ISH NEW INVESTIGATOR AWARD SESSION

ISH NIA OS-01 THE MICRORNA MIR-19A-3P BINDS TO A POLYMORPHISM IN THE GENE FOR THE NORADRENALINE TRANSPORTER AND MAY INCREASE THE RISK OF CARDIOVASCULAR AND PSYCHIATRIC DISEASE

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Objective: Noradrenaline released from sympathetic nerves is removed from the neuroeffector junction via the action of the noradrenaline transporter (NET). NET impairment is evident in several clinically important conditions including essential hypertension, major depressive disorder, panic disorder and the postural orthostatic tachycardia syndrome. Only in rare instances, however, do coding single nucleotide polymorphisms (SNPs) seem to account for a defect in NET. The aim of this study was to determine whether rs7194256 (C/T), a SNP in the 3' untranslated region (UTR) of the NET gene, is associated with diseases associated with NET dysfunction, and to elucidate the mechanism involved.

Design and method: We genotyped by real-time PCR (qPCR) the rs7194256 SNP in a cohort of 55 European-descendent healthy controls and 122 patients (including 44 hypertensives), and validated the results in a larger cohort of 238 controls and 258 cases (124 hypertensives). Bioinformatic analyses identified microRNAs that could bind to the sequence created by the presence of the T allele, and luciferase assays validated it.

Results: Cases had significantly higher prevalence of the T allele, arterial noradrenaline, depression and anxiety scores, clinical and ambulatory systolic and diastolic blood pressures, and larger left ventricular mass index (all $P < 0.05$). Carriers of the T allele also had higher arterial noradrenaline ($P = 0.002$) and 3,4-dihydroxyphenylglycol (the intraneuronal metabolite of noradrenaline, $P = 0.016$). Bioinformatic analyses showed that the T allele created a binding site for the microRNA miR-19a-3p, and luciferase assays validated that this microRNA binds preferentially to the T allele ($P < 0.0001$).

Conclusions: The T allele of the rs7194256 SNP in the 3'UTR of the NET gene is associated with diseases associated with NET dysfunction, including hypertension. This might be explained by the creation of a binding site for the microRNA miR-19a-3p. A defect in NET function may potentiate the sympathetic neurochemical signal, predisposing individuals to increased risk of cardiovascular disease development.

ISH NIA OS-02 ATTENUATION OF HYPERTENSION BY LESS-INVASIVE INTRANASAL VACCINATION AGAINST ANGIOTENSIN II TYPE 1 RECEPTOR IN SPONTANEOUSLY HYPERTENSIVE RATS

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Objective: Previous studies have shown that injectable vaccines against renin-angiotensin system may be effective for the treatment of hypertension, but these injectable vaccines often cause local skin reactions and soreness at the injection site. The aim of this study was to develop a new non-injectable vaccine against angiotensin II type 1 receptor (AT1R) and examine its effect on blood pressure.

Design and method: The peptide, seven-amino-acid sequence from second extracellular loop of rat AT1R was synthesized and then conjugated with pneumococcal surface protein A (PspA) as a carrier protein for the nasal vaccination. 10 ug of AT1R-PspA antigen was mixed with cyclic di-GMP adjuvant to increase its immunogenicity and incorporated into cationic nanometer-sized hydrogel (nanogel) for the effective delivery to the nasal epithelium where was negatively charged. Male spontaneously hypertensive rats (SHRs) (n = 10/group) were treated transiently with five nasal administration of vehicle (cyclic di-GMP and nanogel alone) or AT1R-PspA vaccine at age 4, 5, 6, 7 and 8 weeks, and measured their blood pressures, AT1R-specific serum IgG antibody titers and plasma angiotensin II concentration.

Results: In the preliminary study, nasal immunization with AT1R-PspA (10 ug × 5 times) induced anti-AT1R serum IgG antibodies at the same level as subcutaneous vaccination (20 ug × 3 times). Nasal vaccination of AT1R-PspA also caused a sustained decrease in systolic blood pressure in SHRs (vehicle group 224.1 mmHg vs vaccine group 205.1 mmHg, at 10 weeks after the last vaccination, n = 10/group, $p < 0.01$). Plasma angiotensin II was increased by the vaccination, but the difference was not significant (vehicle 6.30 pg/ml vs vaccine 23.64 pg/ml, n = 5/group, $p = 0.2614$).

Conclusions: These results suggest that the nasal vaccination of AT1R-PspA may be effective for the attenuation of hypertension without injection-associated pain and local skin adverse events.

ISH NIA OS-03 GENETIC DETERMINANTS OF ESSENTIAL HYPERTENSION IN THE POPULATION OF TATARS FROM RUSSIA

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Objective: Systemic inflammation and impaired function of endothelium play a significant role in the development of blood pressure elevation. The population of Tatars residing in the Volga-Ural region of Russia is characterized by a unique combination of European and Asian genetic ancestry, and is an interesting object for genetic study. Our aim was to analyze an association between essential hypertension and the polymorphic markers of genes encoding for molecules involved in blood pressure control and the regulation of endothelial function and inflammation in the group of 530 Tatars from the Republic of Bashkortostan, Russia.

Design and method: The study group consisted of 216 patients with essential hypertension (mean age 48.92 ± 8.8) and 314 healthy individuals (mean age 43.58 ± 7.13) without history of cardiovascular or any other chronic disease. Data were analyzed using IBM SPSS 21.0 program. Fisher's two-tailed exact test was applied to estimate the differences between genotype/allele frequency distribution in the study groups, P-values of < 0.05 were considered significant.

Results: We detected the association of EDNRB (rs5351), EDNRA (rs6842241), VEGFA (–2549(18)I/D), and ADRB2 (rs1042713) polymorphic loci with hypertension, and found that the effect of the rs1042713 polymorphism was more pronounced in individuals with obesity (BMI > 30). We demonstrated that ADRB2 (rs1042713) and ADRB3 (rs4994) gene variants were associated with systolic and diastolic blood pressure level. We also showed that the rs213045 polymorphism in ECE1 gene was associated with cardiac function in patients with essential hypertension.
A Markov chain Monte-Carlo-based approach implemented in the APSampler program was used to analyze association of genotypes and alleles combinations associated with disease phenotypes. After the Bonferroni correction for multiple testing was applied, the most significantly associated with hypertension remained EDNRB*G/G+ADRB2*A+VCAM1*A combination (OR = 4.15, $P_{Bonf} = 5.43*10^{-8}$).

Conclusions: Our results suggest that genetic variation in entothelin-1 system, beta-adrenoreceptors, adhesion molecules and growth factor genes is implicated in the development of essential hypertension in Tatars.

ISH NIA OS-04 P2X3 RECEPTOR ACTIVITY IN THE CAROTID BODY (CB) OF SPONTANEOUSLY HYPERTENSIVE (SH) RATS CONTRIBUTES TO INCREASED CHEMOREFLEX HYPERSENSITIVITY AND HYPERTENSION

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