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MANGANESE INTERACTIONS WITH DOPAMINERGIC SYSTEM

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MANGANESE INTERACTIONS WITH DOPAMINERGIC SYSTEM (Abstract): Manganese is a trace element with important involvement in the central nervous system functioning. The effects of manganese excess on central dopaminergic system in case of both basal nuclei and reward system are linked to important pathologic states such as Parkinsonism and cognitive impairment. Our data show that Mn²⁺ reduces the intensity of experimental morphine addiction in rats (manganese chloride unequally decreases several symptoms of opioid withdrawal syndrome – signs such as compulsive mastication, grooming and teeth chattering being particularly affected). Manganese chloride, administered during conditioning acquisition phase in rats, significantly reduces the intensity of morphine conditioned place preference. We believe that manganese interaction with dopaminergic circuits in the brain reward system represents one of the most important aspects of the action of bivalent cations at central nervous system level. Keywords: MANGANESE, DOPAMINE, BRAIN REWARD SYSTEM, MORPHINE-DEPENDENCE, PLACE PREFERENCE.

Bivalent cations, either macro- or trace elements, are present in different concentrations in the central nervous system (CNS). Most of them play complex roles in the functioning of CNS, neurons, glial tissue or blood vessels. There is increasing evidence referring to the complex regulatory action determined by the bivalent cations on CNS. This regulatory action has three different essential items: modulation of enzymatic activity (most enzymes contain a bivalent cation as co-factor or allosteric modulator); modulation of synthesis and activity of different neurotransmitters (presynaptic release, re-uptake etc); modulation of neurotransmitter action at receptor site.

Manganese is an essential trace element with important catalytic and structural roles. As in the case of other bivalent cations deficiency and excess, in case of Mn²⁺ misbalances dysfunctions in the activity of numerous organs and systems (including CNS) were identified. Mn²⁺ excess is more frequently encountered and has more severe consequences than Mn²⁺ deficiency, determining mainly neurological and psychiatric disturbances.

Human body contains approximately 10 – 20 mg of manganese. It is considered that serum Mn²⁺ level should be lower than 1.4 μg/100 mL. The most important Mn²⁺-dependent enzymes include: glycosyltransferase, phosphoglcomutase, different kinases, hydrolases (including phosphatases), decarboxylases, pyruvate carboxylase, peptidases (arginase), cholinesterase, and mitochondrial superoxide dismutase (1).
The highest CNS Mn\(^{2+}\) concentrations are in nucleus pallidus, as well as in other regions with predominant dopaminergic neurotransmission. Also, brain dopaminergic sites are concentrating most of the Mn\(^{2+}\) excess, both in case of chronic exposure or hepatoportal encephalopathy (2). There is no correspondence relationship between serum and brain Mn\(^{2+}\) concentrations: while increased Mn\(^{2+}\) serum concentration may revert to normal after exposure is stopped, brain Mn\(^{2+}\) levels continue to be increased. Little is known about Mn\(^{2+}\) passage through brain-blood barrier. Aschner et al., 1999 (3), showed that manganese, as a citric acid salt, is better captured by the cerebral tissue compared to free Mn\(^{2+}\) cations. In the lateral choroid plexus, there are mechanisms protecting against Mn\(^{2+}\) ions passage into the cerebral-spinal fluid in case of high blood Mn\(^{2+}\) concentrations (4). Sloot et al., 2004 (5), have shown that Mn\(^{2+}\) is captured by dopaminergic and GABAergic neurons in substantianigra, and that there are mechanisms for the axonal transport of the cation. Also, chronic Mn\(^{2+}\) exposure determines its accumulation into astrocytes (6). The most characteristic aspect regarding Mn\(^{2+}\) excess in the CNS is represented by the occurrence of Parkinson-like disease syndrome. Chronic Mn\(^{2+}\) administration and intoxication are used as experimental models of induced Parkinson disease in animals (7). Extrapyramidal phenomena can be reproduced, for example, by the administration of 5mg/kg/day Mn\(^{2+}\), for 2 to 8 weeks in rats.

