Brain “ouabain” and angiotensin II contribute to cardiac dysfunction after myocardial infarction

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Leenen, Frans H. H., Baoxue Yuan, and Bing S. Huang. Brain “ouabain” and angiotensin II contribute to cardiac dysfunction after myocardial infarction. Am. J. Physiol. 277 (Heart Circ. Physiol. 46): H1786–H1792, 1999.—In chronic heart failure (CHF), sympathetic activity increases in parallel with the impairment of left ventricle (LV) function, and sympathetic hyperactivity has been postulated to contribute to the progression of heart failure. In the brain, compounds with ouabain-like activity (“ouabain,” for brevity) and the renin-angiotensin system contribute to sympathetic hyperactivity in rats with CHF after myocardial infarction (MI). In the present studies, we assessed whether, in rats, chronic blockade of brain “ouabain” or the brain renin-angiotensin system inhibits the post-MI LV dysfunction. In rats, an MI was induced by acute coronary artery ligation. At either 0.5 or 4 wk post-MI, chronic treatment with Fab fragments for blocking brain “ouabain” or with losartan for blocking brain AT$_1$ receptor was started and continued until 8 wk post-MI using osmotic minipumps connected to intracerebroventricular cannulas. At 8 wk post-MI, in conscious rats, LV pressures were measured at rest and in response to volume and pressure overload, followed by LV passive pressure-volume curves in vitro. At 8 wk post-MI, control MI rats exhibited clear increases in LV end-diastolic pressure (LVEDP) at rest and in response to pressure and volume overload. LV pressure-volume curves in vitro showed a marked shift to the right. Intravenous administration of the Fab fragments or losartan at rates used for central blockade did not affect these parameters. In contrast, chronic central blockade with either Fab fragments or losartan significantly lowered LVEDP at rest (only in 0.5- to 8-wk groups) and particularly in response to pressure or volume overload. LV dilation, as assessed from LV pressure-volume curves, was also significantly inhibited. These results indicate that chronic blockade of brain “ouabain” or brain AT$_1$ receptors substantially inhibits development of LV dilation and dysfunction in rats post-MI.

heart; heart failure; left ventricle dilation; ouabain; renin-angiotensin system

In both animals and humans, the progressive remodeling of the left ventricle (LV) after a myocardial infarction (MI) leads to increases in LV end-diastolic and end-systolic volume and pressure and decreases in ejection fraction and cardiac output and clinical chronic heart failure (CHF), with the extent and time course of the changes depending on the size of the MI (11, 18, 24). Stimuli for cardiac remodeling after a MI include increases in diastolic wall stress and (to a lesser extent) systolic wall stress (2). In addition, progressive increases in the activity of the circulatory and/or cardiac tissue renin-angiotensin system (RAS) and in sympathetic activity may further increase wall stress and may cause direct adverse effects on the heart. In CHF, parameters of sympathetic activity increase in parallel with the impairment of cardiac performance (5, 14, 20), and sympathetic hyperactivity has been postulated to contribute to the progression of heart failure (15). Studies on the possible role of sympathetic hyperactivity in disease progression in CHF have used tools such as β-blockers (7, 10), and the results are consistent with the neurohormonal hypothesis (15).

Recent studies in the putative central mechanisms mediating sympathetic hyperactivity in CHF suggest that, in the brain, both compounds with ouabain-like structure (in this paper called “ouabain”) and the RAS play a major role. In the brain, inhibition of the Na$^+$–K$^+$-ATPase enzyme by steroids closely related to ouabain causes sympathoexcitation (8). In rats with post-MI LV dysfunction, ouabain-like activity increases about twofold in the hypothalamus (12), and blockade of brain “ouabain” prevents/reverses sympathetic hyperactivity (12) and the impairment of baroreflex function (9). The brain RAS is also involved in the regulation of sympathetic activity and baroreflex function (19). Recent studies indicate that the brain RAS plays a pivotal role in the sympathetic hyperactivity associated with salt-sensitive hypertension (23) and heart failure. In rats with post-MI LV dysfunction, blockade of the brain RAS reverses sympathetic hyperactivity (4, 25) and impairment of arterial baroreflex function (4, 25).

