INFLUENCE OF CHRONIC ALCOHOL INGESTION ON ACETALDEHYDE-INDUCED DEPRESSION OF RAT CARDIAC CONTRACTILE FUNCTION

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(Received 27 March 2000; in revised form 23 May 2000; accepted 29 May 2000)

Abstract — Long-standing ethanol consumption acts as a chronic cardiac stress and often leads to alcoholic cardiomyopathy. We have recently shown that the acute ethanol-induced depression in myocardial contraction was substantiated by chronic ethanol ingestion. Acetaldehyde (ACA), the main ethanol metabolite, has been considered to play a role in ethanol-induced cardiac dysfunction. To evaluate the ACA-induced cardiac contractile response following chronic ethanol ingestion, mechanical properties were examined using left ventricular papillary muscles and myocytes from rats fed with control or ethanol-enriched diet. Muscles and myocytes were electrically stimulated at 0.5 Hz and contractile properties analysed included peak tension development (PTD) and peak shortening (PS). Intracellular Ca⁺⁺ transients were measured as fura-2 fluorescence intensity changes (ΔFFI). Papillary muscles from ethanol-consuming animals exhibited reduced baseline PTD and attenuated responsiveness to increase of extracellular Ca⁺⁺. Acute ACA (0.3–10 mM) addition elicited a dose-dependent depression of PTD. However, the inhibition magnitude was significantly reduced in ethanol-treated rats. Myocytes from both control and ethanol-treated rats exhibited comparable ACA-induced depression in both PS and ΔFFI. Collectively, these data suggest that the ACA-induced depression of myocardial contraction is reduced at the multicellular level, but unchanged at the single cell level, following chronic ethanol ingestion.

INTRODUCTION

Chronic alcoholism has been considered as a chronic stress on the heart and the major cause of non-ischaemic cardiomyopathy. Alcohol (ethanol)-induced cardiomyopathy is often manifested by left ventricular dilatation, impaired left ventricular contractility, reduced ejection fraction and cardiac output, cardiac hypertrophy and enhanced risk of stroke and hypertension (Steinberg and Hayden, 1981; Regan, 1990; Fernandez-Sola et al., 1994; Preedy and Richardson, 1994; Thomas et al., 1994). The occurrence of cardiomyopathy in chronic alcoholism has been well documented, although its cause is still unclear. Several mechanisms have been postulated including accumulation of triglycerides, altered fatty acid extraction, decreased myofilament responsiveness to Ca⁺⁺ and catecholamines, and impaired cardiac protein synthesis (Preedy and Richardson, 1994; Thomas et al., 1994; Baraona and Lieber, 1998). Altered cardiac morphology, such as a loss or disruption of myofibrils and dilated sarcoplasmic reticulum and metabolism, have also been reported after long-term ethanol consumption (Wynne and Braunwald, 1987). However, neither the precise mechanism of, nor the specific toxic substance(s) responsible for, alcoholic cardiomyopathy have been recognized.

Acetaldehyde (ACA), the major metabolite of ethanol which is found highly concentrated in the heart (Espinet and Argiles, 1984), has been shown to exert biphasic chronotropic and inotropic cardiac effects (Stratton et al., 1981; Brown and Carpenter, 1989; Savage et al., 1995). The positive component including increases in heart rate, cardiac output, coronary blood flow and left ventricular pressure, was often observed at low concentrations and may be associated with stimulation of the β-adrenergic system. Although the negative chronotropic and inotropic effects on myocardial tissue have not been precisely determined, ACA has been shown to elicit myocardial depression independently of cholinergic or purinergic mechanisms (Savage et al., 1995; Brown and Savage, 1996). Our further study confirmed that ACA-induced cardiac depression is likely to be due to its direct inhibition of single ventricular myocyte contraction (Ren et al., 1997; Brown et al., 1999). These data suggest that ACA may play a role in the action of ethanol on cardiovascular dysfunction.

Recently, we reported that ethanol-induced myocardial depression is substantiated by chronic ethanol ingestion (Brown et al., 1998). To determine the action of ACA following chronic ethanol ingestion, the present study examined the impact of chronic ethanol ingestion on ACA-induced cardiac contractile depression using isolated papillary muscles and cardiac myocytes isolated from left ventricles from control animals and those chronically fed with ethanol.

