Adrenomedullin (AM) is a vasoactive and angiogenic peptide that acts through G-protein coupled receptor (GPCR) calcitonin receptor-like receptor (CLR). AM, together with pre-proadrenomedullin N-terminal peptide (PAMP), is encoded by Adm gene. Here, we used adult heterozygous knockout mice with selective disruption of AM alone, with normal PAMP production (Adm+/Δ), to study whether endogenously produced AM plays role in the pathogenesis of lymphedema in normal conditions and after lower limb skin incision surgery. Our data showed that under normal conditions, blood and lymphatic vessel number and diameter were unaltered in the skin of the Adm+/Δ, compared to wild type, mice. After injury, only Adm+/Δ animals developed symptoms and histological changes characteristic of lymphedema: severe limb swelling, high edema score (P<0.001), epidermal thickening (P<0.001) and dermal fibrosis (P<0.01); accompanied by increased diameter, although unaltered number, of blood and lymphatic vessels (P<0.01). These changes were partially, but significantly (P<0.05), reversible upon intra-peritoneal AM supplementation using osmotic mini-pump (effective in 10^-8 to 10^-6 M range). In the skin, CLR was expressed in both blood and lymphatic endothelia. Altogether, these results provide novel evidence that Adm haploinsufficiency (resulting in AM deficiency) alone is sufficient to promote injury-onset lymphedema, and that this condition could be therapeutically corrected, and also that in vivo endogenous AM signaling pathway and GPCR CLR could play a role in the skin and lymphatic endothelial cell biology in health and disease.