Role of Na^+/Ca^{2+} Exchanger Type1 (NCX1) in the Angiogenesis Induced by Lipo-PGE_1 in Murine Hindlimb Ischemia Model

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Abstract：The Na^+/Ca^{2+} exchanger type-1 (NCX1) is considered to be involved in endothelial nitric oxide (NO) production. In this study, we examined the role of NCX1 in angiogenic response to acute hindlimb ischemia by using heterozygous NCX1 knockout ($NCX1^{+/-}$) mice. Furthermore, since Lipo-PGE_1 (prostaglandin E_1 encapsulated into lipid microsphere) is well known as a useful drug for peripheral arterial disease, we examined the effect of Lipo-PGE_1 in hindlimb ischemia-induced angiogenesis. We surgically induced unilateral hindlimb ischemia and monitored the blood flow recovery by Laser Doppler imaging for 4 weeks. Lipo-PGE_1 treatment enhanced the blood flow recovery and capillary density in wild-type mice. Western blotting at 28 day showed that Lipo-PGE_1 increased VEGF and phospho-Akt expression levels in the ischemic muscles. Interestingly, the blood flow recovery in $NCX^{+/-}$ mice was significantly augmented compared with that in wild-type mice, although it was similarly enhanced by Lipo-PGE_1 treatment. Moreover, to study possible involvement of endothelial NO synthase, we administered N^G-nitro-L-arginine methyl ester (L-NAME) to mice with hindlimb ischemia. L-NAME treatment eliminated the enhanced blood flow recovery observed in both $NCX1^{+/-}$ mice and Lipo-PGE_1-treated mice. These results suggest that NCX1, as well as Lipo-PGE_1, is involved in endothelial NO synthase-dependent angiogenesis.

Key words： NCX, Lipo-PGE_1, Angiogenesis, eNOS, VEGF