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Kaolin-induced ventriculomegaly at weaning produces long-term learning, memory, and motor deficits in rats

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ABSTRACT

Ventriculomegaly occurs when there is imbalance between creation and absorption of cerebrospinal fluid (CSF); even when treated, long-term behavioral changes occur. Kaolin injection in the cisterna magna of rats produces an obstruction of CSF outflow and models one type of hydrocephalus. Previous research with this model shows that neonatal onset has mixed effects on Morris water maze (MWM) and motoric performance; we hypothesized that this might be because the severity of ventricular enlargement was not taken into consideration. In the present experiment, rats were injected with kaolin or saline on postnatal day (P)21 and analyzed in subgroups based on Evan's ratios (ERs) of the severity of ventricular enlargement at the end of testing to create 4 subgroups from least to most severe: ER0.4–0.5, ER0.51–0.6, ER0.61–0.7, and ER0.71–0.82, respectively. Locomotor activity (dry land and swimming), acoustic startle with prepulse inhibition (PPI), and MWM performance were tested starting on P28 (122 cm maze) and again on P42 (244 cm maze). Kaolin-treated animals weighed significantly less than controls at all times. Differences in locomotor activity were seen at P42 but not P28. On P28 there was an increase in PPI for all but the least severe kaolin-treated group, but no difference at P42 compared with controls. In the MWM at P28, all kaolin-treated groups had longer path lengths than controls, but comparable swim speeds. With the exception of the least severe group, probe trial performance was worse in the kaolin-treated animals. On P42, only the most severely affected kaolin-treated group showed deficits compared with control animals. This group showed no MWM learning and no memory for the platform position during probe trial testing. Swim speed was unaffected, indicating motor deficits were not responsible for impaired learning and memory. These findings indicate that kaolin-induced ventriculomegaly in rats interferes with cognition regardless of the final enlargement of the cerebral ventricles, but final size critically determines whether lasting locomotor, learning, and memory impairments occur.
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1. Introduction

Ventriculomegaly (VM) occurs when there is an imbalance between the production and absorption of cerebrospinal fluid (CSF). Coupled with a frequent increase of intracranial pressure, VM leads to impairments in widespread regions of the CNS (Air et al., 2010; Budde et al., 2008; Shirane et al., 1992; Tashiro and Drake, 1998; Yuan et al., 2009; Ding et al., 2001a,b) (reviewed in Del Bigio (2004); McAllister et al. (1991)), especially the corpus callosum, periventricular white matter, fornix, internal and external capsules, as well as other white matter regions (Air et al., 2010; Chumas et al., 1994; Del Bigio et al., 1997b; Del Bigio and Zhang, 1998; Jiang et al., 2006; Richards et al., 1995; Shirane et al., 1992; Tashiro and Drake, 1998). White matter damage has been reported to underlie some of the poor behavioral outcomes in children with VM (Del Bigio et al., 2003; Fletcher et al., 1992, 1996), however, current clinical evaluation of such damage remains limited by the inability to quantify damage non-invasively in such a way that is sensitive, specific, and

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predictive. Animal models of VM have been developed to better understand the progression of damage and predict outcome.

While VM can be induced by a number of different processes, one way to induce it mechanically in animals is by kaolin injection in the cisterna magna. Kaolin-induced VM can cause a loss of dopamine neurons in the substantia nigra in adult rats and significantly reduce levels of other monoamines (Chovanes et al., 1988; Hwang et al., 2009; Lovely et al., 1989). These decreases in monoamines are concurrent with reductions in locomotor activity beginning 3 days after treatment and becoming more severe by 4 weeks (Hwang et al., 2009). Similarly, kaolin-treated adult rats spend more time in closed arms of an elevated plus-maze 3 days after injection, but spend less time in closed arms 4 weeks later (Hwang et al., 2011), suggesting that effects on anxiety are transient. In addition to reductions in dopaminergic neurons, kaolin treated rats show increases in cholecystokinin and decreases in neuropeptide-Y 3 days post-treatment, with no differences by 4 weeks. During active avoidance learning, kaolin-treated rats had increased reaction times to escape when classified as having moderate or severe VM compared with controls (Kuchiwaki et al., 1994).

