Obligatory roles of caveolae in excitation-transcription coupling in vascular smooth muscle cells.

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In smooth muscle cells (SMCs), caveolin (cav)-1, an essential component of caveolae, forms Ca^{2+} microdomain accumulating voltage-dependent Ca^{2+} channels (VDCC) and ryanodine receptors (RyR). The functional coupling between VDCC and RyR causes SMC contraction, i.e. excitation-contraction (E-C) coupling. On the other hand, Ca^{2+} influx through VDCC activates Ca^{2+}/calmodulin-dependent protein kinase (CaMK), and promotes gene transcription in neurons, i.e. excitation-transcription (E-T) coupling. E-T coupling is known in SMCs, but its structural basis and physiological function are unknown. Therefore, we examined the relationships between Ca^{2+} microdomain formed by caveolae and E-T coupling in SMCs. When the mesenteric artery was depolarized, the phosphorylation of CREB in the nuclei of SMCs and induction of *c-fos* was detected. These responses were not observed in the tissue of *Cav-1* KO mouse that lacks caveolae in SMCs and those in which caveolae were destroyed by methyl b cyclodextrin. The CREB phosphorylation was significantly attenuated by a CaMKK2 inhibitor STO609 and CaMK2 inhibitor KN93. Furthermore, fluorescence imaging analyses detected a direct molecular coupling between cav1 and CaMKK2. These results suggest that caveolae accumulate Ca^{2+} channels and CaMKK2 and cause not only E-C coupling but also E-T coupling in SMCs.