MATERIALS AND METHODS

Experimental animals and chronic ethanol ingestion

The experimental protocols described in this study were approved by Animal Investigation Committees from Wayne State University and the University of North Dakota and have previously been described (Brown et al., 1998). Male Sprague–Dawley rats were obtained as pairs of littermates weighing ~50 g each. All animals were housed in a temperature-controlled room under a 12-h light/12-h dark illumination cycle and allowed tap water ad libitum. Animals were initially maintained on standard rat chow for a 1-week quarantine period, following which all animals were introduced to a nutritionally complete liquid diet (Shake & Pour Bioserv Inc., Frenchtown, NJ, USA) for a 1-week acclimation period (DeCarli and Lieber, 1967). The use of a liquid diet is based on the observations made by Keane and Leonard (1989) that ethanol self-administration resulted in fewer nutritional deficiencies and less stress to the animals in comparison to

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forced-feeding regimens, intravenous administration, or aerosolized inhalation. Upon completion of the acclimation period, one littermate was maintained on the liquid diet without ethanol, and the remaining littermates began a 7-day period of ethanol introduction. Ethanol-consuming animals were given a diet containing 12%, 24% and 36% of isocaloric ethanol on days 1–4, 5–7 and 8, respectively. An isocaloric (250 kcal/l) pair-feeding regimen was employed to eliminate the possibility of nutritional deficits. Control animals were offered the same quantity of diet that the ethanol-consuming animals drank the previous day. Blood pressure and body weight were monitored weekly. The serum ethanol concentration was determined using a biochemistry analyzer (YSI 2700 Biochemistry Analyzer, Yellow Springs, OH, USA).

**Ventricular papillary muscle isolation and measurement of isometric tension**

Once the animals were sedated, hearts were rapidly excised and immersed in oxygenated Tyrode’s solution at 37°C. Left ventricular papillary muscles were dissected and mounted vertically in a temperature-controlled bath superfused with oxygenated Tyrode’s solution (mM: NaCl 5.4, KCl 136.9, NaHCO₃ 11.9, MgCl₂ 0.50, CaCl₂ 2.70, NaH₂PO₄ 0.45 and glucose 5.6, pH 7.4) at 30°C. Preparations were allowed to equilibrate in Tyrode’s solution for 90 min while electrically driven by a Grass stimulator (S-88) at 0.5 Hz, to establish baseline isometric tension development. Length–tension curves were constructed for each preparation and the peak tension development (PTD) was recorded at ~90% of L₉₀ using a force transducer (Grass, FT 03). Signals were amplified, differentiated and displayed on a chart recorder (Grass-79). PTD was normalized to respective control values and presented as a percentage change to minimize inter-muscle variance. The following parameters were measured: PTD, time-to-PTD (TPT); time-to-90% relaxation (RT₉₀); and the maximum velocities of tension developed and decline (±VT) (Brown et al., 1998).

**Cell isolation procedures**

Ventricular myocytes were enzymatically dispersed from the rat heart as described previously (Ren et al., 1998). Briefly, hearts were rapidly removed and perfused (at 37°C) with Krebs–Henseleit bicarbonate (KHB) buffer containing (in mM): 118 NaCl, 4 KCl, 1.25 CaCl₂, 1.2 MgSO₄, 1.2 KH₂PO₄, 25 NaHCO₃, 10 N-[2-hydro-ethyl]-piperazine-N’-[2-ethanesulphonic acid] (HEPES) and 11.1 glucose. Hearts were digested with Ca²⁺-free KHB containing 223 U/ml collagenase (Worthington Biochemical Corp., Freehold, NJ, USA) and 0.1 mg/ml hyaluronidase (Sigma Chemical, St Louis, MO, USA). After perfusion, ventricles were removed, Minced and filtered through a nylon mesh (300 μm). Cells were initially washed with Ca²⁺-free KHB buffer to remove remnant enzyme and extracellular Ca²⁺ was added incrementally back to the cells, up to 1.25 mM. Cells were not used if they had any obvious saccocellular blebs or spontaneous contractions.

