Studies on the elucidation of the role of an antioxidant, flavangenol, on heat stress in chicks

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論文題名　：Studies on the elucidation of the role of an antioxidant, flavangenol, on heat stress in chicks
（ニワトリヒナにおける暑熱ストレスに対する抗酸化物質フラバンジェノールの作用メカニズム解明に関する研究）

区　　分　：甲

論　文　内　容　の　要　旨

Exposure of an organism to a high ambient temperature (HT) can cause heat stress, which has a huge negative impact on physiological functions. Cellular heat-shock response is activated upon exposure to HT for cellular maintenance and adaptation. However, such a cellular mechanism may not be sufficient under prolonged exposure to HT. Thus, under such a situation, antioxidants are used to support physiological functions in a variety of organisms. Flavangenol, an extract of pine bark, is one of the most potent antioxidants with its complex mixture of polyphenols. Both *in vivo* and *in vitro* studies to investigate the functions of flavangenol in heat-exposed chicks and brain cells by analyzing the gene expression related to cellular defense system were conducted. In the *in vivo* study, both chronic (a single daily oral administration for 14 days) and acute (a single oral administration) administration of flavangenol were performed. Then, the chicks were exposed to an acute HT (40 ± 1°C for 3 h) to examine the effect of oral administered flavangenol on the mRNA expression of heat-shock proteins (HSPs) in the brain and liver. Rectal temperature, plasma corticosterone and metabolites were also determined. The mRNA expressions of HSP-70 and HSP-90 as well as plasma corticosterone were increased by HT. Interestingly, the chronic, but not the acute, oral administration of flavangenol caused a dose-dependent declining in the diencephalic mRNA expression of HSP-70 and HSP-90 as well as plasma aspartate aminotransferase, a marker of liver and other tissue damage, in HT-exposed chicks. The hepatic mRNA expression of HSP-90 was also significantly decreased in HT chicks, which was subjected to a chronic oral administration of flavangenol. These results indicate that chronic, but not acute, oral administration of flavangenol may attenuate HSPs mRNA expression in the central and peripheral tissues due to its possible role in improving cellular protective functions during heat stress. In the *in vitro* study, firstly, the effect of flavangenol on the HSP-70 mRNA expression in heat-exposed slices of chick brain was examined. Flavangenol treatment significantly attenuated the mRNA expression of HSP-70, suggesting a direct function of flavangenol to attenuate the mRNA expression of HSP-70 in the brain tissue during heat stress. Secondly, the effect of flavangenol on the cellular apoptosis and oxidative stress in heat-exposed chick brain cells (mixed neurons and glia cells) was investigated. Chick primary brain cells were isolated from the diencephalon of 14-days-old chicks and cultured at 41.5°C (to mimic the body temperature of young chicks) with the treatment of flavangenol from day 3 of isolation to day 8. Subsequently, the cells in the dish were kept in a water bath at HT (45°C, 20 or 60 min) on day 8 followed by the collection of heat-exposed cells for the analysis of cell viability and HSPs and related other gene expressions. Flavangenol treatment significantly increased cell viability, B-cell lymphoma 2 RNA expression, and attenuated HSP-70 mRNA expression, suggesting an enhanced cellular anti-apoptotic function by flavangenol. Moreover, flavangenol treatment elevated the mRNA expression of glutathione peroxidase in the HT group, which indicates that cellular anti-oxidative ability was strengthened by flavangenol. In conclusion, flavangenol may play a protective role against heat stress-induced cellular

damage in chicks as a whole body and in cultured cells as well. The cytoprotective function of flavangenol against acute heat stress by up-regulating the cellular anti-oxidative and anti-apoptotic ability, which finally results in the lower expression of HSP-70, further suggests that flavangenol could serve as a potential anti-oxidant to protect the adverse effect of heat stress.