学 位 論 文 要 旨

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題　目	Antidepressant effects of Ninjinyoeito in neuropeptide Y deficiency zebrafish and its mechanism (うつ病モデルゼブラフィッシュにおける社交性低下と不安に対する人参養栄湯の改善効果およびその作用機序の解明)

Depression is primarily caused by a decline in brain function and exhibits symptoms such as persistent anxiety and decreased sociability. Currently, antidepressants that increase the amount of monoamine in the brain are widely used. But they have various problems such as slow action, many side effects, and a high relapse rate after discontinuation of medication. Therefore, there is a need for the development of new depression medications. This study focused on the possibility of Ninjinyoeito, one of the Chinese herbal medicines, as an antidepressant. Ninjinyoeito has been reported to have effects on the central nervous system, such as improving memory in mice. However, the effects of Niinjinyoeito on psychiatric symptoms such as anxiety and low sociability are not clear. So, the purpose of this study was to clarify the ameliorative effects of Ninjinyoeito on anxiety and low sociability and its mechanism of action using neuropeptide Y deficiency (NPY-KO) zebrafish that exhibit anxiety and low sociability.

First, NPY-KO zebrafish were fed Ninjinyoeito diet, and changes in social behavior were evaluated by a mirror test. The results showed that Ninjinyoeito treatment increased approach behavior toward the opponent in the mirror, but this behavior was not caused by aggression. Therefore, we analyzed sociability using the 3-chambers test. Nijinyoeito treatment increased the approach behavior of NPY-KO zebrafish to fish group. Nininyoeito treatment decreased gene expressions of glucocorticoid receptor, proopiomelanocortin, corticotropin-releasing hormone, and adrenocorticotropin-releasing hormone in the hypothalamic-pituitary-adrenal system, tyrosine hydroxylase in the sympathetic-adrenal-medullary system, and GABA synthase, and increased expression of oxytocin receptors that regulate social interaction. In addition, NPY-KO zebrafish were fed diets herbs in Ninjinyoeito to identify the active herbals. The effects of Ninjinyoeito on sociability were found to be derived from Cinnamon Bark and Polygala Root.

Next, the anti-anxiety effects of Ninjinyoeito were evaluated. NPY-KO zebrafish showed anxious behaviors such as freezing and swimming along a tank's wall induced by acute stress, but Ninjinyoeito improved these anxious behaviors. In general, noradrenergic neurons are known to be hyperactive when exhibiting anxiety behaviors such as freezing. On the other hand, Ninjinyoeito suppressed the activation of noradrenalin neurons after acute stress in NPY-KO zebrafish. Therefore, we attempted to identify the active herbs in Ninjinyoeito, and found that the nine herbs improved anxious behavior, with four of them showing the more potent effects. Furthermore, schizandrin in the schisandra fruit was identified as one of the active compounds in Ninjinyoeito.

In conclusion, Ninjinyoeito showed sociability- and anxiety-improving effects and has the potential to be used as a new treatment for depression.