Alcohol consumption reduces ischemia-reperfusion injury by species-specific signaling in guinea pigs and rats

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 Departments of 1Medicine (Cardiology), 2Neurology, and 3Cellular and Molecular Pharmacology, and the 4Ernest Gallo Clinic and Research Center, San Francisco General Hospital, University of California, San Francisco, California 94110

Miyamae, Masami, S. Albert Camacho, Hui-Zhong Zhou, Ivan Diamond, and Vincent M. Figueredo. Alcohol consumption reduces ischemia-reperfusion injury by species-specific signaling in guinea pigs and rats. Am. J. Physiol. 275 (Heart Circ. Physiol. 44): H50–H56, 1998.—We recently discovered that regular alcohol consumption reduces ischemia-reperfusion injury to the same degree as ischemic preconditioning in guinea pig hearts. Ischemic preconditioning, like this cardioprotective effect of alcohol, is mediated by adenosine signaling in guinea pigs. In rats, ischemic preconditioning may be mediated predominantly by $\alpha_1$-adrenergic signaling. To be certain that this protective effect of alcohol is a general biological response, we searched for alcohol's cardioprotective effect in rat and identified a potential signaling mechanism. Hearts isolated from alcohol-fed guinea pigs and rats were subjected to ischemia-reperfusion. Hearts from alcohol-fed animals showed greater recovery of left ventricular developed pressure than controls (guinea pigs, 46 vs. 29%; rats, 50 vs. 31%) and decreased myocyte necrosis assessed by creatine kinase release (guinea pigs, 204 ± 42 vs. 440 ± 70 U·ml$^{-1}$·g dry wt$^{-1}$; rats 158 ± 13 vs. 328 ± 31 U·ml$^{-1}$·g dry wt$^{-1}$). Adenosine receptor blockade [8-($p$-sulfophenyl)theophylline] abolished alcohol's protection in guinea pig but not rat hearts. By contrast, $\alpha_1$-adrenergic blockade (prazosin) abolished alcohol's protection in rat but not guinea pig hearts. We conclude that regular alcohol consumption reduces ischemia-reperfusion injury and is mediated by species-specific signaling mechanisms. A major goal of cardiovascular research is to find a pharmacologically induced chronic state of preconditioning. Understanding the mechanisms of alcohol's cardioprotection against ischemia-reperfusion injury may aid in reaching this goal.

Alcohol; pre-conditioning; adenosine; $\alpha_1$-adrenergic receptor; 8-($p$-sulfophenyl)theophylline; prazosin

WE RECENTLY FOUND THAT regular alcohol consumption over 3–12 wk reduces ischemia-reperfusion injury to the same degree as ischemic preconditioning in guinea pig hearts (22). Furthermore, this cardioprotective effect of alcohol requires adenosine $\alpha_1$ receptor activation (22). Attenuation of ischemia-reperfusion injury with regular alcohol consumption could lead to improved myocardial recovery and survival after myocardial infarction (MI). This is consistent with recent clinical evidence that suggests that alcohol drinkers are more likely to survive after MI than abstainers (11, 27, 39). Ischemic preconditioning, like alcohol's cardioprotective effect, requires adenosine receptor activation in many species, including guinea pigs and humans (3, 8, 12, 19, 20, 38). In contrast, conflicting data suggest that $\alpha_2$-adrenergic, and not adenosinergic, signaling is most important in mediating protection in the rat heart (4, 5, 14, 15, 18). To be certain that this cardioprotective effect of alcohol is a general biological response and not unique to guinea pigs, in this study we searched for a similar response in the rat. We also compared the signaling mechanisms that mediate alcohol's protective effect against ischemia-reperfusion injury in guinea pig and rat.

