine and presynaptic adenosine A1 receptors. The importance of caffeine action on adenosine receptors also comes out of the fact that these receptors act as regulators of neurotransmitter release in the brain (Sebastiao and Ribeiro, 2009). Adenosine stimulates all types of adenosine receptors. The omnipresence of A1, A2 and A3 receptors in CNS neurons and neuroglia reflect the major role of adenosine in modulating synaptic activity in many brain regions, including those involved in dependence.

Blockade of adenosine A_{1A} and A_{2A} receptors is involved in the development of caffeine addiction. Burgalassi et al (2009) showed that a substantial number from heavy caffeine drinkers satisfy the research criteria for dependence. Adenosine A_1 and A_2 receptors have a greater involvement in addiction processes well as development of withdrawal syndrome rather than in development of caffeine dependence.

Adenosine and adenosine receptors are also involved in morphine dependence and opioid withdrawal. Adenosine is able to reduce the dose-dependent, naloxone-precipitated withdrawal in

guinea pigs exposed to morphine. Caffeine significantly increases naloxone-precipitated withdrawal (Capasso, 2000). Research on guinea pig isolated ileum exposed to morphine showed that the contraction induced by naloxone was increased by caffeine (P1 antagonist) in a concentration dependent manner (Capasso and Loizzo, 2001). The caffeine effect is amplified by low Mg^{2+} concentration.

A1 receptor antagonists such as caffeine increase the presynaptic release of dopamine and glutamate. This is thought to be the main mechanism for caffeine dependence. A1 receptors are located in presynaptic areas of glutamatergic neurons and Mg can reduce caffeine dependence by blocking NMDA coupled Ca channel activity, reducing the capacity of A_1 receptor antagonists (such as caffeine) to stimulate the glutamate and dopamine release, or by reducing the glutamate stimulation of dopamine presynaptic release. It is not very clear if caffeine enhances magnesium elimination from the human body.

Amphetamine

Amphetamine is a very potent sympathomimetic agent in stimulating the CNS. The main mechanism of action is by release of biogenic amines from their storage sites in presynaptic parts of central synapses. The dependence and stereotypical behavior associated with amphetamine is induced by stimulation of dopamine release. Disturbance of perception and psychotic behavior may be due to release of serotonin and dopamine in the mesolimbic system (Hoffman, 2001). There is also a small stimulating effect of amphetamine on some serotonin receptors. Increased intraneuronal Mg^{2+} concentration is thought to reduce the intensity of psychostimulant addiction. Evidence in favor is the fact that Li^{+} (which increases intracellular magnesium concentration) has an antagonistic effect with amphetamine at the level of the nucleus accumbens. Li^{+} also decreased dopaminergic transmission stimulated by amphetamine (Gray *et al,* 1997). After administration of 1 mg/kg amphetamine, dopamine levels increases by 427% versus the basal level. This dopamine release is calcium potentiated. The replacement of calcium by magnesium reduces the response to amphetamine administration (Warburton *et al,* 1996). It was also remarked that structural brain abnormalities are associated with amphetamine abuse. These differences included lower cortical gray matter quantity and higher striatal volume than in normal subjects (Berman *et al*, 2008). We do not know how magnesium influences these modifications.

Nicotine

Existing data shows that nicotine addiction develops in chronic smokers with over 10-20 cigarettes/day. Chronic smoking decreases the level of serum magnesium (Niemela *et al* 1997; Nechifor *et al*, 2004a), while magnesium administration decreases the number of smoked cigarettes as well as nicotine addiction. Specifically, 2 ampoules/day Magne-B6 administration for four weeks significantly decreased the number of cigarettes smoked by heavy smokers (smokers with over 20 cigarettes/day) (Nechifor *et al*, 2004a). The Fagerstrom score was significantly reduced in the smoker group that received magnesium, from 7.93 ± 0.17 before magnesium to 6.78 ± 0.18 after magnesium ($p<0.05$). Mg^{2+} can potentially reduce nicotine addiction by:

