Miso (Japanese Soybean Paste) Soup Attenuates Salt-Induced Sympathoexcitation and Left Ventricular Dysfunction in Mice with Chronic Pressure Overload

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Miso (Japanese Soybean Paste) Soup Attenuates Salt-Induced Sympathoexcitation and Left Ventricular Dysfunction in Mice with Chronic Pressure Overload

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Abstract

The hypothalamic mineralocorticoid receptor (MR)-angiotensin II type 1 receptor (AT1R) pathway is activated in mice with chronic pressure overload (CPO). When this activation is combined with high salt intake, it leads to sympathoexcitation, hypertension, and left ventricular (LV) dysfunction. Salt intake is thus an important factor that contributes to heart failure. Miso, a traditional Japanese food made from fermented soybeans, rice, wheat, or oats, can attenuate salt-induced hypertension in rats. However, its effects on CPO mice with salt-induced sympathoexcitation and LV dysfunction are unclear. Here, we investigated whether miso has protective effects in these mice. We also evaluated mechanisms associated with the hypothalamic MR-AT1R pathway. Aortic banding was used to produce CPO, and a sham operation was performed for controls. At 2 weeks after surgery, the mice were given water containing high NaCl levels (0.5%, 1.0%, and 1.5%) for 4 weeks. The high salt loading in CPO mice increased excretion of urinary norepinephrine (uNE), a marker of sympathetic activity, in an NaCl concentration-dependent manner; however, this was not observed in Sham mice. Subsequently, CPO mice were administered 1.0% NaCl water (CPO-H) or miso soup (1.0% NaCl equivalent, CPO-miso). The expression of hypothalamic MR, serum glucocorticoid-induced kinase-1 (SGK-1), and AT1R was higher in the CPO-H mice than in the Sham mice; however, the expression of these proteins was attenuated in the CPO-miso group. Although the CPO-miso mice had higher sodium intake, salt-induced sympathoexcitation was lower in these mice than in the CPO-H group. Our findings indicate that regular intake of miso soup attenuates salt-induced sympathoexcitation in CPO mice via inhibition of the hypothalamic MR-AT1R pathway.

Key words: Miso · Mineralocorticoid receptors · Pressure overload · Salt sensitivity · Sympathetic nervous system

Introduction

We recently reported that the hypothalamic mineralocorticoid receptor (MR) and angiotensin II type 1 receptor (AT1R) pathways are activated in mice with chronic pressure overload (CPO). This sensitizes the animals to physiologic levels of sodium in the brain, which ultimately contributes to salt-induced sympathoexcitation and left ventricular (LV) dysfunction. CPO leads to LV hypertrophy, and therefore this model recapitulates the pathophysiology observed in hypertensive heart disease (HHD). HHD is a major risk factor for heart failure during which LV systolic function is preserved (the latter condition is also known as "heart failure with preserved ejection fraction" or "HFpEF"). We previously confirmed that, in CPO mice, the activation of the...
hypothalamic MR pathway and an increase in salt sensitivity occurs before LV systolic function is reduced\(^1\). However, high salt loading in these mice leads to increased salt–induced sympathoexcitation and compromises LV function. Thus, salt–induced sympathoexcitation is an important contributing factor in patients with HFpEF.

Miso, a traditional Japanese food, is made from fermented soybeans, rice, wheat, or oats. Miso contains several types of vitamins, minerals, plant proteins, isoflavones, dietary fiber, and fat. Because various salts are required during the fermentation process, one serving of miso soup contains 1–2 g of NaCl. Despite its high salt content, the intake of misosoup is associated with anti-hypertensive effects in salt-sensitive hypertensive rats\(^6\)\(^7\). This is consistent with the observation that soy–based diets can reduce blood pressure due to inhibition of the angiotensin system. Specifically, soy protein inhibits angiotensin converting enzyme (ACE) activity\(^8\)\(^9\). Therefore, we hypothesized that miso intake may also reduce the prevalence of heart failure associated with salt–induced sympathoexcitation. The experimental model to test this hypothesis and our findings are described below.