METHODS

Animal diet. Male Hartley guinea pigs (275−300 g) and Sprague-Dawley rats (225−250 g) were divided into two groups: a chronic alcohol group (alcohol) and an age-matched control group (control). All animals were fed solid food (guinea pigs: Lab Diet, PMI Feeds; rats: Purina Rat Chow) and water ad libitum. Guinea pigs were started with 2.5% ethanol (vol/vol) in their water to acclimate the animals to drinking alcohol. This was increased to 5% during the second week, 10% during the third week, and 20% thereafter for 13 wk. Rats initially received 5% ethanol. This was increased to 10% during the second week, 20% during the third week, 30% during the fourth week, and 35% thereafter for ~16 wk. Differences in final dosages of ethanol between species were based on the fact that rats metabolize alcohol faster than guinea pigs (9, 41). Alcohol dehydrogenase activity in guinea pigs (2.94 µmol·g liver$^{-1}$·min$^{-1}$) is 58% of that in rats (5.05 µmol·g liver$^{-1}$·min$^{-1}$) (9, 41). Similarly, in vivo alcohol elimination rates are 2.59 µmol·g liver$^{-1}$·min$^{-1}$ in guinea pigs and 3.32 µmol·g liver$^{-1}$·min$^{-1}$ in rats (9, 41).

To rule out that cardioprotection in the setting of regular alcohol consumption was due to the stress of mainnutrition (potentially suggested by the differences in weights between the alcohol and control groups), we also studied a group of guinea pigs given only 2.5% (vol/vol) in their drinking water.

Isolated heart perfusion and measurement of function. Animals were heparinized (1,000 U ip) and anesthetized (60 mg/kg ip pentobarbital for guinea pigs and 1–2 mg/10 g ip ketamine for rats). Hearts were excised and arrested in cold isosmotic saline containing 20 mMolar KCl. Isolated hearts were cannulated via the aorta and perfused at an initial perfusion pressure of 70 mmHg on a nonrecirculating Langendorf perfusion apparatus, using a Krebs-Henseleit perfusate (mmolar/l): 123 NaCl, 6.0 KCl, 2.5 CaCl$2$, 20.0 NaHCO$3$, 1.2 MgSO$4$, 1.2 KH$2$PO$4$, 11.0 glucose, 0.5 EDTA, and 20 U/l insulin. The perfusate was continuously bubbled using 95% O$_2$–5% CO$_2$ and maintained at 37°C. After the sinoatrial node was removed, hearts from guinea pigs were paced at 240 beats/min using two platinum-tipped electrodes connected to a Grass Instruments SD-5 stimulus generator (Grass Instruments, Quincy, MA). Hearts from rats were paced at 300 beats/min.

Left ventricular (LV) developed pressure [LVDP = LV systolic pressure – LV end-diastolic pressure (LVEDP)] was measured using a 2-Fr, high-fidelity micromanometer (Millar Instruments, Houston, TX) passed into a compliant latex balloon. The balloon was connected to a Y adapter, one end of
Table 1. Alcohol’s protection against ischemia-reperfusion injury is abolished by adenosine receptor blockade in guinea pig hearts

<table>
<thead>
<tr>
<th>Hemodynamic Parameter</th>
<th>Preischemia</th>
<th>Reperfusion (48 min)</th>
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<tr>
<td></td>
<td>SPT</td>
<td>SPT</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Developed pressure, mmHg</td>
<td>113 ± 4</td>
<td>117 ± 5</td>
</tr>
<tr>
<td>Diastolic pressure, mmHg</td>
<td>10 ± 1</td>
<td>10 ± 1</td>
</tr>
<tr>
<td>Perfusion pressure, mmHg</td>
<td>70 ± 0</td>
<td>70 ± 0</td>
</tr>
<tr>
<td>Coronary flow, ml/min</td>
<td>35 ± 1</td>
<td>32 ± 1</td>
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</table>

Values are means ± SE. Hemodynamic data are from perfused guinea pig hearts subjected to 45 min of global ischemia and 48 min of reperfusion [regular alcohol consumption (alcohol), n = 8; age-matched controls (control), n = 8]. Experiments were repeated with the adenosine receptor antagonist 8-(p-sulfophenyl)theophylline (+SPT) added to perfusate (alcohol, n = 8; control, n = 8). *P < 0.05 vs. preischemia, †P < 0.05, alcohol vs. control, ‡P < 0.05, +SPT vs. without SPT (−SPT).

