Magnesium in drug dependences

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Abstract. Magnesium decreases the intensity of some drug-induced dependences (e.g. opiates, nicotine, cocaine, amphetamine, ethanol, etc.). The main mechanism involved is a decreasing activity of central glutamatergic synapses, especially those involved in the reward system. There are many particularities of action for each drug dependence. Apart from the effects during emerging dependence, magnesium ions administered only during the withdrawal syndrome decrease the intensity of clinical symptoms. In some cases, Mg2+ decreased the relapse and reinstatement of cocaine and amphetamine intake. Administered alone, in the absence of any abused drug, Mg2+ has moderate stimulatory effects on the reward system and reinforcement, without inducing dependence. The existent data stress a modulatory role of Mg2+ in some drug-induced dependences. Therapeutic administration of magnesium decreases nicotine dependence and cocaine/amphetamine self-administration.

Key words: magnesium, pharmacodependence, morphine, nicotine, amphetamine, ethanol

Magnesium is involved in many central nervous processes both at presynaptic and postsynaptic levels. Changes in magnesium concentration exert diverse influences on neurons, in normal or pathological conditions. Pharmacodependence is a major contemporary medical issue. Addiction is generally defined as drug-induced physical and psychological dependence. Addiction is characterized by compulsive drug consumption, craving and withdrawal syndromes. Emerging addiction supposes different sources of reinforcement, different neuroadapative mechanisms and different neurochemical changes that deregulate the cerebral reward system [1]. Compulsive intake behaviour is the defining characteristic of addiction whereas drug reinforcement is a determinant of drug addiction. Koob and Vogel, analyzing animal models of self-administration, observed that i.v. self-administration is present in all drug-induced pharmacodependences [2]. Substances that induce pharmacodependence induce a strong and prolonged stimulation of reward system.

Neurotransmitters involved in drug-induced dependence

The existent data have shown that for inducing drug dependence there are complex neuronal circuits involved and a number of neurotransmitters that mediate and modulate synaptic transmission. Many neurotransmitters, including dopamine (DA), glutamate, serotonin, acetylcholine, GABA, endocannabinoids, endogenous opioid peptides and others have been involved in the dependence mechanism and in the behavioural abnormalities induced by drugs of abuse [3]. Dopamine is considered the most important molecule that triggers pharmacodependence. All substances that induce dependence strongly increase DA levels in the midbrain. Central DA plays a major role in reward [4-6], but other neurotransmitters are also involved (serotonin, endogenous opioids, excitatory aminoacids). Some substances responsible for pharmacodependence decrease DA re-uptake, whereas others increase DA central presynaptic release. DA acts as an agonist on...
5 types of receptors. Available data strongly support that D1, D2 and D3 receptors predominantly trigger pharmacodependence [7]. Some variations in the number of neuronal DA receptors, especially D2a and D2b receptors, could be involved in some forms of pharmacodependence (e.g. alcohol dependence) [8]. DA release from nigrostriatal nerve terminals and from other DA neurons depends not only on the activity of DA neurons but also on complex presynaptic regulations. Direct glutamatergic control of presynaptic DA release is very important and is mediated by NMDA and AMPA receptors located on DA presynaptic terminals [9]. As a result, magnesium and other bivalent cations acting on the reward system (but not only) may influence the molecular mechanisms of drug dependence.

Abrupt withdrawal of substances imposes neuronal adaptation, especially on the reward system area. Differences in neuroadaptation between glutamatergic and GABA-ergic systems in reward systems have a major role in the mechanism of the withdrawal syndrome [10]. Increasing activity of the glutamatergic system and decreasing GABA-ergic neurotransmission determines the symptoms of withdrawal syndrome. Magnesium depletion produces an increase in activity of the excitatory system by potentiating NMDA receptor stimulation [11] and influences the intensity of the withdrawal syndrome.