In the present studies, we assessed whether chronic blockade of brain “ouabain” or the brain RAS can inhibit the progressive remodeling of the LV and the LV dysfunction in rats post-MI. Central infusion of antibody Fab fragments (Digibind) that bind in vivo and in vitro ouabain and related steroids, such as brain “ouabain,” with high affinity (1, 12) was employed for chronic blockade of brain “ouabain.” For blockade of the brain RAS, central infusions of the AT$_1$ receptor blocker losartan were employed. The results indicate that central blockade by the Fab fragments or losartan indeed can significantly blunt the LV dilation and decrease in cardiac function in rats post-MI.

METHODS

Male Wistar rats (Charles River Breeding Laboratories, Montreal, Canada), weighing 250–300 g, were housed on a 12:12-h light-dark cycle and were given regular rat chow and tap water. All procedures were carried out according to the guidelines of the University of Ottawa Animal Care Committee for the use and care of laboratory animals. After a 5-day acclimatization period, coronary artery ligation was performed as described by Pfeffer et al. (17). Briefly, after the animals were anesthetized with 1.0% halothane in oxygen.

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and the thorax was opened at the 4th or 5th left intercostal space, the left coronary artery was ligated at 2–3 mm from its origin with a 6-0 silk suture attached to anatraumatic needle (K801H; Ethicon). Buprenorphine (0.03 mg/ml, 0.1 ml/rat, twice daily × 3 days) was used to relieve pain. Sham control rats underwent the same surgical procedure without ligation.

Intracerebroventricular Cannulation and Placement of Minipumps

At 0.5 or 4 wk post-MI, under pentobarbital sodium anesthesia (65 mg/kg ip), an L-shaped, 23-gauge stainless steel cannula was placed in the left lateral ventricle (0.5 mm posterior and 1.4 mm lateral to the bregma). The shorter arm of the L-shaped cannula was inserted in the ventricle (3.8 mm from the dura), and the longer arm was connected with a polyethylene (PE; PE-50 fused to PE-60) catheter to an osmotic minipump (model 2002, 12 µl/day; Alza, Palo Alto, CA). The intracerebroventricular cannula was fixed on the skull with dental cement. The minipumps were filled with antibody Fab fragments (Digibind; Glaxo Wellcome, Toronto, Canada), γ-globulins as control (200 µg/day for both; Sigma Chemical, St. Louis, MO), or the AT1 receptor blocker losartan (1 mg·kg⁻¹·day⁻¹). The normalization of parameters of sympathetic hyperactivity in rats with post-MI CHF by infusion of the Fab fragments or losartan at these rates has been previously documented (9, 12, 25). The compounds were all dissolved in artificial cerebrospinal fluid. In two groups of rats after coroinal ligation, instead of placing an L-shaped cannula intracerebroventricularly, a PE-60 catheter was inserted in the left jugular vein and was connected to a minipump filled with the same amount of Fab fragments, or losartan as used for intracerebroventricular infusion. All of the pumps were implanted subcutaneously on the back of the rats. Penicillin G (30,000 IU, Derapen; Ayerst Laboratories, Montreal, Canada) was given intramuscularly after the surgery. Every 2 wk under halothane anesthesia the pumps were replaced with new pumps filled with the same compounds. At the end of the experiments, methylene blue was injected intracerebroventricularly to confirm the accuracy of the intracerebroventricular cannulation.

Protocol for Chronic Treatments

Treatment. 0.5–8 wk post-MI. At 0.5 wk after cardiac surgery, in sham rats, treatment with intracerebroventricular γ-globulins was started, and rats post-MI were randomly allocated to treatment with intracerebroventricular γ-globulins (MI-glob), intracerebroventricular Fab fragments, intracerebroventricular losartan, or intravenous losartan. All assessments were performed at the end of 8 wk of infusion (i.e., from 0.5–8 wk post-MI).