**Cell shortening/relengthening**

Mechanical properties of ventricular myocytes were assessed using a video-based edge-detection system (IonOptix, Milton, MA, USA) as described (Ren et al., 1998). In brief, cells were placed in a chamber mounted on the stage of an inverted microscope (Olympus X-70) and superfused (~2 ml/min at 37°C) with a buffer containing (in mM): 131 NaCl, 4 KCl, 1 CaCl₂, 1 MgCl₂, 10 glucose, 10 HEPES, at pH 7.4. The cells were field-stimulated to contract at a frequency of 0.5 Hz. Changes in cell length during shortening and relengthening were captured and converted to digital signals before being analyzed with pClamp software. The myocyte being studied was rapidly scanned with a camera at 120 Hz to ensure recording with good fidelity. Cell shortening and relengthening were assessed using the following indices: peak shortening (PS), time-to-PS (TPS) and time-to-90% relengthening (TR₉₀), maximal velocities of shortening and relengthening (± dL/dt). Steady state contraction of myocyte was achieved before application of ACA (Aldrich, Milwaukee, WI, USA).

**Intracellular fluorescence measurement**

Myocytes were loaded with fura-2/AM (0.5 μM) for 10 min at 30°C, and fluorescence measurements were recorded with a dual-excitation fluorescence photomultiplier system (Ionoptix) as previously described (Ren et al., 1998). Myocytes were imaged through an Olympus X-70 Fluor ×40 oil objective. Cells were exposed to light emitted by a 75 W lamp and passed through either a 360 or a 380 nm filter (bandwidths were ±15 nm), while being stimulated to contract at 0.5 Hz. Fluorescence emissions were detected between 480–520 nm by a photomultiplier tube after first illuminating the cells at 360 nm for 0.5 s then at 380 nm for the duration of the recording protocol (333 Hz sampling rate). The 360 excitation scan was repeated at the end of the protocol and qualitative changes in intracellular Ca²⁺ concentration ([Ca²⁺]) were inferred from the ratio of the fluorescence intensity at the two wavelengths.

**Data analysis**

For each experimental series, data are reported as mean ± SEM. Differences between group means were assessed using Student’s t-test, whereas within-group comparisons between mean values were calculated by repeated measures analysis of variance (ANOVA). When an overall significance was determined, Dunnett’s post-hoc analysis was incorporated. P < 0.05 was considered significant.

**Table 1. General features of age-matched control and chronic ethanol-consuming animals**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n = 9)</th>
<th>Chronic alcohol ingestion (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>513 ± 4</td>
<td>508 ± 12</td>
</tr>
<tr>
<td>Heart weight (g)</td>
<td>1.27 ± 0.02</td>
<td>1.37 ± 0.04*</td>
</tr>
<tr>
<td>Heart wt/body wt (mg/g)</td>
<td>2.47 ± 0.04</td>
<td>2.70 ± 0.04*</td>
</tr>
<tr>
<td>Liver weight (g)</td>
<td>13.2 ± 0.3</td>
<td>14.4 ± 0.7*</td>
</tr>
<tr>
<td>Liver wt/body wt (mg/g)</td>
<td>25.7 ± 0.6</td>
<td>28.2 ± 1.0*</td>
</tr>
<tr>
<td>Kidney weight (g)</td>
<td>2.83 ± 0.06</td>
<td>3.19 ± 0.12*</td>
</tr>
<tr>
<td>Kidney wt/body wt (mg/g)</td>
<td>5.52 ± 0.09</td>
<td>6.29 ± 0.19*</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td>135 ± 2</td>
<td>143 ± 2*</td>
</tr>
<tr>
<td>Serum ethanol (mg/dl)</td>
<td>0 ± 0</td>
<td>566 ± 72*</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. *P < 0.05 vs control. n, number of animals; wt, weight.
RESULTS

General features of control and chronic ethanol-ingesting animals

The effects of chronic ethanol ingestion on body, heart, liver and kidney weights, and serum ethanol concentration are shown in Table 1. As expected, chronic ethanol consumption was associated with cardiac hypertrophy (both absolute weight and size), hepatomegaly, ren hypertrophy, elevated serum ethanol level and blood pressure compared to those from control animals.

Baseline mechanical properties of papillary muscles and ventricular myocytes

The effects of chronic ethanol ingestion on baseline mechanical properties of left ventricular papillary muscles and ventricular myocytes are shown in Table 2. Papillary muscles from ethanol-consuming animals developed less isometric tension than those of the control group, either in absolute value or when PTD was normalized to muscle weight. The ethanol-induced depression in PTD was associated with significant reduction in contraction and relaxation velocity. The myocardium from ethanol-ingesting animals also exhibited an attenuated tension development in response to elevation of extracellular Ca\(^{2+}\) concentration, compared to that of the control group (Fig. 1), indicating an impaired Ca\(^{2+}\) sensitivity.

