

# Enhancement of social isolation-induced aggressive behavior of young mice by zinc deficiency and effect of Yokukansan

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Neuropsychological behavior via activation of the hypothalamic-pituitary-adrenal (HPA) axis was analyzed using young mice fed a zinc-deficient diet for 2 weeks. Serum corticosterone concentration was significantly increased after 2-week zinc deprivation, whereas zinc concentration in the brain was not decreased. In the resident-intruder test, the rate of mice that exhibited aggressive behavior to the total mice was significantly higher in isolated zinc-deficient mice than in isolated control mice. The duration of aggressive behavior was more in isolated zinc-deficient mice. These results indicate that aggressive behavior of young mice elicited by social isolation is enhanced by zinc deficiency. On the other hand, social isolation-induced aggressive behavior was enhanced in isolated pair-fed mice with food restriction that can activate the HPA axis. Serum corticosterone concentration was also significantly higher in isolated zinc-deficient mice. Interestingly, oral administration of Yokukansan, a herbal medicine, which improves behavioral and psychological symptoms such as agitation, aggression and irritability in 52 patients with dementia including Alzheimer's disease, improved aggressive behavior of isolated zinc-deficient mice. When the relationship between behavioral abnormality and neurotransmitter concentrations in brain tissue were checked, the concentrations of glutamate, aspartate, GABA, and dopamine in brain tissue were more increased in isolated zinc-deficient mice than in isolated control mice. Furthermore, these increases in neurotransmitter concentrations were significantly suppressed by oral administration of Yokukansan. The effect of Yokukansan on aggressive behavior of isolated zinc-deficient mice might be associated with improvement of the abnormal activation of the HPA axis.