Arginine vasopressin relates with spatial learning and memory in a mouse model of spinocerebellar ataxia type 3

Hong-Bo Jiang\textsuperscript{a,b,1}, Ai-Lin Du\textsuperscript{a,c,1}, Hai-Yang Luo\textsuperscript{a}, Jun Yang\textsuperscript{b,⁎}, Xiao-Qiu Luo\textsuperscript{c}, Rui-Qing Ma\textsuperscript{d}, Chang-He Shi\textsuperscript{b,⁎⁎}, Yu-Ming Xu\textsuperscript{b,⁎⁎}

\textsuperscript{a} Department of Neurology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China
\textsuperscript{b} The Third Affiliated Hospital of Xinxiang Medical University, Xinxiang, Henan, China
\textsuperscript{c} Henan Provincial Key Laboratory of Brain Research, Department of Physiology and Neurobiology, Xinxiang Medical University, Xinxiang, Henan, China
\textsuperscript{d} Xinxiang Institute for New Medicine, Xinxiang, Henan, China

\textbf{A B S T R A C T}

Spinocerebellar ataxia is an inherited neurodegenerative disorder that the most prevalent type is type 3 (SCA3). Arginine vasopressin (AVP) is released within the lateral septum for controlling the learning and memory. This communication studied the effect of AVP on the spatial learning and memory of SCA3 mice. The spatial learning and memory were analyzed by Morris water maze test (MWM), and AVP concentration was measured by radioimmunoassay. The results showed that (Alves et al., 2010) the swimming velocity, distance traveled and latency to the platform of MWM in SCA3 mice were reduced slower than those in WT mice over 4 training days ($p < 0.05$, 0.01 or 0.001); (Antunes and Zimmerman, 1978) SCA3 mice showed a lower performance of spatial learning and memory of MWM during the fifth day (test day) compared to WT mice; (Bao et al., 2014) SCA3 mice had a decrease of AVP concentration in cerebral cortex ($6.3 \pm 0.6$ pg/mg vs. $11.4 \pm 1.0$ pg/mg, $p < 0.01$), hypothalamus ($6.1 \pm 1.3$ ng/mg vs. $10.3 \pm 2.1$ ng/mg, $p < 0.05$), hippocampus ($3.2 \pm 0.5$ pg/mg vs. $5.2 \pm 1.0$ pg/mg, $p < 0.01$) and cerebellum ($4.7 \pm 0.9$ pg/mg vs. $8.3 \pm 1.1$ pg/mg, $p < 0.01$), not in spinal cord, pituitary and serum; and (Barberies and Tribollet, 1996) intraventricular AVP could significantly quicken swimming velocity, cut down distance traveled and reduce latency to the platform of MWM in a dose-dependent manner, but intraventricular AVP receptor antagonist weakened the spatial learning and memory of MWM in SCA3 mice during the fifth day. The data suggested that AVP in the brain, not spinal cord and peripheral system of SCA3 mice related with the change of the spatial learning and memory of MWM.

1. Introduction

Arginine vasopressin (AVP), a nonapeptide posterior hormone of the pituitary, is mainly synthesized and secreted in the hypothalamic paraventricular nucleus (PVN) and supraoptic nucleus (SON). This hormone, combined with an apparent carrier protein (neurophysin), is transported along the hypothalamo-hypophyseal pathway to the neurohypophysis, where it is stored for subsequent release (Antunes and Zimmerman, 1978). The remarkable functions of AVP include body fluid homeostasis, cardiovascular control, learning and memory (McEwen, 2004), depression (Yang et al., 2012b), stress (Bao et al., 2014) and pain modulation (Yang et al., 2006b, 2009a, 2012a). AVP is released within the lateral septum under defined stimulus conditions to act not only as neurotransmitter but also as neuromodulator for controlling distinct types of learning and memory (Gülpınar and Yeğen, 2004; Engelmann, 2008).

