Alzheimer's drug candidate, SAK3 enhances the proteasome activity and inhibits amyloid aggregation in Alzheimer‘s disease brain

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[Background and Objectives] Alzheimer's disease (AD) is a progressive neurodegenerative and the most common disease of elderly dementia in the world. Acetylcholinesterase inhibitors such as donepezil and rivastigmine are the most useful drug for AD, but they are only used as symptomatic treatment and not disease-modifying drugs. We here developed a disease-modifying drug, SAK3 which stimulates T-type calcium channels and ameliorates AD pathology. Here, we introduce the novel mechanism through proteasome activation to inhibit Aβ deposition in *App*$^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$ knock-in (NL-G-F) mice.

[Methods] NL-G-F mice were chronically administered with SAK3 (0.5 mg/kg, p.o.) for 3 months. (i) Proteasome activity was assayed by fluorogenic peptides. (ii) Immuno-blotting analyses were conducted to assess CaMKII-Rpt6 pathway. (iii) The number and morphology of spine were assessed *in vivo*. (iv) Behavioral analyses were carried out to assess cognitive functions.

[Results] (i) The decreased 26S proteasome activities in the cortex of NL-G-F mice were restored by SAK3 chronic administration. (ii) The declined levels of phospho-CaMKII and phospho-Rpt6 in the hippocampus of NL-G-F mice were restored by SAK3 administration. (iii) The decreased number and abnormal morphology of spine in the cortex and hippocampus of NL-G-F mice were improved by SAK3 administration. (iv) The impaired cognitive function in NL-G-F mice was improved by SAK3 treatment.

[Conclusions] We defined the novel mechanism of SAK3-induced proteasome activation, thereby inhibiting the amyloid aggregation in AD mice. These results strongly suggest that SAK3 is the disease-modifying therapeutics for AD.