which was used to advance the micromanometer to the latex balloon. The other end of the Y adapter was used to fill the balloon with bubble-free water to set the LVEDP at 10–12 mmHg. The balloon was inserted through the left atrium into the LV. LV pressure was recorded on a Gould series 8000 chart recorder (Gould Electronics, Hayward, CA). Coronary flow was measured by an in-line flowmeter (Gilmont Instruments, Barrington, IL). Coronary pressure perfusion was measured by placing a T connection immediately above the aortic cannulation, which was attached via rigid polyethylene tubing to a Trantec pressure transducer (American Edwards Laboratories, Irvine, CA) placed at the level of the heart.

Creatine kinase release. Creatine kinase release during postischemic reperfusion was measured with a commercially available kit (47–10, Sigma Chemical, St. Louis, MO). Coronary effluent samples were collected every 3 min beginning with initiation of reperfusion for a total of 18 min. Only 7% of the total creatine kinase released was present in the final 3-min sample, suggesting that the majority of creatine kinase had been released by 18 min of reperfusion. Values were corrected for both dry heart weight and coronary flow rates and are expressed in units per milliliter per gram dry weight.

Experimental protocol. To eliminate a direct effect of alcohol on hearts, we withdrew ethanol from the drinking water 14–18 h before the animal was killed. Hearts were isolated 30–60 min after perfusing as described above (n = 8 alcohol, n = 8 control in both species). After a 20-min equilibration period, baseline measurements of LVDP and coronary flow were made. Hearts were then subjected to 45 min of no-flow ischemia, followed by 48 min of reperfusion. Forty-five minutes of ischemia were chosen to guarantee some degree of irreversible myocardial injury (necrosis or infarction). During ischemia, hearts were maintained at 37°C by encasement in a water-jacketed air chamber. Warmed perfusate kept in the lower part of the chamber saturated the air with humidity and prevented cooling of hearts by evaporation. On reperfusion, hemodynamic measurements were repeated every 6 min for a total of 48 min. Hearts were then cleaned of atria and great vessels and dried for 24 h at 80°C. Dried hearts were weighed.

Experiments were also carried out in the presence of the adenosine receptor antagonist 8-(p-sulfophenyl)theophylline (SPT; 10 µM; Sigma Chemical) added to the perfusate 10 min before ischemia (n = 8 alcohol, n = 8 control in both species). Baseline LVDP and coronary flow were measured before and after addition of SPT. This dose of SPT completely abolished the 12% increase of coronary flow associated with infusion of adenosine (10 nM) into the perfusate in a separate group of rat hearts (n = 7; 37.8 ± 0.8 vs. 42.3 ± 0.8 ml/min; P < 0.002).

To determine whether another signaling mechanism might be responsible for mediating this cardioprotective effect of alcohol, we subjected an additional group of rat hearts (n = 10 alcohol; n = 10 control) to ischemia-reperfusion after exposure to the α1-adrenergic receptor antagonist prazosin (0.3 µM; Sigma Chemical). After equilibration, hearts were perfused for 5 min with buffer containing prazosin, followed by 5 min of perfusion with prazosin-free buffer before ischemia. Longer infusions of prazosin resulted in LVDP depression, which might confound the results, as depressed LVDP might itself be cardioprotective against ischemia-reperfusion. Baseline LVDP and coronary flow were measured before and after prazosin treatment to confirm that hemodynamics were not changed. A similar prazosin infusion protocol has already been shown to inhibit ischemic preconditioning in rat hearts (15).

To determine whether α1-adrenergic signaling might also play a role in alcohol’s cardioprotection in guinea pig hearts, we subjected a group of hearts from guinea pigs consuming 2.5% ethanol in their drinking water (n = 8 alcohol; n = 8 control) to ischemia-reperfusion after they were exposed to prazosin (0.3 µM). This group of animals drinking a more moderate amount of alcohol also allowed us to rule out a malnutrition cause for this protective effect against ischemia-reperfusion injury. After equilibration, hearts were perfused for 5 min with buffer containing prazosin, followed by 5 min of perfusion with prazosin-free buffer before ischemia. Baseline LVDP and coronary flow were measured before and after prazosin treatment.

