Cardiac sympathetic nerves as the final common pathway in the induction of adaptive cardiac hypertrophy

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Introduction
A mild to moderate adaptive hypertrophy of a cardiac chamber may be beneficial in increasing the capacity of the heart to cope with an increased work-load. However, in pathological hypertrophy the myocardial muscle cell can hypertrophy to such an extent that myocardial performance deteriorates [1]. To devise a medical treatment that could modify or even prevent the occurrence of adaptive cardiac hypertrophy in response to a pathological work-load, it is necessary that the nature of the triggering event should be understood. In other words, what exactly is the intermediate link between the physiological or pathological condition evoking cardiac hypertrophy and the biochemical events leading to growth of the individual cardiac muscle cell?

Types of cardiac growth
The normal age-related growth of the heart after the early postnatal period does not involve cell division of the cardiac muscle cell but is achieved by an increase in cell size. This age-related growth is dependent on the presence of growth hormone and thyroxine and ceases in hypophysectomized animals [2]. Adaptive or compensatory cardiac hypertrophy, conversely, can be defined as the increase in heart size occurring in response to a physiological or pathological increase in the work-load of the heart. This compensatory growth may be generalized or may involve one chamber only, depending on the cause; but physical exercise, for example, induces adaptive cardiac hypertrophy even in hypophysectomized animals [3] and thus neither growth hormone nor thyroxine is necessary for the occurrence of adaptive cardiac hypertrophy.

Three successive steps occur in the genesis of adaptive cardiac hypertrophy. First, comes the condition that places a greater work-load on the heart. Secondly, there is the intermediate link through which the extra work triggers events at the level of the cardiac muscle cell that lead, thirdly, to the biochemical changes within the cell which cause structural changes leading to growth. The biochemical alterations occurring within the myocardial cell in response to adaptive hypertrophy have been extensively studied, but are not within the scope of this article and the reader is referred elsewhere for detailed reviews [4–6]. In structural terms a sustained increase in the number of myofibrils is seen which gradually leads to a substantial increase in the myofibrillar/mitochondrial ratio. There is an increase in both myocardial cell diameter and in cell length, caused by addition of sarcomeres; the latter process appears to be initiated by proliferation of the intercalated discs [6].

I am concerned here entirely with the intermediate link, or ‘trigger factor’, that initiates the biochemical chain of events; it is important to distinguish this from ‘permissive’ factors that may be necessary (but are not in themselves sufficient) for hypertrophy to occur.

Is the work-load of the heart or a blood-borne factor the trigger for hypertrophy?
As a close association between conditions associated with an increased work-load of the heart and cardiac hypertrophy has been repeatedly observed, ever since the first report by Robinson in 1748 [7], it has become a time-honoured view that an increase in ‘work’ somehow directly causes adaptive hypertrophy. Two
possible mechanisms have been proposed. Firstly, it has been suggested that an increase in wall stress of the heart through increased stretch of muscle fibres could activate the genetic apparatus and lead to enhanced protein synthesis. This hypothesis cannot be verified in vivo, since too many other parameters are altered, and the work in vitro claiming to support this hypothesis is seriously flawed. Schreiber and co-workers [8] have used the perfused working heart preparation in a series of studies on protein synthesis; however, their control hearts worked against a hydrostatic pressure of only 30 mmHg, thereby having a coronary artery perfusion pressure of 30 mmHg. It has been demonstrated that the optimal perfusion pressure in this preparation is 60 mmHg [9]. What Schreiber et al. [8] use as a model of pressure ‘overload’ is a hydrostatic pressure of only 70 mmHg, so the ‘stimulation’ they see is only relative to what is probably a hypoxic control heart. This conclusion is supported by the fact that perfusion at 30 mmHg in hyperbaric oxygen is associated with the same stimulation of protein synthesis as a ‘pressure overload’ and that in hyperbaric oxygen an increase of hydrostatic pressure from 30 mmHg even up to 160 mmHg did not cause any further stimulation of protein synthesis [10].