Interestingly, cells from both the control and ethanol groups exhibited comparable resting cell length and cell shortening, although reduced resting intracellular Ca\(^{2+}\) levels were seen in the ethanol-ingesting group. The duration and velocity of both shortening and re-lengthening was comparable in myocytes from either group. These data suggest that certain non-myocyte components might play a role in the reduced myocardial contraction at the multicellular level following chronic ethanol ingestion.

Acute effects of ACA on force development of papillary muscles

Representative tracings showing the typical negative inotropic response to ACA in papillary muscles from both control and ethanol-treated animals are shown in Fig. 2. The muscle from a chronic ethanol-consuming animal did not develop as much tension as that from a non-ethanol-consuming animal. A 10-min exposure to ACA (10 mM) elicited an appreciable depression in PTD in both groups. The magnitude of inhibition was less in the ethanol-consuming group (28.2%) compared to the control group (38.5%). The dose-dependent response curve (Fig. 2: lower panel) reveals that the magnitude of ACA-induced depression in PTD was attenuated under chronic ethanol ingestion. The ACA-induced inhibition was partially recoverable and was not associated with any alteration in duration and velocity of contraction and relaxation (data not shown).

Acute effects of ACA on cell shortening

To determine whether the altered response of ACA on myocardial contraction during chronic ethanol ingestion reflects dysfunction at the myocyte level, the impact of chronic ethanol exposure on ACA-induced cardiac myocyte shortening was examined. Representative tracings showing the effect of ACA on cell shortening with or without chronic ethanol ingestion are shown in Fig. 3 (top panel). Acute exposure to ACA (10 mM) caused an appreciable decrease in the extent of cell shortening in both control (30.0%) and ethanol-consuming (35.0%) groups. The dose-dependent response curve further indicates that ACA-induced reduction in the ability of ventricular myocytes to shorten is similar in both groups (Fig. 3: lower panel). The ACA-induced attenuation of cell shortening was not associated with alteration in duration or maximal velocities of shortening and re-lengthening (data not shown).

Table 2. Baseline mechanical properties of papillary muscles and isolated ventricular myocytes from control and chronic ethanol-consuming animals

<table>
<thead>
<tr>
<th>Papillary muscles</th>
<th>Control (n = 13)</th>
<th>Chronic alcohol ingestion (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTD (g)</td>
<td>1.82 ± 0.15</td>
<td>1.24 ± 0.09*</td>
</tr>
<tr>
<td>PTD/prep wt (g/g)</td>
<td>147.3 ± 16.5</td>
<td>104.7 ± 13.7*</td>
</tr>
<tr>
<td>+VT (g/s)</td>
<td>25.0 ± 1.8</td>
<td>18.8 ± 1.5*</td>
</tr>
<tr>
<td>–VT (g/s)</td>
<td>–15.1 ± 1.0</td>
<td>–11.2 ± 1.4*</td>
</tr>
<tr>
<td>Ventricular myocytes</td>
<td>(n = 19)</td>
<td>(n = 22)</td>
</tr>
<tr>
<td>Cell length (μm)</td>
<td>136.9 ± 6.6</td>
<td>135.1 ± 4.8</td>
</tr>
<tr>
<td>PS (% cell length)</td>
<td>6.5 ± 0.7</td>
<td>6.7 ± 0.6</td>
</tr>
<tr>
<td>TPS (ms)</td>
<td>55.0 ± 4.6</td>
<td>51.9 ± 2.6</td>
</tr>
<tr>
<td>TR(_{90}) (ms)</td>
<td>70.4 ± 4.0</td>
<td>63.3 ± 5.8</td>
</tr>
<tr>
<td>+dL/dt (μm/s)</td>
<td>172.5 ± 23.6</td>
<td>178.6 ± 19.4</td>
</tr>
<tr>
<td>–dL/dt (μm/s)</td>
<td>–166.8 ± 21.1</td>
<td>–187.6 ± 18.7</td>
</tr>
<tr>
<td>Ventricular myocytes</td>
<td>(n = 25)</td>
<td>(n = 24)</td>
</tr>
<tr>
<td>Baseline 360/380 ratio</td>
<td>0.97 ± 0.02</td>
<td>0.86 ± 0.01*</td>
</tr>
<tr>
<td>Peak 360/380 ratio</td>
<td>1.10 ± 0.02</td>
<td>1.03 ± 0.02*</td>
</tr>
<tr>
<td>t (ms)</td>
<td>249 ± 13</td>
<td>239 ± 9</td>
</tr>
</tbody>
</table>