To exclude the possibility that protection was due to withdrawal, we carried out ischemia-reperfusion experiments on hearts from rats consuming alcohol until they were killed. Serum alcohol levels were drawn on the day of death of each animal (n = 7).

The investigation conforms with the Guide for the Care and Use of Laboratory Animals (NIH Publication No. 85–23, revised 1985).

Statistical analysis. All data are expressed as means ± SE. Comparisons between groups were made using repeated-measures ANOVA with multiple grouping factors. If differences were observed, a Tukey post hoc test was used to confirm the significance of differences between groups. A value of P < 0.05 was considered statistically significant.

RESULTS

Baseline LVDP, coronary flow, and coronary perfusion pressure were similar in hearts from controls and alcohol-treated guinea pigs and rats (Tables 1 and 2, respectively). Figure 1 shows LVDP over the course of the ischemia-reperfusion protocol for alcohol and con-
Table 2. Alcohol’s protection against ischemia-reperfusion injury is unaffected by adenosine receptor blockade in rat hearts

<table>
<thead>
<tr>
<th>Hemodynamic Parameter</th>
<th>Preischemia</th>
<th>Reperfusion (48 min)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Developed pressure, mmHg</td>
<td>119 ± 5</td>
<td>115 ± 6</td>
</tr>
<tr>
<td>Diastolic pressure, mmHg</td>
<td>10 ± 1</td>
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<tr>
<td>Perfusion pressure, mmHg</td>
<td>70 ± 0</td>
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<tr>
<td>Coronary flow, ml/min</td>
<td>24 ± 1</td>
<td>24 ± 1</td>
</tr>
</tbody>
</table>

Values are means ± SE. Hemodynamic data are from perfused rat hearts subjected to 45 min global ischemia and 48 min reperfusion with SPT (+SPT: alcohol, n = 8; age-matched controls, n = 8) or without SPT (−SPT: alcohol, n = 8; control, n = 8). *P < 0.05 vs. preischemia; †P < 0.05 vs. control; ‡P < 0.05, +SPT vs. −SPT.
0.08 × 10⁻⁴; rat 5.16 × 10⁻⁴). Nevertheless, to rule out that alcohol’s cardioprotective effect was due to the stress of malnutrition, we studied an additional group of hearts from guinea pigs given a more moderate amount of alcohol in their drinking water (2.5%). Body weights were similar between alcohol-fed (745 ± 16 g) and age-matched control animals (773 ± 19 g).

Signaling mechanisms of alcohol’s cardioprotective effect. Ischemia-reperfusion experiments were also carried out in the presence or absence of the adenosine receptor antagonist SPT. Baseline LVDP, coronary flow, and coronary perfusion pressure were unchanged by SPT in both guinea pig and rat hearts (Tables 1 and 2).

In guinea pigs, SPT abolished alcohol’s cardioprotective effect against ischemia-reperfusion injury. There was no longer improved LVDP recovery in hearts from alcohol-treated guinea pigs compared with controls (Table 1 and Fig. 1A). Furthermore, LVDP recovery was identical to that of control hearts not treated with SPT. LV diastolic pressure increased similarly in alcohol and control hearts treated with SPT, again identical to that of control hearts not treated with SPT (Table 1). Creatine kinase release was also similar in hearts from alcohol-treated (475 ± 60 U·ml⁻¹·g dry wt⁻¹) and control (446 ± 74 U·ml⁻¹·g dry wt⁻¹) guinea pigs treated with SPT (Fig. 2A). These data show that adenosine receptor blockade abolishes alcohol’s protective effect against ischemia-reperfusion injury in guinea pig hearts.