Secondly, it has been suggested that relative hypoxia in the myocardial fibre exposed to increased tension would cause a feedback activation of protein synthesis through accumulation of metabolites. The above-mentioned results, however, disagree with this hypothesis, and in addition it has been shown that regional ischaemia did not cause the changes in lactate dehydrogenase isoenzyme pattern seen in cardiac hypertrophy [11].

Furthermore there are findings that are not easily accounted for on the work-load hypothesis. For example, it has been shown that the development of cardiac hypertrophy occurs before the onset of hypertension in spontaneously hypertensive rats and that the prevention of hypertension in these rats, by administration of hydralazine, did not prevent the cardiac hypertrophy from developing [12]. Furthermore deoxycorticosterone treatment may induce hypertension without concomitant cardiac hypertrophy [13].

One essential criterion for the trigger factor is that it must be capable of influencing one cardiac chamber in isolation, since adaptive cardiac hypertrophy can be restricted to just one cardiac chamber. This immediately excludes all circulating agents from a causative role, although a circulating factor could still have a ‘permissive’ role. However, no pituitary hormones can play even a ‘permissive’ role in compensatory hypertrophy, as mentioned above.

**Hypothesis: noradrenaline released from cardiac sympathetic nerves is the trigger for cardiac hypertrophy**

The sympathetic nerves innervating the heart would appear to be a logical final common pathway in the induction of compensatory cardiac hypertrophy. After all, the physiological signal that makes the heart increase its rate and/or contractility in response to volume and/or pressure work is increased activity of the sympathetic nerves to the heart. Laks and co-workers [14] have postulated that noradrenaline is the ‘myocardial hypertrophy hormone’ on the basis of experiments with chronic infusions of ‘sub-hypertensive’ doses of noradrenaline, which they claim cause isolated left ventricular hypertrophy. However, increases in left ventricular weight were offset by decreases in weight of right ventricle and interventricular septum (which is largely composed of left ventricular wall), so that total heart weight was unaltered, suggesting that their result arose from a dissection artifact. There are, however, better arguments for a trophic action of sympathetic nerves. Thus sympathetic nerves can cause hypertrophy and hyperplasia in salivary glands, an effect which can be prevented by β-adrenoceptor blockade [15–17], and it has been shown that incorporation of thymidine into regenerating liver is inhibited by sympathetic denervation [18], by α-adrenoceptor [19] and β-adrenoceptor [18] blockade. It has also been shown that noradrenaline increases RNA synthesis in the chick embryo [20].

There are at least two conditions that need to be fulfilled before a role for the sympathetic nervous system in the aetiology of cardiac hypertrophy can be accepted.

Firstly, an anatomical basis for selective sympathetic innervation to individual heart chambers must exist. This condition appears to be fulfilled since the various nerves carrying sympathetic fibres to the heart have been shown to have a very localized projection, and stimulation of distal branches of these trunks elicits a response only in small segments of myocardium [21]. The projections of the various nerves carrying sympathetic inflow appear to permit selective activation of each of the four chambers of the heart [22, 23]. The majority of the nerves innervating the right atrium and right ventricle arise from the right-sided sympathetic trunk and the majority of those innervating the left atrium.
Sympathetic nerves in cardiac hypertrophy

**Table 1. Activity of cardiac sympathetic nerves in various experimental conditions that lead to adaptive cardiac hypertrophy**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cardiac sympathetic activity</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized cardiac hypertrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical exercise</td>
<td>Increased</td>
<td>Rat [25, 26]</td>
</tr>
<tr>
<td>Cold acclimation</td>
<td>Increased</td>
<td>Rat: mouse [2’, 27]</td>
</tr>
<tr>
<td>Isoprenaline administration</td>
<td>Increased</td>
<td>Rat [28, 29]</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Probably unchanged, see [30]</td>
<td></td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coarctation of the aorta</td>
<td>Increased</td>
<td>Rat [31]</td>
</tr>
<tr>
<td>Renal hypertension</td>
<td>Increased</td>
<td>Rat [32, 33]</td>
</tr>
<tr>
<td>Deoxyxycorticosterone-induced hypertension</td>
<td>Increased</td>
<td>Rat [34, 35]</td>
</tr>
<tr>
<td>Genetic spontaneous hypertension</td>
<td>Probably increased</td>
<td>Rat [36]</td>
</tr>
<tr>
<td>Right ventricular hypertrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoxia</td>
<td>Increased</td>
<td>Cat: rat [37, 38]</td>
</tr>
<tr>
<td>Experimental pulmonary hypertrophy</td>
<td>Probably increased</td>
<td>Calf [39]</td>
</tr>
</tbody>
</table>

