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Research report

Influence of magnesium supplementation on movement side effects related to typical antipsychotic treatment in rats

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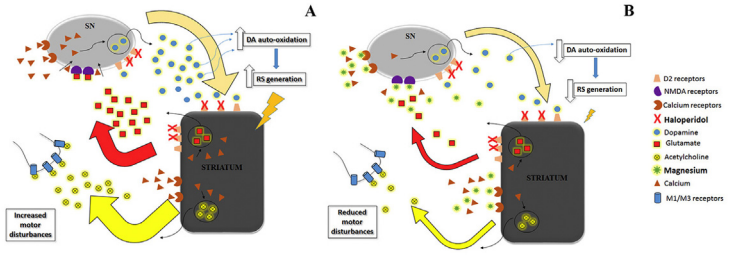
HIGHLIGHTS

- Extrapyramidal disturbances (ED) are side effects consequent to haloperidol treatment.
- ED occurs due to dopamine receptor blockade in the nigrostriatal system.
- ED are related to cholinergic activation and glutamatergic excitotoxicity.
- Mg_2^{++} supplementation inhibits Ca_2^{++} and blockade NMDA receptors.
- Mg_2^{++} supplementation protects against haloperidol-induced movement disturbances.

GRAPHICAL ABSTRACT



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ABSTRACT

Chronic use of typical antipsychotic haloperidolis related to movement disturbances such as parkinsonism, akathisia and tardive dyskinesia which have been related to excitotoxicity in extrapyramidal brain areas, requiring their prevention and treatment. In the current study we evaluated the influence of the magnesium on prevention (for 28 days before-), reversion (for 12 days after-) and concomitant supplementation on haloperidol-induced movement disorders in rats. Sub-chronic haloperidol was related to orofacial dyskinesia (OD) and catalepsy development, increased generation of reactive species (RS) and levels of protein carbonyl (PC) in cortex, striatum and *substantia nigra* (SN) in all experimental protocols. When provided preventatively, Mg reduced the increase of OD and catalepsy time 14 and 7 days after haloperidol administration, respectively. When supplemented after haloperidol-induced OD establishment, Mg reversed this behavior after 12 days, while catalepsy was reversed after 6 days of Mg supplementation.When Mg was concomitantly supplemented with haloperidol administration, OD and catalepsy were prevented. Moreover, Mg supplementation was able to prevent the RS generation in both cortex and SN, reducing PC levels in all brain areas evaluated. When supplemented after haloperidol, Mg reversed RS generation in cortex and striatum, decreasing PC levels in SN and striatum.The co-administration of haloperidol and Mg supplementation prevented RS generation in cortex, striatum and SN, and PC levels in the SN.These outcomes indicate that Mg supplementation may be a useful alternative to prevent movement disturbances resulting of classic antipsychotic pharmacotherapy as haloperidol.

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1. Introduction

Antipsychotic-induced extrapyramidal symptoms (EPS), such as acute dystonia, akathisia, parkinsonism, and tardive dyskinesia (TD), constitute a major problem for patients treated with antipsychotics and compromise treatment adherence and compliance [1–3]. TD is a potentially irreversible disorder associated with chronic first generation antipsychotic exposure and characterized by involuntary, stereotyped, and repetitive movements in different body parts [4]. Although the emerging use of second generation antipsychotics are related to lower risk to TD development, the expectation of being EPS-free antipsychotic drugs is not encouraging since most of the newer atypical antipsychotic agents may also induce varying degrees of EPS [5,6].

The pathophysiology of TD steel poorly understood but it has been suggested that the hypersensitivity of striatal post-synaptic dopamine receptors is implicated on it [7,8]. The exacerbation of dopamine metabolism causing by prolonged blockade of dopamine D2 receptors (D2R), lead to the generation of reactive species particularly in the basal ganglia consequently leading to neurodegeneration [9–11]. An enhancement of the glutamatergic transmission, in response of presynaptic dopamine receptors blockade, also participate on free-radicals formation, which has gained experimental support in the literature on involvement in the etiology of TD [9,12–15].

Magnesium (Mg) is the fourth most abundant mineral in the body and is recognized as a cofactor for more than 300 enzymatic reactions, including energy metabolism and nucleic acid synthesis and also essential for the regulation of blood pressure, insulin metabolism, cardiac excitability [16,17], neuromuscular conduction and neurotransmitter release [18]. In general, its actions are related to its physiological blockade of calcium channels [19–22]. Besides that, Mg plays a role on blocking N-methyl-D-aspartate (NMDA) receptor channels which is believed to have a great importance on physiological modulation of glutamate transmission involved in many neurological diseases, such as Alzheimer's disease, attention deficit hyperactivity disorder (ADHD) and Parkinson's disease [23–26].

