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## A probable protective mechanism for NO/cGMP/G-kinase activity is to raise Nrf2 activity

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Although insufficient bioavailability of NO is not the cause of cardiovascular disease (Int J Mol Sci 2013 Nov 13;14(11):22274-330.), NO signaling through cGMP and G-kinase is protective; the question is how does it work? It is the author's view that the primary mechanism of action of this signaling pathway is likely to be that it raises Nrf2 activity. Protein kinase G has been shown to raise Nrf2 activity, a very important cytoprotective mechanism known to be raised by numerous health promoting factors. Nrf2 is a transcription factor that acts to raise the levels of many different enzymes with antioxidant activities and also lower inflammatory responses while raising levels of enzymes of energy metabolism and stimulating mitochondrial biogenesis. It also acts to raise autophagy, increasing degradation of toxic protein aggregates and dysfunctional organelles. The autophagy response is useful in lowering tissue remodeling, as is another response to Nrf2, stimulation of dedifferentiation fibroblasts, thus lowering fibrosis.

It should not be surprising, given the common role of oxidative stress; chronic inflammation and mitochondrial dysfunction in various chronic inflammatory diseases that Nrf2 helps prevent and/or treat a large number of such diseases including the including atherosclerosis, ischemic cardiovascular disease, vascular endothelial dysfunction and heart failure, at least in animal model studies.

In conclusion, it is likely that raising Nrf2 is an important mechanism by which the NO/cGMP/G-kinase signaling pathway can help prevent or treat various types of cardiovascular disease. Nrf2 may well play a similar role in a variety of NO/ONOO(-) cycle diseases.

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## Disruption of RSK3 binding to muscle A-kinase anchoring protein *in vivo* via adeno-associated virus expression of a competing peptide attenuates pressure overload-induced cardiac hypertrophy

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Cardiac myocyte hypertrophy is the main compensatory response to chronic stress in the heart. p90 ribosomal S6 kinase (RSK) family members are effectors for extracellular signal-regulated kinases that induce myocyte growth. RSK3 contains a unique N-terminal domain that mediates RSK3 binding to the muscle A-kinase anchoring protein (mAKAP $\beta$ ) scaffold. We have published that disruption of RSK3-mAKAP $\beta$  complexes using a competing peptide inhibited the hypertrophy of neonatal ventricular myocytes *in vitro*. *In vivo*, RSK3 gene deletion in mice attenuated the concentric cardiac hypertrophy induced by pressure overload. We hypothesize that RSK3 anchoring to mAKAP $\beta$  in myocytes is required for cardiac hypertrophy *in vivo*. We have used a recombinant adeno-associated virus vector to express a mAKAP $\beta$  RSK3-binding domain (RBD)-GFP fusion protein under the control of the cardiac myocyte-specific cardiac troponin T promoter. 3 day-old C57BL/6 mice were injected intraperitoneally with either AAV-RBD-GFP or AAV-GFP control virus. At 8 weeks of age mice were subjected to transverse aortic constriction to induce pressure overload (TAC) for two weeks. Cardiac hypertrophy was attenuated in mice injected with the AAV-RBD-GFP virus (biventricular weight indexed to tibial length (mg/mm): 7.7, 8.6, and 9.2 for AAV-RBD, AAV-GFP and non-injected TAC cohorts, respectively;  $p < 0.05$  vs. both controls). Echocardiography both corroborated the inhibition of hypertrophy and revealed no deleterious effect on cardiac function attributable to the AAV-RBD-GFP vector. Thus, anchored RSK3 regulates pathologic myocyte growth. AAV can successfully deliver a competing peptide inhibiting pathological hypertrophy and should be investigated further as a prevention and/or treatment for heart failure.

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