

Postprandial cardiac hypertrophy in pythons

This snake can synthesize fresh heart muscle to cope with extra metabolic demand.

Oxygen consumption by carnivorous reptiles increases enormously after they have eaten a large meal in order to meet metabolic demands, and this places an extra load on the cardiovascular system. Here we show that there is an extraordinarily rapid 40% increase in ventricular muscle mass in Burmese pythons (*Python molurus*) a mere 48 hours after feeding, which results from increased gene expression of muscle-contractile proteins. As this fully reversible hypertrophy occurs naturally, it could provide a useful model for investigating the mechanisms that lead to cardiac growth in other animals.

The heart is remarkable for its ability to remodel itself in response to altered functional demands. For example, chronic exercise training in mammals results in ventricular hypertrophy¹, which is beneficial because the resulting increase in stroke volume leads to a decrease in the resting and submaximal heart rates, and to an increase in filling time and in venous return².

Burmese pythons are considered to be an excellent model of extreme physiological upregulation³. While digesting, their metabolic rate may increase by up to 40-fold relative to the fasting rate and may be raised for as long as 14 days (ref. 3). This increase in oxygen consumption is accompanied by rapid remodelling of many physiological systems: within two days of feeding, there is a substantial increase in wet mass of the gastrointestinal system, kidneys, liver, pancreas, lungs, heart and stomach⁴. However, the cause of this remodelling, which could be increased protein synthesis or increased fluid content, is unclear^{3,5}.



Hearty meal: the python's cardiac ventricles grow after feeding.

To investigate the nature of cardiac hypertrophy in pythons following feeding, we obtained ventricles from three groups of Burmese pythons: fasting (fast of 28 days), digesting (two days after consuming rats equal to $25.0 \pm 0.1\%$ body mass) and post-digestion (28 days after the meal). (For methods, see supplementary information.) Oxygen consumption increased sevenfold and ventricular mass increased significantly ($P < 0.003$) by 40% during digestion (Table 1). This increase was fully reversible, as the ventricular mass returned to its fasting mass in post-digestion animals.

There was no change in the ventricular dry/wet mass ratio, indicating that the increased ventricular mass during digestion was not due to water shifts between extra- and intracellular compartments. Total protein, RNA and myofibrillar concentrations on a tissue-mass-specific basis did not change during digestion (Table 1).

Mass-specific DNA concentration significantly decreased ($P < 0.01$), and this is consistent with the ventricular mass increase by cellular hypertrophy found in rats⁶. All of these measurements indicate a rapid new growth of ventricular tissue.

To investigate whether this growth was a result of increased transcription, we sequenced the isoforms of cardiac myosin heavy chains (GenBank accession numbers: AY773093 and AY773094). We found a significant increase in the expression of messenger RNA for heavy-chain cardiac myosin during digestion (Table 1), judging both by polymerase chain reaction with reverse transcription ($P < 0.0001$) and by band intensity on northern blots

($P < 0.0001$; Fig. 1).

We conclude that the newly synthesized protein results from increased transcription of the gene encoding cardiac myosin heavy chains and that cardiac hypertrophy follows from *de novo* addition of contractile elements. This cardiac hypertrophy is likely to have important consequences for oxygen transport and could explain why stroke volume in postprandial pythons is 50% greater than that measured in fasted animals doing maximal exercise⁷.

This ventricular growth in postprandial pythons is very rapid compared with that in mammalian models, in which comparable increments in ventricular size take weeks to develop⁸. In addition, mammalian models may necessitate highly invasive procedures for variable aortic occlusion, such as hydraulic constrictors, inflatable cuffs or angioplasty balloons, which can induce acute congestive failure and aortic rupture

