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POMC neurons expressed in the ARC are essential for energy balance and glucose homeostasis. It has been suggested the involvement of these neurons in the control of endocrine axes, such as the HPA. During fasting, $POMC^{ARC}$ neurons are silenced as an effort to reduce body weight loss and to avoid hypoglycemia. During this process glucocorticoid secretion and activation of enzymes involved in the hepatic gluconeogenesis take place in order to preserve the homeostasis. In this study, to clarify the contribution of $POMC^{ARC}$ neurons to the adaptive changes in energy homeostasis, glucose metabolism and HPA axis activity induced by food deprivation we used DREADDs to specifically activate $POMC^{ARC}$. Bilateral injections of the AAV carrying the excitatory DREADD (hM3DGq) or only the reporter gene (mCherry) have been performed into the ARC of *Pomc-ires-cre* and WT mice. Two weeks later the animals were fasted for 36hr, treated with saline (5 i.p. injections each 8hrs) and blood samples were collected from the facial vein at 10am. Two weeks apart, the same animals were submitted to another period of fasting and treated with CNO (1mg/Kg, 5 i.p. injections each 8hrs). Four hours after the last injection of CNO, the mice were anesthetized, blood and the liver were collected and then the animals perfused for brain harvesting. Body weight measurements have been performed before and after the 36hrs period of fasting. Another set of *Pomc-ires-cre* (hM3DGq or mCherry) and WT animals were fasted (36hrs), treated with CNO (5X) and subjected to GTT. DREADD–induced activation of $POMC^{ARC}$ neurons has been confirmed by the increased cFos/mCherry expression after CNO treatment only in *Pomc-ires-cre* animals expressing hM3DGq. We observed that the specific activation of $POMC^{ARC}$ neurons did not change the fasting-induced activation of HPA axis. Surprisingly, we observed reduced body weight loss and higher plasma glucose in *Pomc-ires-cre* animals expressing the hM3DGq and treated with CNO. The GTT showed an impaired glucose tolerance after activation of $POMC^{ARC}$ neurons. The increased fasting glucose plasma levels was associated with increased *G6pc* (Glucose-6-phosphatase) mRNA expression but with no effect on other hepatic gluconeogenic genes. The present study reveals that $POMC^{ARC}$ neurons are not involved in the increased HPA axis activity in prolonged fasting conditions. Considering the classical anorexigenic/thermogenic and the glucose-lowering action of $POMC^{ARC}$ neurons, the present data reveal an unpredicted reduced body weight loss and impaired glucose tolerance induced by activation of these neurons during fasting. These data reinforce the notion that $POMC^{ARC}$ neurons are heterogeneous and might be playing dual effects on energy homeostasis. Of note, because part of ARC neurons shares a common progenitor, some of the functions ascribed to POMC neurons could be mediated by non-POMC neurons expressing the Cre transgene.

Genetics and Development (including Gene Regulation)

GENETICS AND DEVELOPMENT AND NON-STEROID HORMONE SIGNALING I

Association of Single Nucleotide Polymorphisms of CYP11B2, CYP11B1 and CYP17A1 with Primary Aldosteronism in a Multi-Ethnic Malaysian Cohort

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Abstract: Primary aldosteronism (PA), also known as Conn's syndrome, is a common curable cause of hypertension. Family studies of essential hypertensive patients suggest that heritable genetic factors play a role in blood pressure regulation[1]. Interestingly, single nucleotide polymorphisms (SNP) in genes encoding enzymes involved with adrenal steroidogenesis, *CYP11B2*, *CYP11B1* and *CYP17A1*, associate with increased risk of hypertension[2]. Therefore, we analysed whether selected SNPs in these genes are associated with PA. We performed an association study using genotype imputation for selected SNPs of the steroidogenic enzyme genes *CYP11B2* (rs4546, rs1799998, rs13268025), *CYP11B1* (rs6410, rs149845727), and *CYP17A1* (rs1004467, rs138009835, rs2150927) from a pilot genome wide association study of Malaysian PA patients and healthy controls which was merged with the Singapore Genome Variation Project (SGVP) population dataset[3]. Genotype imputation for minor and major alleles was validated using PCR sequencing (n>10 for each genotype). Further, one SNP from each steroidogenic enzyme (*CYP11B2*:rs1799998, *CYP11B1*:rs6410 and *CYP17A1*:rs1004467) was validated using commercial TaqMan genotyping assays on the ABI 7000 Sequence Detection System which was performed on 149 PA patients and 78 non-hypertensive healthy individuals. Case-control genetic association analysis was performed at http://www.oege.org/software/orcalc.html and the association between genotypes and phenotypes was done using the independent-samples Kruskal-Wallis test on SPSS (version 25). The Minor Allele Frequencies (MAFs) for rs1004467, rs6410 and rs1799998 were similar to East Asian populations but differed significantly different from European, African, American and South Asian populations (rs1004467 MAF: C=0.258/298, rs6410 MAF: A=0.265/298, rs1799998 MAF: C=0.225/298). In Chinese patients matched by gender, heterozygotes for rs6410 had significantly increased risk of PA compared to common homozygotes (OR: 3.15, 95% CI: 1.01–9.8, p=0.04). Across patients of different ethnicity, the distribution of aldosterone levels was significantly different (p=0.039). In summary, only SNP rs6410 in Chinese patients matched by gender showed association with PA in our South East Asian cohort. More functional experiments need to be done to find out whether this is causal for PA or whether the SNP is in linkage disequilibrium with the actual functional causative SNPs. Once the functional SNP is known, identification of these germline variants in asymptomatic family members would allow early screening of PA to be offered and potentially provide novel drug targets to treat the disease.

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