Treatment. 4–8 wk post-MI. At 4 wk after cardiac surgery, in sham rats, treatment with intracerebroventricular γ-globulins was started, and rats post-MI were randomly allocated to treatment with intracerebroventricular γ-globulins (MI-glob), intracerebroventricular Fab fragments, intravenous Fab fragments, or intracerebroventricular losartan. The assessments were done at the end of 4 wk of infusion (i.e., from 4–8 wk post-MI).

Survival rates for MI rats were in the 81–90% range in the 0.5–8 wk post-MI studies and in the 80–94% range in the 4–8 wk post-MI experiments. Both the time course of mortality and death rates did not differ significantly between treatments.

Assessment of Central Hemodynamics

Under halothane anesthesia, a PE-50 catheter was inserted in the right jugular vein, and another catheter was inserted in the LV through the right carotid artery. Four hours after the recovery from the anesthesia and surgery, the rat was placed in a cage in which it could move back and forth. The catheters were connected to a transducer connected to a Grass 7E polygraph as well as a Grass 7E44 tachograph for continuous recording of LV end-diastolic pressure (LVEDP), peak systolic pressure (LVSP), and heart rate.

Measurement of cardiac filling pressures. Pressure overload. After we allowed a 30-min rest to obtain resting hemodynamic values, phylephrine was infused at 4, 8, 12, 16, and 24 µg·kg⁻¹·min⁻¹ with each dose for 1 min.

Volume overload. Thirty minutes after the pressure overload, resting values were again obtained, and volume expansion was performed through intravenous infusions of three doses of 5% dextrose at 15-min intervals: 0.33, 1, and 3 ml/100 g body wt over 30 s.

LVEDP and LVSP were recorded continuously, and peak values were used for statistical analysis.

Determination of Passive Pressure-Volume Relationship

After the assessment of the effects of pressure and volume overload, the rat was killed with 2 M KCl, and the heart was excised. To avoid fluid accumulation and a variable compressive force on the interventricular septum, the right ventricle (RV) was incised. A double-lumen catheter was inserted in the LV with one end connected to the Harvard infusion pump and the other end to a pressure transducer. The LV was isolated by ligation with silk round the atrioventricular groove and was compressed manually to expel blood and create a negative pressure of ~5 mmHg, which was taken as zero volume. Saline (0.9%) was infused in the LV at a constant rate of 0.68 ml/min, whereas LV pressure was recorded continuously over a pressure range of ~5 to 30 mmHg. Two to three reproducible pressure-volume curves were obtained within 10 min of cardiac arrest (before the onset of rigor mortis). From the pressure-volume curve, LV volumes were determined at pressures of 0, 2.5, 5, 10, 15, 20, and 30 mmHg and at the pressure corresponding to the in vivo LVEDP (6).

Assessment of Infarct Size

After the measurement of the pressure-volume relationship, the RV and the LV were separated and weighed. Infarct size was measured as previously described (12). In brief, four to five incisions were made in the LV so that the LV tissue could be pressed flat. The circunferences of the entire flat LV and the visualized infarcted area, as judged from both epicardial and endocardial sides, were outlined on a clear plastic sheet. The difference in weight between the two marked areas on the sheet was used to determine the infarct size. To only include animals with moderate to severe LV dysfunction, data from rats with infarct size <30% were excluded from the analysis. Specifically, for this reason in the 0.5–8 wk experiment, two rats with intracerebroventricular Fab were excluded, and in the 4–8 wk experiment, three rats with intravenous Fab and three with intracerebroventricular Fab were excluded.