I. Mechanisms of manganese-induced central nervous system toxicity

CNS is the main target of Mn\(^{2+}\) toxicity. Even though data on the mechanisms by which Mn\(^{2+}\) determines its toxic effect on the CNS are not very clear, the hypothesis of increased oxidative stress, followed by a reduction in mitochondrial anti-oxidant protection system, is ever more considered (8):

1. Fitsanakis et al., 2006 (9), have demonstrated that intra-cellular Mn\(^{2+}\) is sequestered by the calcium-importer system in the mitochondria, and that neuronal mitochondria are particularly sensitive to Mn\(^{2+}\) toxic activity (Mn\(^{2+}\) inhibits oxidative phosphorylation);

2. A possible explanation for the long term Mn\(^{2+}\) neurotoxic effect related to chronic exposure may be the following: excess brain Mn\(^{2+}\) cation levels are oxidized to superior valence forms, and therefore catecholamine, and particularly dopamine oxidation is enhanced (10; 11);

3. Manganese also determines an increase in H\(_2\)O\(_2\) neuronal generation, probably as a consequence of reduced catalase activity (12);

4. Also, the increased oxidative stress hypothesis to explain Mn\(^{2+}\)-induced neurotoxicity was suggested by Prabhakaran et al., 2008 (13), who incriminated NF-\(\kappa\)B induction and the activation of nitric oxide synthesis through NOS (nitric oxide synthase) as a probable mechanism for Mn\(^{2+}\) CNS toxic effects;

5. Manganese induces caspase activation and DNA fragmentation;

6. Another possible hypothesis for Mn\(^{2+}\) brain cytotoxic effects is linked to metabolism impairment. Glucidic metabolism is particularly affected. Especially in astrocytes, glycolytic activity inhibition may result in the accumulation of toxic glutamine.

Central dopaminergic systems are particularly affected by Mn\(^{2+}\) excess. A significant and long-lasting dopaminergic depletion (tens of years after exposure is stopped) is recognized as a consequence of
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Mn²⁺ exposure. Mn²⁺ excess is considered dopaminergic neurotoxin, and Hamai et al., 2001 (14), show that Mn²⁺ is highly effective in blocking dopaminergic neurotransmission. Chronic exposure to Mn²⁺ is associated with lesions in the basal ganglia neurons. Intrathecal Mn²⁺ administration in rats is followed by dopaminergic depletion, especially in the caudate-putamen regions. Manganese phosphate (MnPO₄) is more potent than manganese sulphate (MnSO₄) and manganese chloride (MnCl₂) in producing dopaminergic depletion (15). The selectivity of Mn²⁺ toxicity for the regions rich in dopamine does not have a clearly elucidated cause, but there are some partial explanations. For example, Anderson et al., 2007 (16), proved that Mn²⁺ accumulation in dopaminergic neurons in globus pallidus is at least partially dependent on dopamine transporter (DAT), as by inhibiting DAT with GBR12909 substance (1 mg/kg, 3 times a week, for 4 weeks) Mn²⁺ accumulation is stopped and Mn²⁺ levels show a significant decrease in that region. A study by Hirata, 2008 (17), contradicts the idea that toxicity determined by Mn²⁺ in the PC12 cell line is DAT-dependent, as Mn²⁺-induced DNA fragmentation is present in both PC12 cells over-expressing DAT and in PC12 control cells (although the latter are affected at slightly higher doses); however DAT inhibitors (such as mazindol, nomifensine, or GBR12909), inhibit MPP⁺-induced DNA fragmentation.

As dopaminergic systems are particularly sensitive to the influence of Mn²⁺ ions, Mn²⁺ causing, as shown above, dopaminergic depletion, several studies were focused on different aspects of the interactions between Mn²⁺ ions and dopaminergic neurotransmission, including dopamine synthesis, release, action at specific receptor site, re-uptake, and metabolism. Different Mn²⁺-induced effects on the above-mentioned aspects of dopaminergic neurotransmission were evidenced. Some of them are quite contradictory and some of the studies do not support the idea that Mn²⁺ impairs dopamine functions at any of its levels.

a. *Dopamine synthesis*. Bonilla et al., 1980 (18) reported that following Mn²⁺ chronic treatment in rats the enzymatic activity of L-tyrosine hydroxylase (an enzyme involved in catecholamine synthesis) is increased. The augmented enzymatic activity persisted in neostriatum, midbrain and hypothalamus on the third month and remained elevated only in neostriatum on the sixth month. After eight months a significant decrease in the activity of the enzyme was found in neostriatum with no changes in the remaining studied regions. Also, in male albino rats exposed to MnCl₂•4H₂O (1 mg/ml) through drinking water there is an initial increase in the stream dopamine level, followed by a period when concentration is almost normal (from 120 to 240 days) (19). Thereafter, the contents of dopamine declined significantly at 300 and 360 days of treatment. Mn²⁺, 125-520 μM in cell culture increases intracellular concentrations of L-Dopa (catecholamine precursor) (20). These findings are in agreement with the fact that human Mn²⁺ intoxication starts with a psychiatric phase bearing similarities to schizophrenia in which the primary disturbance has been suggested to be an over-activity of dopamine neurons. A totally different situation is in newborns compared to adults. Neonatal rats, intubated daily with distilled water, 25 or 50 μg MnCl₂/g/day for 14 or 21 days (starting from the day of birth) did not show significant changes in norepineph-
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Dopamine, serotonin and their metabolites in the striatum, hypothalamus, and nucleus accumbens, though Mn$^{2+}$ brain levels were significantly higher than in controls. The developing CNS may be able to counteract neurochemical changes caused by Mn$^{2+}$ exposure.

