Hypertension Research (2023) 46:1335–1336
https://doi.org/10.1038/s41440-023-01264-4

COMMENT

Mechanical stress is involved in mechanism of hypertensive nephropathy

Masaki Mogi[1]

Keywords Mechanosensor · Piezo2 · Mineralocorticoid receptor · Nephrosclerosis · Salt

Received: 28 February 2023 / Accepted: 3 March 2023 / Published online: 15 March 2023

Mechanobiology research is the study of the role and mechanisms of forces generated in living organisms. In the living body, the function of sensing and feeding back passive forces acting on organs, tissues, and cells is at work, and it has recently been revealed that disruption of this function is involved in the pathogenic mechanisms of many diseases. In the fields of hypertension and nephrology, mechanosensitive ion channels have recently been discovered, and mechanobiology research has been actively pursued.

The piezoelectric effect (also known as the Piezo effect) is the ability of certain materials to generate an electric charge in response to mechanical stress. Piezo was named from the Greek "πίεση" (píesi), which means pressure. In 2010, mechanically activated cation channels, Piezo1 and Piezo2, were reported as the responsible molecules in mechanically activated cells [1]. Mutations in the Piezo genes are responsible for multiple hereditary human diseases such as congenital lymphatic dysplasia, dominant hemolytic anemia, muscular atrophy, and distal arthrogryposis. Thus, dysfunction of the Piezo channels may contribute to the pathophysiology of human disease [2].

In the latest issue of Hypertension Research, Ochiai et al. focused on Piezo2 and examined its expression and localization changes in a model of hypertensive nephropathy [3]. In a previous study, the authors reported that Piezo2 is expressed in glomerular mesangial and renin-producing cells in the mouse kidney, and that Piezo2 expression in mesangial cells decreases with dehydration, and that Piezo2 may regulate renin expression [4]. This paper provides a more detailed examination of the function of Piez2.

Analysis using Dahl salt-sensitive rats fed a normal (0.3%) or high (8%) salt diet for 6 weeks from 4 weeks of age showed that Piezo2 expression was observed in mesangial cells and Ren1-positive cells in normal-salt-fed rats. On the other hand, Piezo2 expression was further enhanced in high-salt-fed rats Fig. 1. Interestingly, this increased expression was restored by treatment with the mineralocorticoid receptor blocker esaxerenone, which ameliorated hypertension and nephrosclerosis induced in high-salt-fed rats and suppressed perivascular mesenchymal cell growth. In vitro studies showed that suppression of Piezo2 expression in mesangial cells upregulated Tgfb1 expression, suggesting that Piezo2 acts in a tissue-protective manner. Interestingly, an increase in Piezo2 was observed not only in Dahl salt-sensitive rats, but also in salt-loaded SHRSP, indicating that it is not specific to this hypertension experimental model. Extended studies, including Piezo2 knockout mice, are expected to further elucidate the function of Piezo2.

Hypertension, as the name implies, is induced by the pressure exerted on blood vessels and is one of the most targeted diseases for mechanobiology research, but research seems to be just getting started. Piezo acts as the long-sought baroreceptor mechanosensors which are critical for acute blood pressure control [5]. Subsequently, Piezo was primarily examined mainly in pulmonary hypertension [6–8], with a focus on Piezo1. This paper provides an important finding that links the mechanosensitive ion channel to hypertension. The mechanisms by which signaling in response to mechanical stress act in an organ-damaging or organ-protective manner are complex, and further research, including mechanobiological studies, is warranted.

✉ Masaki Mogi
mmogi@m.ehime-u.ac.jp

[1] Department of Pharmacology, Ehime University, Graduate School of Medicine, Shitsukawa, Tohon, Ehime 791-0295, Japan

