Translational Initiation Factor eIF-4E
A LINK BETWEEN CARDIAC LOAD AND PROTEIN SYNTHESIS*

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To define the coupling mechanism between cardiac load and the rate of protein synthesis, changes in the extent of eIF-4E phosphorylation were measured after imposition of a load. Electrically stimulated contraction of adult feline cardiocytes increased eIF-4E phosphorylation to 34% after 4 h, as compared with 8% phosphorylation in quiescent controls. However, eIF-4E phosphorylation did not increase upon electrical stimulation in the presence of 7.5 mM 2,3-butanedione monoxime, an inhibitor of actin-myosin cross-bridge cycling and active tension development. Treatment of adult cardiocytes with either 0.1 μM insulin or 0.1 μM phorbol 12-myristate 13-acetate increased eIF-4E phosphorylation to 23 and 64%, respectively, but these increases were not blocked by 2,3-butanedione monoxime. In canine models of acute hemodynamic overload in vivo, eIF-4E phosphorylation increased to 23% in response to left ventricular pressure overload as compared with 7% phosphorylation in controls. Acute volume overload had no effect on eIF-4E phosphorylation. These changes in eIF-4E phosphorylation account for differences in anabolic responses to acute pressure versus acute volume overload. These data suggest that eIF-4E phosphorylation is a mechanism by which increased cardiac load is coupled to accelerated rates of protein synthesis.

In the adult mammal, cardiac muscle grows by hypertrophy of the constituent terminally differentiated muscle cells or cardiocytes (1). In contrast to hyperplastic growth that is regulated at multiple levels, hypertrophic growth is primarily regulated at the level of protein translation, since the eventual increase in mass is a function of the net difference between rates of protein synthesis and protein degradation (2). A nearly universal feature of cardiac hypertrophy in the adult is that it is the basic compensatory mechanism for increased hemodynamic load. The amount of hypertrophy that develops in vivo is dependent upon the type, severity, and duration of the increased ventricular wall stress imposed by a load, and it can be accounted for by quantitative differences in protein synthesis rates that are intrinsic to the cardiocyte (3–7). However, the coupling mechanism between load and hypertrophy is unknown. Therefore, in an attempt to define this mechanism, we focused on the rate-limiting steps involved in regulating protein translation in response to load.

Many studies indicate that the initial acceleration of the rate of protein synthesis in response to an acute increase in load results from increased translational efficiency, in which a greater amount of protein is produced by the preexisting translational machinery in the cardiocyte (3, 4, 6, 8, 9). Increased translational efficiency usually occurs at the level of peptide chain initiation and is controlled by modifying the activities of translational initiation factors via phosphorylation and dephosphorylation (10, 11). Thus, changes in the activity of an initiation factor that is rate-limiting for peptide chain initiation would provide a specific mechanism for accelerating cardiocyte protein synthesis. One such mechanism that regulates the overall rate of protein synthesis is the formation of the 48S initiation complex, which is formed by the binding of mRNA to the 43S initiation complex and is catalyzed by the activities of eIF-4F and eIF-4B (10–12). The eIF-4F complex consists of three components: a cap binding protein referred to as eIF-4E that binds to the m7-GTP cap of mRNA, eIF-4A that functions as a helicase along with eIF-4B to unwind mRNA secondary structure, and eIF-4G that functions as a binding protein for the eIF-4 protein group. The assembly of the eIF-4F complex occurs either prior to mRNA binding or sequentially during the process of mRNA binding to the 40S ribosome (12, 13). Although all of the eIF-4 proteins are phosphorylated with the exception of eIF-4A several lines of evidence indicate that eIF-4E activity, which is a function of its phosphorylation state, is rate-limiting for peptide chain initiation and therefore regulates the rate of protein synthesis. First, a large number of studies have shown a direct correlation between the extent of eIF-4E phosphorylation and the rate of protein synthesis (10–12). Second, it is the least abundant eIF and is present in limiting quantities relative to mRNA and ribosomes (14). Third, eIF-4E activity is increased by phosphorylation on serine 209, which increases its binding affinity for the m7-GTP cap on mRNA and thereby promotes assembly of eIF-4F in the initiation complex (15).

