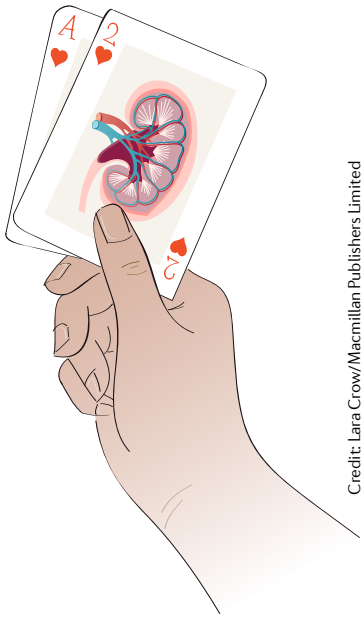
HYPERTENSION

FGF21 ACEs hypertension



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Fibroblast growth factor 21 (FGF21) is an endocrine hormone that regulates energy metabolism and insulin sensitivity and was shown to reduce blood pressure in a rat model of hypertension. Now, the group of Zhuofeng Lin shows that FGF21 functions in hypertension by regulating the renin–angiotensin system.

First, the researchers assessed the levels of FGF21 in mice following hypertension induced by angiotensin II (ANGII) infusion. In wild-type mice, ANGII infusion increased serum FGF21 levels and FGF21 mRNA levels in the liver, but not in adipose tissue. The production of FGF21 by the liver required peroxisome proliferator-activated receptor-α (PPARα), which is a key regulator of the metabolic response to fasting or starvation.

Next, the researchers observed that ANGII-induced hypertension and the associated vascular damage observed in wild-type mice were exacerbated in *Fgf21*$^{-/-}$ mice. Furthermore, in ex vivo arteries, ANGII-induced vascular dysfunction, upregulation of oxidative stress markers and production of reactive oxygen species (ROS) were greater in *Fgf21*$^{-/-}$ mice than in wild-type mice. Conversely, overexpression of FGF21 in wild-type mice suppressed all of these ANGII-induced effects. Thus, FGF21 protects mice against the effects of ANGII-induced hypertension.

Next, the researchers sought the mechanism by which FGF21 protects against ANGII-induced hypertension and vascular damage. The renin–angiotensin system controls blood pressure and fluid balance in mammals and is regulated by angiotensin-converting enzymes (ACEs). Whereas ACE catalyses the production of ANGII (a vasoconstrictor), ACE2 converts ANGII to a vasodilator, angiotensin-(1–7) (ANG-(1–7)). The researchers found that ACE2 protein and mRNA levels in aortic tissue were substantially lower in *Fgf21*$^{-/-}$ mice than in wild-type mice. Furthermore, ANGII infusion upregulated aortic ACE2 mRNA and protein levels in wild-type mice, an effect that was markedly reduced in *Fgf21*$^{-/-}$ mice. Consequently, plasma ANGII levels were higher, and ANG-(1–7) levels were lower, in *Fgf21*$^{-/-}$ mice than in wild-type mice, and ANGII infusion did not markedly increase ANG-(1–7) and ACE2 levels in the plasma of *Fgf21*$^{-/-}$ mice.

Conversely, FGF21 overexpression in wild-type mice increased aortic ACE2 mRNA levels and plasma ACE2 and ANG-(1–7) levels (ANGII levels were decreased), resulting in increased ACE2 levels in aortic tissue and preventing ANGII-induced hypertension and vascular damage. Importantly, in renal tissue, which is a major in vivo source of ACE2, ANG-(1–7) levels were higher and ACE2 and ANGII levels were lower in *Fgf21*$^{-/-}$ mice than in wild-type mice after ANGII infusion. However, whereas renal ACE levels were not affected by FGF21 deficiency, renin and ANGII receptor type 1 (AT1R) expression, ROS production and collagen deposition in kidney tissue were increased in *Fgf21*$^{-/-}$ mice compared with wild-type mice after ANGII infusion. FGF21 overexpression had the reverse effect — increasing ACE2 and ANG-(1–7) levels and decreasing ANGII levels in the kidneys.

To further dissect the relationship between FGF21 and ACE2, the researchers repeated their analyses in *Ace2*$^{-/-}$ mice. The protective effects of FGF21 overexpression in ANGII-induced hypertension, including lowered blood pressure and reduced vascular inflammation, damage, dysfunction and oxidative stress, were predominantly absent in *Ace2*$^{-/-}$ mice. Thus, FGF21 seems to exert its effects on ANGII-induced hypertension through ACE2.

Finally, in vitro experiments showed that the FGF21 induction of ACE2 production is direct — recombinant FGF21 increased ACE2 and ANG-(1–7) production by primary adipocytes and glomerular mesangial cells in a dose-dependent manner. This effect was blocked by treating the cells with a PPARγ antagonist, suggesting that the protective effects of the FGF21 via the ACE2–ANG-(1–7) axis are mediated, in part, through the activity of PPARγ in renal cells.

"In conclusion, the liver-secreted hormone FGF21, which was previously thought to be a potential anti-diabetic agent, potently attenuates ANGII-induced hypertension. Our study raises the possibility that FGF21 or its agonists might be more effective for the treatment of hypertension than diabetes," says Lin.

Grant Otto

> "the liver-secreted hormone FGF21 … potently attenuates ANGII-induced hypertension"

ORIGINAL ARTICLE Pan, X. et al. FGF21 prevents angiotensin II-induced hypertension and vascular dysfunction by activation of ACE2/angiotensin-(1–7) axis in mice. *Cell Metab.* https://doi.org/10.1016/j.cmet.2018.04.002 (2018)