P-107
ASSOCIATION OF METHYLENETERAHYDROFOLATE REDUCTASE POLYMORPHISM C677T WITH HYPERTENSION DEVELOPMENT
Marília Fatela, Luisa Breitenfeld, Paula Alcantara, Helena Moreira, José Braz-Nogueira, Luis Sardinha, Maria J Laires, Manuel Bicho, Metabolism and Endocrinology Centre- Genetic Laboratory, Medical School University of Lisbon, Lisbon, Portugal; Metabolism and Endocrinology Centre- Genetic Laboratory, Medical School University of Lisbon, Lisbon, Portugal; Medicine I, Santa Maria Hospital, Lisbon, Portugal; Health and Exercise department, Physical Education Faculty, Lisbon, Portugal; Medicine I, Santa Maria Hospital, Lisbon, Portugal; Health and Exercise department, Physical Education Faculty, Lisbon, Portugal; Biochemistry laboratory, Medical School University of Lisbon, Lisbon, Portugal; Metabolism and Endocrinology Centre- Genetic Laboratory, Medical School University of Lisbon, Lisbon, Portugal.

Introduction: The Methylenetetrahydrofolate reductase enzyme (MTHFR) converts 5,10-methylenetetrahydrofolate to 5-methitilenehydrofola, a fundamental step in S-adenosylmethionine formation from S-adenosylhomocisteine. The substitution C677T (C677T) in the gene of MTHFR (1p36.3) expresses an enzyme variant, termolabile and with low activity, that may be related with the hypercisteineina development.


Population: The association study of C677T MTHFR polymorphism was done in a population with 142 individuals with Hypertension (81 with stage II hypertension (HT-II) and 61 with stage III hypertension (HT-III)), and a control population with 141 individuals with no history of hypertension or diabetes.

Results: The genotype frequencies of C677T MTHFR polymorphism for the hypertensives were CC- 0.620, CT- 0.345, and TT- 0.035, and for controls were CC-0.546, CT- 0.312, and TT- 0.142 (p<0.008). The allelic frequency for hypertension was C- 0.792 and T- 0.208, and for controls C- 0.702 and T- 0.298 (p<0.02).

Separating the individuals by the type of hypertension we disclosed that the genotype frequencies distribution in the 3 populations were different HT-II (CC-0.44; CT- 0.506; TT- 0.050) vs. controls (p<0.007) and HT-III (CC-0.689; CT- 0.295; TT- 0.016) vs. controls (p<0.0001). The allelic frequencies for HT-II were C- 0.698 and T- 0.302, and for HT-III were C- 0.836 and T- 0.164.

Conclusions: The hypertensive population when compared with the controls showed a significantly higher frequency of TT individuals in the control group. Our results don’t associate the TT genotype with a predisposition for hypertension development. Some studies associate the TT homozigoty to a predisposition for vascular disease. A meta-analysis from the several studies realized until 1998, have concluded that TT genotype is not a determinant factor in a well nourish population, a conclusion supported by our results.

Key Words: Hypertension, genetics, polymorphism

P-108
ALDOSTERONE SYNTHASE (CYP11B2)-344CT POLYMORPHISM IS ASSOCIATED WITH SHORT TELOMERES AND CAROTID ARTERY PLAQUES
Athanasse Benetos, Jeffrey P Gardner, Mahmoud Zareik, Kathy Bean, Abraham Avish, Research, Centre IPC, Paris, France; INSERM U258, Villejuif, France; Hypertension Research, University of Medicine and Dentistry of New Jersey, Newark, NJ.

The aim of this study was to examine the influence of the aldosterone synanse gene (CYP11B2) on two indices of biological aging, namely telomere length in white blood cells and the presence of carotid artery plaques, in men. The study was conducted in a French cohort of 349 males. We studied associations between the ~344 CT polymorphism of the aldosterone synthase gene (CYP11B2) and telomere length assessed in white blood cells, by measuring the length of terminal restriction fragments and detecting the presence of carotid artery plaques.

The presence of the C allele of the ~344 CT polymorphism was significantly associated with shortened telomere length: 8.53 ± 0.12kb in TT, 8.26 ± 0.10kb in TC and 8.17 ± 0.09kb in CC subjects (ANOVA p<0.03). The presence of the C allele was also associated with an increased prevalence of carotid artery plaques: 23% in TT vs. 41% in CT and 38% in CC patients (ANOVA p<0.02). This association was observed only in men with high blood pressure. Among hypertensives, the C-allele carriers had a high prevalence of atherosclerotic plaques, whereas the HT patients did not develop such lesions more frequently than normotensive subjects. Carriers of the ~344 TT aldosterone synthase genotype, with high blood pressure, do not develop more carotid artery atherosclerotic plaques than normotensive subjects. They also exhibit longer telomere length than subjects in the other hypertensive groups, suggesting a less advanced biological age and a possible protection against hypertensive vascular alterations.

