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PHARMACOLOGICAL INHIBITION OF ADENYLYL CYCLASE TYPE 5 (AC5), A NEW THERAPEUTIC MODALITY FOR MYOCARDIAL INFARCTION, DERIVED FROM THE MODEL OF AC5 DISRUPTION, A NOVEL MODEL OF HEALTHFUL LONGEVITY

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Disruption (knock out, KO) of adenylyl cyclase type 5 (AC5) is a model of healthful longevity. Not only do the mice live 32% longer than their wild type, but also are protected against myocardial infarction, heart failure, cancer, obesity and diabetes and exhibit improved exercise capacity. In order to translate these therapies to patients, we developed a novel, pharmacological AC5 inhibitor, C90. Our first goal was to determine the efficacy of C90 in mediating protection against myocardial infarction, even when administered after coronary artery reperfusion. This is important since it is not practical to administer a drug to a patient with myocardial infarction before revascularization and is one reason why so many prior drugs, which reduced infarct size in experimental animals, failed in clinical trials. C90 is the most potent AC5 inhibitor, as exhibited by its IC50 value for AC5 inhibition, which was 5 times lower than the next most potent AC5 inhibitor. Compared with vehicle treatment, C90, administered 5 min after coronary artery reperfusion, and reduced infarct size by 64% at a dose of 0.6 mg/kg. Thus, C90 is a novel, selective and potent AC5 inhibitor that reduces infarct size, when delivered after coronary artery reperfusion, rendering it potentially clinically useful. It also reduces beta-adrenergic receptor signalling, which will provide additional benefit to patients with coronary artery disease or heart failure.

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