immune phenotyping and cardiovascular MRI. Women without prior CVD or diabetes were eligible.
Results: Women were similar in age and BMI (WWH vs. women without HIV: 51 ± 5 vs. 52 ± 6 years, P=0.79 and 32 ± 8 vs. 31 ± 7 kg/m2, P=0.71). There was no significant between-group difference in the percentage of women without menses in the past year (p=0.52) or in the percentage of women with undetectable levels of antimullerian hormone (p=0.71). No women in either group were on estrogen and/or progesterone for treatment of menopausal symptoms. Hot flash frequency (days per week with hot flashes) was higher among WWH versus women without HIV (median [IQR], 7.0 [1.3, 7.0] vs. 0.8 [0.0, 2.1], p=0.01). In sensitivity analyses excluding either women with menses in the past year or with detectable AMH, WWH still reported a significantly higher number of days per week with hot flashes (7.0 [6.3, 7.0] vs. 0.4 [0.0, 2.3], p=0.007, and 7.0 [2.4, 7.0] vs. 0.8 [0.0, 2.1], p=0.01, respectively). Among WWH experiencing (vs. not experiencing) hot flashes in the past year, longer duration of ART use was noted (21.2 [16.0, 22.7] vs. 9.3 [3.3, 16.0] years, p=0.03). Among the entire cohort and among WWH, women with more than one hot flash per day had higher levels of soluble CD14, a marker of monocyte activation, compared to women with one or fewer hot flash per day (p=0.004 and p=0.02, respectively). Among WWH and a history of hot flashes, years since onset of hot flashes related to cardiovascular MRI-derived measures of subclinical pathology. Specifically, years since onset of hot flashes related directly to myocardial steatosis (intramyocardial triglyceride content; ρ=0.80, p=0.02) and inversely to diastolic function (left atrial passive ejection fraction; ρ=−0.70, p=0.03).
Conclusions: WWH experienced a higher frequency of hot flashes compared to women without HIV. Among WWH, hot flash symptomatology related to systemic immune activation and to cardiovascular MRI-derived measures of CVD risk. Additional research is required to improve understanding of mechanisms underlying these relationships and determine if hot flashes are a sex-specific risk factor for CVD in WWH.

Cardiovascular Endocrinology
CARDIOVASCULAR ENDOCRINOLOGY

Mild Autonomous Cortisol Secretion in Primary Aldosteronism Enhances Renal and Hemorrhagic Cerebrovascular Complications

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Background: It is well known that primary aldosteronism (PA) is often associated with renal dysfunction and cardiovascular events (CVEs). However, the synergic effect of mild autonomous cortisol secretion (MACS) on the co-morbidities among PA has not been clarified yet. Thus, we retrospectively assessed whether the presence of MACS in PA patients with adrenal tumor, which may have MACS, to enhance the risk of the complications using a large Japanese multicenter database.
Methods: We enrolled patients with both confirmed PA and obvious adrenal tumor (diameter > 1 cm) on computed tomography. The subtype of PA was diagnosed based on the results of adrenal venous sampling with ACTH stimulation. A total of 575 study subjects were stratified into two groups according to 1-mg dexamethasone suppression test (DST) results (cut-off post-DST serum cortisol 1.8 μg/dL): MACS group (N=174, 30.2%) and non-MACS group (N=401, 69.8%). Decreased estimated glomerular filtration rate (eGFR) was defined as <60 ml/min per 1.73m^2.
Results: The percentage of unilateral PA between the MACS and non-MACS group was equivalent (50.0% vs. 48.1%). Prevalence of decreased eGFR in the MACS group was higher than in the non-MACS group [odds ratio (OR) 1.91, 95% confidence interval (95% CI) 1.20–3.04, P=0.006]. Conversely, prevalence of MACS was higher in patients with decreased eGFR than those without decreased eGFR (42.7% vs 28.0%, P=0.008). Proteinuria was deteriorated with the increase in post-DST serum cortisol concentration as well as the basal plasma aldosterone concentration (PAC) (P=0.028 and P<0.001, respectively), although PAC but not the presence of MACS was selected as an independent factor related with decreased eGFR. Prevalence of cerebral hemorrhage in the MACS group was higher than the non-MACS group. (OR 5.35, 95%CI 1.83–15.6, P=0.002). We found that MACS was the only significant factor which increased the odds of developing cerebral hemorrhage (OR 9.13, 95%CI 2.15–38.90, P=0.003). Prevalence of other CVEs between the two groups was similar. Regardless of the PA subtype, complication rate of decreased eGFR and cerebral bleeding in the MACS group were significantly or tend to be higher than non-MACS group.
Conclusion: Our date strongly suggested that co-secretion of cortisol in PA directly and/or indirectly increase renal and cerebrovascular comorbidities. Given that MACS is common in PA, endocrinological testing with DST is recommended in PA patients, especially those with adrenal tumor on imaging. (Supported by Research Grants of AMED:JP17ek0109122, JP20ek0109352; National Center for Global Health and Medicine:27–1402, 30–1008), and Ministry of Health, Labour, and Welfare, Japan (046).

