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# Metabolic Parameters and Polymorphisms of Stress-related Genes

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Metabolic diseases such as diabetes, obesity and dyslipidemia progress to atherosclerotic vascular diseases unless they are well controlled. Main risk factors of these diseases are life style of food intake and exercise, environment before and after birth and genetic background. One of an important environmental factor is physical or psychosocial stress. Stress response is dependent on each individual with different genetic background.

Representative stress response is a stimulation of hypothalamic-pituitary-adrenal axis. Glucocorticoid from adrenal cortex is well known to enhance visceral obesity, and induces a variety of gene expression in the early differentiation of adipocytes by the study using microarray [1]. Among these molecules, defective adipocyte differentiation in CCAAT/enhancer-binding protein δ (C/EBP- δ) knockout mice suggested that C/EBP- δ was important for the early differentiation of adipocytes [2]. We examined the association of *C/EBP*- δ single nucleotide polymorphisms (SNPs) and metabolic parameters [3]. Participants were 172 healthy subjects (male 52) with mean age 59.3, BMI 22.8 kg/m$^2$, fasting plasma glucose (FPG) 103 mg/dl, triglyceride (TG) 119 mg/dl, HDL-C 65.5 mg/dl, and total cholesterol 221 mg/dl. Minor allele frequency of *C/EBP*- δ SNPs rs15955 and rs5030976 were more than 5 % in Japanese population. SNP rs15955 C/T was significantly and independently attributable to hypertriglyceridemia (>150 mg/dl) with odds ratio 3.003 (95 % CI; 1.057-8.532) (P=0.039) and to high FPG (>110 mg/dl) with 3.02 (95 % CI; 1.092-9.058) (P=0.034) assessed by logistic regression analysis. On the other hand, no association was noted between SNP rs5030976 and metabolic parameters. The mechanism underlying the association between rs15955 SNP and metabolic parameters remained unknown. SNP rs15955, located on the coding region, was not the cause of amino acid substitution.

The other important stress response is a stimulation of sympathetic neuron or adrenal medulla. Not only catecholamine but also neuropeptide Y (NPY) is secreted from sympathetic nerve terminal in response to stress. It is well known that food intake is stimulated by NPY through NPY Y1 receptor [4]. Kuo et al. have reported that NPY causes metabolic syndrome through NPY Y2 receptor (Y2R)in rodents under stress and high caloric diet [5]. We examined the association of *Y2R* SNPs and metabolic parameters. Participants were 317 healthy subjects (male 98) with mean age 61.3, BMI 22.7 kg/m$^2$, FPG 93.4 mg/dl, plasma TG 105 mg/dl, HDL-C 64.8 mg/dl, and LDL-C 131 mg/dl. *Y2R* SNPs rs6857715 and rs56857530 had minor allele frequency more than 5 %, located on promoter regions and had evidences of associations with metabolic disease such as obesity, so these SNPs were selected to study the association with metabolic parameters.

Plasma HDL-C levels were significantly different in subjects with each SNP rs6857530; GG<GA<AA or rs6857715; TT<TC<CC [6].

In order to know the underlying mechanism, we constructed pGL3-basic plasmid containing *Y2R* gene promoter with rs6857530GG+rs6857715TT (G+T) or rs6857530AA+ rs6857715CC (A+C) [7]. Luciferase activity of (G+T) was detected in human hepatoma cell line HepG2, but not in macrophages that were differentiated from human acute monocytic leukemia cell line THP-1, adipocytes that were differentiated from mouse 3T3-L1, and human umbilical vein endothelial cell

line HUEhT-1. Luciferase activity of (A+C) was slightly detected in macrophages but not in the other cells described above. The around sequence of rs6857530G than rs6857530A was similar to the consensus sequence of SP1; stress-responsive transcription factor. Therefore, electro-mobility shift assay was carried out after binding the nuclear extracts of HepG2 cells and the florescence-labeled oligonucleotide containing rs6857530G or rs6857530A. The specific shifted band was noted when oligonucleotide with SNP G but not A was used. Taken together, it was speculated that this nucleotide with SNP G bound to the activator of *Y2R* gene transcription in HepG2 cells, thereby causing SNP- and cell type-dependent *Y2R* gene transcription.

*Y2R* SNPs of HepG2 cells were rs6857530G/A and rs6857715T/C by direct sequencing. Therefore, we tested the effect of potent Y2R antagonist BIIE0246 on gene expressions in HepG2 cells [8]. By using real time PCR, BIIE0246 failed to change apolipoprotein A1 (ApoA1) and ApoA1 binding protein mRNA levels. BIIE0246 tended to inhibit cholesterol ester transfer protein (CETP), scavenger receptor-B1 (SR-B1) and hepatic lipase mRNA levels, although the difference was not statistically significant. By using microarray, BIIE0246 up-regulated 743 transcripts and down-regulated 492 transcripts. BIIE0246-upregulated genes were significantly involved in 11 gene ontology including 3 biological processes; chylomicron remodeling, negative regulation of cholesterol transport, and negative regulation of sterol transport ($P<0.001$). BIIE0246-upregulated genes were also significantly involved in 22 pathways including lipid metabolism ($P=0.0048$). BIIE0246-downregulated genes were significantly involved in 44 pathways including sterol responsive element binding protein signaling ($P<0.01$). These data supported not only the association but also causal relation between *Y2R* gene SNPs and plasma HDL-C levels. Although the quality rather than quantity of HDL is recently known to be important for cardiovascular disease prevention [9], more selective Y2R antagonist might be a candidate drug for dyslipidemia in subjects with specific Y2R SNPs under stress.

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