There are at least 3 mechanisms for this last action:
- decreasing Ca2+ entry in neurons through the L-type Ca2+-channels;
- the glutamate action as the main excitatory amino-acid is important during the withdrawal syndrome. It has been proved that the Ca2+-channel blocker (e.g. nimodipine) decreases the intensity of symptoms during withdrawal syndrome [12]. Magnesium acts in the same way;
- Vaupel et al. [13] have shown that NO- synthetase (NOS) inhibitors such as L-nitroarginine (L-NAME) reduce several signs of opiate withdrawal. This fact sustains the involvement of NO in the pathogeny of the withdrawal syndrome. Since Mg2+ also inhibits NOS, it may also decrease the intensity of the withdrawal syndrome. Opiate-induced withdrawal syndrome is the result of hyperactivity in presynaptic glutamate receptors [14].

There is a deficit in the intracellular concentration of Mg in heroin users, both in neurons and in the smooth vessel muscular cells [15, 16]. Mg2+ strongly inhibits the amplitude of NMDA-evoked potentials (EPSCs) in nucleus accumbens slices in control and morphine treated rats [17].

### Opiate dependencies

All narcotic analgesics (morphine-like drugs) determine drug dependence but heroin (diacetyl morphine) is the most frequent. Morphine-like substances produce a dose-dependent increase in dopaminergic activity in both ventral tegmentum and substantia nigra. In the brain, morphine has no direct effect on DA release and acts only via stimulation of NMDA receptors [18].

Naloxon, a µ receptor antagonist, does not significantly influence activity of DA neurons. Some data indicate an allosteric link between occupation of the NMDA-linked Ca2+ channels by Mg2+ ions and closure of the permeation gate [19]. Also, agonist binding on glutamate metabotropic receptors (mGluR1 and mGluR4) requires Ca2+ cations. It is important to observe that acting on µ receptors, morphine increases the presynaptic release of glutamate. This will stimulate DA release, which is strongly involved in drug dependence. Simultaneously, morphine acts directly on NMDA receptors and has a non-competitive antagonistic effect, decreasing calcium entry through channels linked with NMDA receptors [20]. Chronic administration of morphine decreases the sensitivity of NMDA receptors for binding magnesium (which behave as a partial agonist of Ca2+) [20]. Some metabotropic glutamate receptor subtypes require different bivalent cations for ligand bindings [21].

We consider that Mg2+ may decrease the intensity of morphine-induced drug dependence (and consequently the withdrawal syndrome) in rats through various mechanisms:
- by decreasing presynaptic release of catecholamines (including DA) - essential for the molecular mechanism of morphine dependence;
- by decreasing the glutamate effect on NMDA receptors in the brain. Intracellular Mg2+ acts directly on the Ca2+-NMDA receptor linked pathway and decreases the stimulation of these receptors [22]. Mg2+ links on N-site arginine in the NR1-subunit of NMDA receptor Ca2+ channels. An essential fact to explain the Mg2+ capacity for decreasing the intensity of morphine-induced pharmacodependence is its ability to significantly reduce presynaptic DA release resulting from glutamate activity on NMDA receptors. This magnesium effect can be seen at 1.2 mM Mg2+ concentrations, which can easily be reached in the human body [23]. Mg ions, both extracellular and intracellular, act on NMDA receptors. Li-Smerin et al. [24] have shown that intracellular Mg2+ ions block the single channel currents and modulate the gating kinetics of NMDA receptors.
Mg\(^{2+}\) deficiency during morphine-induced pharmacodependence decreases the intensity of naloxone-induced withdrawal signs in animals. This is not a direct effect of Mg\(^{2+}\) on the withdrawal syndrome because the magnesium administration ceased 24 h before naloxone administration [25, 26]. Our data are in agreement with Handy et al. [27], that showed that co-administration of dizocilpine (a non-competitive NMDA-receptor antagonist) and morphine prevented the development of morphine-induced dependence in the rat. The main mechanism for alleviating the intensity of dependence seems to be a magnesium-induced decrease in NMDA receptor activity (if it is administered during morphine-induced addiction). The brain DA level in mice was significantly increased following i.c.v. administration of CaCl\(_2\). Magnesium inhibits this Ca-induced DA release [9];