and left ventricle from the left-sided trunk; it is therefore relevant that central pathways involved in cardiovascular control can be selectively activated on the right and left sides [24].

Secondly, there should be increased cardiac sympathetic activity in conditions that lead to compensatory cardiac hypertrophy. There is experimental evidence for this in both generalized and localized cardiac hypertrophy (Table 1). In the papers quoted, altered sympathetic nervous activity has been documented either by electrophysiological recording from cardiac sympathetic nerves or by measurement of the rate of turnover of noradrenaline in the heart. Thus, of the experimental models of cardiac hypertrophy studied so far, apart from thyroxine-induced cardiac hypertrophy, which will be discussed below, only genetic spontaneous hypertension in rats has not been shown unequivocally to be associated with increased cardiac sympathetic nervous activity.

The great difficulty of interpreting the results of research on spontaneously hypertensive rats is knowing what constitutes a proper control, and workers who have found unaltered or even decreased cardiac sympathetic nervous activity in spontaneously hypertensive rats have not used closely related rat strains as controls [30]. Those who use closely related strains do in fact find an increased sympathetic nervous activity in the heart of spontaneously hypertensive rats [36].

As regards thyroxine-induced cardiac hypertrophy, this can probably be considered as a pathological developmental hypertrophy rather than a true compensatory cardiac hypertrophy, since thyroxine has been shown to have a direct growth-promoting effect on [40] cultures of human myocardial cells in vitro.

In summary, therefore, there appears to be much circumstantial evidence in support of the hypothesis that cardiac sympathetic nerves are the final common pathway in the induction of adaptive cardiac hypertrophy. More direct evidence to test the hypothesis will now be discussed.

**Tests of the hypothesis**

The most direct experimental test is to see whether adaptive cardiac hypertrophy still occurs when the cardiac sympathetic nerves have been destroyed.

Previous studies, involving stellate ganglionectomy, were inconclusive [41]. This is hardly surprising because not even removal of caudal cervical ganglia, stellate ganglia and seven upper thoracic ganglia produces a complete sympathetic denervation of the heart [42].

Another approach is to use chemical sympathectomy brought about by chronic administration of high doses of guanethidine; this permanently destroys at least 97% of the sympathetic ganglion cells without affecting the central nervous system or the adrenal medulla [30, 43]. Rats treated in this way are able to maintain a normal resting blood pressure and to undertake strenuous exercise because increased secretion of adrenal catecholamines enables them to increase their cardiac output [30, 44]. When rats chemically sympathectomized in this way were subjected to a strenuous programme of daily swimming sessions for 3 months there was no detectable increase in their heart weight; conversely, exercised rats with an intact sympathetic nervous system showed adaptive cardiac hypertrophy (Fig. 1). This strongly suggests that the presence of intact cardiac sympathetic nerves, as
distinct from moderately elevated levels of circulating catecholamines, is necessary for the occurrence of compensatory cardiac hypertrophy in response to physical exercise.