Recently, a study from our group demonstrated a preventive and protect role of Mg supplementation in a reserpine-induced model of OD [27]. However, there is no more studies related withMg and the extrapyramidal effects.Therefore, the aim of this study is evaluate the influence of different periods of Mg supplementation in a sub-chronic haloperidol-induced model of OD.

2. Methods

2.1. Animals

Male *Wistar* rats weighing 250–320 g (about 3 months old) were used. Groups of three (±1) animals were kept in Plexiglas cages with free access to food (standard chow) and water in a room with controlled temperature (22–23 °C) and 12 h-light/dark cycle with lights on at 7:00 a.m. Animals were fed with standard chow *ad libitum* (PuroTrato®, RS, Brazil), which contains adequate levels of Mg following recommendations from the National Research Council (NRC, 1995), during all experiments. The experimental protocols were approved by the Animal Ethics Committee (Universidade Federal de Santa Maria – UFSM 064/2013), which is affiliated to the Council of Animal Experiments (CONCEA), following international norms of animal care and maintenance.

2.2. Drugs

Haloperidol decanoate (Haloperidol decanoate – Janssen-Cilag) was dissolved in Tween® and diluted to a final concentration of 1% Tween® with distilled water. The vehicle consisted of a 1%Tween® solution. Magnesium aspartate (Fragon do Brasil Farmacêutica Ltda) was dissolved in deionized water.

2.3. Experimental procedure

2.3.1. Experiment 1: preventive influence of Mg supplementation on the development of sub-chronic haloperidol-inducedOD

Twenty-eight rats were randomly designated to two groups of fourteen animals each (n = 14) and orally supplemented (once a day, by gavage) with magnesium aspartate solution (40 mg/kg of body weight in 1 mL deionized water) (Mg – magnesium group) [27,28] or deionized water (C – control group). After 28 days of oral supplementation, basal behavioralassessments were performed and subsequently one-half of each experimental group was administrated once a week with haloperidol solution (12 mg/kg of body weight in 1 mL vehicle – 1% Tween, intramuscular-i.m.) or vehicle (1% Tween® solution) [29,30], for 4 weeks. As a result, 4 experimental groups were established: control group (C); haloperidol group (H); magnesium group (Mg) and magnesium + haloperidol (MgH). Before each haloperidol injection all animals were submitted to the behavioral evaluations. One week after the lasthaloperidol/vehicle administration all animals were submitted to last behavioral evaluations as described (Fig. 1A).

2.3.2. Experiment 2: influence of Mg supplementation on the reversal of sub-chronic haloperidol-induced OD

Twenty-eight rats were randomly designated to two groups of fourteen animals each (n = 14) and administrated with haloperidol solution (H group- 12 mg/Kg/mL; i.m.) or vehicle (C group), once a week, for 4 weeks. Seven days after the first H/vehicle administration, OD development and catalepsy time was quantified (basal) and subsequently, one-half of each experimental group was immediately supplemented once a day (by gavage) with magnesium aspartate (40 mg/Kg/mL) (Mg and MgH groups) or deionized water (C and H groups). OD and catalepsy time was quantified during the subsequent days (each 72 h). Mg supplementation was maintained throughout the behavioral assessment period until a significant difference between MgH and H groups was observed (15 consecutive days) (Fig. 1B).

2.3.3. Experiment 3: influence of Mg supplementation together with haloperidol administration on the development of OD

Twenty-four rats were randomly designated to four groups (n = 6): C (control), H (haloperidol), Mg (magnesium) and MgH (magnesium + haloperidol). All the animals were submitted to an evaluation of OD and immediately after administrated with haloperidol solution (H and MgH group – 12 mg/Kg/mL) or vehicle (C and Mg groups), once a week for four weeks. Concomitantly, animals were orally supplemented with magnesium aspartate (Mg and MgH groups – 40 mg/Kg/mL) or deionized water (C and H groups). OD was quantified previously to each haloperidol administration and catalepsy time one time seven days after de last haloperidol administration. Mg supplementation was maintained throughout the protocol (total of 28 days) (Fig. 1C).

2.4. Behavioral assessments

2.4.1. Orofacial dyskinesia (OD)

Rats were placed individually in cages (20 × 20 × 19 cm) containing one mirror under the floor and one behind the back wall of the cage to allow behavioral quantification when the animal

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