Statistical Analysis

All values are expressed as means ± SE. Using SAS software (SAS Institute, Cary, NC), one-way ANOVA was performed to determine the effects of treatments and MI on...
the various parameters. When F ratios were significant, a
Duncan's multirange test followed as a post hoc test for
locating the differences between means of the groups. Least-
squares linear regression was performed to compare the
changes in LVEDP in relation to LVPSP induced by phenyleph-
rine infusion and the pressure-volume relationship in vitro.
For the latter, exponential transformation of LV pressures
was performed to make the data suitable for linear regression
analysis (6). Statistical significance was defined as P < 0.05.

RESULTS

General Characteristics

Infarct size was ~40% of the LV and similar for all MI
groups. In MI rats, resting LVPSP was significantly
decreased, and resting LVEDP increased (Table 1). LVPSp was not affected by any of the treatments. The
increase in LVEDP was significantly attenuated by
treatment with intracerebroventricular Fab fragments
from 0.5 to 8 wk post-MI and somewhat less [not
significant (NS)] by intracerebroventricular losartan. Treatment from 4 to 8 wk post-MI had only minor (NS)
effects on resting LVEDP. Heart rate was similar in all
groups and was not affected by the treatments.

RV weight was significantly increased in the control
(MI-glob) group compared with the sham groups, and
these increases were attenuated by both intracerebro-
ventricular losartan and intracerebroventricular Fab
fragments.

Hemodynamic Responses to Pressure Overload

Phenylephrine increased LVPSP in a dose-related
manner (Fig. 1). Compared with the sham groups, in
MI-glob groups, this increase was significantly attenu-
ated. This attenuation was improved by both intracere-
broventricular losartan and intracerebroventricular Fab
fragments from 0.5 to 8 wk post-MI or from 4 to 8 wk
post-MI. Increases of LVEDP by pressure overload were
higher in the two control MI-glob groups versus sham
groups relative to the increase in LVPSP (P < 0.01).
The relationship of increases in LVEDP relative to
LVPSP was improved significantly by treatment of MI
rats with both intracerebroventricular losartan and
intracerebroventricular Fab fragments from 0.5 to 8 wk
post-MI or from 4 to 8 wk post-MI (Fig. 1). In contrast,
treatment of MI rats with intravenous losartan or
intravenous Fab fragments at the same rates did not
improve this relationship. The pressor effects of phenyl-
ephrine were associated with significant rate-related
decreases in heart rate, as expected (9), significantly
more in the sham versus MI groups (data not shown).

Hemodynamic Responses to Volume Overload

LVEDP was increased by volume overload in a dose-
related manner (Fig. 2). Relative to sham rats, a
further increase (P < 0.05) was observed in the two
control MI-glob groups. In both studies, this increase
was normalized by treatment of MI rats with intracere-
broventricular losartan or intracerebroventricular Fab
fragments. However, intravenous losartan or intrave-
nous Fab fragments did not affect this response (Fig. 2).

Volume overload caused minor increases in LVPSP in
sham rats but decreases in the two control MI-glob
(groups (Table 2). In the MI groups treated with intrace-
broventricular losartan or intracerebroventricular Fab
fragments, changes of LVPSP induced by volume
overload were not different compared with the sham
group. In contrast, treatment of MI rats with intrave-
nous losartan or intravenous Fab fragments at the
same low intracerebroventricular rates did not attenu-
ate MI-induced changes in LVPSP.

