Actomyosin-dependent PIEZO1-mediated mechanotransduction amplifies aldosterone production

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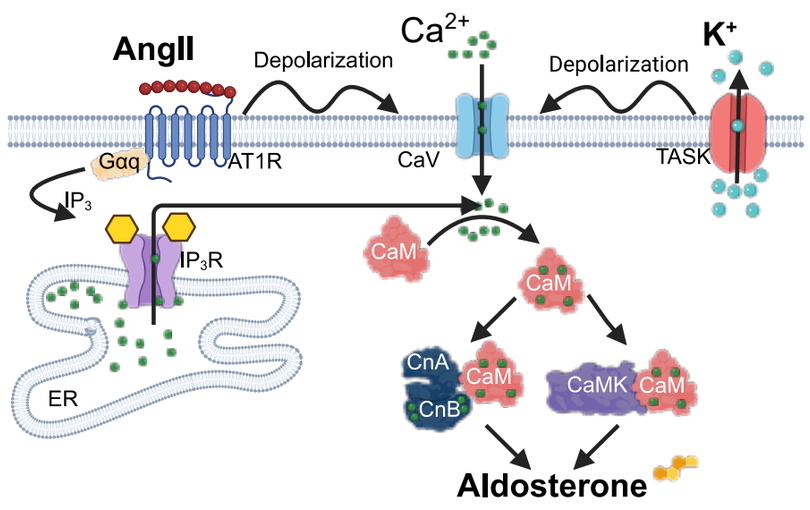
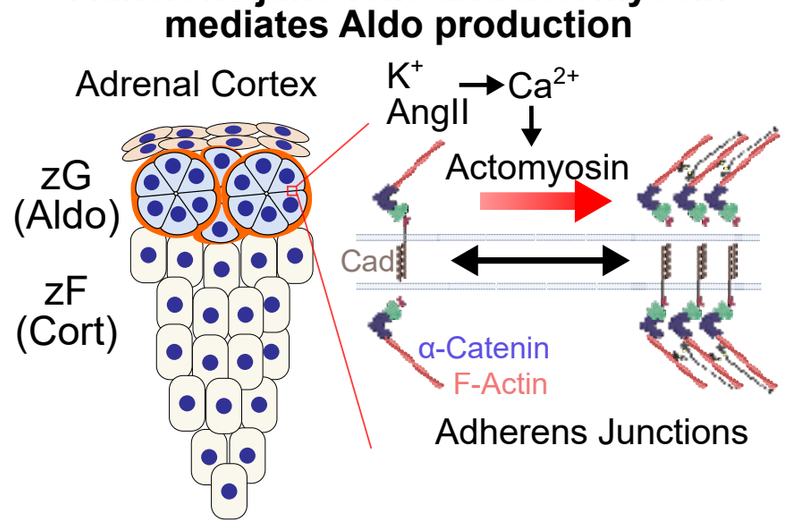
Background

Aldosterone (**Aldo**) is produced by zona glomerulosa (**zG**) cells of the adrenal cortex in response to elevated extracellular K^+ and angiotensin II (**AngII**). It helps maintain blood pressure and electrolyte homeostasis by promoting renal Na^+ retention and K^+ excretion. Autonomous Aldo production, as occurs in primary aldosteronism, is a common cause of secondary hypertension. In zG cells, Aldo synthesis is primarily regulated by Ca^{2+} signaling. zG cells connected by adherens junctions (**AJs**) form rosette structures. We found that Aldo secretagogues regulate AJ dynamics and promote actomyosin assembly at AJs, while AJ disruption reduces Aldo production. However, how AJs regulate Aldo synthesis remains unknown.