**Methods**

**Animals**

The study was reviewed and approved by the Committee on Ethics of Animal Experiments, Kyushu University Graduate School of Medical Sciences, and was conducted according to the Guidelines for Animal Experiments of Kyushu University and the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH publication no. 85–23, revised 1996). We used 10–week–old male mice for all experiments (Institute of Cancer Research [ICR] general purpose mice ; SLC, Hamamatsu, Japan).

**CPO mouse model**

To induce CPO, mice were placed under anesthesia with sodium pentobarbital (25–40 mg/kg i.p.) and isoflurane inhalation (1.5–2.0%), and the suprarenal abdominal aorta was banded. Subsequently, the abdominal aorta was constricted at the suprarenal level with 5–0 silk sutures guided by a blunted 27–gauge needle, which was withdrawn as quickly as possible. Sham–operated (Sham) mice served as controls\(^1\)\(^–\)\(^3\).

**Evaluation of salt sensitivity in CPO mice**

Two weeks post–surgery, both Sham and CPO mice were given drinking water containing 0.5%, 1.0%, or 1.5% NaCl for 4 weeks. We then evaluated the relationship between uNE excretion (a marker of sympathetic activity) and uNa excretion (a marker of sodium intake)\(^10\).

**Effects of miso soup in CPO mice**

A separate cohort of CPO mice was divided into 2 groups at 2 weeks after surgery ; the mice in group 1 (CPO–H mice) were given drinking water containing 1.0% NaCl for 4 weeks, and those in group 2 (CPO–miso mice) were given miso soup (containing salt equivalent to the 1% NaCl water). The red miso powder was kindly provided by Central Miso Institute, Tokyo, Japan. After 4 weeks of high–salt water or miso loading, we compared the 2 groups with respect to body and organ weight, echocardiograph results, and expression of selected proteins (see below). Blood pressure and heart rate were also measured 2 and 4 weeks post–initiation of high–salt water and miso loading.

**Evaluation of sympathetic activity**

Sympathetic activity was evaluated by measuring 24–h uNE by using high–performance liquid chromatography (SRL Inc., Tokyo, Japan)\(^11\)\(^–\)\(^3\).

**Measurement of organ weight**

After completion of the experiments, the mice were euthanized with an overdose of sodium pentobarbital, and the heart and lungs were
removed and weighed.

**Evaluation of LV function**

LV systolic function was evaluated by serial M-mode echocardiography using the SSD5000 echocardiography system (Aloka, Tokyo, Japan) with a dynamically focused 10-MHz linear array transducer; the mice were placed under light sodium pentobarbital anesthesia with spontaneous respiration. M-mode tracings were recorded from the short-axis view at the level of the papillary muscle 1

LV end-diastolic diameter (LVDD), LV end-systolic diameter (LVSD), and LV wall thickness (LVWT) were measured. LVWT was calculated as the mean thickness of the inter-ventricular septum and the posterior LV wall. Percent fractional shortening (%FS) was calculated as follows:

\[
%FS = \frac{LVDD - LVSD}{LVDD} \times 100
\]

**Western blot analysis**

The animals were sacrificed using an overdose of sodium pentobarbital, and the hypothalamus tissue was excised. The tissues were homogenized in a lysing buffer containing 40 mmol/L 4-[2-hydroxyethyl]-1-piperazineethanesulfonic acid (HEPES), 1% Triton X-100, 10% glycerol, 1 mmol/L sodium orthovanadate, and 1 mmol/L phenylmethylsulfonyl fluoride. Protein concentration was determined using a bicinechonic acid protein assay kit (Pierce Chemical Co., Rockford, IL). A 15-µg aliquot of protein from each sample was separated on a polyacrylamide gel containing 10% sodium dodecyl sulfate. The proteins were subsequently transferred onto polyvinylidene difluoride membranes (Immobilon-P membranes; Millipore, Billerica, MA). The membranes were then incubated in an immunoreaction enhancer solution (Can Get Signal; Toyobo, Osaka, Japan) with rabbit polyclonal immunoglobulin G (IgG) antibody against mineralocorticoid receptor (MR, 1 : 1000; Santa Cruz Biotechnology, Santa Cruz, CA), rabbit polyclonal antibody against serum glucocorticoid-induced protein kinase-1 (SGK-1, 1 : 1000; Abcam, Cambridge, UK), or rabbit polyclonal IgG antibody against angiotensin II type 1 receptor (AT1R, 1 : 1000, Santa Cruz Biotechnology). The membranes were then incubated with horseradish peroxidase-conjugated horse anti-rabbit or anti-goat IgG antibody (1 : 10,000; Santa Cruz Biotechnology). Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as the internal control. Immunoreactivity was detected by enhanced chemiluminescence autoradiography (ECL western blotting detection kit; Amersham Pharmacia Biotech, Uppsala, Sweden), and the film was analyzed using the public domain software NIH Image (developed at the US National Institutes of Health and available on the Internet at http://rsb.info.nih.gov/nih-image/).

