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Continuous infusion of manganese improves contrast and reduces side effects in manganese-enhanced magnetic resonance imaging studies

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ABSTRACT

The ability to administer systemically high doses of manganese as contrast agent while circumventing its toxicity is of particular interest for exploratory MRI studies of the brain. Administering low doses either repeatedly or continuously over time has been shown to enable the acquisition of satisfactory MRI images of the mouse brain without apparent side effects. Here we have systematically compared the obtained MRI contrast and recorded potential systemic side effects such as stress response and muscle strength impairment in relation to the achieved contrast. We show in mice that administering $MnCl_2$ via osmotic infusion pumps allows for a side-effect free delivery of a high cumulative dose of manganese chloride (480 mg/kg bodyweight in 8 days). High contrast in MRI was achieved while we did not observe the weight loss or distress seen in other studies where mice received manganese via fractionated intraperitoneal injections of lower doses of manganese. As the normal daily conduct of the mice was not affected, this new manganese delivery method might be of particular use to study brain activity over several days. This may facilitate the phenotyping of new transgenic mouse models, the study of chronic disease models and the monitoring of changes in brain activity in long-term behavioral studies.

1. Introduction

The ability of the paramagnetic manganese ion Mn^{2+} to enter neurons via voltage-gated calcium channels makes it a unique and valuable magnetic resonance contrast agent which allows monitoring the activation pattern of the entire brain. Manganese as a contrast agent was shown to be directly sensitive to brain activation, accumulating in higher amounts in the more active brain regions (Lin and Koretsky, 1997). Hereby it increases the visibility of these brain regions (Natt et al., 2002) in a manner assumed proportional with their neuronal density, function, and the presence of bivalent metal transporters (Thompson et al., 2007). This is of particular interest for studies of brain activation in rodents without confounding effects of anaesthesia.

Visualizing the entire brain requires that manganese is administered systemically. Due to limited blood-brain barrier penetration, it is necessary to administer high doses (Lee et al., 2005), in order to ensure a sufficiently high manganese uptake in the brain. At high doses however, manganese displays systemic toxicity. While in humans and other primates the presence of high amounts of manganese in the body mainly leads to Parkinson-like side-effects (Pal et al., 1999), in rodents these neurological side-effects are less pronounced (Dodd et al., 2005) and are replaced by systemic toxicity in the form of acute liver and heart failure (Gerber et al., 2002). In manganese-enhanced magnetic resonance imaging (MEMRI) studies in rats with doses of 80 mg/kg, side effects included locomotor deficits, weight loss and reduced food intake (Eschenko et al., 2010a). These systemic side effects associated with manganese toxicity may interfere with the experimental design and outcome, particularly in studies of brain activation under prolonged activity. While manganese has been used as an MRI contrast agent for several decades, its systemic toxicity remains a challenge up to this day (Malheiros et al., 2015).

Therefore, alternative protocols of systemic administration of manganese have been suggested, meant to circumvent its systemic toxicity. The fractionated approach consists of repeated intraperitoneal (i.p.) injections of small amounts of manganese at regular intervals (usually daily), which has been shown to lead to an increase in contrast in the rodent brain (Bock et al., 2008). At doses as low as 30 mg/kg

Abbreviations: Kg, kilogram; I.P., intra-peritoneal; MEMRI, manganese-enhanced MRI; Mg, milligram; $MnCl_2$, manganese chloride; S.C., subcutaneous

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bodyweight injected daily intra-peritoneally and cumulating to a total dose of 240 mg/kg bodyweight over 8 days, the manganese administration circumvented acute systemic toxicity and severe stress response in mice (Grunecker et al., 2010), although more subtle side effects such as weight loss were still present. Another study reports having to euthanize mice after i.p. injections of 60 mg/kg bodyweight due to obvious toxicity symptoms such as tremor or convulsion persisting for longer than 3 min after injection, or lethargy observed 24 h post injection (Bade et al., 2015). In rats, subcutaneous injections of as little as 32 mg/kg bodyweight manganese chloride significantly decreased wheel-running activity in a dose-dependent and long-lasting manner (Eschenko et al., 2010a). The infusion approach involves administering the manganese continuously with the aid of an implanted osmotic pump, which produces in time a satisfactory amount of contrast in the rodent brain (Eschenko et al., 2010a; Mok et al., 2012; Sepulveda et al., 2012). In mouse models, daily doses of manganese as low as 30 mg/kg bodyweight administered via osmotic pumps have allowed a significantly increased contrast after 3 weeks of continuous administration, but have been accompanied by significant changes in gait parameters (Sepulveda et al., 2012). In a comparable manner, Mok and colleagues have been able to administer daily manganese doses of 60 mg/kg bodyweight for 3 days and obtained a significant increase in contrast with no observable alterations of the animals' well-being (Mok et al., 2012). In rats, a cumulative manganese dose of 80 mg/kg bodyweight has been infused continuously over 7 days with no significant changes in food and water intake and no significant decrease in wheel-running activity (Eschenko et al., 2010b). Although these protocols have successfully been used in both mice and rats studying e.g. stress and anxiety (Knapman et al., 2012; McGuire et al., 2013), learning (Gildish et al., 2012; Kleinknecht et al., 2012), reward and addiction behaviour (Dudek et al., 2014; Hoch et al., 2013), and traumatic brain injury (Rodriguez et al., 2015) very little still is known about potential systemic side effects, such as motor impairment or a stress response that may confound the outcomes of such studies (Eschenko et al., 2010a; Jackson et al., 2011).

