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Cognitive recovery by chronic activation of the large-conductance calcium-activated potassium channel in a mouse model of Alzheimer's disease

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ABSTRACT

We previously showed that activity of the large conductance calcium-activated potassium (Big-K; BK) channels is suppressed in 3xTg Alzheimer disease (AD) model mice. However, its behavioral significance is not known. In the present report, ventricular injection of the BK channel activator isopimaric acid (ISO) was conducted to examine whether BK channel activation ameliorates cognition in 3xTg mice. The novel object recognition (NOR) test revealed that chronic injection of ISO improved non-spatial memory in 3xTg mice. In the Morris water maze, the probe test demonstrated an improved spatial memory after ISO injection. Electrophysiological underpinnings of the ISO effect were then examined in slices obtained from the mice after behavior. At hippocampal CA1 synapses, the basic synaptic transmission was abnormally elevated and long-term potentiation (LTP) was partially suppressed in 3xTg mice. These were both recovered by ISO treatment. We then confirmed suppressed BK channel activity in 3xTg mice by measuring the half-width of evoked action potentials. This was also recovered by ISO treatment. We previously showed that the recovery of BK channel activity accompanies reduction of neuronal excitability in pyramidal cells. Here again, pyramidal cell excitability, as assessed by calculating the frequency of evoked spikes, was elevated in the 3xTg mouse and was normalized by ISO. ELISA experiments demonstrated an ISO-induced reduction of $A\beta_{1-42}$ content in hippocampal tissue in 3xTg mice. The present study thus suggests a potential therapeutic utility of BK channel activators for AD.

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1. Introduction

Amyloid plaques and neurofibrillary tangles deposited in brain tissue have been regarded as the cause of Alzheimer's disease (AD) since Alzheimer's original description (Goedert and Spillantini, 2006 for review). However, such a causative link appears to be controversial. A review of a clinical trial in retrospect failed to demonstrate a clear correlation between cognitive improvement and plaque clearance in recipients of anti-amyloid vaccination (Schenk et al., 1999; Holmes et al., 2008). In clinical imaging studies, cognitively normal people exhibit intracerebral amyloid distribution patterns essentially indistinguishable from that of AD subjects (Klunk et al., 2004; Mintun et al., 2006), agreeing with the earlier pathological evidence (Crystal et al., 1988). It is currently considered that onsets of dementia in humans may not necessarily be correlated with the emergence of amyloid plaques (Morris and Price, 2001; Perrin et al., 2009). In AD model mice also, cognitive impairment is often manifested before age-dependent appearance of amyloid deposits (Oddo et al., 2003). Soluble Aβ in turn has been a focus of attention as a key to link cognitive dysfunction and underlying molecular events in AD pathogenesis (Hardy and Selkoe, 2002; Kamenetz et al., 2003; Haass and Selkoe, 2007; Brody and Holtzman, 2008). Moreover, the dynamic turnover of soluble $A\beta_{1-42}$ between the brain parenchyma and cerebrospinal fluid

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(CSF) has been regarded as a prognostic index predicting the risk for a full clinical manifestation of AD in the future (Sunderland et al., 2003; Fagan et al., 2009).

Not just soluble $A\beta_{1-42}$ in the extracellular space or CSF, but also its intracellular accumulation is among the early pathological events in AD (Oddo et al., 2003; Gouras et al., 2000). How intracellular $A\beta_{1-42}$ affects physiological processes has been fragmentarily demonstrated. Intracellular injection of $A\beta_{1-42}$ into the presynaptic terminal blocks synaptic transmission in the squid giant axon (Moreno et al., 2009). The width of action potentials in neocortical pyramidal cells are broadened by intracellular $A\beta_{1-42}$ injected into wild-type mouse neurons or by that accumulated innately in AD model mouse neurons, which we showed is attributed to suppression of the large-conductance calcium-activated potassium (BK) channels (Yamamoto et al., 2011). Calcium fluorimetry further revealed that the abnormally wider spike in 3xTg mouse neurons leads to an enhanced *per spike* calcium entry, thereby acting as a threat to calcium homeostasis (Yamamoto et al., 2011). In reverse, facilitation of BK channels by the BK channel activator isopimaric acid normalizes the spike width. It is plausible that the reversal of spike width by isopimaric acid may not just be a cellular phenomenon, but also cause a beneficial effect on behavior. The data here, obtained by using the Morris water maze and novel object recognition tests, indeed showed that chronic infusion of the BK channel activator into the ventricular-subarachnoid system ameliorates learning performance of 3xTg mice. We then sought its underlying mechanisms in the later part of this report. The AD mice we used were 4-to-5-month-old 3xTg mice (Oddo et al., 2003), in which intracellular Aβ is notably accumulated prior to the extracellular deposit of plaques (LaFerla et al., 2007).

