Molecular mechanism in the control of central obesity and atherosclerosis by androgen and its target molecule

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【Outline of survey】

We have long accumulated many research outcomes in the molecular mechanisms of androgen receptor (AR) action and androgen insensitivity. Although physiological significance of androgens in metabolic syndrome (MS) and atherosclerosis has not been well elucidated, we have recently clarified the mechanism of late-onset obesity observed in ARKO mice (kindly provided by Prof. Kato S, Tokyo University), namely abnormalities of adipose tissue metabolism and energy balance. In this research project, to clarify the significance of androgens, testosterone (T) and dehydroepiandrosterone (DHEA) in MS and atherosclerosis, the following 3 experiments will be done. (1) We clarify the significance of androgen in the central regulatory mechanism of energy balance through the analysis of ARKO mice and search target molecules of AR. (2) We aim at developing SARM (selective androgen receptor modulator) which has anti-obesiy effect without any effect on prostate. (3) We have recently identified a DHEA-inducible P38 MAP kinase phosphatase, DHEA-enhanced dual specificity protein phosphatase (DDSP). We aim at clarifying a mechanism of anti-obesity effect of DDSP suggested from DDSP-transgenic mice and developing new drugs which targets DDSP.

【Expected results】

It is not clear that androgen action *in vivo* is a direct action of androgen itself or an indirect action mediated through the conversion to estrogens. However, since androgen action is completely blocked in ARKO mice, conclusive results on the significancee of endogenous androgen in MA or atherosclerosis will be expected. And there is a possibility that signal interaction between AR and known or unknown molecules that regulates energy balance may be clarified, giving a new insights on AR action in brain other than sexual behavior. In addition, this research project may lead to the development of new drugs (SARM and inducer or activator of DDSP) for life-style related diseases.

【References by the principal researcher】

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2)Ashida K, Goto K, Zhao Y, Okabe T, Yanase T, Takayanagi R,Nomura M, Nawata H: Dehydroepiandrosterone negatively regulates the p38 mitogen-activated protein kinase pathway by a novel PTPN7 locus-derived transcript. Biochem Biophys Acta 1728: 84-94, 2005

【Term of project】 FY 2005 - 2007 | 【Budget allocation】 74,100,000 yen

【Homepage address】 http://www.med.kyushu-u.ac.jp/intmed3/general_1.html