**Measurement of blood pressure and heart rate**

Under isoflurane anesthesia (1.5–2.0%), a catheter (stretched PE50 tubing) was inserted into the right carotid artery. Tubing was tunneled subcutaneously from the neck incision to the back of the neck. After recovery from anesthesia (3 h after the surgical procedure), the waking blood pressure and heart rate were measured.

**Statistical analysis**

All values are expressed as mean ± SE. An unpaired t-test was used to compare the value of uNE /uNa excretion ratio and organ weights between the 2 groups. One-way analysis of variance, followed by the Bonferroni multiple-comparison post-test, was used to compare LVDD, LVSD, LVWT, %FS, protein expression level, blood pressure, and heart rate among the experimental groups. Two-way analysis of variance was used to test whether there were any significant effects of CPO or drinking water Na concentration, or a combination of both with respect to uNE excretion. The Bonferroni multiple-comparison post-test was used to determine whether there were significant differences between Sham and CPO mice at each Na concentra-
Differences were considered significant at $P < 0.05$.

**Results**

*Acquisition of salt sensitivity due to increased sympathetic activity in CPO mice*

In Sham mice, uNE excretion did not change for any of the NaCl concentrations administered. In CPO mice, however, uNE excretion increased in an NaCl concentration-dependent manner (Fig. 1A). uNE excretion in CPO mice was higher than that in Sham mice for NaCl concentrations of 1.0% and 1.5% (Fig. 1A). We also evaluated the uNE/uNa excretion ratio and found that it was significantly higher in CPO mice than in Sham mice. This indicates that CPO mice acquired salt sensitivity likely due to increased sympathetic activity (Fig. 1B).

**Physiological characteristics of Sham and CPO-H mice**

Both the heart weight and relative heart weight (heart weight/body weight) increased in the CPO-H mice as compared to the Sham mice (heart weight, $0.22 \pm 0.01$ g versus $0.25 \pm 0.02$ g, $P = 0.001$, $n = 8$ for each; relative heart weight, $4.6 \pm 0.1$ mg/g versus $5.6 \pm 0.1$ mg/g, respectively; $P < 0.0001$, $n = 8$ for each). The relative lung weight (lung weight/body weight) was also higher in the CPO-H mice (relative lung weight, $5.6 \pm 0.3$ mg/g vs. $6.2 \pm 0.3$ mg/g, respectively; $P = 0.035$, $n = 8$ for each).

Echocardiography (Fig. 2) revealed that LV dimension and LVWT were higher and that the LV%FS was lower in the CPO-H mice than in the Sham mice.

The expression of hypothalamic MR, SGK-1 and AT1R proteins was significantly higher in the CPO-H mice than in the Sham mice (Fig. 3).

The mean blood pressure (MBP) was higher in the CPO mice as compared to the Sham mice at 2 weeks after aortic banding. Two weeks following high salt loading, the MBP in CPO mice was also greater than that of Sham mice; however, 4 weeks after high salt loading, levels were equivalent in the 2 groups. There was no difference in heart rate between the CPO and Sham mice 2 weeks after aortic banding. However, following high salt loading, heart rate was consistently elevated in the CPO-H mice compared to Sham mice (Table 1).