In rats, however, SPT had no effect on alcohol’s cardioprotection against ischemia-reperfusion injury. Contractile recovery was similar in hearts from alcohol-treated rats in the presence and absence of SPT (Fig. 1B and Table 2). Creatine kinase release was also similar in the presence (97 ± 12 U·ml⁻¹·g dry wt⁻¹) and absence (157 ± 12 U·ml⁻¹·g dry wt⁻¹) of SPT (Fig. 2B). To confirm that this dose of SPT blocked adenosine receptors in rat hearts, we gave seven additional hearts adenosine boluses in the presence and absence of SPT. Adenosine (10 mM) consistently produced a 12% increase in coronary flow that was completely blocked by SPT. These data suggest that adenosine receptor blockade by SPT was effective but did not prevent alcohol’s cardioprotective effect in rat hearts.

On the basis of these findings, we next searched for evidence that α₁-adrenergic receptors are involved in alcohol’s protective effect against ischemia-reperfusion injury in rat hearts, possibly like ischemic preconditioning. Ischemia-reperfusion experiments were repeated with rat hearts in the presence or absence of the α₁-adrenergic receptor antagonist prazosin. Baseline LVDP, coronary flow, and coronary perfusion pressure were unchanged by treatment with 0.3 µM prazosin (Table 3). However, prazosin abolished the alcohol’s cardioprotective effect. LVDP and LV diastolic pressure recovered similarly in hearts treated with prazosin from alcohol-treated and control rats (Table 3). Creatine kinase release was also similar (alcohol-treated rats 343 ± 32 U·ml⁻¹·g dry wt⁻¹; control rats 333 ± 47 U·ml⁻¹·g dry wt⁻¹) with prazosin treatment. These data indicate that in rats α₁-adrenergic receptor blockade prevents alcohol’s protective effect against ischemia-reperfusion injury.

A final group of guinea pig hearts was studied for two purposes. The first purpose was to determine whether α₁-adrenergic signaling plays a role in alcohol’s protective effect against ischemia-reperfusion injury in guinea pig hearts. The second purpose was to determine whether alcohol’s cardioprotective effect was due to the stress of malnutrition.

Table 3. Alcohol’s protection against ischemia-reperfusion injury is attenuated by α₁-adrenergic receptor blockade in rat hearts

<table>
<thead>
<tr>
<th></th>
<th>Preischemia</th>
<th>Alcohol</th>
<th>Reperfusion</th>
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<tr>
<td></td>
<td>Before prazosin</td>
<td>After prazosin</td>
<td>Before prazosin</td>
</tr>
<tr>
<td>Developed pressure, mmHg</td>
<td>127±5</td>
<td>126±4</td>
<td>129±6</td>
</tr>
<tr>
<td>Diastolic pressure, mmHg</td>
<td>10±1</td>
<td>10±1</td>
<td>10±1</td>
</tr>
<tr>
<td>Coronary flow, ml/min</td>
<td>27±1</td>
<td>26±1</td>
<td>26±1</td>
</tr>
<tr>
<td>Creatine kinase, U·ml⁻¹·g dry wt⁻¹</td>
<td>333±47</td>
<td>343±32</td>
<td></td>
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</table>

Values are means ± SE; n = 10 regular alcohol consumption rats and n = 10 age-matched controls. Hemodynamic and creatine kinase release data are from perfused rat hearts subjected to 45 min global ischemia and 48 min reperfusion in the presence of the α₁-adrenergic receptor antagonist prazosin (0.3 µM). *P < 0.05 vs. preischemia.
pig hearts. The second purpose was to rule out a contribution to alcohol’s protective effect from the potential stress of malnutrition associated with heavy alcohol consumption. Therefore, this group was only exposed to 2.5% ethanol in their drinking water. Just like at heavier levels of alcohol consumption, hearts from animals consuming 2.5% alcohol demonstrated improved contractile recovery and decreased creatine kinase release compared with control hearts (Table 4). These experiments were performed after treatment with 0.3 µM prazosin. α1-adrenergic blockade had no effect on alcohol’s protective effect (Table 4).