Spinocerebellar ataxia (SCA) is an inherited neurodegenerative disorder (Durr, 2010; Klockgether, 2011; Seidel et al., 2012; Rüb et al., 2013; Lin et al., 2016). The disease has no effective treatments that alleviate major symptoms or modify disease progression (Rüb et al., 2013), although several strategies are under investigation including: (i) inhibitors of histone deacetylases (Chou et al., 2008) to correct transcriptional dysregulation; (ii) interference RNA to reduce the translation of the mutated protein (Alves et al., 2010); and (iii) activation of autophagy to eliminate protein aggregates (Menzies et al., 2010; Nascimento-Ferreira et al., 2013; Silva-Fernandes et al., 2014).

The most prevalent type is type 3 (SCA3) or Machado-Joseph disease, which is caused by a polyglutamine expansion in a protein called...
ataxin-3 (Paulson, 2012). SCA3 has numerous clinical features, including ataxia, ophthalmoplegia, pyramidal signs, basal ganglia symptoms and peripheral neuropathy (Nakano et al., 1972). Although a little studies have pointed that the clinical learning and memory function might reduce in SCA3 (Durr, 2010; Jacobi et al., 2013; Rübl et al., 2013), it is difficult to find the relationship between the learning and memory development and AVP variety in central nervous system of SCA3 (Bürk et al., 2003). This communication was designed to investigate the effect of AVP in central nervous system on the spatial learning and memory of Morris water maze test (MWM) in a mouse model of SCA3, which compared to those in a wild type (WT) mouse.

2. Materials and methods

2.1. Animals

2.1.1. Source of SCA3 mouse

Gordon Holmes syndrome (GHS) is a rare Mendelian neurodegenerative disorder characterized by ataxia and hypogonadism. It was suggested that disordered ubiquitination underlies GHS though the discovery of eoxme mutations in the ubiquitin (E3) ligase RNF216 and deubiquitinase OTUD4. We performed exome sequencing in a family with two of three siblings afflicted with ataxia and hypogonadism and identified a homozygous mutation in STUB1 (NM-005861) c.737C → T, p.Thr246Met, a gene that encodes the protein CHIP (C-terminal of HSC70-interacting protein). CHIP plays a central role in regulating protein quality control, in part through its ability to function as an E3 ligase. Loss of CHIP function has long been associated with protein misfolding and aggregation in several genetic mouse models of neurodegenerative disorders. Loss of CHIP function in mice resulted in behavioral and reproductive impairments that mimic human ataxia and hypogonadism (Shi et al., 2014).

SCA3 mice were generated in Dr. Xu’s Laboratory (Shi et al., 2014), which were identified by the polymerase chain reaction (PCR, One step mouse genotyping kit, Vazyme Co.) with the specific primers. Yeast artificial chromosomes (YAC) and MJD1 genes, which included CAG76 and CAG84 repeat, were constructed by the homologous recombination. Then the YAC DNA was purified and injected into the F2 oocytes of the mouse prkaryotic (C57BL/6 J × CBA/Ca) at a low concentration. The transgenic mice with active backcross (human ataxin-3-84Q/CHIP−/−) mated with the parental C57BL/6 J mice (Shi et al., 2014; Scaglione et al., 2011).

SCA3 mouse were certified by PCR with the identification primers that had 3 pairs of stream primers, where the stream primer SCA3-Ide-F/SCA3-Ide-R1 is more stable (Table 1).

SCA3 mouse developed the spinocerebellar ataxia symptoms on 8–11 months after its birth.

2.1.2. Source of WT mouse

WT mice were also called control mice, which were generated in Dr. Xu’s Laboratory (Shi et al., 2014). The mice with non-active backcross in the littermate mice (human ataxin-3-84Q/CHIP−/−) mated with the parental C57BL/6 J mice.

WT mouse were also certified by PCR with the identification primers that had 3 pairs of stream primers, where the stream primer SCA3-Ide-F/SCA3-Ide-R1 is more stable (Table 1).

