Studies on the Enhancement of Energy Metabolism by Transient Receptor Potential Vanilloid 1 Antagonists in Mice

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論文題名　：Studies on the Enhancement of Energy Metabolism by Transient Receptor Potential Vanilloid 1 Antagonists in Mice
（Transient Receptor Potential Vanilloid 1 アンタゴニストによるエネルギー代謝亢進作用に関する研究）

区　　分　：甲

論　文　内　容　の　要　旨

Obesity is one of the risk factors for lifestyle-related diseases. Enhancing the energy metabolism in exogenous manners leads to the prevention and improvement of obesity. Since transient receptor potential vanilloid 1 (TRPV1) is involved in the development of acute pain, it has been expected that an inhibitor (antagonist) targeting TRPV1 is valid as an analgesic. However, as a side effect, it has been revealed that the TRPV1 antagonists cause a transient hyperthermia. TRPV1 antagonists also induce thermogenesis as well as its agonists. In this thesis, the enhancement of energy metabolism (hypermetabolism) and anti-obesity effects of TRPV1 antagonists were examined.

At first, changes of energy metabolism (EM) by three TRPV1 antagonists in mice were measured by using respiratory gas analysis. As results, intragastric (IG) or intraperitoneal (IP) administration of AMG517 and AMG9810 increased VO2 and CHO in mice. In addition, IG and IP administration of AMG517 enhanced EM, whereas IP administration of AMG9810 enhanced VO2 and fat oxidation more than IG administration. However, neither IG nor IP administration of JYL1421 changed VO2 and CHO under normal conditions. Interestingly, in the case of IG co-administration of JYL1421 and capsaicin, CHO was increased more than IG administration of CAP alone. These results suggest that that the inhibition of TRPV1 activated by protons, endogenous TRPV1 modulators (capsaicin analogs), body temperature and exogenous capsaicin increases EM in mice. Therefore, it is considered that the type of TRPV1 antagonists and route of their administration have different effects on EM in mice. These findings will help to reveal the roles of TRPV1 and to promote the development of new drugs and supplements for regulating EM.

Next, the mechanisms underlying hypermetabolism by AMG517, a TRPV1 antagonist, were explored. In the mice desensitized to sensory nerves expressing TRPV1 by pretreatment of capsaicin, IG administration of AMG517 did not change EM. To clarify the involvement of the SNS, the effect of propranolol on AMG517-induced hypermetabolism was confirmed. Treatment of propranolol partially suppressed hypermetabolism by IG administration of AMG517. On the other hand, treatment of propranolol almost abolished hypermetabolism by IP administration of AMG517. These results suggest that IG administration of AMG517 enhances EM via afferent sensory nerves expressing TRPV1, and IP administration of AMG517 enhances EM by increasing the sympathetic nerve activity in mice. However, AMG517 did not affect hypothalamic monoamine concentration, plasma catecholamine concentration, and expression levels of metabolism-related genes.

Then, I examined the effects of AMG517 on obesity induced by a high-fat diet to clarify whether TRPV1 antagonists might be candidates for drugs against obesity. The effects of chronic administration on body

weight, food intake, resting EM, glucose tolerance and tissue weights including WAT were demonstrated. However, no significant difference was found between the AMG517 group and the control group in any experiment. Although it is seemed that these results were due to attenuation of effect of AMG517 on EM by continuous administration, and physical and mental stress at the time of administration, it is considered that AMG517 does not prevent induction of obesity by a high-fat diet.

Finally, changes in EM by antagonists of transient receptor potential ankyrin 1 (TRPA1) and anoctamine 1 (ANO1), which were co-expressed and interaction with TRPV1, were measured to explore whether ANO1 and TRPA1 were also involved in hypermetabolism by TRPV1 antagonists. However, no definitive evidences were obtained. Thus, it is supposed that these receptors are not involved in hypermetabolism by TRPV1 agonists and antagonists, and TRPV1 alone plays an important role in the EM.

In conclusion, this study demonstrated that the inhibition of TRPV1 by its antagonists also enhanced EM in mice, and the type of TRPV1 antagonists and the routes of its administration had different effects on EM. Furthermore, it is suggested that IG administration of AMG517 enhanced EM via afferent sensory nerves expressing TRPV1, and IP administration of AMG517 enhanced EM by increasing the sympathetic nerve activity in mice. On the other hands, it is considered AMG517 does not prevent induction of obesity, although it is possible that AMG517 may affect obesity in obese mice. Furthermore, it is considered that ANO1 and TRPA1 are not involved in hypermetabolism by TRPV1 agonists and antagonists, and TRPV1 alone plays an important role in the EM.