b. Dopamine release. Semama et al., 1995 (21) have demonstrated partial Mn$^{2+}$ blocking of calcium channels in renal blood vessels. If this action also takes place in the cerebral tissue, this may explain a possible Mn$^{2+}$-induced alteration of glutamate ability to stimulate dopamine release. On the other hand, chronic Mn$^{2+}$ exposure results in a marked decrease of in vivo dopamine release, in the absence of a change in markers of dopamine terminal integrity or dopamine receptors in the striatum (22).

c. Dopamine – specific receptors binding. Butterworth et al., 1995 (23) showed that Mn$^{2+}$ potentiates dopamine binding to specific receptors. On the other hand, Mn$^{2+}$ seems to determine a reduction in dopamine receptors antagonists binding to their specific sites. In monkeys with Mn$^{2+}$ intoxication, the specific D1 receptors antagonist SCH 23.390 expresses a lower binding to specific receptors compared to controls (24). Chronic manganism is associated with markedly decreased D2 receptor density, especially in the striatum (25).

d. Dopamine re-uptake. Chen et al., 2006 (26) proved in a study on primates (baboons) that acute manganese sulphate (MnSO$_4$) administration determines a decrease in dopamine binding to DAT (dopamine transporter), but a significant increase in DAT level (probably compensatory to the decrease in dopamine binding capacity), while dopamine re-uptake is inhibited.

Our data show a reduction in the intensity of both morphine physical dependence and morphine-induced conditioned place preference by Mn$^{2+}$. We have found a significant reduction in morphine dependence intensity by the administration of MnCl$_2$ (0.1 mEq/kg/day, 10 days) (27, 28). Compulsive mastication, teeth chattering and grooming are particularly reduced by manganese administration (p<0.01 vs. morphine-only treated group), while locomotor activity, weight loss, aggressive postures are moderately reduced (p<0.05). Global withdrawal score GellertHolzmann is also reduced (p<0.01). The influence on withdrawal symptoms is therefore unequal and dose-dependent (MnCl$_2$ administration, 0.05 mEq/kg/day, has no influence on morphine global withdrawal score, reducing only teeth chattering and grooming, 0.01<p<0.05). As MnCl$_2$ was administered during morphine dependence induction phase and not during withdrawal, we consider this not to be a direct effect of manganese on morphine withdrawal, but on the intensity of morphine dependence. The intensity of morphine induced conditioned place preference in rats is reduced by MnCl$_2$, (0.1mmol/administration, administered 2 hours before morphine, in the conditioning acquisition phase; 0.01mmol/kg/day, 10 days before preconditioning) (29). We believe that decreases in both morphine dependence intensity and morphine behavioral effects represent important proofs of the consequences of Mn$^{2+}$ excess and support that their mechanism is related to dopamine neurotransmission impairment. Glutamatergic system is particularly sensitive to manganese actions, glutamate being one of the neurotransmitters mainly involved in the addictive processes. A subacute manganese exposure (7 to 21 days) in mice is sufficient to alter presynaptic do-
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I. Manganese interactions with the dopaminergic system

Dopamine release in the striatum (30).

II. Clinical consequences of the interactions between manganese and dopaminergic neurotransmission and of manganese excess

Chronic Mn\(^{2+}\) intoxication is characterized by weakness, headache, muscle cramps, loss of appetite, apathy, insomnia, diminished libido, which are associated with psychotic reactions known as “locura manganica”. This “manganese madness” is characterized by aggressive manifestations and emotional lability. Characteristic clinical signs often include extrapyramidal symptoms such as bradykinesezia, tardive dyskinesia (myoclonic movements), akathisia, dystonia (31). Other symptoms are less common and include behavioral impairment. As a consequence of manganese toxicity, symptoms such as confusion, monotone voice, un-expressive face, spastic movements and disturbed gait, hallucinations, renal failure may also appear. Mn\(^{2+}\) excess also impairs cognitive capacity (learning and memorization skills). There is a very clear relationship between manganese excess and dopamine central circuits which explain the behavioral disorders and cognition impairment associated with Mn\(^{2+}\); taking this into consideration, new perspectives are opened for human clinical studies.

REFERENCES