DISCUSSION

The major new finding of this study is that regular alcohol consumption protects against cardiac ischemia-reperfusion injury through species-specific signaling mechanisms. Alcohol’s protective effect against ischemia-reperfusion injury was demonstrated in both guinea pig and rat hearts, suggesting a general biological response. Adenosine receptor blockade abolished alcohol’s protection against ischemia-reperfusion injury in guinea pig hearts [previously shown by us at shorter durations of alcohol exposure (22)]. In rats, adenosine receptor antagonism had no effect, whereas α1-adrenergic receptor blockade attenuated alcohol’s cardioprotection. Conversely, α1-adrenergic receptor blockade had no effect on alcohol’s protective effect against ischemia-reperfusion injury in guinea pig hearts. Therefore, the protective effect of regular alcohol consumption against ischemia-reperfusion injury, like that of ischemic preconditioning, may be mediated through signaling mechanisms that are specific for different species.

Ischemic preconditioning (i.e., brief episodes of ischemia and reperfusion before prolonged ischemia) is an experimental intervention that reduces ischemia-reperfusion injury (3, 12, 18–20, 38). Ischemic preconditioning has been documented in many species, including human myocardium (3, 4, 8, 12, 18–20, 38). Despite the finding of a general biological response to ischemic preconditioning, species-specific signaling appears to mediate protection. In most species, including guinea pigs and humans, ischemic preconditioning requires activation of adenosine receptors at the time of ischemia to effect protection (3, 8, 12, 19, 20, 38). In rat, there are conflicting data regarding the role of adenosine signaling in ischemic preconditioning. Whereas some studies find no role for adenosine in ischemic preconditioning (5, 18), another recent study does (14). Others have found α1-adrenergic signaling to be important in protection against ischemia-reperfusion injury in rat hearts (4, 15), although there are also conflicting data (5, 24).

Our findings suggest that at the time of ischemia, alcohol’s protection against ischemia-reperfusion injury is mediated through species-specific mechanisms, analogous to ischemic preconditioning. However, in contrast to ischemic preconditioning, alcohol’s cardioprotective effect appears sustained with regular consumption. We previously showed in time-dose studies that 6 wk of moderate alcohol consumption were necessary to induce protection against ischemia-reperfusion injury [full protection was seen at 3 wk with higher alcohol levels (22)]. Furthermore, protection was still present at 12 wk of regular alcohol consumption (22). In contrast, ischemic preconditioning’s protection disappears after 3–4 days of continued preconditioning with 5-min occlusive episodes before prolonged ischemia and reperfusion (7). Thus, although activation of alcohol’s or ischemic preconditioning’s cardioprotection may be mediated by similar mechanisms at the time of ischemia, regular alcohol consumption may induce more lasting responses that produce sustained protection that are not induced with ischemic preconditioning. These may include changes in gene expression and/or sustained activation of preconditioning factors with regular alcohol consumption. For example, sustained activation of protein kinases [e.g., protein kinase C (PKC) or protein kinase A translocation to activation sites (23)] or increased production of antioxidants or heat shock proteins may potentiate the effects of protective signaling at the time of ischemia. Thus alcohol’s cardioprotective effect may be analogous more to preconditioning’s second window of protection (28, 30) than to protection seen within minutes of ischemic preconditioning. Inhibition of PKC has been shown to abolish preconditioning’s second window of protection (31). We recently found that inhibiting PKC activity abolishes alcohol’s cardioprotective effect as well (21). Studies are under way to determine how regular alcohol consumption induces long-term protection against ischemia-reperfusion injury.

Acute alcohol exposure has been shown by several investigators to transiently increase adenosine (10, 26) and norepinephrine (1, 16) levels. Episodic, as opposed to continuous, activation of adenosinergic and adrenergic...
gic signaling with intermittent drinking could induce hypersensitization (rather than desensitization with continuous stimulation) of these signaling pathways, leading to augmented protective responses to ischemia-reperfusion. Supporting this theory, hypersensitivity of cAMP production via adenosine A1 receptors with chronic alcohol exposure has been demonstrated in hepatocytes (25). It remains to be determined whether chronic, intermittent exposure to alcohol (i.e., drinking once or more a day) alters the number or activity of these receptors, leading to a cardioprotective state.