Given the regulatory potential of a rate-limiting translation factor, we hypothesized that eIF-4E phosphorylation might be the coupling mechanism by which an acute change in load accelerates the rate of protein synthesis. We determined whether changes in eIF-4E phosphorylation, a direct measure of its activity, occur in response to acute changes in load by using an in vitro model of electrically stimulated contraction of adult feline cardiocytes in primary culture and in vivo models of canine left ventricular pressure and volume overload. In electrically stimulated cardiocytes in vitro, prior studies had demonstrated that the rate of protein synthesis was acutely accelerated in response to the active as opposed to the passive

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tension component of cardiocyte contraction, and long term stimulation resulted in a sustained increase in protein synthesis and hypertrophic growth (4, 16). In the experimental models of hemodynamic overload in vivo, we have previously shown that the rate of myosin synthesis was significantly increased in response to acute pressure overload but not in response to acute volume overload (3). Therefore, in this study, both the in vitro and in vivo models were employed to determine whether eIF-4E phosphorylation is a mechanism for accelerating rates of protein synthesis in response to increased mechanical load.

**MATERIALS AND METHODS**

Electrical Stimulation Model—Adult feline cardiocytes were isolated for primary culture by collagenase digestion in combination with mechanical agitation as described previously (4). Following cell isolation, the eIF-4E–deficient cardiocytes were cultured in M199 (Life Technologies, Inc.) medium with Earle’s balanced salts at a concentration of 50,000 rod-shaped cells/ml. The cardiocytes were plated onto four-well culture trays (Nunc); the dimensions of each well were 2.5 × 6.5 cm. To facilitate adhesion, the wells were coated with laminin and the cardiocytes plated in M199 medium at a density of 2 × 10^6 rod-shaped cells/well. Cardiocyte contractile function was monitored by digital video microscopy every 15 min. Following an overnight incubation, the cultures were rinsed to remove nonadherent cardiocytes and incubated in a chemically defined serum-free medium consisting of M199 medium supplemented with 250 μM ascorbic acid and 1.8 mM sodium acetate. Adult feline cardiocytes, which are normally quiescent in culture, exhibit contractile activity by electrical field stimulation as described previously (16). Cardiocyte contraction was stimulated at a frequency of 1 Hz and pulse duration of 5 ms.

**Canine Models of Acute Pressure and Volume Overload—**The canine models of acute hemodynamic overload were prepared as described (3). In the acute pressure overload model, averaged hemodynamic data over 6 h demonstrated that systolic pressure was increased by 44% over that of control dogs and was accompanied by significant increases in stroke work, pulmonary wedge pressure and diastolic pressure. In the acute volume overload model, hemodynamic data showed that the average regurgitant fraction was 67 ± 6% of control, and the stroke volume and pulmonary wedge pressure were increased by 57 and 130%, respectively.

**Phosphorylation and Immunoprecipitation of eIF-4E from Canine Cardiocytes—**Canine cardiocytes were rinsed twice with ice-cold M199 medium and scraped in a buffer containing 20 mM Tris, pH 7.5, 0.5 mM EDTA, 0.1 mM phenylmethylsulfonyl fluoride, 1 μM benzamidine, 0.5 mM sodium orthovanadate, 1 μM okadaic acid, 1 μM microcystin LR, 25 μM leupeptin, 2 units/ml aprotinin, and 20 μM chymostatin. The material from eight wells (two culture trays) was pooled and homogenized by means of a Dounce homogenizer. 20 μl of washed m7-GTP-Sepharose 4B (Pharmacia Biotech Inc.) was added to each sample and incubated for 1 h at 4 °C. The m7-GTP-Sepharose was pelleted, washed and resuspended in 48 μl of HB buffer consisting of 20 mM PEPES, pH 7.5, 100 mM KCl, 0.2 mM EDTA, 80 mM 2-glycerophosphate, 50 mM NaF, 1 mM dithiothreitol, 0.2 mM phenylmethylsulfonyl fluoride, 1 mM benzamidine, 0.5 mM sodium orthovanadate, 1 μM okadaic acid, and 1 μM microcystin. 12 μl of solution D (10% SDS, 150 mM dithiothreitol) was added, and the samples were boiled for 3 min and allowed to cool to room temperature. 4 μl of solution E (65 mM dithiothreitol, 4% (w/v) CHAPS, 9 mM urea) was then added, and the samples were frozen using liquid N2 and stored at −70 °C prior to isoelectric focusing.

