Kamisyoyosan, a Japanese traditional Kampo medicine, ameliorates sex-dependent ADS-like behavior caused by decrease of brain allopregnanolone

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Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by sociability deficit and restrictive repetitive behaviors and is suggested to be in part due to GABAergic dysfunction in brain. In our previous study, a decrease of endogenous allopregnanolone (ALLO), a positive allosteric modulator of GABAA receptors, by a type I 5α-reductase inhibitor (SKF105111: SKF)-induced ASD-like behavior in male mice, suggesting a role of endogenous ALLO in the regulation of ASD-like behaviors. To investigate availability of traditional Kampo medicine for ASD, we investigated the effects of kamisyoyosan (KSS), a Kampo formula which has been used for the anxiety-related symptoms, on SKF-induced ASD-like behaviors in mice.

Six-to-9-week old male/female ICR mice were administrated SKF (40 mg/kg, i.p.) 3-6 hrs before starting behavioral and neurochemical studies. Drugs except KSS were administrated i.p. 30 min before behavioral experiments. KSS was given p.o. at doses 1-3 times more than the dose used for human therapy. Sociability was elucidated by 3-chamber paradigm and/or resident-intruder paradigm. An open-field test was used to analyze stereotyped grooming behavior as an index of restrictive repetitive behaviors. ALLO content in brain was measured using an ALLO ELISA system.

The administration of SKF induced ASD-related behavior such as sociability deficits and an increase of repetitive grooming behavior in male mice. These abnormalities were abolished by exogenously administrating ALLO (1 mg/kg). Similarly, SKF reduced ALLO contents in brain in a manner that is reversed by exogenous ALLO administration. However, neither behavior abnormalities nor ALLO contents decline were observed in SKF-treated female mice. The oral administration of KSS ameliorated SKF-induced ASD-related behavioral abnormalities, without affecting SKF-induced decrease in brain ALLO content. The effects of KSS were attenuated by a dopamine D₁ antagonist as well as by a GABAA receptor antagonist.

These results suggest that ALLO content in brain plays an important role in the regulation of ASD-like behavior, and that a sex-dependent decrease in brain ALLO content causes ASD-like behavior in male mice. Moreover, the present findings that KSS ameliorates SKF-induced ASD-like behavior via dopaminergic and GABAergic mechanisms suggest that KSS can be used as a novel therapeutic agent against ASD symptoms.