- by stimulating synthesis and action, at the receptor level, of the main inhibitory neuroaminoacids, GABA and taurine;
- by direct Mg\(^{2+}\) action on serotonin receptors and by increasing activity in the mesolimbic serotoninergic system. It has been proved that serotonin binding to 5-HT receptors in the hippocampus is magnesium-related. The activity of serotoninergic receptors is modulated by different bivalent cations (Mg\(^{2+}\), Ca\(^{2+}\), Zn\(^{2+}\)) [28]. The agonist binding to hippocampal 5-HT1A receptors is relatively insensitive to guanine nucleotides in the absence of Mg\(^{2+}\) [29]. In the absence of Mg\(^{2+}\), imbalances are produced between dopaminergic and serotoninergic systems toward dopaminergic one and an enhancement of dependence. In addition, Mg\(^{2+}\) increases sensitivity to agonists of some serotonin receptors [30].

Besides the capacity of Mg\(^{2+}\) to decrease the intensity of the withdrawal syndrome if administered during the induction of opiate addiction, Mg has shown beneficial effects if administered only during the withdrawal syndrome, too.

Chronic morphine treatment significantly decreases the sensitivity of NMDA EPSCs to Mg\(^{2+}\). One week after morphine withdrawal, the Mg\(^{2+}\)-effect was still significantly lower than in the control slices [17].

We consider there is a double influence of magnesium:

- on induction of drug addiction. For emerging pharmacodependence, the necessary time may vary considerably, as well as the number of substance administrations. This period may be as long as two weeks in the case of morphine and other opiates, but it may reach months/years in case of ethanol. Mg\(^{2+}\) ions, administered during the inducing of dependence, may modify the synthesis of neurotransmitters and the release profile, and therefore neurotransmitter action at the receptor level. The intensity of the withdrawal syndrome is reduced compared to the group that did not receive magnesium during the emergence of opiate dependence. As has been proved, withdrawal symptoms are directly correlated with dependence intensity, so it may be stated that magnesium significantly reduced the intensity of opiate dependence:

- a direct action on processes and symptoms during the withdrawal syndrome. There are data that Mg\(^{2+}\)-administered only during the withdrawal syndrome (after opiate ceasing) decreased some symptoms of withdrawal. This means a direct action on neuronal mechanisms is involved in withdrawal. This might be correlated with the fact that morphine decreased plasmatic and cellular magnesium levels [31].

In contrast to morphine-induced dependence (decreased by Mg\(^{2+}\)), morphine-induced analgesia is increased by Mg\(^{2+}\) [32]. Magnesium administration alone induces a significant analgesic effect in neuropathic and diabetic rats. At the same doses, magnesium enhances the analgesic effect of morphine in low doses.

The mechanisms involved in the enhanced Mg-induced analgesia are different from the Mg\(^{2+}\)-effect in opiate-induced dependence. Treatment using magnesium l-aspartate (732 mg/day) for 12 weeks decreases the frequency of relapse in heroin addicted patients treated with methadone. The urinary test was positive for 22.6% in the group of patients who received magnesium vs 46.4% in the placebo group [33]. Mg administration decreased the reintroduction of heroin intake during a methadone-maintenance program [34].

**Psychostimulant-induced dependence**

Psychostimulants are widely used and include amphetamine and its derivatives, cocaine, nicotine and caffeine. The intensity and time for emerging dependence vary according to the substance.

Each of these psychostimulants has some particularities regarding the mechanisms of action and the induction of pharmacodependence.

**Caffeine dependence**

Caffeine produces a weak dependence. It is considered that this dependence is mainly psychic. Caffeine and other methylxanthines act through more than one mechanism. The most important is the action as a
A competitive antagonist at the level of some adenosine receptors. This inhibitory effect is decreased by Mg$^{2+}$.