- acting as a partial antagonist of calcium entry into neurons, thereby decreasing glutamate release and glutamatergic transmission which is stimulated by nicotine;
- decreasing nicotine-induced pre-synaptic release of dopamine and other catecholamines;
- increasing magnesium concentration in the neuron producing a decrease in sodium concentration. This decreases the stimulant effect of nicotine on nicotine receptors.
- decreasing the nicotine addictive effect by diminishing the nicotine effect on GABA synthesis. Nicotine diminishes GABA synthesis and release in some brain areas by stimulation of nicotine presynaptic receptors;
- enhancing some of the GABA effects and diminishing some effects of the excitatory amino acids in drug dependence. GABA antagonizes some of the glutamate-induced stimulatory effects of NMDA receptors.

Like nicotine, synaptically released acetylcholine stimulates nicotinic receptors and in this way enhances glutamatergic activity (Guo *et al*, 2005).

The release of DA from the nucleus accumbens and substantia nigra was stimulated by glutamate, and nicotine enhanced this release (Marien *et al,* 1983). Such DA secretion induced by glutamate and nicotine is Ca^{2+} dependent and was inhibited by Mg^{2+}. We think that this is an essential mechanism for magnesium action to reduce the nicotine dependence.

Ethanol dependence

Alcohol induced dependence is one of the most widespread dependencies. Abuse and addiction depend, at least partially, on the activation of mesolimbic dopaminergic systems. The activation of these systems is achieved directly by ethanol, but also by acetaldehyde, which results from ethanol metabolism. Acetaldehyde increases dopaminergic neuronal activity in the nucleus accumbens, ventral tegmental area and in other parts of the CNS (Foddai *et al*, 2004; Diana *et al*, 2008). Alcohol-dehydrogenase drastically inhibits the effects of ethanol on dopaminergic neurons of the ventral tegmental area (VTA). We consider that magnesium could reduce the stimulating effect of ethanol on dopaminergic systems by directly reducing the presynaptic release of dopamine, but also by decreasing acetaldehyde production.

There is important evidence implicating the endogenous opioids in the processes of reward and reinforcement (Gianoulakis, 2009). Endogenous opioids, like morphine, induce an increase of dopamine concentration in the nucleus accumbens, which is considered the most important structure for drug addiction. This is considered a common effect for many drugs involved in abuse. Ethanol increases beta endorphin release. The stimulation of opioid receptors (especially of μ receptors) seems to be important for ethanol addiction, with low morphine doses increasing ethanol consumption (Hertz, 1997). Magnesium reduces receptor binding of morphine and other μ receptor agonists (Mendez *et al*, 2001; Rodriguez *et al*, 1992). This way, magnesium could reduce the stimulation of dopamine synthesis produced by large quantities of opioid peptides, which themselves are induced by ethanol in the nucleus accumbens and VTA. We therefore consider that Mg^{2+} could decrease ethanol addiction and hypomagnesemia could increase alcohol consumption. Mendez et al (2001) showed that the reinforcing properties of ethanol may be partially mediated by ethanol regulation of μ receptors in dopaminergic neurons from mesolimbic systems. A modulation of μ receptors from the frontal and prefrontal cortex is also possible.

There are also findings that suggest that mGluR5 receptors modulate ethanol self-administration in rats (Schroeder *et al,* 2005). Dopamine is the most important neurotransmitter involved in the reward mechanism and it influences the development of alcohol dependence and relapse. Two polymorphisms of the D2 dopamine receptors seem to suffer 2.5 times more risk to develop ethanol dependence (Prasad *et al*, 2010). Embry and Lippman (1987) considered that magnesium deficiency plays an important role in the alcohol-withdrawal system. There are data that show that magnesium administration decreases the intensity of symptoms from the withdrawal syndrome. The alcohol induces hypomagnesemia and increases urinary magnesium loss. Low concentrations of ethanol deplete free intracellular magnesium (Babu *et al*, 1999). Consistent with Shane and Flink (1992), we believe that magnesium deficiency is involved not only in the intensity of the alcohol withdrawal, but also in the development of alcohol dependence.