In the present study we therefore investigated the possibility of administering cumulative doses of 240 and 480 mg/kg $MnCl_2$ over a period of 8 days via either daily i.p. injections (IP) or osmotic pump infusion (OP). The aims of this study were: (1) to compare the MRI signal enhancement over time while employing two different methods of administering manganese chloride systemically to normally behaving C57BL/6J mice, and (2) to assess potential systemic side effects such as stress response and muscle strength impairment and relate them to the obtained MRI contrast.

2. Materials and methods

2.1. Animal groups

C57Bl6J 10 weeks old male mice were administered daily doses of $MnCl_2$ for 8 days. As shown in Table 1, group IP30 (n=8) received daily i.p. injections of 30 mg/kg $MnCl_2$, and groups OP30 (n=7) and OP60 (n=10) received continuous infusions of 30 mg/kg and 60 mg/kg $MnCl_2$ respectively (Sigma Aldrich, St Louis, MO, USA).

Table 1
Experimental groups.

Treatment group	N	Administration route	Manganese daily dose (mg/kg bodyweight)	Manganese cumulative dose (mg/kg bodyweight)
IP30	8	I.P. injections	30	240
OP30	7	S.C. osmotic pump	30	240
OP60	10	S.C. osmotic pump	60	480
OP0	4	S.C. osmotic pump	0	0
Blank	4	No treatment	0	0

Two aspects were of consequence for the formation of the groups and the number of mice attributed to each group. Firstly, while both daily manganese doses of 30 and 60 mg/kg bodyweight are given via osmotic pumps, only 30 mg/kg bodyweight manganese is administered via i.p. injections. A corresponding IP60 group would have to receive daily injections of manganese at a dose of 60 mg/kg bodyweight. Previous studies (Bade et al., 2015; Grunecker et al., 2010) have already reported visible side effects after injecting mice with manganese doses of 60 mg/kg bodyweight, and even having to euthanize mice as a consequence of the incurred toxicity. Secondly, the three groups receiving manganese were initially planned to contain 7 animals. An extra animal was added to group IP30 and 3 extra animals were added to group OP60 in order to accommodate possible exclusions due to unforeseen events and, in the case of group OP60, possible toxicity due to the high dose and long exposure time. As neither occurred, all the animals that were employed in the study could be included in the analysis.

Continuous administration was achieved via ALZET mini-osmotic pumps model 1002 (DURECT Corporation, Cupertino, CA, USA). The metal flow moderators were replaced with PEEK flow moderators for MRI compatibility. Over 8 days, this resulted in cumulative doses of 240 mg/kg $MnCl_2$ for groups IP30 and OP30, and 480 mg/kg $MnCl_2$ for group OP60. Two additional control groups were used: group OP0 (n=4) which was implanted with osmotic pumps containing phosphate buffer 0.09% saline solution to account for the potential discomfort caused by the presence of the pump, and group Blank (n=4) which did not receive any treatment.

All animals were housed individually in enriched ventilated cages, were granted 14 days of accommodation prior to the experiments and were kept in an isolated room, secluded from any other experimental activity and interference. The light/dark cycle was set to 7 a.m./7 p.m. and the cages were enriched with tissue paper and cardboard tunnels. The behavior and health status of the mice, as well as the body weight, were evaluated daily according to the European Mouse Phenotyping Resource of Standardized Screens guidelines (EMPRESS) (Brown et al., 2005) by two independent observers blinded to the experimental setup. Markers included body position, tremor, palpebral closure, coat appearance, whiskers, lacrimation, defecation, gait, and tail elevation. At pre-decided time points, the animals were submitted to muscle strength tests and blood sampling to determine corticosterone levels, according to the scheme depicted by Fig. 1. Prior to the experiment, the mice were submitted to three muscle strength tests for training purposes.

2.2. Osmotic pump implantation

Manganese chloride tetrahydrate BioReagent (Sigma Aldrich) was used for preparing the manganese solutions. Appropriate amounts were dissolved in 1x sterile phosphate buffered saline (10x, BioPerformance Certified, Sigma Aldrich) for each mouse, dependent on its body weight, to create individual stock solutions. Osmotic pumps filled with phosphate buffered saline 1x were made for the control group OP0. The pumps were subsequently primed overnight in sterile 0.9% saline solution (BioXtra, Sigma Aldrich) at 37 °C.

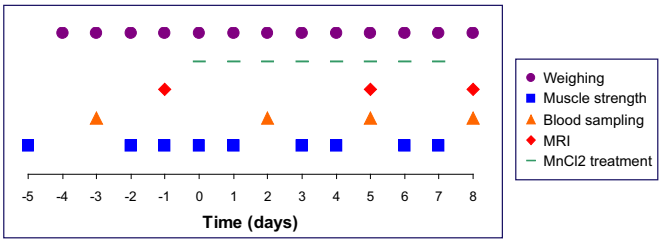

Fig. 1. Experimental setup.

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