**Immunoprecipitation of eIF-4E from Feline Cardiocytes—**Cardiocyte cultures were rinsed twice with ice-cold M199 medium and scraped in a buffer containing 20 mM Tris, pH 7.5, 0.5 mM EDTA, 0.1 mM phenylmethylsulfonyl fluoride, 0.4 mM dithiothreitol, 0.1% Nonidet P-40, 0.1% SDS, 0.5 μg/ml leupeptin, 1 mM sodium orthovanadate, 80 mM β-glycerophosphate, 1% sodium deoxycholate, 50 mM NaF, and 10 mM Na4P2O7. The homogenate was incubated on ice for 1 h, centrifuged for 10 min at 13,000 × g, and incubated overnight with eIF-4E antibody. eIF-4E was immunoprecipitated by incubating for 1 h with Protein A-Sepharose (Pierce). The samples were pelleted, washed, and subjected to SDS-PAGE following Western blotting with eIF-4E antibody.

**Western Blot Analysis of Total Cell Protein—**Cardiocyte cultures were rinsed and homogenized in LCB buffer using a Dounce homogenizer as described above. Protein concentration was determined using the BCA method (Pierce). 100-μg aliquots of total cell protein were subjected to SDS-PAGE using 15% polyacrylamide gels, followed by Western blotting. For canine myocardial samples, frozen samples from the left ventricle and companion right ventricle were homogenized in LCB buffer by means of a Polytron followed by Dounce homogenization. 100-μg aliquots of total tissue protein were electrophoresed by SDS-PAGE using 15% polyacrylamide gels followed by Western blotting.

**RESULTS**

Changes in eIF-4E activity, as measured by the extent of eIF-4E phosphorylation on isoelectric focusing gels, were assessed in cardiocyte homogenates following purification by affinity chromatography with m7-GTP-Sepharose and detection by Western blotting using a polyclonal antibody for eIF-4E. The validity of this approach is demonstrated in Fig. 1 by five criteria. First, as shown previously (17), human recombinant eIF-4E bound to an m7-GTP-Sepharose affinity column and was eluted by m7-GTP (Fig. 1A); the eIF-4E antibody recognized recombinant eIF-4E on Western blots. Second, eIF-4E was purified from homogenates of both quiescent control and electrically stimulated cardiocytes using the m7-GTP-Sepharose affinity column; a protein of the same electrophoretic mobility as human eIF-4E (28 kDa) was detected by Western blotting (Fig. 1C). Third, to further demonstrate the specificity of the polyclonal antibody, eIF-4E was immunoprecipitated from the cardiocyte homogenate by the m7-GTP-Sepharose affinity purification step (Fig. 1C); a single protein band having the same electrophoretic mobility as human recombinant eIF-4E was immunoprecipitated from the cardiocyte homogenate by the m7-GTP-Sepharose affinity purification step (Fig. 1C).
Our previous studies showed that electrically stimulated contraction of adult cardiocytes resulted in a time-dependent increase in protein synthesis that reached 43% after 4 h (4). In order to determine whether the rate of protein synthesis was increased by a mechanism involving phosphorylation of eIF-4E, cardiocytes were electrically stimulated to contract at a frequency of 1 Hz, and the extent of eIF-4E phosphorylation was measured as a function of time (Fig. 2). There was a time-dependent increase in the percentage of eIF-4E phosphorylation from 4% in the quiescent controls to 33% after 4 h of electrically stimulated contraction. Our previous studies also showed that the rate of protein synthesis was accelerated by the mechanical component of cardiocyte contraction, as defined by active tension development and shortening. To determine whether load in the form of mechanical contraction was the stimulus that increased eIF-4E phosphorylation, cardiocytes were electrically stimulated for 4 h in the presence and absence of 2,3-butanedione monoxime (BDM), and the extent of eIF-4E phosphorylation was measured. BDM is a chemical agent that blocks actin-myosin cross-bridge cycling and force development without any significant effects on calcium transients at concentrations lower than 10 mM, in effect uncoupling electrical excitation from contraction (19). We have shown that 7.5 mM BDM completely blocks the ability of electrical stimulation to accelerate the rate of cardiocyte protein synthesis; concurrently it reduces both the extent and velocity of sarcomere shortening by 70% and the extent of cell shortening by 90% (4). In the absence of BDM, electrically stimulated contraction for 4 h significantly increased eIF-4E phosphorylation as compared with that of quiescent controls (Fig. 3). In contrast, eIF-4E phosphorylation was not increased when cardiocytes were electrically stimulated in the presence of 7.5 mM BDM. BDM had no effect on eIF-4E phosphorylation of quiescent controls. Thus, the extent of eIF-4E phosphorylation correlates with changes in the rate of protein synthesis since both were increased in response to a work load consisting of active tension development during cardiocyte contraction.

