Abstract

Objective: Recently studies have demonstrated that inflammatory reaction and neurotoxic effect caused by activated microglia which induced by hippocampal gene expression of apoptosis of brain cell deposition plays an important role in the development of AD.

To investigate the effect of intestinal endotoxemia (IETM) on learning and memory ability in rats with Alzheimer’s disease (AD) and its possible mechanisms.

Methods: The AD model of wistar rats were produced by injecting D-galactose and AlCl₃, intraperitoneally for 90 days. Subsequently, learning and memory ability of the rats were evaluated by Morris water maze; the level of lipopolysaccharide (LPS) and tumor necrosis factor-α (TNF-α), IL-1, IL-10, TNF-α, NO were determined by ELISA; the apoptosis of brain cell were detected by TUNEL.

Results: The learning and memory ability of the rats were observed by Morris water maze. The results indicated that compared with the normal control, the learning and memory ability of model rats and AD rats is markedly decreased; LPS and IL-1, IL-10, TNF-α, NO in blood in AD rats were increased (P<0.05); indicated that compared with the normal control, the incidence rate of the brain cell apoptosis of model rats and AD rats is markedly increased (P<0.01).

Conclusions: The rat model of Alzheimer’s disease is accompanied IETM and that apoptosis of hippocampus of brain cell may plays an important role in the development of AD.

Key words: Alzheimer’s disease; Intestinal endotoxemia; LPS; TNF-α; apoptosis of brain cell

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Alzheimer disease therapeutics candidate, SAK3 improves the cognitive functions through inhibition of amyloid beta accumulation in APP23 mice.

Hisanao Izumi, Yasushi Yabuki, Yasuharu Shinoda, Kohji Fukunaga
Department of Pharmacology, Graduate School of Pharmaceutical Sciences, Tohoku University, Sendai, Japan

Abstract

As Alzheimer disease therapeutics candidate, we have developed SAK3 [Ethyl 2’3’-dihydro-8-methyl-2’4-dioxo-2-peperidinospiro[2-cyclopentene-1,3’-imidazo[1,2-a’]-pyridine]-3-carboxylates] (PCT/JP2013/051388). SAK3 stimulates T-type voltage-gated Ca²⁺ channels (T-VGCC) in mouse cortical slices (Moriguchi et al., J Neurochem 2012;121:44–53). We also reported that SAK3 stimulates acetylcholine release and promotes long-term potentiation in mouse hippocampus (Neuroscience 2014 abstract 265.21). We here tested whether SAK3 reduced amyloid beta (1–42) accumulation in Alzheimer model (APP23) mice. APP23 mice aged 6 and 9 months were treated for two or three months with SAK3 (0.5mg/kg, p.o.) and measured amyloid beta (1–42) levels. Consistent with the reduced amyloid beta (1–42) levels, the numbers of amyloid plaques assessed by thioflavin staining were significantly reduced by the chronic SAK3 treatment. Furthermore, the cognition assessed by novel object recognition task was improved by the chronic administration. Using LC/MS/MS system, we established high sensitivity quantification system in blood to obtain proof-of-concept of SAK3 safety in human. Taken together, the novel T-type calcium channel stimulator SAK3 restored cognition ability in APP23 mice and reduced the amyloid beta (1–42) accumulation/