It should be noted that LVDP recovery during post-ischemic reperfusion was greater in prazosin-treated hearts from alcohol-fed rats than from control rats (Tables 2 and 3), suggesting some degree of protection against ischemia-reperfusion injury despite the presence of prazosin. However, LVDP recovery was still significantly reduced in the presence of prazosin compared with LVDP recovery in hearts from alcohol-fed rats in the absence of prazosin, suggesting a role for α1-adrenergic signaling in mediating alcohol's cardioprotective effect. Several possibilities may account for the greater LVDP recovery in the presence of prazosin compared with control. First, cardioprotection may be mediated by multiple signaling pathways in rat hearts (with a common pathway merging at, e.g., PKC activation). Thus α1-adrenergic blockade might only partially inhibit alcohol's cardioprotective effect against ischemia-reperfusion injury. Second, prazosin may have been underdosed, leading to a partial protective effect. Third, there may have been attenuation of simultaneous detrimental effects of increased catecholamines during ischemia with adrenergic blockade. Nevertheless, α1-adrenergic blockade did significantly reduce contractile recovery and increase creatine kinase release in hearts from rats chronically consuming alcohol compared with hearts not exposed to prazosin. This suggests that α1-adrenergic signaling does play an important role in alcohol's protective effect against ischemia-reperfusion injury in rat hearts.

Another issue worth noting is the difference between our finding of a lack of importance of adenosine signaling in mediating alcohol's protection against ischemia-reperfusion injury in rat hearts and the recent data of Headrick (14) demonstrating the requirement of adenosine receptors in the protective effect of ischemic preconditioning in rat hearts. Headrick used a much higher dose of the adenosine receptor antagonist SPT, suggesting we may have underdosed SPT in our experiments on rat hearts. Thus we cannot completely rule out a role for adenosine signaling in alcohol's cardioprotective effect. Interestingly, in the data presented by Headrick, the protective effect of ischemic preconditioning does not appear to be completely abolished by high-dose SPT, similar to the partial attenuation of alcohol's cardioprotection with α1-adrenergic blockade in our experiments on rat hearts. This suggests a role of both signal pathways in protecting rat hearts, where α1-adrenergic signaling predominates. This is in contrast to the situation in guinea pig hearts, in which adenosine signaling predominates in mediating alcohol's cardioprotective effect against ischemia-reperfusion injury.

A major goal of cardiovascular research is to find a pharmacologically induced chronic state of preconditioning. A due to achieving this goal may lie in this sustained protective effect of regular alcohol consumption against ischemia-reperfusion injury. Recent evidence suggests that regular alcohol consumption, in addition to decreasing the incidence of MI (13, 17, 33, 36), may also improve survival after MI (11, 27, 39). For example, an analysis of 14,407 subjects followed for more than 20 years in the National Institutes of Health Alcohol Epidemiologic Data System (11) showed that regular drinkers are more likely to survive MI than abstainers. However, the mechanisms underlying alcohol's benefit on survival after MI are not known.

Reducing ischemia-reperfusion injury, especially in this era of emergent reperfusion therapies, improves myocardial recovery and survival. We recently found that 3–12 wk of moderate to heavy alcohol consumption reduces ischemia-reperfusion injury to the same degree as the acute effect of ischemic preconditioning in guinea pig hearts (22). In the present study, we demonstrate that alcohol's cardioprotective effect is present whether animals consumed alcohol until they were killed or did not drink for 14–18 h before death. This suggests that regular alcohol consumption induces long-term protection against ischemia-reperfusion injury, which is sustained for at least 18 h after alcohol exposure. Our hope is that further studies to understand how alcohol's cardioprotective effect is produced may aid in the development of therapies to produce a chronic preconditioning state in patients at risk for MI.

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