The NMDA receptors from the nucleus accumbens and the mesolimbic structures are involved in drug reward and reinforcement. Ethanol sensitivity of NMDA receptors from the nucleus accumbens is important for ethanol induced neuroadaptation of the reward system. Chronic alcohol administration results in an increased glutamate binding to the NMDA receptors (Hu and Ticku, 1995). This highlights the importance of glutamate action in development of alcohol addiction. The activation of NMDA receptors in rats increases during the alcohol withdrawal syndrome (Sanna *et al* 1993). Electrolyte abnormalities are common in chronic alcoholics and during alcohol withdrawal syndrome (Stasinkyniene, 2002). Alcohol consumption is one of the major causes for hypomagnesemia, which is one of the most important cation imbalances in alcoholic patients and during withdrawal (Carl and Halzbach, 1994). In alcoholic patients urinary magnesium loss

increases 2-3 fold (Romain, 2008) and brain intracellular Mg^{2+} level are reduced (Li *et al*, 2001; Pasternak, 1999). Low ethanol concentrations deplete type 2 astrocytes of intracellular free magnesium (Babu *et al*, 1999). The Mg^{2+} dependent decay off-rate of NMDA miniature synaptic currents (mEPSes) was also significantly reduced by ethanol (Zhang *et al*, 2005), suggesting that ethanol not only contributes to increase the release of magnesium from the body, but also to increase magnesium's effect at the NMDA receptor level.

Mg^{2+} ions modulate neuronal excitability and are involved in alcohol-related behaviors. Uusi-Oukari et al (2001) found that the putative Mg^{2+} binding sites differ between alcohol insensitive (AT) and alcohol sensitive (ANT) rats lines. In the presence of GABA, the effect of low Mg^{2+} concentration was higher in cerebral cortex and in the caudate-putamen of AT rats than in the ANT animals. Alcohol sensitive rats have alterations of the alpha 6 subunit – containing GABA A receptors. It is possible that these receptors might be involved in the sensitivity of different lines of rats to alcohol and also in the different sensibility of animals to sedative drugs (Uusi-Oukari M *et al*, 2001). Magnesium administration only during the withdrawal syndrome of ethanol addicts reduced the clinical symptoms.

Hallucinogens (psychedelic substances)

Hallucinogens are substances that induce hallucinations, disorders of thinking and delusions. The most potent hallucinogen is LSD (lysergic acid diethylamide) that produces a significant hallucinogen effect at a dose of as little as 25-50 ug. Other psychedelic drugs are derivatives with indolaminic structure (psylocibine, DMT and others) and substances with phenethylaminic structure (mescaline, MDMA, and DOM). The precise mechanism of action of these substances is not yet known, but a positive correlation between the relative affinity of hallucinogens for serotonin 5-HT2 receptors and their potency to induce hallucination has been observed (Titeler *et al*, 1988).

The hallucinogens (LSD, phencyclidine, psilocybin, mescaline, DMT and others) give a strong psychic dependence, but the concept of addiction is controversial. The presence of withdrawal from hallucinogens has not been clearly established because these drugs don't seem to induce physical dependence. The most utilized hallucinogen is LSD.

There are data that favor the idea that all phencyclidine receptors in the brain are associated with NMDA receptors. Notably, there is an interaction of L-glutamate and magnesium with the phencyclidine recognition site in the brain (Loo *et al*, 1987). The agonists of NMDA receptors induce a high affinity state in the phencyclidine receptors. This is another possibility by which Mg^{2+} can influence phencyclidine action. Mg^{2+} inhibits MK-801 (a ligand for the NMDA ion channel phencyclidine site) binding in the cortex (Chahal *et al*, 1998). It is possible for magnesium to also decrease phencyclidine action this way. However, Rothman et al (1989) demonstrated the existence of a high-affinity phencyclidine binding site associated with the dopamine reuptake carrier. The hallucinogen could therefore influence synaptic dopamine concentration. It is still unknown how Mg^{2+} influences dopamine reuptake.