Adenosine receptors regulate both DA and glutamate levels. Nevertheless, the roles of A1 and A2A receptors are different. A2A receptor antagonists, such as MSX-3, significantly reduce DA and glutamate levels in the nucleus accumbens [35], [17]. A1 receptor antagonists such as caffeine increase the levels of these two neurotransmitters inducing dependence. As magnesium reduces the capacity of A1 receptor antagonists to stimulate DA release, this may be considered a mechanism that contributes to a reduction in the intensity of caffeine dependence.

Development of tolerance to caffeine-induced DA release in nucleus accumbens may explain its weak addictive properties. The influences of Mg$^{2+}$ on caffeine dependence are shown in Figure 1.

Figure 1. Influence of Mg$^{2+}$ on caffeine dependence (+ stimulating effect; - inhibiting effect).

A1 receptors are located pre-synaptically, in the region of glutamatergic fibers in the nucleus accumbens. Their antagonists (such as caffeine) increase glutamate levels. Glutamate stimulates DA release. Magnesium decreases NMDA receptor stimulation by glutamate, and this can be considered a second mechanism by which magnesium decreases caffeine dependence.

Nicotine dependence
Nicotine and opioids enhance DA release from the nucleus accumbens and substantia nigra evoked by L-glutamic acid (NMDA receptor stimulation). Magnesium reduces this DA release. Nicotine-induced stimulation of DA release is calcium dependent. We think that this is an essential mechanism by which Mg$^{2+}$ decreases nicotine and opiate dependence.
Mg\textsuperscript{2+} \[36\].

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 [9]. In this way, it appears as an increase in activity of NMDA receptors. Consequently the reward system is stimulated. Lena and Changeux [37] have shown that stimulation of pre-synaptic nicotine receptors into the brain lead to increased calcium concentrations.

Nicotine-induced stimulation of the reward system and reinstatement of drug seeking behaviour, studied by conditioned place preference paradigms in rats, show that calcium channels blockers (e.g. nimo-

dipine) attenuate the reinstatement of nicotine-induced place preference [38]. These facts conclude that Mg\textsuperscript{2+} (a partial antagonist of Ca\textsuperscript{2+} entrance through membrane channels) may decrease the nicotine stimulation of the reward system. Our data [25] and also that of Niemela et al. [39] have shown that in chronic smokers (more than 10 cigarettes/day), the plasmatic level of magnesium was significantly decreased compared with non smoking healthy subjects. We consider that the low levels of serum magnesium contribute to the emergence of nicotine dependence.

Stimulation of nicotine neuronal receptors induces an increase in the calcium entry into neurons and also increases glutamate release. It has been shown that nicotine also stimulates DA release in some brain areas similarly to opiates and other substances inducing dependence [36]. The intensity of nicotine addiction in heavy smokers (i.e. the number of daily smoked cigarettes) was significantly decreased after Mg\textsuperscript{2+} administration for 4 weeks [25].

The main mechanisms influenced by Mg\textsuperscript{2+} in nicotine dependence are: decreasing glutamate transmission (increased by nicotine) and activity of postsynaptic NMDA receptors in some brain areas (by blocking in part calcium channels coupled with these receptors). Mg\textsuperscript{2+} ions produce some effects close to psychomotor stimulants in a variety of behavioural situations. The intensity of effect is reduced compared to classical psychostimulants [40].

- Magnesium (as a partial antagonist of calcium entrance into the neuron) decreases glutamate release and glutamatergic transmission, stimulated by nicotine

- Magnesium decreases nicotine-induced pre-synaptic release of DA and other neuromediators.

- Increased magnesium concentration into the neuron decreases the sodium concentration and as a consequence decreases the stimulant effect of nicotine on nicotine receptors.

- Nicotine diminishes GABA synthesis and release in some brain areas by stimulation of nicotine pre-synaptic receptors. Magnesium may decrease the nicotine effect on GABA synthesis [37]. Also, GABA antagonizes some of the glutamate-induced stimulatory effects of NMDA receptors. Mg\textsuperscript{2+} may enhance some of the GABA effects and diminishes some effects of the excitatory aminoacids in drug dependence.