WT mouse did not show the spinocerebellar ataxia symptom in its lifetime.

2.1.3. Qualification of SCA3 mouse and wild type (WT) mouse

The male SCA3 mice and male WT mice weighing 20–23 g, age 12 months, were used in all experiments. The animals were housed individually in polycarbonate cages (12 × 12 × 25 cm) in a specific pathogen free (SPF) animal laboratory with controlled humidity (40 ± 1%) and temperature (21 ± 2 °C), and a 12 h light/dark cycle (light on at 8:30 AM) for the food and water available ad libitum. All procedures were approved by the Animal Care and Use Committee of Xinxiang Medical University.

2.2. Materials

AVP and d(CH2)5Tyr(Et)DAVP (AVP receptor antagonist) were obtained from Peninsula Laboratories International, Inc., San Carlos, CA, USA. 125Iodine was brought from GE Healthcare Amersham Pharmacia Biotech UK Ltd., Buckinghamshire, England. The other chemicals were bought from Sigma-Aldrich Co., Darmstadt, Germany.

Rabbit anti-mouse AVP serum was made by Department of Neurobiology, Second Military Medical University, Shanghai, China (Liu et al., 1987; Yang et al., 2009b). The antisera specifity was more than 99.9% reactive with AVP and less than 0.1% reactive with other similar peptides including lysine vasopressin, oxytocin, vasotocin, vasoactive peptide, leucine- enkephalin, methionine-enkephalin, β-endorphin, dynorphin A1-13, and neurotensin. The dilution of the antisera was 1:80,000 for radioimmunooassay.

2.3. Surgery

With the Paxinos and Franklin (2001) mouse brain atlas as reference, we used a stereotaxic apparatus (Jiangwan 1-C, Shanghai, China) to implant a stainless steel guide cannula (0.4 mm outer diameter) into the lateral ventricle (Bregma: 1.0 mm, LR 1.0 mm, H 2.5 mm) for microinjection under sodium pentobarbital anesthetization (35 mg/kg, intraperitoneal injection). The guide cannula was fixed to the skull by dental acrylic. All operations were carried out under sterile conditions and the animals needed at least 14 days to recover after surgery.

2.4. Morris water maze test (MWM)

The spatial learning and memory were evaluated in a water maze adapted from that previously described by Morris (1984) and was based on Van Dam et al. (2003), Javed et al. (2011) and Galeano et al. (2014).

The test was performed in a circular galvanized steel pool of 90 cm in diameter and 40 cm height, filled with 20 cm of water tainted with a non-toxic white paint (acrylic paint, 20,503 white, Apple Barrel). As it is known that the standard Morris water maze can interfere with physiology, likely due to the stress of heat loss (Ivonen et al., 2003), we opted to refine this method to be less stressful by not maintaining it at room temperature (21 ± 2 °C), but instead between room and central body temperature (37 °C), i.e., at 29 ± 2 °C. The pool was virtually divided into four equal quadrants, labeled north-south-east-west. A camera connected to a video tracking system was mounted above the maze.

During the beginning 4 days for training, a platform (10 cm in Table 1

<table>
<thead>
<tr>
<th>Name</th>
<th>Upstream primer</th>
<th>Downstream primer</th>
<th>Fragment (bp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCA3-Ide-F/SCA3-Ide-R1</td>
<td>CCAGTGACTCTTGTGATTG</td>
<td>CTTACCTGAGTACTCCCAA</td>
<td>About 500</td>
</tr>
<tr>
<td>SCA3-Ide-F/SCA3-Ide-R2</td>
<td>CCAGTGACTCTTGTGATTG</td>
<td>TGGCCTTCTCAGTGATGAAA</td>
<td>About 550</td>
</tr>
<tr>
<td>SCA3-Ide-F/SCA3-Ide-R3</td>
<td>CCAGTGACTCTTGTGATTG</td>
<td>GATGTGACCCACATCT</td>
<td>About 700</td>
</tr>
</tbody>
</table>
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