![Fig. 1](image-url)  
**Fig. 1** A, Sympathetic activity evaluated on the basis of uNE excretion in each group. *$P < 0.05$ Sham vs. CPO, $n = 8$ in each group. Open bar graphs indicate Sham, Square–block bar graphs indicate CPO. B, The ratio of uNE/uNa excretion, indicating uNE excretion per uNa excretion of 1 mEq, as a marker of sympathetic activation in response to salt intake (**$P < 0.0001$ Sham vs. CPO, $n = 24$ for each). Sham, sham operated control mice; CPO, chronic pressure overload mice; uNE, 24-h urinary norepinephrine excretion; ANOVA, analysis of variance.
**Effects of miso intake in CPO mice**

Both the heart weight and relative heart weight (heart weight/body weight) in the CPO-miso mice were lower than those in the CPO–H mice (heart weight, $0.22 \pm 0.02$ g versus $0.25 \pm 0.01$ g, $P < 0.0001$, $n = 8$ for each; relative heart weight, $5.2 \pm 0.2$ mg/g versus $5.6 \pm 0.1$ mg/g, respectively; $P = 0.0075$, $n = 8$ for each). The relative lung weight (lung weight/body weight) was also higher in the CPO–H mice than in the CPO-miso mice (relative lung weight, $5.5 \pm 0.3$ mg/g versus $6.2 \pm 0.2$ mg/g, respectively; $P = 0.0028$, $n = 8$ for each).

The LV function (LV dimensions and LV%FS) was also better in CPO-miso mice than in CPO–H mice (Fig. 2).

The hypothalamic expression of SGK-1 and AT1R was lower in CPO-miso mice than in CPO–H mice (Fig. 3).

![Fig. 2](image1.png)

**Fig. 2** Left ventricular function evaluated by echocardiography in each group. LVDD, left ventricular end-diastolic diameter; LVSD, left ventricular systolic diameter; LVWT, LV wall thickness; LV%FS, LV percent fractional shortening. **P < 0.01 Sham vs. CPO–H, #P < 0.05, ##P < 0.01 CPO–H vs. CPO-miso, n = 8 in each group. Sham, sham operated control mice; CPO–H, chronic pressure overload mice with 1.0% NaCl water; CPO-miso, CPO mice with miso soup intake.

![Fig. 3](image2.png)

**Fig. 3** Representative western blots showing hypothalamic MR, SGK-1, and AT1R expression in mice from each group. The graph shows the means from 4–6 separate experiments. Data are expressed as the relative ratio to GAPDH expression. **P < 0.05 Sham vs. CPO–H, #P < 0.01 CPO–H vs. CPO-miso. Sham, sham operated control mice; CPO–H, chronic pressure overload mice with 1.0% NaCl water; CPO-miso, CPO mice with miso soup intake; MR, mineralocorticoid receptor; SGK-1, serum glucocorticoid-induced protein kinase-1; AT1R, angiotensin II type 1 receptors; GAPDH, Glyceraldehyde 3-phosphate dehydrogenase.
At two weeks post high salt loading, miso intake reduced the MBP of the CPO mice. However, by 4 weeks, the MBP in the CPO-miso mice was lower than that in the CPO-H mice (Table 1).

In the CPO-miso mice, uNE excretion was lower, while uNa excretion was higher in comparison with CPO-H mice (Fig. 4A, B). Accordingly, the uNE/uNa excretion ratio was significantly lower in the CPO-miso group when compared with the CPO-H animals (Fig. 4C).

**Discussion**

In the present study, we demonstrated that regular miso soup intake suppresses activation of the brain hypothalamic MR pathway and inhibits AT1R expression. We also found that miso soup can prevent salt-induced sympathoexcitation in CPO mice. Sodium intake, presumed by urinary sodium excretion, was greater in the CPO-miso mice than in their CPO-H counterparts; however, sympathetic activity was lower and LV%FS was higher in the CPO-miso animals. These results indicate that regular miso soup intake can prevent the harmful effects of excessive sodium intake, particularly with regard to sympathetic activity and LV function.