Insulin has been shown to increase both protein synthesis and eIF-4E phosphorylation (20). Because we have found that insulin acutely accelerates the rate of protein synthesis in quiescent cardiocytes (16), the effect of 0.1 mM insulin on eIF-4E phosphorylation was determined (Fig. 3). As measured after 4 h, insulin stimulated eIF-4E phosphorylation in quiescent cardiocytes to the same extent as did electrically stimulated contraction. However, in contrast to electrical stimulation, BDM did not affect the insulin-stimulated increase in eIF-4E phosphorylation, indicating that insulin has a signaling mechanism for eIF-4E phosphorylation that is distinct from that utilized by cardiocyte contraction. eIF-4E has also been shown to be a substrate for protein kinase C in vitro, and eIF-4E phosphorylation occurs in response to phorbol ester treatment in several cell types (20). Because protein kinase C activation may have an important role in regulating hypertrophic growth of cardiocytes (7, 21), we examined whether direct activation of the catalytic subunit of protein kinase C by phorbol ester treatment increased eIF-4E phosphorylation (Fig. 3). Phorbol ester treatment of quiescent cardiocytes for 4 h caused a marked increase in eIF-4E phosphorylation that was approximately

**Phosphorylation of eIF-4E in Cardiac Muscle**

8361

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twice that observed in response to either contraction or insulin. BDM treatment had no effect on eIF-4E phosphorylation in phorbol ester-treated cardiocytes. Thus, three distinct stimuli for accelerating the rate of protein synthesis, namely load as induced by electrically stimulated contraction, insulin treatment, and activation of protein kinase C with phorbol ester, share a common anabolic end point of eIF-4E phosphorylation, even though they utilize unique signaling mechanisms. The fact that BDM did not affect eIF-4E phosphorylation in response to either insulin or phorbol ester treatment shows that its inhibition of eIF-4E phosphorylation in electrically stimulated cardiocytes is caused by blockade of active tension development and cell shortening and is not the result of a phosphatase activity or other nonspecific effects on phosphorylated eIF-4E.

To determine whether the mechanical effects of cardiocyte contraction on eIF-4E phosphorylation in vitro have relevance to load-induced cardiac hypertrophy in vivo, eIF-4E phosphorylation was measured in experimental canine models of acute pressure and volume overload in vivo (3). These two distinct types of left ventricular hemodynamic overload exert different types and severities of wall stress. Aortic stenosis (AS) is a pressure overload characterized by an increase in systolic wall stress as the stroke volume is pumped under higher pressure into the aorta. Sustained pressure overload results in the development of concentric hypertrophy and increased wall thickness. In contrast, mitral valve regurgitation (MR) is a volume overload in which the excess volume is ejected into the left atrium under low pressure. There is an increase in diastolic wall stress that causes the development of eccentric hypertrophy, but the amount of hypertrophy produced by MR is generally much less than that produced by substantial pressure overload (3). Indeed, we have determined that AS accelerates the rate of myosin synthesis by 45%, whereas MR has no significant effect on the rate of myosin synthesis (3). Therefore, the phosphorylation of eIF-4E in response to AS and MR was compared in the same cardiac tissue samples in which the disparate effects of AS and MR on the rate of myosin synthesis had been found. As shown in Fig. 4, pressure overload of the left ventricle by AS caused an increase in eIF-4E phosphorylation as compared with the left ventricle of sham-operated control dogs. In contrast, volume overload of the left ventricle by MR did not stimulate eIF-4E phosphorylation. As an internal, more normally loaded, control for each heart, there was no significant effect on eIF-4E phosphorylation in the companion right ventricles in any of the treatment groups. Thus, increased eIF-4E phosphorylation was dependent upon the type of wall stress imposed upon the myocardium, consistent with previous findings that the rate of protein synthesis is accelerated in response to an increase in systolic wall stress produced by acute pressure overload, but not in response to an increase in diastolic stress produced by acute volume overload.