Cohen [45] has suggested that myocardial adrenergic nerve terminals are not required for the cardiac hypertrophy caused by deoxycorticosterone-induced hypertension on the basis of experiments with rats chemically 'sympathectomized' with 6-hydroxydopamine. However, the dose of 6-hydroxydopamine used was not sufficient to produce maximal sympathectomy and to prevent rapid regeneration of adrenergic nerve terminals [30, 46], and thus the results of Cohen [45] are not a sufficiently critical test of the hypothesis. The claim by Cutilella et al. [47] that immunosympathectomy does not prevent cardiac hypertrophy occurring in spontaneously hypertensive rats, arises from an experimental artifact since they expressed cardiac hypertrophy only in the form of a ratio of left ventricular weight to body weight, which is not a valid way of comparing heart size in groups of animals of different body size because the heart ratio continually decreases with increasing body size [48]. If one uses the results of Cutilella et al. [47] to calculate the mean left ventricular weight, it is seen that immunosympathectomy reduces the left ventricular weight of spontaneously hypertensive rats by approximately 11%, which indicates a reversal of the 9% cardiac hypertrophy observed when intact spontaneously hypertensive rats were compared with normotensive control rats.

There is further, albeit indirect, evidence that in conditions other than exercise the trigger for cardiac hypertrophy may also be the cardiac sympathetic nerves. Sen et al. [12] reported that whereas treatment with either α-methyldopa or hydralazine significantly reduced the blood pressure in spontaneously hypertensive rats, only α-methyldopa significantly reduced the heart weight. Although hydralazine maintained blood pressure at normotensive levels it failed to prevent the occurrence of cardiac hypertrophy. These results fit well with the hypothesis under discussion. Thus α-methyldopa has a central hypotensive action which produces a relative bradycardia as well as a decrease in lumbar sympathetic impulse outflow [49, 50]; it would therefore tend to diminish the exaggerated heart rate and blood pressure responses precipitated by external stimuli in spontaneously hypertensive rats [51]. The hypotensive action of hydralazine, conversely, is predominantly due to relaxation of vascular smooth muscle and both heart rate and stroke volume are increased, presumably due to reflex-induced increase in cardiac sympathetic nervous activity as hydralazine-induced tachycardia can be prevented by ganglion blockers and β-adrenoceptor antagonists [52]. Hydralazine would not, therefore, diminish the pathologically increased activity in cardiac sympathetic nerves in spontaneously hypertensive rats and so would not inhibit the induction of cardiac hypertrophy. This interpretation is supported by the finding that in experimental renovascular hypertension, hydralazine reduced the blood pressure without influencing cardiac hypertrophy [53].

Furthermore, Tomanek et al. [54] found that α-methyldopa treatment in a dose that did not prevent hypertension, nevertheless prevented the occurrence of the compensatory cardiac hypertrophy in spontaneously hypertensive rats. Likewise, Fernandes et al. [55] found that propranolol treatment reduced the development of cardiac hypertrophy in renal hypertensive rats even though their blood pressure remained as elevated as in the untreated hypertensive rats; however, they did not measure to what extent the bradycardia caused by the β-adrenoceptor blockade had reduced cardiac work. In a pilot study in rats it was found that high-dose oral propranolol treatment reduced the compensatory cardiac hypertrophy occurring in response to experimental coarctation of the aorta by 73% (P < 0.001), although cardiac work expressed as the product of average 24 h heart rate and systolic pressure was only reduced by 6% (because of the larger stroke volume, the peak systolic pressure was higher in the propranolol-treated rats) (I. Östman-Smith, unpublished work).

**Which substance is the trophic factor?**

Since sympathetic nerves are known to release not only noradrenaline but also secretory proteins [56] one
cannot immediately draw the conclusion that release of noradrenaline is the essential trigger factor. There are, nevertheless, many observations that point to noradrenaline. Firstly, the trophic effects of sympathetic nerves in other organs can be blocked by β- and, occasionally, α-adrenoceptor antagonists (see above); secondly, regular administration of low doses of the β-adrenoceptor agonist isoprenaline causes a generalized cardiac hypertrophy [45, 57]. Thirdly, long-term treatment of rabbits with β-adrenoceptor antagonists reduces the growth of the heart [58]. Lastly, it has been shown that isoprenaline treatment can still induce cardiac hypertrophy in chemically sympathectomized rats, which shows that secretory proteins from the sympathetic nerves are not required for cardiac hypertrophy to take place [30]. The finding that a moderate elevation of the circulating levels of catecholamines is not sufficient to induce cardiac hypertrophy [44] suggests that high local concentrations of noradrenaline, such as occur at the site of release from sympathetic nerve terminals, are required for the triggering of the hypertrophic response in the myocardial cell.

