GS03-6 PK/PD analyses of SAK3 for development of Alzhemier's disease therapeutics

○Keita SATO[1], Hisanao IZUMI[1], Kohji FUKUNAGA[1]
[1]Tohoku Univ. Grad. Sch. of Pharm. Sci.

We recently defined that T-type calcium channel is novel Alzheimer's disease (AD) therapeutic target and developed SAK3 as T-type calcium channel enhancer. SAK3 enhances hippocampal acetylcholine release and improves cognition in various AD model mice. We here addressed pharmacokinetic and pharmacodynamics analyses to define the proof of concept (POC) of SAK3 as AD therapeutics. We first established LC-MS/MS system to define pharmacodynamics of SAK3 in mice and rats. In male rats, the SAK3 concentration was peaked at 30 min after oral administration and disappeared for serum with 24 hours. We next determined the dynamics in brain using deuterium isotope of SAK3 to eliminate the disturbed endogenous signal. As expected, SAK3 concentration in both mice and rats was peaked 30 min after oral administration and disappeared within 24 hours. The time course was closely associated with SAK3 effects of hippocampal ACh release and cognitive improvement in mice. We next assessed cognitive improvement effects of SAK3 in 10-month years old APP23 mice. Oral administration of SAK3 for 3 months significantly inhibited the amyloid beta accumulation and its plaques in APP23 mice. The inhibition of amyloid beta accumulation was closely associated with cognitive improvement. Taken together, we obtained the POC of pharmacokinetics and pharmacodynamics to develop SAK3 as novel AD therapeutics. This work was supported by AMED project.