Values are means ± SEM. *P < 0.05 vs respective control group.
PTD, peak tension developed; PTD/prep wt, peak tension developed normalized to muscle weight; + VT, maximum velocities of tension development and decline; PS, peak shortening; TPS, time-to-90% PS; TR\(_{90}\), time-to-90% re-lengthening; ±dL/dt, maximal velocities of shortening and re-lengthening; \(\tau\) = fluorescence decay rate.
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Fig. 2. Effect of acetaldehyde (ACA) on myocardial contraction in papillary muscles isolated from control (CONT) and ethanol (ETOH)-consuming animals.

Top panel: Solid and dotted lines indicate representative myocardial contraction before and 10 min after ACA (10 mM) exposure. Lower panel: The dose-dependent response of ACA (0.3–10 mM) on peak tension development (PTD) in myocardium from control and ethanol-consuming animals. PTD is expressed as a percentage change from the respective control value. Values are mean ± SEM (bars), *P < 0.05 vs baseline, #P < 0.05 vs control group, n = 13 for control group and 12 for ETOH group.

Fig. 3. Effect of acetaldehyde (ACA) on cell shortening in ventricular myocytes isolated from control and ethanol (ETOH)-consuming animals.

Top panel: Solid and dotted lines indicate representative myocyte shortening before and 10 min after ACA (10 mM) exposure. Lower panel: The dose-dependent response of ACA (0.3–10 mM) on peak shortening (PS) in myocytes isolated from control and ethanol-consuming animals. PS is expressed as a percentage change from the respective control value. Values are mean ± SEM (bars), *P < 0.05 vs baseline, n = 19 for control group and 22 for ETOH group.
Acute effects of ACA on intracellular Ca\(^{2+}\) transients

To determine whether the ACA-induced depression of myocyte shortening was due to changes in \([\text{Ca}^{2+}]_i\), we used fluorescence dye fura-2 to estimate \([\text{Ca}^{2+}]_i\), in the myocytes from both the control and ethanol-consuming groups. The time course of the fluorescence signal decay (fluorescence decay time, \(\tau\)) was calculated to assess intracellular Ca\(^{2+}\) clearing rate. Myocytes from both groups exhibited similar clearing rates, whereas myocytes from the ethanol-consuming animals displayed significantly lowered baseline fura-2 fluorescence intensity (FFI) (representing resting intracellular Ca\(^{2+}\) levels). Representative tracings depicting ACA-induced inhibition of intracellular Ca\(^{2+}\) transient in both control and chronic ethanol-consuming groups are shown in Fig. 4 (top panel). Consistent with its effect on cell shortening, ACA exerted a comparable dose-dependent decrease in intracellular Ca\(^{2+}\) transients recorded from ventricular myocytes in both groups (Fig. 4: lower panel). Neither resting FFI nor \(\tau\) was affected by ACA (data not shown).

DISCUSSION

The basis of this study stems from the fact that acute ethanol-induced cardiac contractile depression is substantiated following chronic ethanol ingestion (Brown et al., 1998). The major findings of the present work include a reduced ACA-induced myocardial contraction and comparable ACA-induced myocyte shortening as well as intracellular Ca\(^{2+}\) changes between the control and chronic ethanol-ingesting animals. Additionally, hearts from chronic ethanol-consuming rats showed depressed PTD, ±VT, Ca\(^{2+}\) responsiveness and resting \([\text{Ca}^{2+}]_i\) despite no obvious difference in basal myocyte contraction, compared to the control group.

Altered contractile function has been reported to be associated with chronic ethanol exposure (Thomas et al., 1994). However, the mechanisms responsible for the altered tension development and velocity of contraction and relaxation are not well known. Consistent with this study, several laboratories have shown depressed cardiac contraction following chronic ethanol exposure (Kino et al., 1981; Tepper et al., 1986; Capasso et al., 1991; Figueredo et al., 1998). However, conflicting results regarding the impact of chronic ethanol ingestion on velocity of contraction and relaxation have included increased (Tepper et al., 1986), no change or decreased parameters (Kino et al., 1981; Capasso et al., 1991, 1992). Such discrepancies may be related to multiple factors such as animal models, dosages and duration of exposure to ethanol.