Table 1 Cardiac hypertrophy following digestion in Burmese pythons

Phase	Fasting	Digesting	Post-digestion
Pre-feeding body mass (kg)	0.702 \pm 0.045	0.783 \pm 0.126	0.721 \pm 0.070
Oxygen consumption (ml O ₂ min ⁻¹ kg ⁻¹)	0.67 \pm 0.056	4.49 \pm 0.385 *	0.54 \pm 0.070
Ventricular mass (g wet mass)	0.95 \pm 0.070	1.34 \pm 0.202 *	1.07 \pm 0.062
Ventricular mass (% body mass)	0.136 \pm 0.006	0.168 \pm 0.004 *	0.137 \pm 0.007
Dry/wet mass of ventricles (%)	22.4 \pm 1.470	23.1 \pm 1.91	20.3 \pm 0.06
Total protein (μ g per mg ventricle)	236 \pm 17	208 \pm 10	249 \pm 24
DNA (ng per mg ventricle)	2.93 \pm 0.11	2.54 \pm 0.12 *	3.09 \pm 0.12
RNA (μ g per mg ventricle)	0.96 \pm 0.064	1.11 \pm 0.080	1.08 \pm 0.080
Myofibrillar protein (μ g per mg ventricle)	32.9 \pm 2.25	34.8 \pm 3.78	30.7 \pm 2.89
Ventricular Mhc mRNA (Mhc/18S)	0.97 \pm 0.163	2.11 \pm 0.221 *	0.78 \pm 0.139
Ventricular Mhc mRNA (intensity)	2,320 \pm 526	31,650 \pm 5,280 *	5,140 \pm 1,020 *

Mhc, cardiac myosin heavy chain; fasting, 28 d fasted; digesting, 48 h postprandial; post-digestion, 28 d postprandial. Ventricular Mhc mRNA expression was determined by semiquantitative reverse-transcription polymerase chain reaction (RT-PCR) and by northern blot (Fig. 1). In RT-PCR, Mhc mRNA is shown as a ratio (Mhc/18S) of 18S ribosomal subunit mRNA expression, which is considered to be constant. Quantitative mRNA expression measured by northern blot is given as intensity. $N = 6$ per group. Values are means \pm 1 s.e.m. All experiments were carried out under University of California at Irvine Animal Research Committee Protocol Number 1999-2123.

*Significantly different ($P < 0.05$) from fasting value by one-tail t -test.

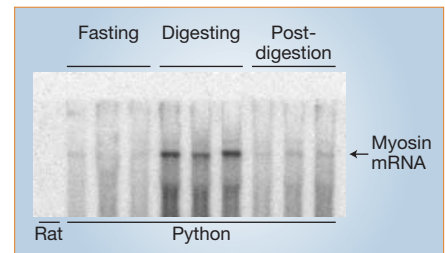


Figure 1 Northern blot showing increase in myosin mRNA in the cardiac ventricles of postprandial Burmese pythons. Each lane represents RNA from an individual python ventricle, hybridized to a probe specific to the ventricular myosin heavy-chain isoform. The same blot hybridized with a probe for the python atrial isoform gave no detectable signal. The lane immediately to the left of the fasted samples contains rat ventricular RNA, showing that the probe does not crossreact. Fasting phase, 28 d fasted; digesting phase, 48 h postprandial; post-digestion phase, 28 d postprandial.

as well as hypertrophy. Because Burmese pythons naturally undergo a 40%, fully reversible increase in ventricular mass in the two days after a meal, they could provide an attractive model for investigating the fundamental mechanisms that lead to cardiac remodelling and ventricular growth⁹. The physiological stimuli underlying this hypertrophy are still unknown, but are likely to include neural and humoral factors.

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Synaesthesia

When coloured sounds taste sweet

Synaesthesia is the involuntary physical experience of a cross-modal linkage — for example, hearing a tone (the inducing stimulus) evokes an additional sensation of seeing a colour (concurrent perception). Of the different types of synaesthesia, most

have colour as the concurrent perception¹, with concurrent perceptions of smell or taste being rare^{2,3}. Here we describe the case of a musician who experiences different tastes in response to hearing different musical tone intervals, and who makes use of her synaesthetic sensations in the complex task of tone-interval identification. To our knowledge, this combination of inducing stimulus and concurrent perception has not been described before.

E.S. is a 27-year-old professional musician who is female, right-handed and of average intelligence⁴ (IQ, 115). Whenever she hears a specific musical interval, she automatically experiences a taste on her tongue that is consistently linked to that particular interval (Table 1). Besides this exceptional interval-to-taste synaesthesia, she also reports the more common tone-to-colour synaesthesia, in which each particular tone is linked to a specific colour (for example, C and red; F sharp and violet).

Both synaesthetic perceptions have always been consistently reproducible. We repeatedly tested E.S. for over a year and have confirmed that her interval-to-taste synaesthesia is unidirectional: she does not hear tone intervals when exposed to taste. In addition, E.S. applies this synaesthesia in identifying tone intervals (which is evidence of a synaesthesia–cognition cascade).

