

P009 Agonist-evoked intralobular calcium waves and the regulation of mitochondrial metabolic responses in the intact liver.

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Glycogenolytic hormones, such as α_1 -adrenergic agonists and vasopressin, evoke transient increases or spikes in cytosolic free calcium ($[Ca^{2+}]_i$) by stimulating the production of the Ca^{2+} -mobilizing second messenger, inositol 1,4,5-trisphosphate ($InsP_3$). In the intact liver, $InsP_3$ -dependent $[Ca^{2+}]_i$ increases can be communicated to neighbouring cells giving rise to intercellular Ca^{2+} waves that spread across the entire lobule. These intercellular Ca^{2+} waves originate from a small number of hepatocytes located just outside of the portal tract, and then spread in a radial fashion into the portal vein and outwards towards the pericentral zone. Agonist-evoked $[Ca^{2+}]_i$ spikes are associated with a concomitant reduction in the mitochondrial pyridine and flavin nucleotide pools and this mitochondrial response follows the Ca^{2+} wave as it propagates across the lobule. The rise in NAD(P)H decays more slowly than $[Ca^{2+}]_i$ spike resulting in a sustained mitochondrial redox response at a low rate of $[Ca^{2+}]_i$ spiking. Challenging the liver with sub-threshold agonists concentrations generates asynchronous $[Ca^{2+}]_i$ spikes, which do not propagate as a coordinated intercellular Ca^{2+} wave across the lobule. Under these conditions, the mitochondrial NAD(P)H responses are not sustained and limited to the portal tract. These studies suggest that intercellular Ca^{2+} waves provide a mechanism to coordinate the functional metabolic responses of the liver.