It has been reported that impaired intracellular Ca\(^{2+}\) handling, such as decreased sarcoplasmic reticulum Ca\(^{2+}\) uptake and

![Fig. 4. Effect of acetaldehyde (ACA) on intracellular Ca\(^{2+}\) transients in ventricular myocytes isolated from control and ethanol (ETOH)-consuming animals.](image-url)

Top panel: Solid and dotted lines reflect representative fura-2 recording taken before and 10 min after ACA (10 mM) exposure. Lower panel: The dose-dependent response of ACA (0.3–10 mM) on intracellular Ca\(^{2+}\) transient fura-2 fluorescent intensity (FFI) in myocytes isolated from control and ethanol-consuming animals. FFI is expressed as percentage change of respective control value. Values are mean ± SEM (bars), * \(P < 0.05\) vs baseline, \(n = 25\) for control group and 24 for ETOH group.
binding, may be mainly responsible for altered cardiac contraction following chronic ethanol exposure (Sarma et al., 1976; Kino et al., 1981; Segel et al., 1981; Guarneri and Lakatta, 1990; Danziger et al., 1991; Thomas et al., 1994). In the present study, despite comparable myocyte mechanical parameters with chronic ethanol exposure, diastolic Ca\(^{2+}\) level was found to be reduced, but associated with a normal intracellular Ca\(^{2+}\) decay rate in the ethanol-consuming group. Acute ethanol exposure has been reported to reduce the peak amplitude of cytosolic Ca\(^{2+}\) increase without affecting basal (diastolic) Ca\(^{2+}\) concentration (Thomas et al., 1994). It is possible that inhibition by ethanol of certain Ca\(^{2+}\) regulatory proteins, such as Ca\(^{2+}\) pumps and channels, may play a role in the decreased cytosolic Ca\(^{2+}\) concentration. However, recent evidence has suggested that chronic ethanol-associated changes in myocardial contractility do not result from altered Ca\(^{2+}\) handling, but, rather, from changes at the level of the myofilament that do not involve myosin heavy chain isofrom shifts (Figueroedo et al., 1998).

ACA is the major metabolic product of ethanol metabolism and has been shown to bind to proteins to form adducts. The role of ACA in cardiac function is still somewhat controversial. Long-term ethanol consumption leads to accumulation of ACA and increased reaction with protein-bound Amadori products (Thieie et al., 1996). The formation of ACA–protein adducts effectively removes Amadori products, the precursors to advanced glycation endproduct which leads to the development of diabetes- and age-related cardiovascular disease. This ACA–protein adduct has been considered the possible role of ACA in cardiac function is still somewhat controversial, (Al-Abed et al., 1999). In contrast, although one report indicates that ACA has no influence on the function of the cardiovascular system after the ingestion of ethanol (Pawlak et al., 1993), accumulating evidence has also shown that ACA depresses myocardial contraction, attenuates intracellular Ca\(^{2+}\) mobilization and inhibits membrane voltage-dependent Ca\(^{2+}\) channels (Savage et al., 1995; Morales et al., 1997; Ren et al., 1997; Brown et al., 1999). Transgenic over-expression of alcohol dehydrogenase to elevate cardiac exposure to ACA displayed ultrastructural as well as functional damage in the myocardium consistent with chronic ethanol ingestion-induced cardiomyopathy (Li et al., 1999). The ACA-induced myocardial depression may play a role in ethanol-induced myocardial depression in both human and experimental animals.

In this study, we observed a disparate response to ACA at the papillary muscle, but not the myocyte, level. Although the mechanism responsible for such difference is unknown, the non-myocyte component is speculated to play a role. Chronic ethanol ingestion is associated with a reduction in the amount of contractile proteins and an adaptive increase in fibrillar protein synthesis, which may be responsible for the increased myocardial stiffness and fibrosis (Rajiyah et al., 1996). Despite prolonged exposure to heavy ethanol, cardiac contractile changes are relatively modest, and the majority of alcoholics demonstrate subclinical contractile abnormalities. Future work will be focused on whether blood ACA concentrations obtained from metabolism of ethanol at commonly acceptable doses are sufficient to impose overt cardiac effect, and if so, the mechanism of action to altered contractile function.

Acknowledgements — This research was supported in part by grants from NIH (MH47181, GM08167) to R.A.B. and a University of North Dakota New Faculty Scholar Award to J.R. The authors wish to acknowledge Melissa Natavio and Andrew Jeffery for technical assistance.

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