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Elucidation of Roles of NCX/TRPC Coupling in Vascular Spasm and Its Applications

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Summary

α_1-adrenoceptor contributes to the sympathetic regulation of various arteries. However, the molecular mechanisms underlying α_1-adrenoceptor-mediated vasocontraction remain obscure. We found that phenylephrine -induced cytosolic Ca^{2+} elevation and contraction were significantly greater in mesenteric arteries from NCX1-transgenic mice (vascular smooth muscle-specific promoter), as well as from TRPC3-transgenic mice, compared to wild-type mice. In these two kinds of transgenic mice, a bolus injection of norepinephrine elicited ST-segment elevation and Atrio-Ventricular block (coronary spasm), both of which were suppressed by a selective inhibitor for NCX1 or TRPC3. When we crossed NCX1-transgenic mice with dominant negative TRPC3 -transgenic mice and TRPC3-transgenic mice with NCX1-knockout mice, their offspring mice did not exhibit α1-adrenoceptor-mediated hypervasoreactivity. Coimmunoprecipitation, sucrose gradient fractionation, and immunolocalization experiments revealed that NCX1 and TRPC3 are interactively enriched in caveolar raft domains of vascular myocytes. These findings indicate that TRPC3/NCX1 coupling plays a pivotal role in regulating arterial tonus via α_1- adrenoceptor.