Cardiovascular Endocrinology
CARDIOVASCULAR ENDOCRINOLOGY

Modulation of Calcium Signaling by Chemogenetic Tools to Elucidate the Pathogenesis of Primary Aldosteronism

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Primary aldosteronism (PA) is the most frequent form of secondary arterial hypertension. The identification of germline or somatic mutations in different genes coding for ion channels (*KCNJ5*, *CACNA1D, CACNA1H* and *CLCN2*) and ATPases (*ATP1A1* and *ATP2B3*) defines PA as a channelopathy. These mutations promote increased intracellular calcium concentrations and activation of calcium signaling, the main trigger for aldosterone biosynthesis.
The aim of our study was to elucidate the mechanisms underlying the development of PA by modulating calcium signaling using chemogenetic tools.
We have generated two different adrenocortical H295R_S2 cell lines stably expressing different chimeric ion channels generated by fusing the mutated extracellular ligand binding domain of the α7 nicotinic acetylcholine receptor to the ion pore domain of large Cys-loop receptor ion channel family; these receptors constitute PSAM (Pharmacologically Selective Actuator Modules). The mutations introduced in the ligand-binding domain allow to use synthetic ligands, PSEM (Pharmacologically Selective Effector Molecules) to activate the PSAM. We used two different PSAM: the chimeric receptor α7-5HT3 or a mutated acetylcholine receptor nAchR, allowing respectively modulation of sodium or calcium entry into the cells in response to the specific PSEM: Varenicline for α7-5HT3 or Compound 9S for mutated nAChR. The cells lines were characterized in terms of intracellular calcium concentrations, cell proliferation, aldosterone production and steroidogenic gene expression.
Cells expressing α7-5HT3 treated for 24h with increasing concentrations of Varenicline (10^{-9} to 10^{-5}M) showed increased intracellular calcium concentrations and an increase in expression of steroidogenic genes such as *StAR CYP17A1, CYP21A2 and CYP11B2*. Cell proliferation was not affected. Calcium entry into cells expressing the mutated nAChR receptor treated for 24h with increasing concentrations of Compound 9S (10^{-9} to 10^{-5}M) induced an increase in expression of steroidogenic genes such as *StAR*, *CYP21A2* and *HSD3B2,* but not *CYP11B2*. Similarly to the results obtained in cells expressing α7-5HT3, cell proliferation was unaffected in response to Compound 9S.
These cell lines, in which we can modulate the intracellular calcium concentration « on demand », are a useful tool for a better understanding of the alterations of intracellular ion balance and calcium signaling in the pathophysiology of PA.

Cardiovascular Endocrinology
CARDIOVASCULAR ENDOCRINOLOGY

Muscle Function is Associated With Presence, New-onset, or Worsening of Hepatic Steatosis Assessed by Biochemical Parameters, Independent of Muscle Mass

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Non-alcoholic fatty liver disease (NAFLD) becomes a major health problem leading to metabolic complications and end-stage liver disease, lacking effective therapeutic interventions. Skeletal muscle deficit, or sarcopenia, is related to accelerated accumulation of ectopic fat at liver. Skeletal muscle can be a novel intervention target of NAFLD. However, previous studies focused on the association between muscle mass and NAFLD, whereas the association of muscle function with NAFLD, a more clinically relevant assessment regarding skeletal muscle, remains unclear. Among participants enrolled between 2013 to 2014 in cardiovascular and Metabolic Diseases Etiology Research Center (CMERC) study (n=807), a cohort of community-dwelling Korean adults to study cardiovascular risk factors, a total of 500 individuals were recruited for 5-year follow-up. Hepatic steatosis was defined by hepatic steatosis index 36 or higher (HSI=8X(AST/ALT)+BMI+2 [if diabetes]+2 [if female]). New-onset of hepatic steatosis was defined as newly developed hepatic steatosis at current follow-up compared to baseline and worsening of HSI was defined as the highest quartile of HSI changes (2 or higher HSI increase). Muscle function was assessed by peak countermovement jump power relative weight (W/kg), 5 times chair rise test (CRT; in seconds), and grip strength (GS; in kg). Appendicular lean mass (ALM) was measured using bioimpedance analysis (InBody770, Biospace, Seoul, Korea). A total of 439 subjects (women 74%; mean age 57 ± 8 year) were analyzed after excluding those with excessive alcohol intake (n=51) and any missing values (n=10). Hepatic steatosis was present in 40% of subjects, which was increased from baseline period (33%, p<0.001). Low peak jump power (adjusted odds ratio [aOR] 1.14 per 1 W/kg decrease), GS (aOR 1.08 per 1kg decrease), and CRT performance (aOR 1.09 per 1 second increase; p<0.05 for all) were all associated with elevated odds of hepatic steatosis, after adjustment for age, gender, height, ALM, and metabolic syndrome components. Compared to those without hepatic steatosis at baseline and follow-up, those with persistent hepatic steatosis had significantly lower jump power in both men and women (33 vs. 40 W/kg in men, p=0.027; 26 vs. 29 W/kg in women, p<0.001). Jump power remained as robust predictor for new-onset hepatic steatosis or worsening of HSI (aOR 1.05 per 1W/kg decrease, p=0.044), whereas GS, CRT, and ALM were not. Muscle function measured by jump power was associated with presence or worsening of hepatic steatosis assessed by biochemical parameters, independent of muscle mass. Acknowledgement: We thank CMERC participants and all research staffs for this work. Funding: This study was supported by research grants from Hanmi Pharmaceutical Co.,Ltd. (4-2018-0845).