Abstract citation ID: bvac163.596

Cardiovascular Endocrinology

12428

Modulation Of Calcium Signaling On Demand To Decipher The Molecular Mechanisms Of Primary Aldosteronism

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Disclosure: B. Fedlaoui: None. T. Cosentino: None. Z.R. Al Sayed: None. I. Giscos-Douriez: None. J. Hulot: None. T. Simon: None. S. Baron: None. F.L. Fernandes-Rosa: None. M. Zennaro: None. S. Boulkroun: None.
Primary aldosteronism (PA) is the most frequent form of secondary hypertension and is due to autonomous aldosterone production by the adrenal gland. During the last decades, major advances have been made in our understanding of the disease with the identification of germline or somatic mutations in ion channels and pumps. These mutations enhance calcium signaling, the main trigger of aldosterone biosynthesis. The objective of our work was to elucidate, using chemogenetic tools, the molecular mechanisms underlying the development of PA by modulating sodium entry into the cells “on demand” leading to calcium signaling activation. We have developed an adrenocortical H295R-S2 cell line stably expressing a chimeric ion channel receptor formed by the extracellular ligand-binding domain of the $\alpha_7$ nicotinic acetylcholine receptor fused to the ion pore domain of the serotonin receptor 5HT3a named $\alpha_7$-5HT3. Its activation by a selective agonist, the PSEM-817, leads to sodium entry into the cells and activation of calcium signaling. In parallel, we have developed a mouse model expressing the $\alpha_7$-5HT3 receptor specifically in the adrenal cortex. Cells expressing the $\alpha_7$-5HT3 receptor recapitulate the major characteristics of KCNJ5 mutations, the most frequent genetic alteration identified in aldosterone producing adenoma. Stimulation of the $\alpha_7$-5HT3 receptor by PSEM-817 resulted in a significant increase in intracellular calcium concentrations, CYP11B2 mRNA expression, and aldosterone biosynthesis and was associated with a decrease in cell proliferation. RNA sequencing and steroidome analyses revealed unique profiles associated with sodium entry. Exploration of adult mice expressing the $\alpha_7$-5HT3 receptor specifically in the adrenal cortex, generated in our laboratory, is ongoing. Preliminary results revealed a significant increase in plasma aldosterone and 18-hydroxycorticosterone levels in male and female mice expressing the $\alpha_7$-5HT3 receptor after four weeks of treatment with PSEM-817 but no major adrenal abnormalities. Our results suggest that increased sodium influx leading to increased calcium signaling is not sufficient to promote both increased aldosterone production and cell proliferation, strongly supporting the need for additional mechanisms for the development of aldosterone producing adenoma. Overall, this work provides valuable insights into the role of sodium-induced calcium signaling in the development of PA and paves the way for the development of new therapeutic strategies.

Presentation: 6/1/2024