Regarding other hallucinogens such as psilocin (from Psilocybe mushrooms) and phenylethyl-amine, subchronic experimental intoxication in rats disturbs magnesium concentrations (Majdanik *et al*, 2007). Low magnesium concentration also resulted from chronic mescaline and LSD administration. Hypomagnesemia is associated with an increased intracellular entrance of Ca^{2+} in these conditions. In cerebral vasospasm, which appears in chronic hallucinogen intoxication, both magnesium and the calcium antagonist verapamil block this effect (Altura and Altura, 1983). The NMDA receptor is coupled with an ion channel and has regulatory sites for phencyclidine, glycine, and also for magnesium and zinc. In this way, it might be possible for an interaction between magnesium and phencyclidine to exist with respect to the activity of NMDA receptors.

Lerma et al (1991) suggest that interactions between Mg^{2+} and phencyclidine at the level of the NMDA channels are competitive. Indeed, 0.5 mM Mg caused a four-fold decrease in phencyclidine potency. In vitro incubation of phencyclidine stimulated brain slides with 1.2 mM $MgC1_2$ shows that Na efflux produced by the NMDA receptor stimulation is decreased.

Benzodiazepines

Magnesium aspartate decreases benzodiazepine addiction (lorazepam, alprazolam, or bromazepam) (Hantouche *et al*, 1998). The decrease in addiction intensity was manifested as prolonged delay in benzodiazepine reintake, reduction of withdrawal intensity, and reduction of anxiety during benzodiazepine discontinuation. In benzodiazepine withdrawal syndrome, strong anxiety is present. This phenomenon is associated with a potentiation of AMPA receptor activity and AMPA receptor currents in hippocampal pyramidal neurons. Calcium/ Calmodulin–dependent protein kinase II has a contribution by enhancing the glutamatergic synaptic activity during benzodiazepine withdrawal (Shen *et al*, 2010). In some patients that received Mg L-aspartate, cessation of benzodiazepines was obtained without onset of withdrawal syndrome. It is possible that magnesium ions acting at the level of AMPA receptors influence the calcium/calmodulin dependent PK II to reduce the anxiety and other clinical symptoms present in benzodiazepine withdrawal syndrome.

Cannabinoids

Delta 9-tetrahydrocannabinol is the principal psychoactive compound in marijuana, although it is widely used in a number of forms. It induces an important psychic dependence, but only a modest physical dependence. Bac and Germain Fattal (2006) showed that magnesium deficiency increased the neurotoxicity of THC at low doses in rats. Hyperagressiveness and THC induced muricidal behavior in rats was also increased by magnesium deficiency. Otherwise, there is very little data regarding the influence of magnesium and other bivalent cations in cannabinoid addiction.

Conclusion

Regarding the involvement of magnesium in addiction, we consider that is important not only at the neuronal level, but also at neuroglial level. According to data that shows that the glial cells are involved in addictive behavior mainly through the regulation of glutamate transport and activity, we believe that magnesium acts at the neuroglial level by reducing the action of glutamate. There are NMDA receptors at the glial level (in oligodendrocytes, microglia and astrocytes) (Verkhratsky and Kirchhoff, 2007), and at both these receptors and the neuronal NMDA receptor level, there is a calcium channel that can be influenced by magnesium.

We consider that the ability of magnesium to reduce addiction to different substances and reduce the intensity of addiction to different substances is essentially related to the association of two different factors:

- its ability to produce a moderate stimulation of the brain reward system (Nechifor *et al*, 2010);
- its capacity to reduce the activity of glutamatergic substances, importantly involved in compulsive use disorders.

Compulsive drug-taking behavior is an important characteristic element in addiction. The existence of a strong reinforcement activity is a determining factor for drug addiction (Koob and Bloom, 1988). Reducing the intensity of dependence on different compounds involves reducing their reinforcing proprieties. Response-reinforcement learning is dependent on NMDA receptor activation (Kelley *et al*, 1997). We consider that magnesium reduces reinforcing proprieties of different compounds by action on these NMDA receptors.

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