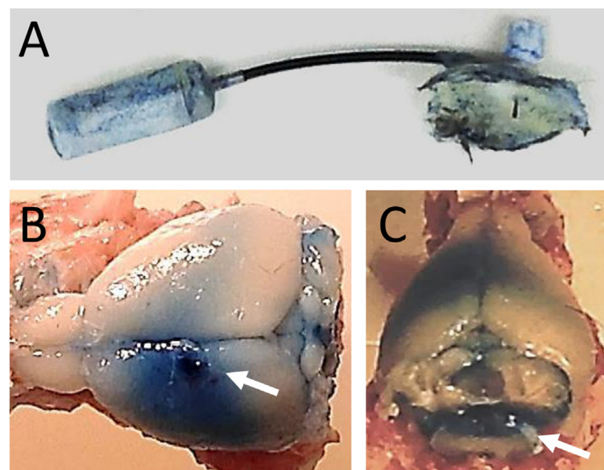

Fig. 1. Assembly of pump and cannula used for chronic injection. A, Osmotic pump and cannula removed from a mouse. The pump (left) was loaded with a 2% pontamine sky blue to verify the method of implantation. Connection was made by a vinyl tubing (middle) between the pump proper (left) and the head piece located on the top of the skull (right), which is the white plastic piece containing a stainless tubing inside. The tip of the stainless tubing, which once was located into the left lateral ventricle, is seen here below the skull. B, View of the injected cerebral cortex. The left hemisphere was penetrated by the stainless tubing through the indicated point (arrow). The lateral ventricle was densely stained by the injected dye. Despite the lack of a direct injection, the right lateral ventricle was also stained albeit much less densely, presumably by diffusion from the left ventricle through the ventricular continuity. C, Posterior oblique view of the brain. A dense staining is seen between the cerebellum and brain stem, corresponding to the forth ventricle. This staining is most attributable to diffusion through the ventricular system rather than spillover through the parenchyma, because the tissue between the injection site and the forth ventricle is almost dye-free. The symmetrical staining pattern in the cerebral cortex (B) supports the interpretation that the dye was delimited within the ventricular system.

2. Materials and methods

All the experiments were performed in accordance with the guiding principle of the Physiological Society of Japan and were approved by the Animal Care Committee of Kanazawa Medical University.

2.1. Animals

Triple transgenic AD model mice (3xTg) with 129/C57BL6 hybrid background (Oddo et al., 2003), provided from Dr LaFerla (University of California, Irvine), were kept in our in-house colony under an automatic day–night control (12:12 h), and allowed to free access to food and water. Male 3xTg mice of 4–5 months of age were used. As the age-matched control, non-transgenic mice from the same hybrid background were used (wild-type).