Table 1. Resting hemodynamics and cardiac anatomy in rats at 8 wk post-MI

<table>
<thead>
<tr>
<th></th>
<th>MI Treatment, 0.5–8 wk post-MI</th>
<th>MI Treatment, 4–8 wk post-MI</th>
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<tbody>
<tr>
<td></td>
<td>Sham icv Glob</td>
<td>icv Glob</td>
</tr>
<tr>
<td>n</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>LVPSp, mmHg</td>
<td>133 ± 2</td>
<td>117 ± 3*</td>
</tr>
<tr>
<td>LVEDP, mmHg</td>
<td>2 ± 0.3</td>
<td>16 ± 2*</td>
</tr>
<tr>
<td>LVEDVI, ml/kg body wt</td>
<td>0.62 ± 0.03</td>
<td>3.03 ± 0.27*</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>373 ± 8</td>
<td>365 ± 5</td>
</tr>
<tr>
<td>RV weight, mg/100 g body wt</td>
<td>42 ± 1</td>
<td>67 ± 6*</td>
</tr>
<tr>
<td>Infarct size, %</td>
<td>38 ± 2</td>
<td>38 ± 4</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of rats. MI, myocardial infarction; glob, γ-globulin; Los, losartan; LVPSp, left ventricle (LV) peak systolic pressure; LVEDVI, LV end-diastolic pressure; LVEDVI, LV end-diastolic volume index; RV, right ventricle. *P < 0.05 vs. sham. †P < 0.05 vs. MI-glob. ‡P < 0.05 vs. MI icv Los or icv Fab.
In Vitro Pressure-Volume Relationship

At each level of LV pressure, LV volumes measured in the potassium-arrested heart were significantly increased in all MI groups compared with the sham group (Fig. 3). In both studies, in the pressure range 5–30 mmHg, LV volumes were significantly decreased in the MI groups treated with intracerebroventricular losartan or intracerebroventricular Fab fragments compared with control MI-glob groups. Treatment of MI rats with intravenous losartan or intravenous Fab fragments at the same rates caused only minor, nonsignificant changes in LV volumes. Left ventricular end-diastolic volume index (LVEDVI) in vitro at the resting LV end-diastolic pressure (LVEDP) was significantly higher in all MI groups (Table 1). This increase in LVEDVI was significantly attenuated by treatment of MI rats with intracerebroventricular Fab fragments or intracerebroventricular losartan in both studies.

DISCUSSION

The present study provides a major new finding that chronic blockade of either brain “ouabain” or the brain renin-angiotensin system inhibits the development of LV dilation and dysfunction in rats post-MI.

Post-MI LV Remodeling and Dysfunction

LV remodeling defined as “progressive loss of ventricular function along with LV cavity dilatation” (11) post-MI involves a cycle of events extending from the MI to late heart failure (Fig. 4 in Ref. 11). Consistent with many previous studies, in the present experiments, infarct sizes in the 40% range resulted by 8 wk post-MI in a marked shift to the right of LV pressure-volume curves in vitro. RV weight increased, likely related to progressive LV failure resulting in increases in RV systolic and diastolic wall stress. As assessed in conscious, unrestrained animals, LV function decreased post-MI, as reflected by a significantly higher resting LVEDP, larger increases in LVEDP in response to volume overload, and larger increases in LVEDP relative to increases in LVPSP caused by phenylephrine. Initiation of blockade of either brain “ouabain” or brain AT1 receptors early post-MI significantly inhibited the development of LV dysfunction. Thus intracerebroventricular Fab fragments or losartan inhibited ~50% of the post-MI LV dilation, as assessed from the pressure-volume curves. Increases in RV weight tended to be inhibited by either

Fig. 1. Increases in left ventricle (LV) end-diastolic pressure (EDP) relative to increases in LV peak systolic pressure (LVPSP) during infusion of phenylephrine at increasing rates in sham-operated rats or myocardial infarction (MI) rats treated from 0.5 to 8 wk post-MI (A) or 4 to 8 wk post-MI (B) with either γ-globulins (glob), Fab fragments icv (icv Fab) or iv (iv Fab), or losartan icv (icv Los) or iv (iv Los). * Sham glob; † MI glob; ‡ MI icv Fab; †† MI icv Los; ‡‡ MI iv Fab. Values represent mean ± SE changes in LVEDP relative to change in LVPSP at a given rate of phenylephrine (see Table 1 for no. of rats). *P < 0.05 vs. sham; †P < 0.05, MI icv Fab or icv Los vs. MI glob.