There are data that a magnesium deficit is involved in some clinical symptoms of drug dependencies. The influences of Mg\textsuperscript{2+} on nicotine dependence are shown in figure 2.

**Cocaine and amphetamine dependence**

Cocaine elevates extracellular DA level in the brain by inhibiting DA re-uptake. Selective destruction of mesolimbic DA neurons eliminates cocaine self-administration [41]. The nucleus accumbens is the most important area for cocaine reinforcement action [42]. Cocaine induces a rapid and significant loss of intracellular free Mg\textsuperscript{2+} [16]. A severe cerebrovascular spasm is favoured by this depletion. Cocaine (1-5 mg/kg) administered systemically in rats induces a significant and progressive deficit of intracellular free Mg\textsuperscript{2+} in whole brain [15].

Activation of NMDA receptors in DA receptor-containing cells is required in order to elicit the addictive properties of psychostimulants (cocaine, amphetamine, etc.) [43]. Activation of mesolimbic neurons is essential but is not the only important process involved in psychostimulant-induced dependence. It is considered that the balance between DA and 5-HT transmission is critical for dependence. Changes in this ratio are considered to be important for decreasing the intensity of amphetamine-induced addiction [44]. Data about serotoninergic neurons have shown an inhibitory effect upon mesolimbic DA neurons. An increase in extracellular 5-HT attenuates the stimulant effects produced by DA release from amphetamine-like drugs [45]. Among serotonin receptors, 5-HT2C exerts a tonic inhibitory influence over DA neurotransmission in the ventral tegmental area (VTA). Serotoninergic receptors inhibit DA transmission at VTA level by 2 ways: 1.a direct way - stimulation of 5-HT2C receptors on DA neurons decrease their activation and 2.a indirect way - stimulation by activation of 5-HT2C receptor agonists of GABA neurons in the ventral tegmentum. These neurons have an inhibitory effect on dopaminergic neurons. The presence of 5HT2C receptors at the level of
GABA neurons was confirmed [46]. Serotonin inhibits NMDA receptor currents [47].

5-HT and magnesium inhibition of NMDA receptor calcium channels is a very important feature to prevent over-activation of this receptor. Kloda and Adams [47] have shown that both substances bind differently the NMDA receptor-channel subunits. An NR1 subunit mutation strongly reduced the block induced by 5-HT. On the contrary, the block produced by Mg²⁺ is achieved by binding this cation to the NR2 subunit. These data suggest that both magnesium and 5-HT are necessary to decrease stimulation of NMDA receptors. The psychostimulant effect of cocaine depends on the serotonergic system [48]. Receptors for serotonin could be an important target for the development of drugs in treatment of cocaine addiction. Mg²⁺ influences serotonin - receptor binding and may influence in this way the intensity of cocaine addiction. Pharmacological influences in the 5-HT system may efficiently counteract the effects of cocaine withdrawal and can prevent relapse. Data show that the intake of magnesium L-aspartate decreased cocaine self-administration in cocaine dependent individuals [34]. Cocaine craving was lower in the Mg group (732 mg Mg/day, 12 weeks) compared to the placebo group.

In cocaine-dependent rats, MgCl₂ may replace cocaine for self-administration. The rats were kept in this way for 10 days without cocaine. In mice, after 0.5 mg/kg/day cocaine for 15 days, 125 mg/kg MgCl₂ in acute administration prevented the effect of chronic cocaine administration on mouse aggressivity [40, 49].

**Ethanol dependence**

Ethanol induces disturbances of DA and 5-HT transmission in the nucleus accumbens [50]. A decrease in plasmatic and cellular concentration of magnesium was observed in ethanol dependence that increases the activity of glutamate on NMDA receptors [51].

