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The Pathophysiological Clarification Based on Inwardly Rectifying K Channel and the Development of Newly Antihypertensive Treatment in Salt Sensitive Hypertension

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Summary

***Objectives*:** Some aldosterone-producing adenoma (APA) has somatic mutation in *KCNJ5* coding for inwardly rectifying K channel (Kir3) which is mediated by G protein-coupled receptors (GPCRs). We aimed to detect novel genes associated with GPCRs in APA, and elucidate the mechanisms underlying aldosterone production.

Methods: Microarray analysis targeting GPCR-associated genes was conducted using APA without known mutations (APA-NM) samples (n = 8) and APA samples with the KCNJ5 mutation (APA-KCNJ5; n = 6). Since gonadotropin-releasing hormone receptor (*GNRHR*) was one of the highest expression in APA-NM by microarray analysis, we investigated the effects of gonadotropin-releasing hormone (GnRH) stimulation on aldosterone production.

Results: Expression levels of mRNAs encoding GNRHR were highest in APA-NM samples according to our microarray analysis. The quantitative polymerase chain reaction (qPCR) assay results revealed higher GNRHR expression levels in APA-NM samples that in APA-KCNJ5 samples ($P < 0.05$). There was a significant and positive correlation between GNRHR expression and aldosterone increase via GnRH stimulation according to univariate and multivariate analyses. Consistent with the correlation, patients with APA-NM (n = 9), which showed GNRHR mRNA levels, had significantly higher GnRH-stimulated aldosterone response than those with APA-KCNJ5 (n = 13) ($P < 0.05$). We observed an aldosterone response in 55.6% (5/9) of patients with APA-NM, while none of the APA-KCNJ5 patients exhibited an aldosterone response. A partial aldosterone response was seen in 22.2% (2/9) and 23.1% (3/13) of APA-NM and APA-KCNJ5 patients, respectively. Multiple regression analysis revealed that the presence of the KCNJ5 mutation was linked to GNRHR mRNA expression ($\beta = 0.94$ and $P < 0.01$). HAC15 cells with KCNJ5 gene carrying T158A mutation exhibited a 0.64-fold increase in GNRHR expression than that in control cells ($P < 0.05$).

Conclusions: We clarified increased expression of GNRHR in APA-NM, and the expression positively correlated with aldosterone production mediated by GnRH stimulation. Aberrant GNRHR expression in APA-NM could be one of the mechanisms by which aldosterone production is modulated.