Fig. 2. Increases in LVEDP at 3 rates of volume expansion in sham-operated rats or MI rats treated from 0.5 to 8 wk post-MI (A) or 4–8 wk post-MI (B) with either γ-globulins (glob), Fab fragments icv (icv Fab) or iv (iv Fab), or losartan icv (icv Los) or iv (iv Los). * Sham glob; † MI glob; ‡ MI icv Fab; †† MI icv Los; ‡‡ MI iv Los; ‡‡‡ MI iv Fab. Values represent means ± SE (see Table 1 for no. of rats). *P < 0.05 vs. sham; †P < 0.05, MI icv Fab or icv Los vs. MI glob.
intracerebroventricular treatment. Moreover, in vivo increases in resting LVEDP were blunted, and the enhanced responses of LVEDP to volume or pressure overload were normalized.

The first phase of LV remodeling, representing up to 50% of the shift of the pressure-volume curves in vitro, occurs within 4 wk after MI in rats (18). Initiation of blockade of brain “ouabain” or the brain RAS at this stage still caused positive effects on LV size and function. Post-MI LV dilation as assessed by the pressure-volume curves and post-MI increases in RV weight were significantly blunted. In addition, whereas effects on resting LVEDP were only minor, the enhanced responses of LVEDP to pressure and volume overload were still normalized by either intracerebroventricular blockade. This may indicate that central mechanisms particularly contribute to this second component in the LV dilation and dysfunction after MI. Further experiments evaluating effects of treatment during specific phases post-MI are needed to address this aspect.

Peripheral administration of losartan or Fab fragments at the same rate as used for central infusion did not improve any of the parameters of post-MI LV dysfunction. It is obvious from the findings with intracerebroventricular versus intravenous infusion that the pattern of changes caused by the central infusion of losartan or Fab fragments cannot be explained by leakage of centrally administered agents into the peripheral circulation. Whether higher central infusion rates of losartan or Fab fragments would more completely block the brain RAS and brain “ouabain” and induce additional changes in central hemodynamics and LV remodeling cannot be excluded. On the other hand, it is likely that higher intravenous infusion rates of losartan and perhaps the Fab fragments will cause improvements in central hemodynamics and LV remodeling. However, assessment of peripheral actions was not the goal of the present studies.

Sympathetic Activity and Post-MI LV Dysfunction

As reviewed by Capasso et al. (2), Packer (15), and Parmley (16), stimuli for post-MI LV remodeling include increases in diastolic and systolic wall stress and progressive increases in sympathetic activity, renin activity, and other neurohormones. Activation of the sympathetic nervous system, either cardiac specific or in addition to other organs such as the kidneys, can lead directly or indirectly to a negative outcome via many mechanisms (for reviews, see Refs. 3, 15, 16).

### Table 2. Changes in LVPSP in response to volume overload in rats at 8 wk post-MI

<table>
<thead>
<tr>
<th>Treatment, 0.5–8 wk post-MI</th>
<th>Sham icv Glob</th>
<th>icv Glob</th>
<th>icv Los</th>
<th>icv Fab</th>
<th>iv Los</th>
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<tbody>
<tr>
<td>ΔLVPSP, mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>0.33 ml/100 g body wt</td>
<td>2±1</td>
<td>1±1</td>
<td>0±1</td>
<td>2±1</td>
<td>0±1</td>
</tr>
<tr>
<td>1 ml/100 g body wt</td>
<td>2±2</td>
<td>-5±2*</td>
<td>2±1</td>
<td>2±1</td>
<td>11±3*</td>
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<tr>
<td>3 ml/100 g body wt</td>
<td>-1±2</td>
<td>-13±3*</td>
<td>-10±3</td>
<td>-6±2</td>
<td>-14±2*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment, 4–8 wk post-MI</th>
<th>Sham icv Glob</th>
<th>icv Glob</th>
<th>icv Los</th>
<th>icv Fab</th>
<th>iv Fab</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔLVPSP, mmHg</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>0.33 ml/100 g body wt</td>
<td>1±1</td>
<td>1±0.4</td>
<td>-1±2</td>
<td>2±1</td>
<td>0±1</td>
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<td>1 ml/100 g body wt</td>
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<td>2±2</td>
<td>0±3</td>
<td></td>
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<tr>
<td>3 ml/100 g body wt</td>
<td>2±5</td>
<td>-6±2*</td>
<td>1±4</td>
<td>3±2</td>
<td>-4±4*</td>
</tr>
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</table>

Values are means ± SE. See Table 1 for no. of rats. Δ, Change. *P < 0.05 vs. sham. †P < 0.05 vs. iv Los.