There are potentially two ways to increase the activity of eIF-4E in the cardiocyte: increased phosphorylation of eIF-4E and/or an increase in the amount of eIF-4E. We measured the relative amounts of eIF-4E in total cardiocyte or total myocardial tissue homogenates by Western blotting (Fig. 5). The data in Fig. 5A show that eIF-4E levels did not increase after 4 h of electrically stimulated contractile activity, insulin treatment, or phorbol ester treatment when compared with control levels. There were no differences in eIF-4E levels among any of the treatment groups as determined by digital image analysis of the autoradiograms. Values are the mean ± S.E., n = 3 experiments. Statistical comparisons were made by analysis of variance followed by a Student-Newman-Keuls test. *, p < 0.01 as determined by an analysis of variance followed by a Student-Newman-Keuls test.
was 4.4%. The data in Fig. 5B show that eIF-4E levels did not increase after 6 h in the canine models of either pressure overload from AS or volume overload from MR. As determined by digital image analysis, the coefficient of variation in eIF-4E levels was 6.8% (two experiments). Thus, changes in eIF-4E phosphorylation occurred without increases in the overall amount of eIF-4E protein.

**DISCUSSION**

These studies demonstrate a link between the mechanical stimulus of load on the cardiocyte and phosphorylation of eIF-4E. By increasing the activity of eIF-4E through phosphorylation, a specific coupling mechanism is established for enhancing peptide chain initiation and thereby accelerating the steady state rate of protein synthesis. This same mechanism applies to acute models of load-induced hypertrophy in vivo since eIF-4E was phosphorylated in response to the severe increase in systolic stress caused by a pressure overload but not in response to increased diastolic stress produced by a volume overload. Thus, the mechanism involved in eIF-4E phosphorylation distinguishes between the types of wall stress associated with pressure versus volume overload, and the quantitative difference in the rate of protein synthesis observed in these two models correlates with the extent of eIF-4E phosphorylation. In a terminally differentiated cell such as the adult cardiocyte, this type of translational mechanism could coordinate the acceleration of total protein synthesis in response to load. Thus, constitutively expressed proteins of high abundance, which are translated efficiently, could be increased both rapidly and proportionally by effectively competing for the limited amount of eIF-4F that is assembled either prior to or at the start of the process of 48S initiation complex formation (12, 13, 20). Many other initiation factors including eIF-4A and eIF-4B are phosphorylated, but their functional significance has not been determined. Another protein that can regulate eIF-4E activity is the eIF-4E-binding protein PHAS-1 (25, 26). The activity of phosphorylated eIF-4E is inhibited by its binding to PHAS-1, even though the affinity for the m7-GTP cap is unaffected. In insulin-treated cells, phosphorylation of PHAS-1 prevents binding to eIF-4E, thereby removing its inhibitory effect on eIF-4E function. Given the observation that PHAS-1 is phosphorylated through several kinase pathways (25), it could potentially be an additional mechanism for regulating eIF-4E activity in response to mechanical load.

In summary, a specific anabolic end point has been identified that links an acute increase in mechanical load to an accelerated rate of cardiocyte protein synthesis. The change in eIF-4E phosphorylation provides a mechanism coupling load to increased peptide chain initiation and thus to accelerated protein synthesis. While applicable to the terminally differentiated cardiac muscle cell, this mechanism may have much broader implications for other systems in which mechanical forces regulate growth (27). For example, a considerable fraction of the protein synthesizing machinery, including initiation factors, mRNA, and polyribosomes, are physically associated with cytoskeletal components in all cells (28), such that eIF-4E may be a coupling molecule to convert mechanically induced changes in the cytoskeleton into an anabolic response.

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Phosphorylation of eIF-4E in Cardiac Muscle

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