In the first part of the study, we confirmed that salt sensitivity was associated with increased sympathetic activity in CPO mice. We initiated high salt loading 2 weeks after aortic banding, since we previously determined that this was the time required for activation of the MR pathway to occur. Here, we performed high salt loading by administering water containing high amounts of salt. This procedure elicited NaCl concentration-dependent increases in uNE excretion. In addition, we evaluated the uNE/uNa excretion.

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**Table 1** Blood pressure and Heart rate in each group

<table>
<thead>
<tr>
<th></th>
<th>MBP (mmHg)</th>
<th>HR (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sham</td>
<td>99.7 ± 4.9</td>
<td>494 ± 8</td>
</tr>
<tr>
<td>CPO</td>
<td>117.5 ± 2.2</td>
<td>498 ± 11</td>
</tr>
<tr>
<td>CPO-H</td>
<td>100.5 ± 3.6</td>
<td>493 ± 9</td>
</tr>
<tr>
<td>CPO-miso</td>
<td>112.8 ± 2.8</td>
<td>491 ± 9</td>
</tr>
</tbody>
</table>

MBP, mean blood pressure; HR, heart rate; Sham, sham operated control mice; CPO, chronic pressure overload mice; CPO-H, chronic pressure overload mice with 1% NaCl water for 2 weeks; CPO-miso, chronic pressure overload mice with miso soup for 4 weeks. n = 5 for each.

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**Fig. 4** A. Sympathetic activity evaluated on the basis of uNE excretion for each group. ###P = 0.0001, n = 8 for each. B, Na intake presumed by uNa excretion for each group. ##P = 0.0001, n = 8 for each. C, The ratio of uNE / uNa excretion, indicating uNE excretion per uNa excretion of 1 mEq, as a marker of sympathetic activation in response to salt intake. ###P < 0.0001, n = 8 for each. CPO-H, chronic pressure overload mice with 1% NaCl water; CPO-miso, CPO mice with miso soup intake.
ratio as a marker of sympathetic activation in response to salt intake\(^{10}\). This ratio was higher in CPO mice than in Sham mice, indicating that the acquisition of salt sensitivity was associated with increased sympathetic activity in the CPO mice.

We found that miso soup intake attenuated the high-salt-induced sympathoexcitation. uNE excretion in the CPO-miso group was significantly lower than that in the CPO-H animals. In the present study, we equalized the NaCl concentration to 1% for the CPO-H and the CPO-miso groups to ensure that changes in taste did not alter uptake of food and water. Because the CPO mice drank the miso soup willingly, the precise normalization of actual sodium intake was rather difficult. Therefore, we evaluated uNa excretion as a proxy marker of sodium intake. Surprisingly, the amount of sodium intake was greater in the CPO-miso than in the CPO-H animals. Yet, despite their increased sodium intake, the CPO-miso mice had lower sympathetic activity. A previous report indicated that drinking miso soup reduced uNa excretion in Dahl salt-sensitive hypertensive rats, suggesting that it attenuated absorption of sodium from the intestine\(^7\). The mechanism underlying the decreased intestinal absorption of sodium remains unclear. However, the lower levels of sodium loading may be attributed to the reduction of salt-induced hypertension in Dahl salt-sensitive rats. In contrast, uNa excretion was greater in CPO-miso mice than in the CPO-H animals, suggesting that intestinal absorption of sodium was not reduced in the former group. Here, we used ICR mice, which have a different genetic background when compared with Dahl salt-sensitive rats. Thus, some of the discrepancies between the two studies may be attributable to genetic differences.

We have previously reported that the brain hypothalamic MR–AT1R pathway is involved in salt-induced sympathoexcitation in CPO mice\(^{11-13}\). Therefore, we evaluated the effects of miso soup intake on the expression of hypothalamic MR, SGK–1 (a marker of MR activity), and AT1R. Consistent with our previous results, the expression of hypothalamic MR, SGK–1, and AT1R increased in the CPO–H animals. Indeed, the expression of hypothalamic SGK–1 and AT1R was significantly lower in the CPO-miso mice than in their CPO-H counterparts. This finding indicates that habitual miso soup intake inhibited salt-induced sympathoexcitation due to attenuations of the hypothalamic MR–AT1R pathway activation.