Fig. 3. LV pressure-volume curves in sham-operated rats or MI rats treated from 0.5 to 8 wk post-MI (A) or 4–8 wk post-MI (B) with either γ-globulins (glob), Fab fragments icv (icv Fab) or iv (iv Fab), or losartan icv (icv Los) or iv (iv Los). Pressure values on the y-axis are presented in a log scale. ○, Sham glob; ●, MI glob; ■, MI icv Fab; ▲, MI icv Los; ●, MI iv Los; ▼, MI iv Fab. Values represent means ± SE (for LV volume) at specific LV pressure (see Table 1 for no. of rats). *P < 0.05 vs. sham; †P < 0.05, MI icv Fab or icv Los vs. MI glob.
Sympathetic hyperactivity may contribute to the progression of adverse LV remodeling by either direct cardiac effects or through hemodynamic and renal effects increasing diastolic and systolic wall stress. Clinical trials using β-blockers (7, 10) provide evidence for an adverse role of sympathetic activity in CHF. However, such studies do not assess whether β-receptor-mediated sympathetic activity per se versus sympathetic hyperactivity plays a role. Also, these studies do not assess α-receptor-mediated events.

The present studies indicate that central mechanisms contribute to a substantial degree to the development of post-MI LV dilation and dysfunction. Blockade of brain “ouabain” or the brain RAS can both prevent and reverse sympathetic hyperactivity post-MI, as assessed by measurements of renal sympathetic nerve activity or plasma catecholamines (9, 12, 25). It is therefore tempting to conclude that brain “ouabain” and the brain RAS contribute to post-MI LV remodeling and LV dysfunction by being part of the central pathways leading to sympathetic hyperactivity, specifically renal and generalized sympathetic drive. Considering the extensive evidence for regional control of sympathetic activity in CHF (e.g., Ref. 20), one cannot assume that central control of cardiac sympathetic activity follows a similar pattern. Further studies are needed to assess the effects of chronic blockade of brain “ouabain” or the brain RAS on cardiac sympathetic activity relative to the development of post-MI LV dysfunction. From a mechanisms point of view, one has to consider that the central blockade of brain “ouabain” or AT1 receptors may affect directly or indirectly other mechanisms centrally, such as nitric oxide (13), or peripherally, such as vasopressin release from the pituitary or renin release from the kidneys, which may affect disease progression. The present study therefore demonstrates that brain mechanisms play an important role in the disease progression after MI but does not establish the actual pathways or mechanisms involved.

Limitations of the Present Study

To assess their effects, Fab fragments or losartan were chronically infused in the left lateral cerebral ventricle. The results with the Fab fragments point to a major role for compound(s) with ouabain-like structure in the central control of LV remodeling and LV dysfunction post-MI, and the results with losartan point to a major role for AT1 receptor stimulation. These findings do not address the actual stimuli or the central pathways involved. The use of losartan does not provide insights regarding the components of the brain RAS activated post-MI. Similarly, considering their specificity (1, 21, 22), the use of the Fab fragments establishes that a compound(s) with ouabain-like structure plays a role but does not provide insights into its structure or regulation.

In conclusion, the present results demonstrate that, in rats post-MI, chronic blockade of either brain “ouabain” or brain AT1 receptors has a substantial positive impact on the development of LV dysfunction after MI. Based on these findings, one may speculate that post-MI treatment with blockers of the RAS causing blockade of both the peripheral and brain RAS will be more beneficial for outcome than treatment with blockers of RAS “only” blocking the peripheral RAS.

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