MCI-154: A Second Generation Ca\(^{2+}\) Sensitizer That Does Not Impair Relaxation — A Novel Approach to the Treatment of Heart Failure

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ABSTRACT

With the negative results of the cyclic AMP-dependent positive inotropic agents in clinical trials, great interest has been focused on the development of agents that directly activate cardiac myofilaments. These drugs are called “Ca\(^{2+}\) sensitzers”; they are expected to represent a possible new pharmacological approach to the therapy of chronic heart failure. MCI-154 is one of the most powerful and promising Ca\(^{2+}\) sensitzers currently in clinical trials. In preclinical studies, the positive inotropic action of MCI-154 was observed at the concentrations at which the drug did not increase intracellular Ca\(^{2+}\). In skinned cardiac muscle fiber bundles from various animal species MCI-154 shifted p_{Ca} (–log [Ca\(^{2+}\)] M)-force relation upward and to the left, suggesting that this drug not only increases sensitivity of myofibrils to Ca\(^{2+}\), but also enhances cross-bridge interaction. In regard to the molecular mechanism of action of MCI-154, the earliest experiments showed that MCI-154 at the high concentration (10\(^{-4}\) M) stimulated binding of Ca\(^{2+}\) to troponin (Tn) C. However, MCI-154-(at concentrations lower than 10\(^{-5}\) M)-induced increase in the affinity of TnC to Ca\(^{2+}\) led to the complex formation of TnC with TnI and TnT. This effect of the drug on Ca\(^{2+}\) regulation and interaction between troponin subunits was discovered using fluorescence spectroscopy. At 10\(^{-4}\) M MCI-154 decreased binding of Ca\(^{2+}\) to TnC. The Ca\(^{2+}\) sensitizing effect of MCI-154 disappeared when cardiac TnI was exchanged for skeletal TnI. Taken together, it can be concluded that TnI may represent a target protein for the positive inotropic action of MCI-154. The long-term treatment with MCI-154 prolonged the life span of cardiomyopathic hamsters, Bio14.6, a model that resembles human heart failure. Unlike PDE inhibitors, MCI-154 did not aggravate arrhythmias generated in the two-stage coronary ligation-, digitalis- and catecholamine-induced canine arrhythmia models. In clinical studies MCI-154 improved contractile function in patients with left ventricular dysfunction after myocardial infarction. Its effect was not associated with an increase in myocardial oxygen consumption or impaired relaxation. In conclusion, MCI-154 could be promising in the treatment of chronic heart failure. Clinical studies with MCI-154 are currently in progress.