Regular miso soup intake also improved LV systolic function. The LV dimensions were smaller and LV%FS was higher in the CPO-miso mice than in the CPO-H mice. Blood pressure is an important determinant of LV systolic function and is affected by miso intake. Therefore, the improvement in LV systolic function following miso intake may have been an indirect effect of reduction in blood pressure. In addition, uNa excretion increased in the CPO-miso mice due to decreased sympathetic activity. Therefore, volume reduction in the CPO-miso mice might also have contributed to the improvement in LV systolic function.

The mechanisms involved in the attenuated activation of the hypothalamic MR–AT1R pathway following miso intake remain unclear. Sources of soy protein, including miso, are known to block the effects of ACE\(^{89}\). In fact, a soy-based diet reduces blood pressure in salt-sensitive hypertensive rats\(^{67}\). In addition, miso intake triggers the release of antihypertensive peptides (which then act as ACE inhibitors) during the fermentation process\(^{11}\). Therefore, the ACE-inhibitory effects of miso may have contributed to our present results. Whether the ingested miso directly decreases hypothalamic MR activity remains unclear. However, the active ingredient of miso that contains ACE-inhibitory effects was reported to be a small peptide\(^{11}\). Such an anti-ACE small peptide may therefore have direct effects on hypothalamic MR pathway activation. In addition, miso paste intake reportedly increases scavenging of free radicals and inhibits lipid peroxidation\(^{12}\). Reactive oxygen
species (ROS) in the brain also contribute to increased sympathetic activity\(^\text{13}\); therefore, miso-dependent anti-ROS activity in the brain may also lead to the attenuation of salt–induced sympathoexcitation. Further studies are needed to clarify these points.

In conclusion, we found that regular miso intake inhibits the activation of the hypothalamic MR–AT\(_1\)R pathway in response to high-salt intake in CPO mice, thereby attenuating high salt-induced sympathoexcitation and LV dysfunction.

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**Conflicts of interest :** None

**Source of funding :**

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圧負荷心肥大モデルにおける習慣的味噌摂取は食塩感受性交感神経活性化を抑制し、左心機能低下を軽減する

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【背景】圧負荷心肥大モデルでは、脳内視床下部におけるミネラルコルチコイド受容体（MR）―アンジオテンシンⅡタイプ1受容体（AT1R）経路の活性化により、食塩感受性交感神経活性化が引き続き左心機能低下を生じる。これは、塩分摂取が心不全病態に大きく影響することを示したものです。近年、日本において急激に増加している含塩発酵性調味料である味噌が、食塩感受性高血圧モデルの血圧上昇を軽減することが示されており、本研究において、圧負荷心肥大モデルにおける習慣的味噌摂取の効果を検討した。

【方法・結果】2週間の腹部大動脈 Banding により圧負荷心肥大モデルを作成し（対照群には Sham 手術）、その後4週間の食塩水（0.5, 1.0, 1.5% NaCl）を投与した。24時間尿中カテコラミン排泄量で交感神経活動を評価し、圧負荷心肥大モデルでのみ食塩摂取量に応じた食塩感受性交感神経活性化が生じることを確認した。次に、圧負荷心肥大モデルを用いて、1.0%食塩水摂取群を対照群に、塩分濃度を1.0%に調整した味噌水溶液を4週間投与した。マウスの味噌水溶液摂取量は、1.0%食塩水摂取量よりも多く、Na摂取量の指標である尿中Na排泄量も味噌摂取群で有意に高かった。しかし、味噌摂取群における交感神経活動は1.0%食塩水摂取群にて有意に抑制された。また、1.0%食塩水摂取群で認めた心機能低下も味噌摂取群では軽減された。1.0%食塩水摂取群で認めた脳内視床下部における MR, serum glucocorticoid-induced kinase-1（MR活性化指標）、AT1R発現も、味噌摂取群では有意に抑制された。

【結論】以上より、圧負荷心肥大モデルにおける習慣的味噌摂取は、視床下部 MR-AT1R経路活性化の抑制により食塩感受性交感神経活性化を抑制し、心不全を軽減する可能性が示唆される。