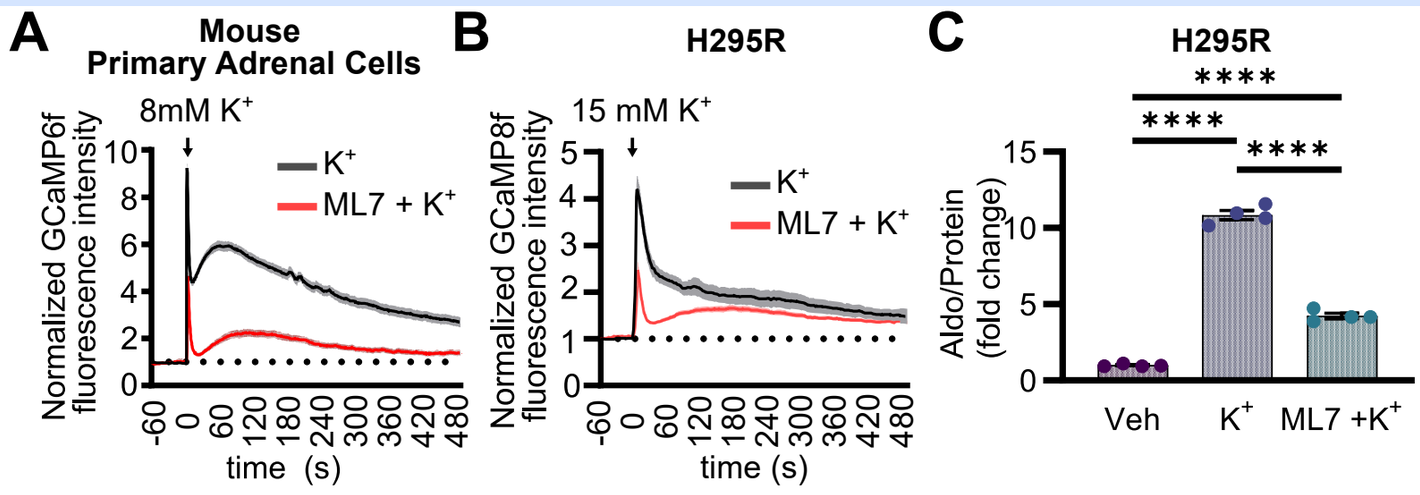
Aldo production is regulated by Ca^{2+} signaling.



Adherens junctions and actomyosin mediates Aldo production

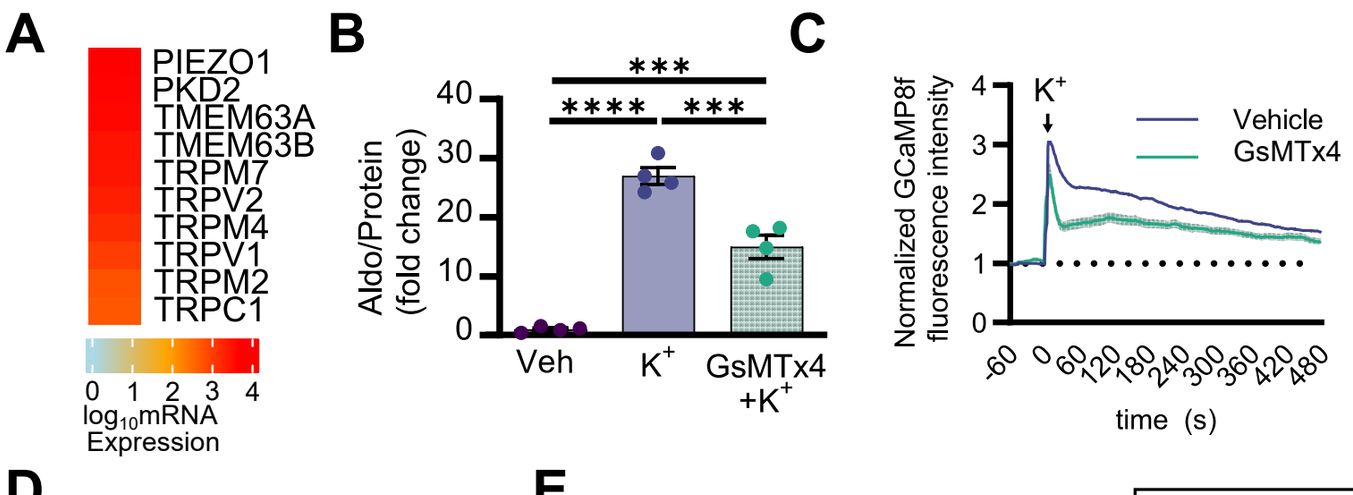


1. Actomyosin contractility regulates Ca^{2+} influx and Aldo production.



(A-C) Myosin light chain kinase inhibtion with ML7 blunts K^+ induced Ca^{2+} influx **(A-B)** and Aldo production **(C)** in primary mouse cells and human adrenocortical cell line (H295R).

