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EDITORIAL COMMENT

The Rise and Fall of Myotrophin in Heart Failure*

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In just over one decade since it was first isolated from the hearts of spontaneously hypertensive rats, much has been learned about the actions of the soluble 12-kd protein myotrophin (1). Although ubiquitous, the cardiac effects of myotrophin have remained the focus of research over this period (2–8). Myotrophin stimulates protein synthesis in cardiomyocytes (and hypertrophy of these cells), as well as the expression of a number of cardiac genes (e.g., beta-myosin heavy chain and atrial natriuretic peptide) and proto-oncogenes (e.g., c-*myc*, c-*fos*, and c-*jun*) (2–8). Myotrophin has similar hypertrophic effects in skeletal muscle cells (9). Myotrophin appears to bring about this effects by interacting with nuclear factor-kappa B (NF-kappa B) (2–8). Indeed, myotrophin has a close structural homology for inhibitory-kappa B (I-kappa B), a regulatory peptide controlling the activity of NF-kappa B (2–8).

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Sometime ago Sil et al. (10) found that myotrophin levels are increased in the hearts of patients with dilated cardiomyopathy (the etiology is not stated in their report). Although it is considered a cytosolic protein, O'Brien et al. (11), in this issue of the *Journal,* have now shown that myotrophin circulates in the blood of healthy subjects and patients with chronic heart failure (CHF), regardless of whether the etiology is ischemic or nonischemic. Plasma concentrations of myotrophin were higher in patients than in control subjects but, curiously, were *inversely* related to clinical severity (i.e., patients with higher New York Heart Association functional class CHF had lower myotrophin concentrations). Men with CHF also had higher myotrophin levels than women with CHF.

These recent observations raise many new questions about myotrophin in CHF. What is the source of circulating myotrophin in CHF? As cardiac hypertrophy tends to increase with increasing severity of CHF (and tends to be greater in women than in men [12]), perhaps the heart is not the origin. Skeletal muscle is an alternative source. Skeletal muscle mass tends to be lower in women than in men and may reduce as CHF advances (e.g., with the development of cachexia) (13). The disconnect between plasma atrial natriuretic peptide (ANP) and myotrophin concentrations also argues against a cardiac origin (given that myotrophin stimulates ANP expression in cardiomyocytes) (14).

Alternatively, if the heart is the source of myotrophin, then these new findings may be describing something very unusual in CHF—that is, the decline or exhaustion of a potential "compensatory" mechanism in this condition. Without exception, other candidate compensatory responses are persistently activated in CHF and are more activated in more severely ill patients. If the present findings indicate that cardiac myotrophin production declines as CHF advances (or might it be that CHF advances because myotrophin production declines?), this could be of great clinical and therapeutic significance. The present findings may also be very important if they are telling us something new about the origin of skeletal muscle dysfunction and wasting in CHF, the latter being of ominous prognostic significance (13).

Another obvious question raised by the observations of O'Brien et al. (11) is: what, if any, role does *circulating* myotrophin have? Is it just a marker of muscle production or does it act as a hormone in its own right, in the conventional sense? Of course, we have assumed plasma concentrations of myotrophin reflect tissue production, whereas these may equally reflect reduced clearance, the mechanisms of which are unknown.

Clearly we need to learn much more about myotrophin in CHF and, in particular, the cardiac production of this peptide during the progression of CHF.

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