Susceptibility to juvenile isolation stress-induced aggressive behaviors in synaptic vesicle protein 2A (SV2A)-mutant rats

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Background: Synaptic vesicle glycoprotein 2A (SV2A) facilitates action potential-dependent exocytosis of neurotransmitter. We have recently developed SV2A-mutant (*Sv2a*^{L174Q}) rats carrying a missense mutation (L174Q) in *Sv2a* gene and showed that the *Sv2a*^{L174Q} mutation markedly facilitates the development of epileptogenesis (Tokudome et al., Sci. Rep., 6, 27420, 2016; Front. Pharmacol., 7, 210, 2016). In this study, we investigated the effects of the *Sv2a*^{L174Q} mutation on juvenile isolation stress-induced behavioral responses to clarify the role of SV2A in modulating emotional disturbances.

Methods: Male *Sv2a*^{L174Q} or F344 (control) rats were used. Animals received social isolation stress for 5 weeks (isolation rearing from 3 to 8 weeks of age) and were subjected to social interaction/aggressive behavior test and Y-maze test. Immunohistochemical staining of Fos protein, a biological marker for neural excitation, was performed to explore the brain regions responsible for behavioral alterations. In addition, in vivo microdialysis experiments were conducted to evaluate synaptic dopamine release in the nucleus accumbens.

Results: In control rats, social isolation stress slightly increased both social interaction and aggressive behaviors. However, the social isolation stress-induced aggressive behaviors, but not social interaction, were significantly enhanced by the *Sv2a*^{L174Q} mutation. Short-term memory evaluated by Y-maze test was not affected either by the social isolation or the *Sv2a*^{L174Q} mutation. Immunohistochemical analysis of Fos protein expression using the social isolation stress-loaded animals revealed that the *Sv2a*^{L174Q} mutation caused significant and region-specific increases in Fos expression in the shell region of the nucleus accumbens and the agranular insular cortex. Furthermore, in vivo microdialysis studies showed that *Sv2a*^{L174Q} mutation significantly enhanced high K⁺ (depolarization)-induced dopamine release in the nucleus accumbens.

Conclusions: The present study demonstrates that dysfunction of SV2A by the *Sv2a*^{L174Q} mutation augments social isolation stress-induced aggressive behaviors via neural activation of the nucleus accumbens and the agranular insular cortex, which seems to result from enhanced synaptic release of dopamine. These results imply that SV2A plays an important role in modulating the vulnerability to psychotic disorders.