2. PIEZO1 mediates actomyosin-dependent K^+-induced Aldo production.

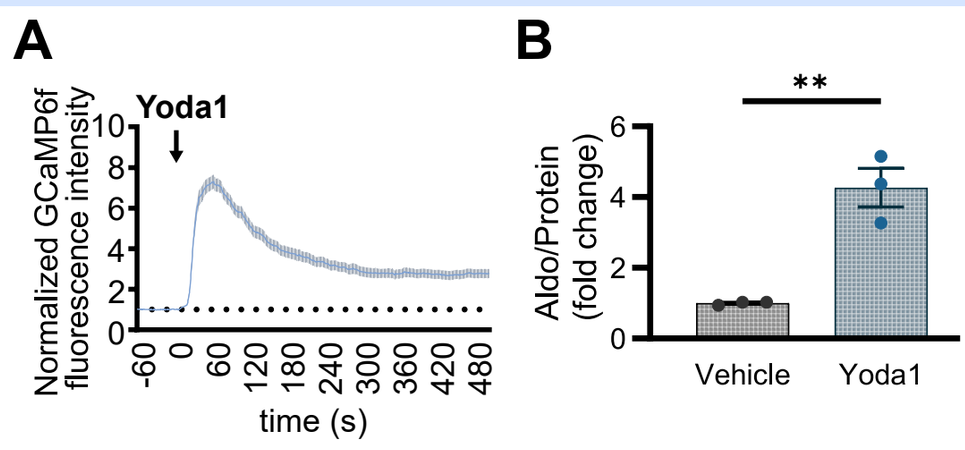


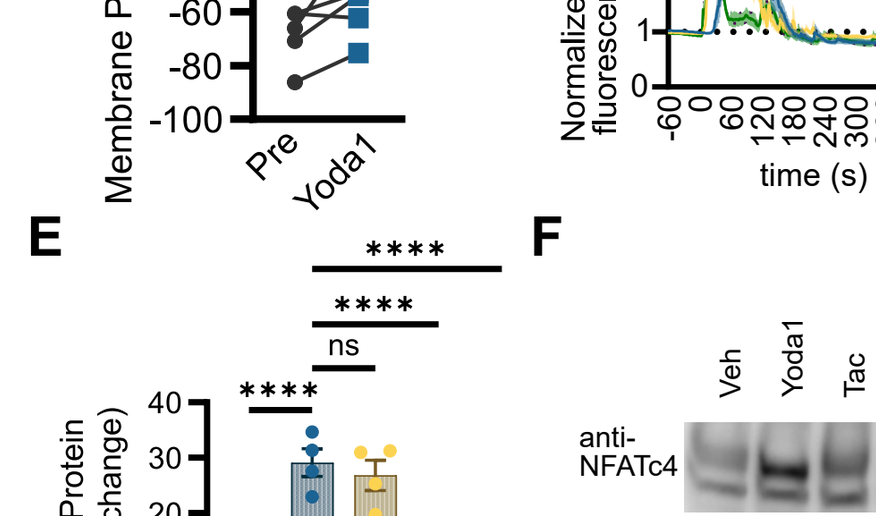
(A) Heatmap showing expression of mechanosensitive Ca^{2+}-permeable channels in human adrenal tissue. **(B-C)** Pharmacologic inhibition with GsMTx4 blunts K^+-induced Aldo production **(B)** and Ca^{2+} influx **(C)**. **(D)** *In vivo*, zG-specific PIEZO1 knockout mice show a blunted Aldo response to a high-K^+ diet. **(E)** Loss of PIEZO1 reduces Aldo production and abolishes additional suppression by actomyosin inhibition, consistent with PIEZO1 acting downstream of K^+-induced actomyosin contractility. **(F)** Schematic model illustrating regulation of PIEZO1 by K^+-triggered actomyosin contractility.

Conclusions

- Actomyosin contractility is required for K^+-induced Ca^{2+} influx and Aldo production.
- PIEZO1 acts downstream of K^+-triggered contractility to couple mechanical signaling to Aldo production.
- PIEZO1 activation is sufficient to stimulate a depolarization→Ca^{2+} →Calcineurin→NFATc4 pathway that promotes Aldo production.

3. PIEZO1 regulates Aldo production via L-type Ca^{2+} channels and calcineurin/NFAT signaling.





(A-B) Yoda1 induces Ca^{2+} influx in primary mouse adrenal cells **(A)** and increases Aldo production **(B)**. **(C)** Yoda1 causes membrane depolarization in human adrenocortical cell lines. **(D)** Inhibition of the voltage-dependent L-type Ca^{2+} channel with nifedipine shortens Yoda1-induced Ca^{2+} influx. **(E)** Inhibition of the L-type Ca^{2+} channel with nifedipine and inhibition of calcineurin with tacrolimus abolishes Yoda1-induced Aldo production. **(F)** Yoda1 induces calcineurin-dependent NFATc4 dephosphorylation. **(G)** Schematic illustrating regulation of Aldo production by the PIEZO1 channel.

Acknowledgement

This work was supported in part by an American Heart Association Postdoctoral Fellowship.