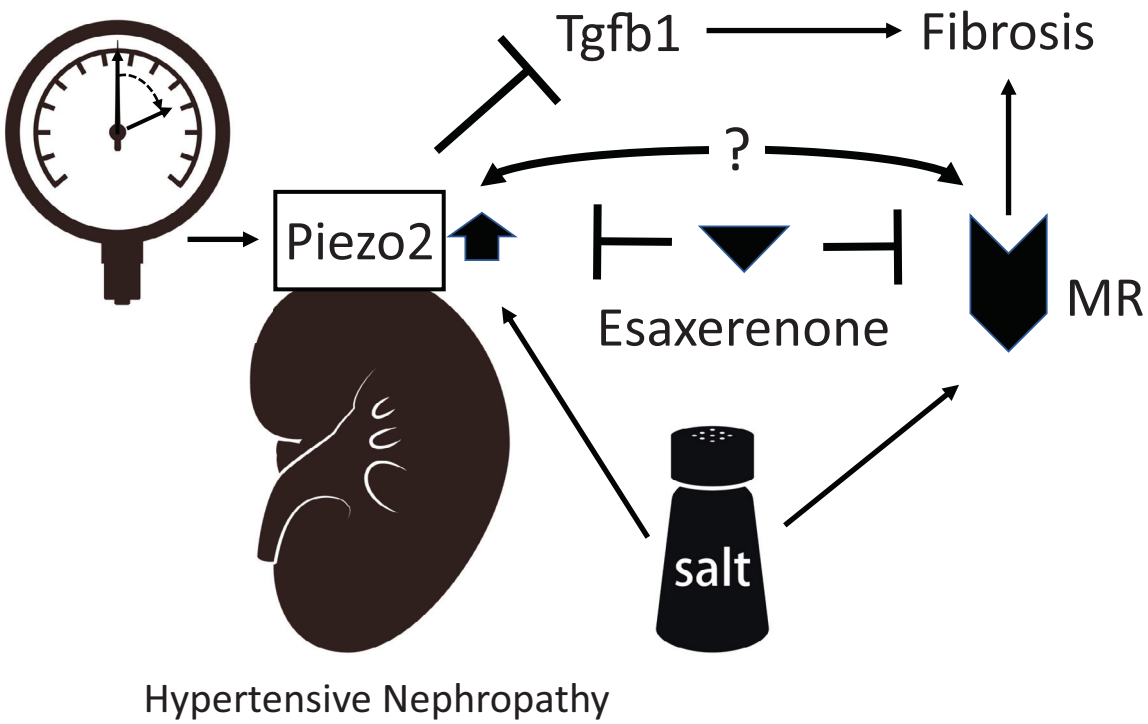

Fig. 1 Schematic presentation of possible interaction between Piezo2 and mineralocorticoid receptor (MR). Piezo2 is upregulated in Dahl salt-sensitive rats. Treatment with a MR blocker, esaxerenone, reduces the increase in Piezo2 expression. Knock down of Piezo2 upregulates Tgfb1 expression. Thus, Piezo2 may have a renoprotective effect. However, the relationship between Piezo2 and MR signaling remains to be elucidated. MR mineralocorticoid receptor

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Coste B, Mathur J, Schmidt M, Earley TJ, Ranade S, Petrus MJ, et al. Piezo1 and Piezo2 are essential components of distinct mechanically activated cation channels. Science 2010;330:55–60.
2. Alper SL. Genetic diseases of PIEZO1 and PIEZO2 dysfunction. Curr Top Membr. 2017;79:97–134.
3. Ochiai K, Mochida Y, Nagase T, Fukuhara H, Yamaguchi Y, Nagase M. Upregulation of Piezo2 in the mesangial, renin, and perivascular mesenchymal cells of the kidney of Dahl salt sensitive hypertensive rats and its reversal by esaxerenone. Hypertens Res. 2023. https://doi.org/10.1038/s41440-023-01219-9.
4. Mochida Y, Ochiai K, Nagase T, Nonomura K, Akimoto Y, Fukuhara H, et al. Piezo2 expression and its alteration by mechanical forces in mouse mesangial cells and renin-producing cells. Sci Rep. 2022;12:4197.
5. Zeng WZ, Marshall KL, Min S, Daou I, Chapleau MW, Abboud FM, et al. PIEZOs mediate neuronal sensing of blood pressure and the baroreceptor reflex. Science. 2018;362:464–7.
6. Barbeau S, Gilbert G, Cardouat G, Baudrimont I, Freund-Michel V, Guibert C, et al. Mechanosensitivity in pulmonary circulation: pathophysiological relevance of stretch-activated channels in pulmonary hypertension. Biomolecules. 2021;11:1389.
7. Liao J, Lu W, Chen Y, Duan X, Zhang C, Luo X, et al. Upregulation of Piezo1 (Piezo type mechanosensitive ion channel component 1) enhances the intracellular free calcium in pulmonary arterial smooth muscle cells from idiopathic pulmonary arterial hypertension patients. Hypertension. 2021;77:1974–89.
8. Wang Z, Chen J, Babicheva A, Jain PP, Rodriguez M, Ayon RJ, et al. Endothelial upregulation of mechanosensitive channel Piezo1 in pulmonary hypertension. Am J Physiol Cell Physiol. 2021;321:C1010–C27.