Calpain translocation and activation as pharmacological targets during myocardial ischemia/reperfusion

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Calpains contribute to reperfusion-induced myocardial cell death. However, it remains controversial whether its activation occurs during ischemia or reperfusion. We investigated the regulation and time-course of calpain activation secondary to transient ischemia and the efficacy of its inhibition at reperfusion as a therapeutic strategy to limit infarct size. In isolated rat hearts (Sprague-Dawley), ischemia induced a time-dependent translocation of m-calpain to the membrane that was not associated with calpain activation as assessed by proteolysis of its substrate ?-fodrin. Translocation of calpain was dependent on Ca2+ entry through reverse mode Na+/Ca2+-exchange and was independent of acidosis. Calpain activation occurred during reperfusion, but only after intracellular pH (pHi) normalization, and was not prevented by inhibiting its translocation during ischemia with methyl-?-cyclodextrin. The intravenous infusion of MDL-28170 in an in vivo rat model with transient coronary occlusio