



P2 Calcium Induced Intramitochondrial cAMP Signalling Enhances Aldosterone Secretion

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ABSTRACT

Elevation of plasma $[K^+]$ and [angiotensin II] (Ang II), two major physiological stimuli of adrenal zona glomerulosa cells, increase aldosterone production by triggering cytosolic Ca^{2+} signalling. Cytosolic Ca^{2+} signals are accompanied by mitochondrial Ca^{2+} elevations which further strengthen this steroidogenic response. It has recently been recognized that such mitochondrial Ca^{2+} signals activate the mitochondrial soluble adenylyl cyclase (sAC) thus evoking intramitochondrial (matrix) cAMP elevations during Ca^{2+} signalling. We hypothesised that this Ca^{2+} induced mitochondrial cAMP production, too, contributes to the hypersecretion of aldosterone. Using human adrenocortical H295R cells we found that silencing of sAC decreased mitochondrial cAMP production and, at the same time, decelerated Ca^{2+} accumulation by the organelle. On the other hand, inhibition of the mitochondrial phosphodiesterase (PDE2A) intensified matrix cAMP production and accelerated mitochondrial Ca^{2+} uptake. More importantly, both pharmacological inhibition and knock-down of sAC mitigate AngII-induced aldosterone production. Finally, overexpression of wild-type sAC within the mitochondrial matrix increased mitochondrial cAMP formation, accelerated mitochondrial Ca^{2+} uptake and, most prominently, potentiated aldosterone production as compared to the enzymatically inactive mutant enzyme. Altogether, Ca^{2+} -induced mitochondrial cAMP signalling supports aldosterone production by favouring additional Ca^{2+} influx into the organelle. This positive feed-back loop may expedite the hormonal response when immediate hypersecretion of mineralocorticoids is crucial for cardiovascular compensation (e.g. exsiccation, blood loss).

REFERENCES

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