2.2. Implantation of osmotic mini-pumps

ALZET osmotic pumps (Model 1004; Durect Corporation, Cupertino, CA, USA) were loaded with the BK channel activator isopimaric acid (ISO groups; 1 mM, 100 μl, solved in DMSO) or DMSO only (vehicle groups; 100 μl). The pump was assembled with an ALZET Brain Infusion Kit III, which is a metal cannula incorporated into a plastic base (Fig. 1). After 48-h incubation in saline, the assembly was implanted into the brain, with the cannula inserted to the lateral ventricle. For the implantation, the male mice (21.2–30.1 g) were placed to a stereotaxic apparatus under sodium pentobarbital anesthesia (60 mg/kg). A small hole was made on the left skull with a dental drill (0.6 mmφ, Leuter K1106, NSN Co. Ltd, Kawanishi, Japan) at 0.4 mm posterior to the bregma and 1.0 mm lateral from the midline, following a stereotaxic atlas (Franklin and Paxinos, 2007). The tip of the cannula attached to the Infusion Kit was introduced from the hole to the depth of 2 mm, targeting the lateral ventricle, with the aid of a stereotaxic holder. Then the Infusion Kit was fixated to the skull with dental cement (Unifast Trad, GC Dental Products Corp., Kasugai, Japan). The pump proper was inserted under the back skin, and the skin over the neck was sutured. After 2-week-long survival, mice were subjected to behavior. During this period, the loaded solution was expected to be pumped out at the rate of 0.11 μl/h. To check the implanted assembly works appropriately, dummy experiments were done in two additional mice. Two pumps were loaded with 2% pontamine sky blue solution in saline, and implanted in the two mice in the same way. Two weeks later, the mice were sacrificed with the brain dissected out. Macroscopic observation by naked eyes showed that the dye reached the fourth ventricle below the cerebellum (Fig. 1). In the parietal cortex, two symmetrical blue-stained bands were observed, with the left side much more darkly stained. These regions are likely to represent the dye-filled lateral ventricles seen through the cortex, indicating that the dye was not only injected into the ipsilateral ventricle but also diffused into the contralateral side. Thus, it was demonstrated that the tip of the cannula can be positioned reliably in the left ventricle by using the present method.

2.3. Behavioral tests

For the novel object recognition test, a cuboid-shaped arena made of plastic (L 26 cm × W 44 cm × H 20 cm) were used (Fig. 2). Mice were allowed to explore on the rectangular bottom of the arena for 3 min, and removed from the arena. Five minutes later, two identical objects (approximately L and W or diameter 5 cm × H 10 cm) were positioned on the bottom 20 cm apart, and then mice were placed again into the area and allowed to explore for 3 min. Behavior was video-recorded, digitized, and stored in a PC for later off-line analysis by using the SMART software (Panlab s.l.u., Cornella, Spain). In the analysis, how often and how long the mice approached the objects was examined. Namely, the time spent within 2 cm from the boundary of each object was measured (d1 and d2). The cases in which the mice came within the 2-cm vicinity of the two objects for less than 10 s in total (i.e., $d1 + d2 < 10$ s) were discarded. On the 2nd day, at a 24-h interval, we positioned one of the same familiar objects that were previously encountered, and a new unfamiliar object of a similar size with a different shape. Then the mice were allowed to explore the arena for 3 min. Again, the time spent with the 2-cm vicinity of the objects was measured separately for the familiar object (d3) and novel object (d4). The discrimination index was defined as $d4/(d3 + d4)$. The larger the discrimination index is, the better will be the memory retrieval on the familiar object encountered 24-h before. By contrast, if the index points to 0.5, it means that the mice approached the novel and familiar objects evenly and therefore failed to recognize the familiar object shown on the previous day. This is based on the well-known fact that mice tend to spend more time interacting with a new object rather than the one that they have previously encountered.

For the *Morris water maze test*, a plastic cylindrical tank (120 cmφ) that is surrounded by a wall of 45 cm high and filled with opaque water (25 °C) was used. A transparent plastic platform (10 cmφ) was hidden below the water surface with its base fixated to the floor of the tank. Four large, differently-colored objects were placed above the edge of the tank as geographical external cues. On each of 5 consecutive days, mice were given 4 sessions of swim. For each session, the mice were released from a starting point pseudo-randomly chosen from the 4 prefixed positions, and the time spent to reach the platform (escape latency) was measured. If mice were not able to reach the platform within 60 s, they were placed on the platform by the experimenter and allowed to stay there for 60 s. The average of the

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