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### PPAR Receptors and the Causal Relationship between Vascular Dysfunction and Salt-induced Hypertension

Jing Wu, Larry N Agbor, Shi Fang, Masashi Mukohda, Anand R Nair, Pablo Nakagawa, Avika Sharma, Donald A Morgan, Justin L Grobe, Kamal Rahmouni, Robert M Weiss, James A McCormick, Curt D Sigmund. Failure to Vasodilate in Response to Salt Loading Blunts Renal Blood Flow and Causes Salt-Sensitive Hypertension. *Cardiovasc Res.* 2020 May 19;cvaa147. doi: 10.1093/cvr/cvaa147.

A little more than two decades ago, a mutation in the peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) was shown to be associated with severe and early insulin resistance, diabetes mellitus, and hypertension (HTN). Years later, a similar but selective PPAR $\gamma$  receptor mutation in vascular smooth muscle was shown to simulate in a mouse model the HTN seen in patients. This demonstrated that PPAR $\gamma$  receptors participate in the regulation of blood pressure through a direct action mechanism on peripheral vascular resistance. More recently, different studies have shown that the loss of this receptor promotes vascular dysfunction and HTN through a lower nitric oxide (NO) bioavailability, a lower response of vascular smooth muscle to the dilating action of NO, and alterations of intracellular pathways that regulate muscle contraction. However, the role of PPAR $\gamma$  receptors in the pathophysiology of renovascular regulation in salt-induced HTN remains unclear.

In this work, Jing Wu et al. used transgenic mice that selectively expressed a dominant negative mutation in the PPAR $\gamma$  protein gene in vascular smooth muscle, similar to that involved in the pathophysiology of HTN in humans. These mice developed a progressive increase in blood pressure during a four-week high-salt diet, simulating a condition of salt-sensitive HTN. Ex vivo studies using renal and carotid artery segments from these mice demonstrated a deterioration of both renal and systemic induced vasodilation. Interestingly, involvement of vasodilation begins to manifest early, from the third day after the start of salt feeding, preceding the onset of HTN, and thus suggesting a bi-

phasic role of PPAR $\gamma$  receptors in the pathogenesis of salt-sensitive HTN. The decrease in the systemic vascular response to NO differs from the reduction in its endogenous renal production, although the vasodilator response to exogenous NO in the renal artery was preserved. As a whole, the transgenic mice showed an increase in blood pressure without changes in cardiac output, evidencing an increase in peripheral vascular resistance and, in addition, a decrease in renal blood flow. The decrease in the renal bioavailability of NO was accompanied by a decrease in diuresis and natriuresis, as demonstrated in previous studies. Finally, the diuretic and natriuretic capacity of NO was recovered with the administration of a Na<sup>+</sup>-K<sup>+</sup>-2Cl<sup>-</sup>-cotransporter inhibitor (NKCC2), thus avoiding the increase in blood pressure.

*Jing Wu et al. demonstrate for the first time that the activity of PPAR $\gamma$  receptors in the smooth muscle cells of blood vessels play a crucial role in the pathogenesis of salt-sensitive HTN, since vascular dysfunction precedes the manifestation of increased blood pressure. Thus, PPAR $\gamma$  receptors are required for an adequate renal and systemic adaptive vasodilator response to high salt intake. These receptors belong to the subfamily of type II nuclear receptors, that is, protein regulatory genes. They are widely distributed in various tissues, and they have an important role in glucose metabolism and fatty acid storage. It is well known that PPAR $\gamma$  receptors have a relevant role in various cardiovascular risk factors, such as obesity, metabolic syndrome, and diabetes mellitus. It is also known that thiazolidinedione binding to these receptors activates genes that promote or facilitate the action of insulin, favoring carbohydrate metabolism. However, the heterogeneous action of receptors caused numerous collateral effects of these drugs in patients who could have benefited from their antidiabetic effects. Therefore, although the role of PPAR $\gamma$  receptors in the pathophysiology of salt-sensitive HTN appears to be highly relevant and a potential therapeutic target, there may still be a long way to go considering the complexity of their functions.*

#### Ethical considerations

Not applicable.