BACKGROUND

Myocardial infarctions (MIs) characterized by the loss of cardiomyocytes that are replaced by non-cardiac scar tissue. During reperfusion, cell damage is compounded by the increase in inflammatory and free radicals, inducing cell death. Reducing cardiomyocyte death would reduce scar formation, improve cardiac function, and reduce the risk of heart failure.

We have previously shown that Celastrol, a compound isolated from an oriental medicinal plant and known as a modulator of HSP90 activity, activates HSF1, limits cell damage, and preserves heart function in a model of permanent ischemia reperfusion (I/R) damage. Celastrol induces the overexpression of HSPs, including the potent cardiac antiapoptotic factor Hsp27 (HSP27), an endogenous HSP70 (HSP70) homologue. The protective activity of Celastrol is associated with the efficiency of heat shock element (HSE) and the antioxidant response element (ARE), as measured by the expression of inducible antioxidant proteins (e.g., HSP27, HSP70).

METHOD

Primary Screening in H9c2 cells (Viability following 2 components of I/R damage)

Validation in H9c2 and iPSC-derived human mature cardiomyocytes

RESULTS

Primary screening: H9c2 cells subjected to 48h Ischemia or 1h oxidative stress

Compared to control, some compounds, including commercially available Celastrol protect form 48h ischemia (H9c2). In the ischemic and oxidative conditions, the green represent alive cells, and the red dead cells.

Compared to control, some compounds, including commercially available Celastrol protect form oxidative stress. Interestingly, some compounds are more potent than Celastrol.

Compared to control, some of the tested compounds, including commercially available Celastrol induce the activity of the heat shock element (HSE) and the antioxidant response element (ARE), as measured by the expression of inducible stress proteins in transfected H9c2 cells (H9c2-ARE).

Compared to control, some of the selected compounds showed a protective effect on H9c2 cells subjected to I/R Stress (H9c2-ARE).

CONCLUSIONS

We have identified and validated Celastrol as a novel infarct sparing agent and identified as well other analog compounds with superior potency. These candidate compounds are tested and compared to Celastrol ex vivo (using a Langendorff preparation; see Can J Cardiol, Vol 32, Issue 10, S192-3) as a first step towards developing a novel drug designed as a first line medication for the treatment of MI and adjunct therapy to reperfusion procedures.

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DISCLOSURES

I, the undersigned, am in compliance with the Sunshine Act of 2011 and have no financial interest in the research that may result from my presentation.

Do you have any conflict of interest to disclose? (Yes/No)

1. YES - If you answered YES, you must disclose this to the audience within your presentation.

2. No

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