Stimulation of the glutamatergic system is important for ethanol addiction [51]. Clinical magnesium deficiency in alcohol-addicted patients was first
described in 1934. Administration of this cation decreases the symptoms during ethanol withdrawal syndrome. Data available show that the main mechanisms of magnesium action in decreasing the intensity of ethanol dependence are: (i) counteracting Ca\(^{2+}\) in some neurons, (ii) presynaptic releasing of excitatory aminoacids, (iii) activation of NMDA receptors by a declining Ca\(^{2+}\) entry into the channels linked with these receptors. Magnesium antagonizes calcium-induced stimulatory effects of ethanol action in the brain. The ability of calcium to prolong ethanol-induced sleep was inhibited by the administration of magnesium chloride. Ethanol increases the urinary elimination of magnesium [52]. Calcium channels appear to be involved in the regulation of ethanol intake. Antagonists of Ca\(^{2+}\) L-type channels decrease ethanol intake in Wistar rats and also the ethanol preference in the place preference paradigm [53]. Increasing GABA and GABAergic activities decreases the motivational properties of alcohol intake in rats [54]. Magnesium increases the activity of the GABAergic system and decreases ethanol dependence in this way. The mechanisms of Mg\(^{2+}\) on decreasing ethanol dependence intensity are shown in figure 3.

**Cannabinoid dependence**

In cannabis, delta-9 tetrahydrocannabinol (THC) is the active compound that induces dependence. Animals with a magnesium deficit exhibit enhanced THC effects. THC induces an aggressive behaviour in rats. Bac and German-Faltal [55] showed that THC-induced hyper-aggressiveness in rats increased with the severity of the magnesium deficiency. Endocannabinoid release (anandamide and 2-arachidonoyl-
glycerol) in the brain is calcium dependent [56]. We consider that Mg may decrease cannabinoid dependence, antagonizing this Ca$^{2+}$ effect.

**Hallucinogen dependence**

Hallucinogen substances induce a strong dependence, quite different to that induced by the above-mentioned substances. The main hallucinogen dependencies includes LSD and phencyclidine dependence.

There are no clear data referring to magnesium influence on LSD. It is proved that increasing magnesium and decreasing calcium concentration in the synaptic cleft determines LSD synaptic action. Kass et al. [57] suggested that LSD determines an inhibition, in some of the synapses, of the pre-synaptic re-uptake of neurotransmitters. Phencyclidine also produces a strong pharmacodependence. After stimulation of NMDA receptors, the noradrenalin (NA) efflux is decreased in incubated brain slices stimulated with phencyclidine and MgCl$_2$ 1.2 mM. There is a binding site for the phencyclidine within the complex of the receptor channel for the glutamate NMDA receptor [58]. Phencyclidine receptors are associated in the brain with NMDA receptors [59]. A partial blockade by Mg$^{2+}$ of the NMDA-coupled calcium channel could determine a decrease in activation of the phencyclidine receptor. Lerma et al. [60] have shown interactions between Mg$^{2+}$ and phencyclidine at the level of Ca$^{2+}$ channels coupled with NMDA receptors. Co-expression of NMDA and phencyclidine receptors as described by Kushner et al. [60] might facilitate Mg action to decrease the activity of phencyclidine receptors after cation action at the NMDA receptor level.

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**Figure 4.** Influence of Mg$^{2+}$ on drug dependence (- inhibiting effect).
Effects of magnesium on the reward system

Besides marking magnesium action in different forms of drug dependencies another problem is, what action does magnesium alone administer on the reward system and does its administration induce pharmacodependence? MgCl₂ produces psychomotor stimulant effects in some behavioral situations, but these effects are of more reduced intensity [40].

The influences of Mg²⁺ on drug dependence are summarized in figure 4.

Pharmacodependence was not observed after chronic administration of magnesium either in human clinics or in experiments on animals. There are influences of magnesium on the reward system. It was shown that during conditioned place preference (CPP), using MgCl₂, 15 mg/kg and 30 mg/kg influence rat behaviour and have a positive action, increasing the animal’s preference for the Mg-associated compartment [61]. The CPP paradigm indicates if a substance has an influence on the reward system. The fact that the animals prefer the Mg-associated compartment shows that this cation has a stimulant effect on the reward system (reinforcing properties).

References

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