Key Words: Atherosclerosis, aldosterone synthase, telomeres

P-109
ACE GENE POLYMORPHISM IS ASSOCIATED WITH EXERCISE-INDUCED CHANGES IN NA+ EXCRETION IN AFRICAN AMERICAN HYPERTENSIVES
Michael D. Brown, Matthew R. Weir, Thomas C. Dowling, Robert E. Ferrell, Jennifer J. Johnson, David Vizcaino, Michael D. Brown, Matthew R. Weir, Thomas C. Dowling, Robert E. Ferrell, Jennifer J. Johnson, David Vizcaino, Kinesiology, University of Maryland, College Park, MD; Medicine, University of Maryland, Baltimore, MD; Pharmacy Practice and Science, University of Maryland, Baltimore, MD; Human Genetics, University of Pittsburgh, Pittsburgh, PA; Kinesiology, University of Maryland, College Park, MD; Kinesiology, University of Maryland, College Park, MD; Kinesiology, University of Maryland, College Park, MD; Kinesiology, University of Maryland, College Park, MD; Pharmacy Practice and Science, University of Maryland, Baltimore, MD; Medicine, Howard University, Washington, DC.

We previously showed that short-term aerobic exercise training (AEX) increased 24-hr Na+ excretion in hypertensive African Americans. We sought to determine whether changes in urinary Na+ excretion in response to short-term AEX were associated with the angiotensin converting enzyme (ACE) Insertion/Deletion (I/D) gene polymorphism in 26 (age 55 ± 1 yrs) sedentary and mildly hypertensive (BP 146± 2/88± 2 mmHg) African Americans. Subjects were. Subjects underwent a 24-hr period of ambulatory BP monitoring and urine collection at baseline and 14-18 hrs after the last exercise session. AEX consisted of 7 or 8 consecutive days, 50 min/day at 65% of heart rate reserve. Dietary intake was similar during the testing periods before and after AEX as determined by food records. The I/D polymorphism in intron 16 at the ACE gene locus was genotyped using standard PCR techniques and resulted in
the following genotype groups: (II n=6, ID n=11, DD n=9). Baseline 24-hr systolic and diastolic BP, BMI, and Na+ and K+ excretion were similar in the three genotype groups. Average Na+ excretion for the entire group increased after AEX (108±9 vs. 143±12 mmol/d, p=0.03). Na+ excretion was significantly increased in the II (114±22 vs. 169±39 mmol/d, p=0.04), but not in the ID (100±8 vs. 133±17 mmol/d, p=0.12) or DD (114±18 vs. 138±11 mmol/d, p=0.12) genotype groups. This resulted in increases of 48, 33, and 21% in the II, ID, and DD genotype groups, respectively, suggesting a dosage effect of the I allele. Changes in K+ excretion were not significantly different in any of the genotype groups. In the II genotype group, the increase in Na+ excretion was significantly and inversely correlated with the change in 24-hr diastolic (r=-0.87, p=0.02) and mean (r=-0.94, p=0.004) BP. These preliminary results suggest that African American hypertensives with the ACE II genotype may be more likely to change their Na+ balance with AEX and their BP may be more sensitive to changes in Na+ excretion than those with the ID and DD genotypes.

Key Words: Exercise, genetics, sodium

P-110
CARDIOVASCULAR RISK FACTORS, SALT SENSITIVITY AND \(\alpha\)-ADDUCIN POLYMORPHISM IN VENEZUELAN SUBJECTS
Ana M Castejon, Irene S Hoffmann, Appu Rathinavelu, Luigi X Cubeddu. School of Pharmacy, Central University of Venezuela, Caracas, DF, Venezuela; School of Pharmacy, Nova Southeastern University, Fort Lauderdale, FL.

Human salt sensitivity (SS) most likely results from combined effects of genetic and environmental factors. Several gene candidates have been proposed to determine SS via an effect on renal sodium handling. Gly460Trp polymorphism, which resulted in the genetic variant of amino acid residue 460 of \(\alpha\)-adducin protein, has been associated with SS hypertension (HT). However, the results have been controversial. We studied whether \(\alpha\)-adducin gene polymorphism (Gly460Trp) was associated with SS, blood pressure (BP), dyslipidemia and other cardiovascular risk factors. A total of 91 healthy adult Venezuelan subjects (Age: 40.3±1.3 y; M/F: 39/52; BMI: 28.9±0.6 kg/m²; SBP/DBP: 119±4/80.0±1.1 mmHg; HR: 67.5±0.9 b/min) were studied. The Gly460Trp mutation was found in 29.7 % of subjects. Compared to the group of subjects carrying the wild type (G/G) gene, those with the G460T mutation had significantly higher BMI (G/T = 30.7±1.1kg and G/G = 28.0±0.6 kg/m², p=0.05), LDL-C (G/T = 153±9 and G/G = 118±7 mg/dL, p<0.01), glucose AUC after 75g of oral glucose (G/T = 87±17 and G/G = 58.5±6 mg/dL.hr, p=0.05) and family history of obesity. The genotype frequencies of \(\alpha\)-adducin polymorphism showed a non significant association with SS in these subjects (G/G = 39 % SS and 61 % SR, vs. G/T = 40.7 % SS and 59.3 % SR). This study shows that the Venezuelans have a G/G and G/T distribution comparable to that of European and American subjects. In this population of healthy normotensive adults, the 460 Trp allele was not found related to SS; although it was associated with risk factors such as dyslipidemia, hyperglycemia, obesity, and family history of obesity. However, we can not rule out that the dysmetabolic features associated to G/T polymorphism could be determined by the larger BMI present in these subjects.

