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Mitochondria regulate TRPV4 mediated release of ATP

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Abstract

Background and Purpose Ca^{2+} influx via TRPV4 triggers Ca^{2+} release from the IP_3-sensitive internal store to generate repetitive oscillations. While mitochondria are acknowledged regulators of IP_3-mediated Ca^{2+} release, how TRPV4-mediated Ca^{2+} signals are regulated by mitochondria is unknown. We show that depolarised mitochondria switch TRPV4 signalling from relying on Ca^{2+}-induced Ca^{2+} release at IP_3 receptors, to being independent of Ca^{2+} influx and instead mediated by ATP release via pannexins. **Experimental Approach** TRPV4 evoked Ca^{2+} signals were individually examined in hundreds of cells in the endothelium of rat mesenteric resistance arteries using the indicator Cal520. **Key Results**TRPV4 activation with GSK1016790A(GSK) generated repetitive Ca^{2+} oscillations that required Ca^{2+} influx. However, when the mitochondrial membrane potential was depolarised, by the uncoupler CCCP or complex I inhibitor rotenone, TRPV4 activation generated large propagating, multicellular, Ca^{2+} waves in the absence of external Ca^{2+}. The ATP synthase inhibitor oligomycin did not potentiate TRPV4 mediated Ca^{2+} signals. GSK-evoked Ca^{2+} waves, when mitochondria were depolarised, were blocked by the TRPV4 channel blocker HC067047, the SERCA inhibitor cyclopiazonic acid, the phospholipase C (PLC) blocker U73122 and the inositol triphosphate receptor (IP_3 R) blocker caffeine. The Ca^{2+} waves were also inhibited by the extracellular ATP blockers suramin and apyrase and the pannexin blocker probenecid. **Conclusion and Implications** These results highlight a previously unknown role of mitochondria in shaping TRPV4 mediated Ca^{2+} signalling by facilitating ATP release. When mitochondria are depolarised, TRPV4-mediated release of ATP via pannexin channels activates plasma membrane purinergic receptors to trigger IP_3 evoked Ca^{2+} release.

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