A novel signaling pathway involved in thromboxane A_2 receptor-mediated vascular contraction

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Thromboxane A_2 (TXA_2) is one of the eicosanoids produced by the arachidonate cascade, and its biological activity is mediated by G protein-coupled TXA_2 receptors, i.e., TP receptors. Although TXA_2 is well known as a potent vasoconstrictor, the detailed understanding of the signaling pathways involved in TP receptor-mediated contraction remains to be fully elucidated. We have previously shown that low concentrations ($\leq$ 30 nM) of U46619, a stable TXA_2 analog, induces extracellular Ca^{2+}-dependent contraction mediated via voltage-dependent Ca^{2+} channels (VDCC) and cation channels in rat aorta. In the present study, we focused on lipid signaling, which may be involved in the Ca^{2+} influx induced by U46619.

U46619 (20 nM) induced contraction and $[Ca^{2+}]_i$ elevation in the ring preparations of isolated rat aorta. These effects were not inhibited by U73122, an inhibitor of phosphatidylinositol-specific phospholipase C (PI-PLC) that produces inositoltriphosphate (IP_3) and diacylglycerol (DAG) from phosphatidylinositol. The α_1 adrenergic agonist phenylephrine, which activates PI-PLC, elicited a transient increase in $[Ca^{2+}]_i$, possibly mediated by IP_3, in Ca^{2+}-free extracellular solution, whereas U46619 had no effect on $[Ca^{2+}]_i$. These results suggest that Ca^{2+} release from sarcoplasmic reticulum (SR) is involved in the $[Ca^{2+}]_i$ elevation mediated by α_1-adrenoceptors, but not by TP receptors. In contrast, the U46619-induced contraction and $[Ca^{2+}]_i$ elevation were abolished by D609, a phosphatidylcholine-specific phospholipase C (PC-PLC) that produces DAG from phosphatidylcholine. Although the involvement of DAG was suggested, the effects of U46619 were not inhibited by GF109203X, a protein kinase C (PKC) inhibitor.

Taken together with these results, we propose the following mechanism: U46619 stimulates PC-PLC, which increases DAG production. The produced DAG opens cation channels independently of the activation of PKC, which leads to VDCC activation via depolarization. Then, extracellular Ca^{2+} influx via VDCC and cation channels increases $[Ca^{2+}]_i$, thereby eliciting vascular contraction.