Conclusions

In conclusion, therefore, it is suggested that increased nervous activity in cardiac sympathetic nerves induces compensatory growth of cardiac muscle cells, and that the trophic action is mediated by noradrenaline acting via a β-adrenoceptor. It is furthermore suggested that in most or all conditions leading to adaptive cardiac hypertrophy the sympathetic nervous system is the final common pathway through which increased physiological or pathological demands for cardiac work trigger the biochemical events in the cardiac muscle cell resulting in adaptive growth (Fig. 2).

Clinical implications

Such a hypothesis carries some implications for clinical medicine. In pathological hypertrophy the myocardial muscle cell may hypertrophy to an extent that causes myocardial performance to deteriorate [1]. The cause of the deterioration in function is not entirely clear but it is probably related to at least two different factors. Firstly, because the myocardial cell is mononucleate and does not divide in compensatory hypertrophy, the increased volume of cytoplasm probably reaches an upper limit beyond which the cell cannot increase its size without increasing its DNA content [59]. Secondly, in pathological hypertrophy there is not necessarily a compensatory increase in the number of capillaries to supply the hypertrophied muscle cells [60] and the capillary network becomes more irregular with segmental areas of absent perfusion [61]. A particularly illustrative example of the deleterious effects of excessive hypertrophy is seen in patients with pure aortic stenosis where the concentric hypertrophy may aggravate the outflow obstruction and where the small diastolic volume and the thick ventricular wall cause considerable problems during aortic valve replacement surgery; in such patients subendocardial necrosis and the development of 'stone heart' are major causes of operative mortality [62].

It could be argued that it is undesirable to interfere with the adaptive hypertrophy of the heart and that hypertrophy might be necessary to cope with an increased work-load; however, it has been demonstrated that, in patients with chronic heart disease, the increased ventricular mass is associated with low work efficiency and increased total oxygen consumption [63]. Furthermore, in animal studies where a compensatory cardiac hypertrophy in response to an increased pressure or volume load of the heart has been prevented by means of propranolol or α-methylldopa treatment, or by chemical sympathectomy, no evidence of cardiac decompensation has been reported [53, 54, 58]. Propranolol-treated rats have been found to be able to maintain a blood pressure of 245/173 with no signs of cardiac decompensation (I. Östman-Smith, unpublished work).
In animals cardiac hypertrophy can regress rapidly if the original growth stimulus is withdrawn [64, 65]. In clinical medicine this approach may not always be possible. However, should the present hypothesis prove true, it might still be beneficial to limit hypertrophy in the presence of a continuing stimulus, e.g. hypertension and valvular disease, by using a therapy which interferes with the activity of the sympathetic nervous system (see Fig. 2).

It also follows from the hypothesis that the long-term use of non-selective \( \beta \)-adrenoceptor agonists, in conditions such as atrioventricular conduction disturbances and in asthma, and of \( \beta \)-adrenoceptor antagonists with intrinsic sympathomimetic actions, might lead to an undesirable stimulus for cardiac growth. Lastly, the current enthusiasm for reducing after-load in chronic heart failure ought to be tempered by the awareness that some of the drugs used, in particular hydralazine, cause a reflex increase in cardiac sympathetic nervous activity [51], and that hydralazine may even have direct \( \beta \)-adrenoceptor-stimulating properties [46]; these are all actions which might have undesirable consequences in the long term.

Finally, although there are some clinical studies showing regression of the electrocardiographical signs of left ventricular hypertrophy with anti-hypertensive therapy [67, 68] the reduction of cardiac work-load was not accurately assessed and it would clearly be useful to assess whether drugs currently used in antihypertensive treatment, that act at one or more sites in the chain of events illustrated in Fig. 2, will reduce compensatory cardiac hypertrophy by a mechanism which is distinct from their effect on cardiac work-load.

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References


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