To assess the influence of E.S.'s synaesthetic gustatory perception on her ability to identify tone intervals, we adapted the Stroop task⁵ (for methods, see supplementary information). Four selected tone intervals (seconds and thirds) were presented while applying four differently tasting solutions (sour, bitter, salty and sweet) to E.S.'s tongue. Her task was to identify the tone intervals by pressing a particular button for each interval on a computer keyboard. Reaction times and errors were measured for trials in which the applied taste was either congruent or incongruent with the tone interval; tone intervals were also presented without taste stimulation.

We found that E.S.'s tone-interval identification was perfect and was significantly faster during the congruent condition compared with all the other conditions (Fig. 1). Five non-synaesthetic musicians were tested as controls using the same procedure: no significant between-condition differences were found. The reaction times of the controls were comparable to those of E.S. in the no-taste condition (Fig. 1).

To exclude conceptual priming effects as an explanation for these results (for example, the subject might imagine sourness when presented with 'sour' as either a taste or word), we also tested E.S. by showing her the word(s) describing each taste. We found no between-condition difference in this conceptual task (Fig. 1).

Together, these results indicate that E.S.'s

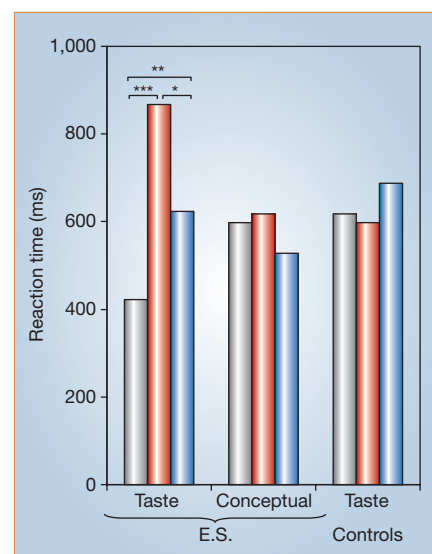


Figure 1 Mean reaction times in a gustatory Stroop task linking perception of tone intervals with different tastes for congruent-taste (grey), incongruent-taste (red) and no-taste (blue) conditions for synaesthete E.S. and for five non-synaesthetic musicians (controls). In the 'Taste' condition, musical intervals were presented while solutions of different taste (citric acid, 20 g litre⁻¹; quinine, 60 mg litre⁻¹; salt, 10 g litre⁻¹; sucrose, 120 g litre⁻¹) were delivered to the subject's tongue. The 'Conceptual' condition followed the same procedure, except that words describing the tastes, instead of the tastes themselves, were visually presented 2 s before the tone interval. Non-parametric randomization tests were used for statistical comparison. For E.S., all statistical comparisons in the taste condition were associated with *P* values of less than 0.01 (**P* < 0.05, ***P* < 0.01, ****P* < 0.001). For control subjects and for the conceptual condition, none of the comparisons revealed significant differences. The reaction time of E.S. in the no-taste condition is similar to those of the controls, but is faster in the congruent condition and slower in the incongruent condition.

performance in the gustatory Stroop task is most likely to be due to her extraordinary type of synaesthesia, in which a complex inducing stimulus leads to a systematic, concurrent gustatory sensation. This case differs from another gustatory synaesthete, S., who reported blended gustatory sensations (such as specific meals) in response to simple auditory stimuli (tones and sounds)². E.S.'s application of her synaesthetic sensations in identifying tone intervals — a complex task that requires formal musical training — demonstrates that synaesthetics may be used to solve cognitive problems.

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Table 1 Tastes triggered by tone intervals

Tone interval	Taste experienced
Minor second	Sour
Major second	Bitter
Minor third	Salty
Major third	Sweet
Fourth	(Mown grass)
Tritone	(Disgust)
Fifth	Pure water
Minor sixth	Cream
Major sixth	Low-fat cream
Minor seventh	Bitter
Major seventh	Sour
Octave	No taste

Tastes experienced by synaesthete E.S. in response to different musical tone intervals are shown; in the case of the fourth and tritone intervals, however, complex visual and emotional perceptions, respectively, are induced. Note that dissonant tone intervals induce unpleasant tastes and consonant ones induce pleasant ones (for example, the minor second intervals induce sour tastes, and the major thirds induce sweet ones). There is also an apparent symmetry in some of the responses: the minor second and major seventh, which are mirror-image intervals in terms of octave equivalence, are both rated as sour, and the major second and minor seventh are both rated as bitter.