Kaolin-induced VM on postnatal day 1 (P1) produces reductions in weight gain in rats classified as having severe VM by P19 compared with controls (Khan et al., 2006). Magnetic resonance imaging of VM severity on P7 and P21 in the Khan et al. (2006) study showed that enlargement of the ventricles was stable throughout the 14 days between scans, such that animals did not change from mild to severe VM during this time or vice versa. Furthermore, the kaolin-induced VM animals showed no developmental delays in a number of behaviors, although some impairment in Morris water maze (MWM) latency to reach the escape platform was observed in the most severely affected VM rats compared with controls (Khan et al., 2006). This increase in latency to find the platform may be explained by the slower swimming speeds of the VM animals reported in this study (Khan et al., 2006). Consistent with a lack of spatial learning changes, these authors were unable to demonstrate MWM deficits when animals were injected with kaolin on P21 (Khan et al., 2003). These kaolin-treated animals also showed no changes in body weight, locomotor activity, or swimming ability. Inconsistent differences in MWM learning (i.e., deficits on one trial of a day but not the last trial of the day) were observed in another study where animals received kaolin on P21 (Del Bigio et al., 1997a). The kaolin-treated animals showed body weight reductions suggesting a greater effect was achieved in this experiment. Previous reports have also demonstrated weight reductions with this model (Deren et al., 2009, 2010; McAllister et al., 1985). While a number of reasons related to timing of injection or other procedures may explain the lack of effect following kaolin in some experiments, one major factor not accounted for above is the severity of VM. The VM induced by kaolin is not consistent between animals (McAllister et al., 1985, 1991), therefore identifying the magnitude of VM in relation to outcome may improve the model and explain past inconsistencies. In order to characterize in vivo changes to white matter, diffusion tensor imaging (DTI) can be useful. VM increases astrogliosis and microgliosis (Deren et al., 2010; Miller and McAllister, 2007) and these changes correlate with abnormal DTI measures (Yuan et al., 2010). The abnormal DTI data in a series of WM regions of interest from a subset of the animals used in the present study have been reported previously (Yuan et al., 2012). In the present study, the behavioral outcome data were analyzed in association with the DTI data to explore the potential underpinnings of functional changes. It should be noted that the present study was designed to examine the behavioral consequences of kaolin-induced VM that begins at a time in brain development that correlates with human infancy based on comparative anatomy (Clancy et al., 2007), since the infantile period is when hydrocephalus most commonly develops clinically. We also accounted for the severity of VM after testing to address what appears to be inconsistencies identified in this area of research as noted above. In order to do this, we analyzed the behavioral data by Evan's ratio (ER) subgrouping.

2. Materials and methods

2.1. Animals and treatments

Male Sprague-Dawley rats (Charles River, Raleigh, NC) were obtained on P14 with their dams and allowed to acclimate to the housing conditions of the vivarium at Cincinnati Children's Research Foundation. The vivarium is fully accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care. The vivarium is pathogen free and uses the Modular Animal Caging System (Alternative Design, Siloam Spring, AR) with HEPA filtered air that is supplied via the Flex-Air System (Alternative Design, Siloam Spring, AR) at 30 air changes/h. Water was provided ad libitum with the Lixit automated system (SE Lab Group, Napa, CA). Each cage (polysulfonate cages 26 cm × 48 cm and 20 cm tall) had ad libitum food, contained woodchip bedding, and a semicircular stainless steel enclosure to provide environmental enrichment (see Vorhees et al. (2008)). Animals were maintained on a 14 h light:10 h dark cycle. All procedures were approved by the Institutional Animal Care and Use Committee of Cincinnati Children's Research Foundation and conform to animal use guidelines set forth by the National Institutes of Health.

On P21, the animals were weaned and divided into two groups: kaolin injected (VM, $n = 30$ with 2 deaths, final $n = 28$) or saline injected (SAL, $n = 30$ with 2 deaths, final $n = 28$). VM animals were anesthetized with isoflurane (1–4%) and injected with a solution of 30–50 μl kaolin (25%, w/v in sterile saline) percutaneously over 10 s into the cisterna magna as described previously (Yuan et al., 2010, 2012). For the SAL animals the same volume of sterile physiological saline was injected using the same procedures. Animals recovered all reflexes prior to being housed with a littermate for 1 week prior to the start of behavioral testing. All animals were weighed one day before surgery, daily for 1 week after surgery, and weekly thereafter (P35, 42, 49).

2.2. Behavioral assessment

Animals had behavioral testing at two ages: firstly, one week following surgery (starting on P28) and then secondly, three weeks after surgery (starting on P42). All behavioral tests were conducted by a technician blinded to the condition of each animal, although VM was observable in some of the animals.

2.3. Locomotor activity

On P28, animals were tested for spontaneous locomotor exploration/activity in 41 cm × 41 cm test chambers (Accuscan Instruments, Columbus, OH). Animals were allowed to explore the chamber for 60 min and data were captured in 5 min intervals. The dependent measure was the amount of horizontal activity (measured in photobeam interruptions). Animals were retested in the same apparatus on P42. The chambers were cleaned with 70% ethanol between animals.

2.4. Acoustic startle with prepulse inhibition (PPI)

Acoustic startle with prepulse inhibition was tested beginning at least 1 h after locomotor activity. Acoustic startle reactivity was measured in an SR-LAB apparatus (San Diego Instruments, San Diego, CA). Animals were placed in an acrylic cylindrical holder mounted on a platform with a piezoelectric accelerometer as the force transducer attached to the underside of the platform. The platform was located inside a sound-attenuated chamber. Each animal had a 5 min acclimation period prior to a 5 × 5 Latin square sequence of trials of 5 types: no stimulus, startle stimulus with no prepulse, or 70, 75, or 80 dB prepulse followed by the startle stimulus.

Each set of 25 trials was repeated 4 times with an intertrial interval of 8 s for a total of 100 trials. The startle signal was a 20 ms 110 dB sound pressure level (SPL) mixed frequency sound burst with a background of 67 dB and the startle recording window of 100 ms following startle signal onset. All prepulses preceded the startle-eliciting stimulus by 70 ms (onset to onset). The dependent measure was startle amplitude measured as voltage change (mV). Trials of the same type were averaged together. Chambers were cleaned with 70% ethanol between animals.

2.5. Straight channel swim

On P28 after PPI, animals were assessed in a 244 cm straight swimming channel (width 15 cm) filled with room temperature water to test for swimming ability and motivation to escape to a submerged platform at one end. This task also taught animals that escape was possible. Each animal was given four consecutive trials with a limit of 2 min/trial. All trials were started when the animal was placed in the water facing the end wall and ended when the animal found the platform located at the opposite end. Trials were timed by the experimenter.

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