From: Hamster Information Service, Vol 8, No 4, pp 3-6, 1986.

EDITORIAL

Hamster Cardiomyopathy: Understanding the Pathogenesis of Heart Failure

by

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Congestive heart failure is a major cause of disability and premature death in modern western societies. Surgical models of heart failure have been valuable contributors to our understanding of the hemodynamic and neurohumoral responses to myocardial failure. These models, however, have several disadvantages. For example, the surgical lesion usually results in a disorder with a relatively acute or sub-acute course, limiting the relevance of these surgical paradigms to the more protracted course taken by human disease. The surgical procedure, itself, often results in disturbances of relevant cardiac autonomic nerves, limiting information pertaining to the neurohumoral response to heart failure. Finally, surgically-induced heart failure gives little insight into the mechanisms underlying a particularly poorly understood group of clinical disorders, the primary congestive cardiomyopathies.

The cardiomyopathic Syrian hamster is a reproducible, spontaneous (genetically transmitted as an autosomal recessive), gradual model of cardiac hypertrophy, dilatation, and failure. Animals younger than 40 to 50 days of age display little gross or light microscopic evidence of heart disease. At this time, they enter the "necrotic" phase of the disease, developing multiple focal areas of myocytolytic necrosis in the heart. All cardiac muscle layers and chambers are involved. The number of these lesions begins to decrease at approximately 100 days of age, although they continue to form at a reduced rate as the heart gradually hypertrophies. These lesions are replaced in the heart by fibrotic, calcified deposits. The terminal phase of the disease is characterized by progressive cardiac dilatation and decompensation and, ultimately, premature death at 7 to 14 months of age, depending on the strain; approximately one half of the deaths are sudden and appear to be from arrhythmias, whereas the remainder of the animals die of actual congestive heart failure.

Skeletal muscle is also affected, but, in contrast to the onset of cardiac lesions, involvement is seen even in neonates. Selection of best brother-sister pairs for breeding may be made on the basis of calcification and ulcers seen on the underside of the tongue in young animals; the best animals for breeding exhibit tongue lesions between 20 and 30 days of age.

Currently, three major strains of hamsters are in use in North America. BIO 14.6 animals are bred in Massachusetts by Bio-Breeders, Inc., in Fitchburg. These animals are commercially available and exhibit a somewhat greater degree of myocardial hypertrophy than other hamsters. Life expectancy, however, is approximately one year, and thus is somewhat longer than

for other strains. The University of Montreal maintains a strain known as UM-X7.1, which has a life expectancy of approximately 8 to 11 months; these animals are not commercially available. A new strain, T.O., has been developed recently at the University of Toronto, and is now in the 15th generation; this strain was derived from Bio 53.58 animals originally from the Bio-Research Institute, Inc., in Cambridge, Massachusetts. The life expectancy of these animals is approximately 7 to 8 months. These animals are not for commercial sale, but they are available to a limited group of collaborating investigators.

A large variety of bio-chemical alterations have been described during the clinical course of hamster heart disease (1,2). Our laboratory has used this model to study the neurochemistry and the molecular biology of myocardial failure.

Sympathetic Innervation of the Failing Heart (reviewed in 3)

The sympathetic nervous system is important for the appropriate regulation of cardiac mechanical and electrical function in response to physiological demands. Myocardial failure, however, is accompanied by profound derangements in this control mechanism. Surgical models have shown that congestive heart failure is associated with the depletion of cardiac norepinephrine and a reduction of tyrosine hydroxylase, the rate-limiting enzyme for norepinephrine synthesis. Studies in the hamster have revealed that such alterations are not true for all forms of heart failure. Hamster heart failure, like that induced by surgery, is accompanied by a decrease in cardiac norepinephrine stores (4). Associated with this decrease, however, is an increase in tyrosine hydroxylase (5,6), norepinephrine turnover, and cardiac dopamine stores (7). In hamster heart failure, the rate-limiting step for norepinephrine synthesis no longer appears to be tyrosine hydroxylation but rather is the rate at which dopamine can be transported across the membrane of the noradrenergic vesicle for hydroxylation to norepinephrine (7). Recently, a pattern of norepinephrine-dopamine distribution similar to that found in the hamster has been confirmed for human cardiomyopathic hearts (8).

