Brain Research 1689 (2018) 54–62

Contents lists available at ScienceDirect

Brain Research

journal homepage: www.elsevier.com/locate/bres

Research report

Memantine treatment of juvenile rats with kaolin-induced hydrocephalus

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ARTICLE INFO

Article history:
Received 18 December 2017
Received in revised form 9 March 2018
Accepted 1 April 2018
Available online 3 April 2018

Keywords:
Behavior
Corpus callosum
Excitotoxicity
Hydrocephalus
Memantine
NMDA receptor

ABSTRACT

Memantine is a selective, non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist that has previously been shown to have neuroprotective qualities in some animal models of neurologic disease. We hypothesized that memantine therapy would improve behavioral, neuropathological, and/or biochemical outcomes in juvenile rats with kaolin-induced hydrocephalus. Three-week old rats received an injection of kaolin (aluminum silicate) into the cisterna magna. Magnetic resonance imaging was performed one week later to assess ventricle size and stratify rats to three treatment groups. Rats were blindly treated daily for three weeks with saline or 10 or 30 mg/kg/day memantine. Behavior measures were performed weekly. Histologic and biochemical evaluations were performed at termination. Hydrocephalic rats showed no differences in weight among treatment groups. Memantine treatment stabilized ventricular enlargement in both low and high dose groups. The high dose group exhibited increased motor activity in open field chambers compared to the vehicle-treated group. However, there were no significant differences between the three hydrocephalic treatment groups for other behavioral tasks. Ventriculomegaly was associated with periventricular white matter damage. Glial fibrillary acidic protein (GFAP) content was higher in the low dose memantine group compared to vehicle-treated group, but there were no differences in GFAP-immunoreactive astrocytes or Iba-1- immunoreactive microglia between groups. Memantine therapy stabilized ventricular expansion and improved some behavioral measures but did not reduce brain tissue changes in juvenile rats with kaolin-induced hydrocephalus.

1. Introduction

Hydrocephalus is a characterized by enlargement of the cerebral ventricles due to altered flow of cerebrospinal fluid (CSF) (Rekate, 2009). The brain damage has contributions from both mechanical forces and metabolic changes (Del Bigio, 2004). As ventriculomegaly progresses, the surrounding white matter is compressed with an associated reduction in blood flow and eventually dysfunction and destruction of axons and oligodendroglia (Del Bigio, 2010). In rats with kaolin-induced hydrocephalus, mRNA expression of the extracellular glutamate/aspartate transporter (GLAST) was shown to increase in periventricular regions (Masago et al., 1996). The excitatory amino acids glutamate and aspartate were increased in the cerebrum of immature rats with kaolin-induced hydrocephalus (Del Bigio and Vriend, 1998). The same amino acids are increased in the CSF of hydrocephalic humans (Engelson et al., 1985). Together these suggest that excitotoxicity might contribute to hydrocephalic brain damage.

Glutamatergic excitotoxic effects can occur through specific ionophoric receptor subtypes including N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-4-isoxazolpropionic acid (AMPA), and kainate receptors (Wang and Qin, 2010). Memantine (1-amino-3,5-dimethyladamantane) is a moderate affinity, non-competitive extrasynaptic antagonist that selectively binds to NMDA receptor-operated cation channels, thereby stabilizing the Ca^{++}-dependent desensitized state (Glasgow et al., 2017; Majlath et al., 2016). Numerous experimental studies have shown that memantine protects neurons and axons in a variety of neurological conditions including acute ischemia, excitotoxicity, allergic encephalomyelitis, glaucoma, and repetitive traumatic brain injury (Mei et al., 2018; Parsons et al., 1999). Memantine has been used in

Abbreviations: ANOVA, analysis of variance; CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; GFAP, glial fibrillary acidic protein; MR, magnetic resonance; NMDA, N-methyl-D-aspartate; SVZ, subventricular zone.

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https://doi.org/10.1016/j.brainres.2018.04.001
0006-8993/

a large number of clinical trials for stroke, psychiatric diseases, pain, migraine, Alzheimer disease, and vascular dementia (Majlath et al., 2016; Peng et al., 2013); in the latter, chronic white matter hypoperfusion is similar to that which occurs in hydrocephalus.

Memantine is considered safe for use in adults with dementia (up to 50 mg daily) (Kavirajan, 2009) and children age 6–12 years with autism (up to 15 mg daily) (Aman et al., 2017). Anecdotal evidence also suggests the possible value and tolerance of memantine for managing some types of childhood epilepsy (Pierson et al., 2014). Adverse effects of memantine are typically minor and rare: they include dizziness, irritability, and somnolence. Memantine does not appear to be toxic to the developing rat brain (Manning et al., 2011), and is a candidate drug for treating neonatal brain injury (Juul and Ferriero, 2014), but there are no specific data concerning safety or efficacy in very young humans.

