No. 2319

Pathophysiology of Skin Renin-Angiotensin System and Sodium Accumulation in the Development of Hypertension

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Summary

Recent studies suggest skin sodium accumulation and vasoconstriction are associated with hypertension. The skin has a localized renin-angiotensin system (RAS), a key regulator of blood pressure (BP), but its functional role remains unclear. We have shown that ATRAP (type-1 angiotensin II (Ang II) receptor (AT1R)-associated protein), which selectively inhibits pathological AT1R signaling, prevents the development of non-communicable diseases, including hypertension. This study aims to investigate the role of skin RAS in hypertension with a focus on "skin sodium accumulation" and "skin vasoconstriction". To investigate the relationship between skin RAS and hypertension, mice lacking ATRAP in keratinocytes (KO: $K14^{Cre}$; $ATRAP^{flox}$) were generated. Ang II (500 ng/kg/min)-induced hypertension and related cardiac hypertrophy were exacerbated in KO mice compared to their littermate control mice. KO mice showed increased skin expression of angiotensinogen and AT1R, suggesting enhancement of tissue RAS activity in the skin. Unexpectedly, skin water and sodium amounts estimated by the ashing method were compatible between the genotypes with Ang II treatment. On the other hand, skin blood flow and transepidermal water loss (TEWL) were significantly decreased in KO mice compared to their controls, suggesting "skin vasoconstriction" is associated with the exacerbated Ang II-induced hypertension in KO mice. In conclusion, enhanced skin RAS activity may be associated with BP elevation via skin vasoconstriction. Further studies are necessary to elucidate the causal relationship between skin RAS and hypertension.