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Supporting Online Material
www.sciencemag.org/cgi/content/full/334/6055/525/DC1
Materials and Methods
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Fatty Acids Identified in the Burmese Python Promote Beneficial Cardiac Growth

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Burmese pythons display a marked increase in heart mass after a large meal. We investigated the molecular mechanisms of this physiological heart growth with the goal of applying this knowledge to the mammalian heart. We found that heart growth in pythons is characterized by myocyte hypertrophy in the absence of cell proliferation and by activation of physiological signal transduction pathways. Despite high levels of circulating lipids, the postprandial python heart does not accumulate triglycerides or fatty acids. Instead, there is robust activation of pathways of fatty acid transport and oxidation combined with increased expression and activity of superoxide dismutase, a cardioprotective enzyme. We also identified a combination of fatty acids in python plasma that promotes physiological heart growth when injected into either pythons or mice.

The mammalian heart is a highly adaptable organ that demonstrates remarkable cellular remodeling in the face of both pathological and physiological stimuli. Pathological hypertrophic signaling cascades, including those mediated by the α1-adrenergic and endothelin receptors, can be activated by insults such as myocardial infarction, chronic hypertension, or genetic mutations affecting sarcomeric or calcium-handling proteins. This ultimately results in increased cell size, enhanced sarcomere assembly, and activation of a "fetal" gene program, with increased expression of β-myosin heavy chain (β-MHC), α–skeletal actin, atrial natriuretic peptide, and brain natriuretic peptide, accompanied by reduced expression of α-MHC and SERCA2 (sarcoplasmic reticulum Ca^{2+} adenosine triphosphatase–2) (*1*–*3*).

Pathological insults also typically result in a switch in metabolic substrate utilization from lipid oxidation to glucose utilization and increased apoptosis and fibrosis (*1*, *3*). Conversely, physiological cardiac hypertrophy resulting from postnatal growth, pregnancy, or exercise is primarily mediated by insulin-like growth factor–1 (IGF-1) signaling and activation of phosphatidylinositol 3-kinase (PI3K)–Akt signaling in the absence of fetal gene program activation (*4*, *5*). Unlike pathological cardiac hypertrophy, this adaptive hypertrophy does not appear to be detrimental to cardiac function. In fact, exercise-induced physiological cardiac growth protects the heart against pathological stimuli such as pressure overload (*6*).

The infrequently feeding Burmese python (*Python molurus*) has been described as a model of extreme metabolic regulation in which many organs, including the heart, increase in mass after a large meal (*7*, *8*). Whereas most mammalian models of physiological hypertrophy typically demonstrate modest hypertrophy (~10 to 20%) after weeks of stimulation, the python heart grows in mass by 40% within 48 to 72 hours after consumption of a large meal (*7*–*9*). This remarkable cardiac hypertrophy is accompanied by increased cardiac output and appears to be an adaptive response to support the large (factor of ~44) increase in postprandial metabolic rate, accompanied by increased systemic nutrient transport and widespread organ growth, required to accommodate such a large meal (*7*–*12*). The cardiac hypertrophy observed in *P. molurus* has

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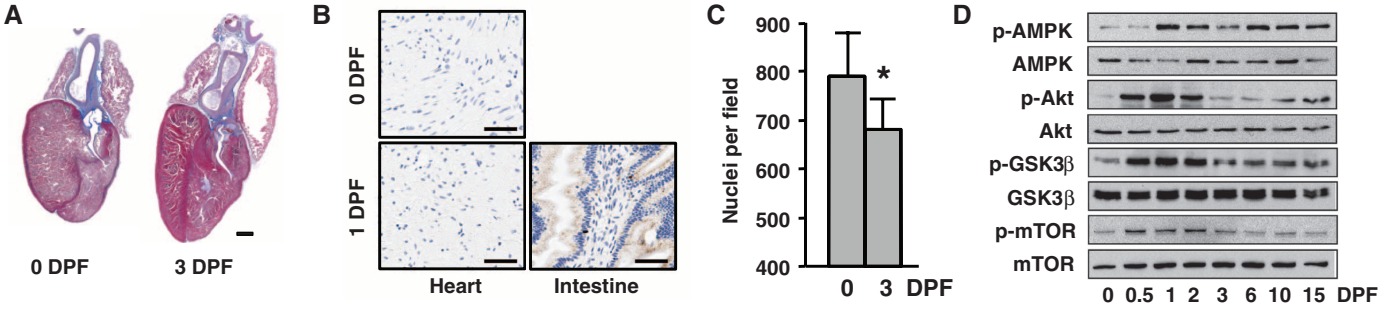

Fig. 1. Postprandial cardiac growth in the python is characterized by cellular hypertrophy and activation of protein synthesis pathways. (**A**) Masson trichrome–stained python hearts depicting pronounced postprandial cardiac hypertrophy. Scale bar, 2 mm. (**B**) BrdU staining of 0- and 1-dpf python hearts shows no evidence of postprandial cellular proliferation. Python small intestine is included as a positive control (brown nuclear staining). Scale bar, 50 μm. (**C**) The number of nuclei per field is reduced post-feeding. Error bars represent ±SE; $n = 4$ per condition; $^*P < 0.05$ versus 0 dpf. (**D**) Immunoblot analysis reveals increased phosphorylation of AMPK, Akt, GSK3β, and mTOR in the postprandial python heart.