Studies of the neurochemical integration of cardiac sympathetic tone in the central nervous system during hamster heart failure have also been performed. These studies have identified a specific brain serotonergic pathway which appears to participate in the modulation or integration of the increased cardiovascular sympathetic efferent response found in hamster heart failure (9).

There is considerable evidence which suggests that an increase in cardiac sympathetic tone may be of importance in the etiology of hamster heart disease. Neonatal cardiomyopathic hamsters are exquisitely susceptible to myocardial calcium accumulation and necrosis following exogenous catecholamine administration (10). There is also evidence for an increase in the maximum number of binding sites for the radioligands 3H-prazosin (an α-1 antagonist) and 3H-dihydroalpranolol (a β antagonist) in cardiomyopathic hearts as compared to controls (11). Aortic smooth muscle from cardiomyopathic hamsters exhibits an increased contractile response

(but normal sensitivity) to norepinephrine or serotonin as compared to control animals (12). Factor and co-workers perfused normal and myopathic hamster hearts with liquid silicone rubber (Microfil), and were able to demonstrate that the onset of the cardiomyopathy was associated with numerous areas of microvascular constriction, narrowing, and irregularity in the heart (13). Both the cardiomyopathic and vascular disorder were prevented by pre-treating animals with either the calcium antagonist, verapamil (13,14), or the α-1 antagonist, prazosin (15). Thus, these data suggest that an increase in sympathetic tone together with a defective handling of calcium by myocardial and vascular smooth muscle sarcolemma may be of fundamental importance for the phenotypic expression of hamster heart disease.

Molecular Biology of Myocardial Failure

A genetically-transmitted model of heart disease particularly lends itself to the investigation of the molecular biology of myocardial failure. DNA-associated chromosomal proteins play a significant role in dictating the structural properties of the eukaryotic genome and the regulation of gene expression. Dr. C.C. Liew, in collaboration with our laboratory, has made several contributions to the molecular biological aspects of hamster heart disease. We have been able to demonstrate alterations in the composition of a group of cardiac non-histone chromosomal proteins which appear to be important for the processing of heterogeneous nuclear RNA (16,17). These alterations appear to be functionally important, for we have also been able to demonstrate a reduction in both nuclear RNA synthesis and polyribosomal RNA levels in myopathic hamster hearts, as compared to controls (17). We have also been able to show similar alterations in cardiac non-histone chromosomal proteins in a familial form of human heart disease, hypertrophic obstructive cardiomyopathy (18). We were not able to demonstrate such abnormalities in surgically-induced animal models of myocardial hypertrophy or in acquired forms of human cardiac enlargement.

Our laboratories have also begun to apply recombinant DNA technology to the study of myofibrillar proteins in hamster heart disease. Cosmid DNA libraries of both normal and cardiomyopathic hamsters (T.O.) and a cardiac cDNA library of normal hamsters have been established. Clones for α and ß myosin heavy chain genes have been isolated and partially sequenced (19). These clones exhibit a >90% homology between each other and with those for rat myosin heavy chain genes. The 3' untranslated regions, however, show very little homology between the α and ß myosin heavy chain genes. These heterologous regions have provided an opportunity for the construction of discrete probes to follow the pattern of myosin heavy chain gene expression during the course of cardiomyopathy. We have recently used S_1 mapping techniques, which have demonstrated clearly a shift from the synthesis of α myosin heavy chains to that of the ß isoform with the evolution of the cardiomyopathy (20), supporting data from myofibrillar protein studies (2).

Finally, Jasmin and co-workers (21) have recently reported the presence of hypothyroidism during the course of the cardiomyopathy in UM-X7.1 animals. The relevance of this hormonal disturbance to other strains and the biochemical features of the heart disease remains to be determined.

Biochemical abnormalities described in the hamster paradigm of congestive cardiomyopathy have predicted successfully similar abnormalities in human cardiomyopathic hearts. The application of recombinant DNA to this genetic model of heart disease now provides investigators with particularly exciting opportunities for the understanding of primary myocardial disease.

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