Key Words: Salt sensitivity, \(\alpha\)-adducin, polymorphism

P-111
HUMAN PRESSOR RESPONSES: HERITABILITY ESTIMATIONS IN TWINS, AND GENOTYPIC ASSOCIATIONS AT ADRENERGIC AND RENIN/ANGIOTENSIN LOCI
Rubin Chandran, Fangwen Rao, Peter E Cadman, Alice Y Chen, Kathy Nguyen, Anna Bolotnikova, Guangfa Zhang, Brinda K Rana, Paul A Insel, Nicholas A Schork, Daniel T O’Connor. Department of Medicine & Center for Molecular Genetics, UCSD & VASDHS, San Diego, CA; Department of Psychiatry, UCSD, San Diego, CA.

Repeated pressor responses may ultimately result in sustained hypertension in individuals at genetic risk. The purpose of the study was to investigate heritability of pressor responses, evaluating blood pressure (BP, mmHg) and heart rate (HR, beats/min) variation in twins using the cold pressor test (CPT), and to correlate the cardiovascular responses with adrenergic (ADR) and renin-angiotensin-aldosterone system (RAAS) genetic loci.

145 pairs of twins (102 monozygotic [MZ], 43 dizygotic [DZ]) were studied. BP and HR were recorded continuously and non-invasively with a calibrated radial artery application device and dedicated software during CPT (immersion of non-dominant hand in ice water for 1 minute). Since MZ twins share 100% and DZ ~50% of alleles, the difference in trait correlation can be used to estimate heritability. Allergic association studies were done using single nucleotide polymorphisms (SNPs) at loci hypothesized to be important in pressor responses as well as the etiology of hypertension, including ADR B1 (ADRB1; Ser49Gly, Gly389Arg Lys324Arg), ADR B2 (ADRB2; 11 SNPs), angiotensin converting enzyme (ACE; intron 174), and angiotensin II type 1 receptor (AGTR1; 2 SNPs).

Heritability estimates for CPT were 0.24 for ΔSBP, 0.20 for ΔSBP and 0.26 for ΔHR. Preliminary genotypic analysis showed significant associations at ADRB1 Ser49Gly for ΔSBP (p=0.005) and ΔHR (p=0.018), while ΔDBP was only marginally significant (p=0.083). At ADRB1 Gly389Arg, %ΔSBP approached significance (p=0.083); no significance was noted for ΔDBP or ΔHR. ADRB1 Ser49Gly and ADRB1 Gly389Arg were in linkage disequilibrium by chi² analysis (D²=1, p=0.0216). There were no significant (all p>0.1) associations between CPT responses and SNPs at ADRB1 Lys324Arg, ADRB2, ACE, or AGTR1.

We conclude that pressor responses to environmental (cold) stress are heritable, and our preliminary data suggest that variability in such responses is predicted by allelic variation at ADR loci, such as ADRB1 Ser49Gly. Further genetic linkage/association studies in larger numbers of twins and siblings are ongoing to better characterize the involvement of ADR and RAAS genetic loci.

Key Words: Hypertension, twin, heredity

P-112
SALT INTAKE, URINARY NITRIC OXIDE METABOLITE EXCRETION AND GLY460TRP \(\alpha\)-ADDUCIN POLYMORPHISM
Luigi X Cubeddu, Anna B. Alfieri, Ana M. Castejon, Appu Rathinavelu, Irene S. Hoffmann, Pharmaceutical Science, School of Pharmacy, Nova Southeastern University, Fort Lauderdale, FL; Pharmacology, School of Pharmacy, Central University of Venezuela, Caracas, DF, Venezuela.

Changes in salt intake have been shown to differentially alter nitric oxide metabolite (NOx) excretion in salt sensitive (SS) and salt resistant (SR) subjects. Changes in salt intake do not alter the NOx excretion in SR; however, in SS subjects, high salt intake decreases NOx excretion, an effect reversed by salt restriction. Because SS has been linked to Gly460Trp alpha-adducin polymorphism, in this study we investigated whether the NOx excretion pattern induced by high and low salt intake was associated to Gly460Trp alpha-adducin polymorphism. A total of 73