Memantine was previously reported to have therapeutic effects in experimental hydrocephalus. Three-week old rats were given memantine (20 mg/kg intraperitoneal) daily for 2 weeks starting 1 day after kaolin injection, although it was not determined if hydrocephalus had been successfully induced. Histologic evaluation showed degenerative changes in the CA1 and CA2 hippocampal regions of hydrocephalic rats, and a partial reduction of this change in association with memantine treatment. The authors also reported a slight decrease in nitric oxide synthase immunoreactive neurons after memantine treatment (Cabuk et al., 2011).

Because the data concerning protection in hydrocephalus are limited, we thought it important to expand the investigation of memantine in experimental hydrocephalus. We have previously used 3-week-old rats with kaolin-induced hydrocephalus to screen for structural, behavioral, and histologic therapeutic effects (Del Bigio and Massicotte, 2001; Di Curzio et al., 2014; Khan et al., 2003). We hypothesized that memantine would be associated with a therapeutic effect in young rats with kaolin-induced hydrocephalus.

2. Results

2.1. Mortality

Of the 39 rats injected with kaolin on P21, 9 rats developed tonic-clonic seizures, a complication we have not previously seen (see Discussion); they died shortly after kaolin injection. Seizures were averted by gradually reversing the anesthesia. We were left with 30 rats (n = 29 kaolin injected, n = 1 saline injected). One rat experienced major neurological deficits due to severe hydrocephalus and was euthanized at P35. The remainder completed the 3-week drug trial and were sacrificed at ~P52.

2.2. Ventricle size on magnetic resonance imaging

MR images obtained 2 days after the kaolin injections showed mild ventricular enlargement in the lateral and fourth ventricles of all kaolin injected rats. At 7 days post-kaolin injection (P28), MR images demonstrated progressive ventriculomegaly (both $p < 0.01$, ANOVAs) (Figs. 1 and 2). Hydrocephalic rats were then strat-

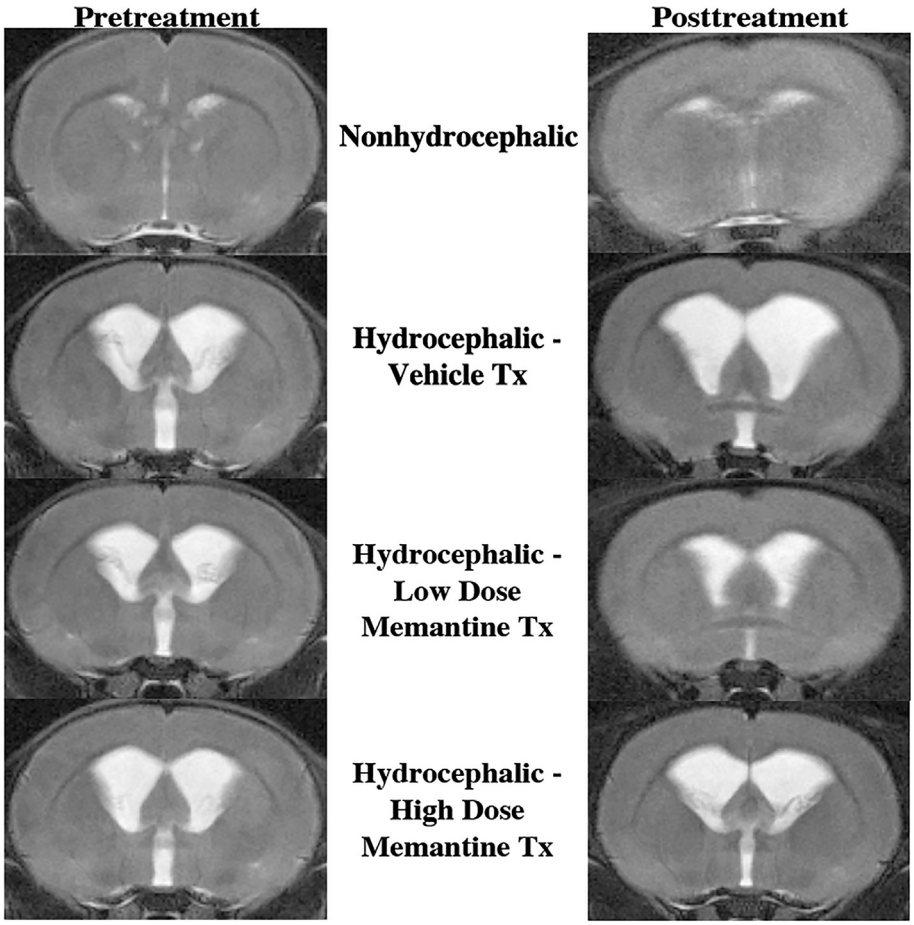

Fig. 1. T2-weighted magnetic resonance (MR) images of rat brain coronal slices showing ventricular enlargement 1 week after kaolin injections (Pretreatment column) and after 3 weeks drug therapy (Tx) (Posttreatment column). Cerebrospinal fluid (CSF) appears white in the lateral and third ventricles. The nonhydrocephalic rat brain had very small lateral ventricles. Hydrocephalic rats that received vehicle treatments had slightly larger ventricles than memantine treated hydrocephalic rats (see Fig. 2 for quantitative data).