Sardine Peptide with Angiotensin I-Converting Enzyme Inhibitory Activity Improves Glucose Tolerance in Stroke-Prone Spontaneously Hypertensive Rats

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An enzymatic hydrolysate of sardine protein (sardine peptide, SP) derived from sardine muscle possesses angiotensin I-converting enzyme (ACE) inhibitory activity. In the present study, we investigated the effect of SP on the blood glucose levels in stroke-prone spontaneously hypertensive rats (SHRSPs). Ten-week-old SHRSPs were assigned to three groups. The control group was given tap water for 4 weeks, while the experimental groups were given water containing SP (1 g/kg/d) or an ACE inhibitor, captopril (8 mg/kg/d). Treatment with SP and captopril decreased ACE activity in the kidney, aorta, and mesentery. There were no differences in fasting blood glucose levels among the three groups, whereas SP and captopril administration significantly suppressed the increase in blood glucose after glucose loading in the control SHRSPs. No difference was observed in plasma insulin levels among the three groups. Thus treatment with captopril and ACE-inhibitory sardine peptides ameliorated the glucose tolerance of this rat strain.

Key words: sardine peptide; stroke-prone spontaneously hypertensive rats; blood glucose; angiotensin I-converting enzyme

According to the National Health and Nutrition Survey of 2006 in Japan, 50–70% of Japanese individuals aged 65 years or more suffer from hypertension. Furthermore, cerebrovascular disease and ischemic heart disease, which are secondary to hypertension, are the second and third most prevalent causes of death in Japan. Hypertension patients often have other diseases, such as obesity, impaired glucose tolerance, and hyperlipidemia.1,2 In hypertension patients, glucose tolerance weakens with an increase in blood pressure; hence, the incidence of diabetes in these patients is approximately 3 times higher than in individuals with normal blood pressure.3-4 The same finding is true for animals; stroke-prone spontaneously hypertensive rats (SHRSPs), which are considered to be the best genetic model of essential hypertension and stroke in humans, have been reported to exhibit hyperglycemia;5,6 and abnormal glucose transport.7,8 Hypertension and diabetes onset are thus closely associated with each other.

The renin-angiotensin-aldosterone system (RAAS) plays a key role in the regulation of blood pressure and electrolytes.9,10 Angiotensin II (AII), a component of the RAAS, has been reported to be associated with the pathophysiology of hypertension and insulin resistance. AII has also been found to inhibit insulin signaling; in large-scale clinical trials, an angiotensin I-converting enzyme (ACE) inhibitor, which inhibits the generation of AII, inhibited the onset of diabetes in hypertension patients.11,12 Inhibition of the RAAS is expected to be linked not only to hypotensive action but also to improvements in abnormal glucose metabolism.

A number of foods have been approved as Foods for Specified Uses for mildly hypertensive people. A sardine peptide preparation was produced by hydrolysis of sardine muscle and has been found to possess ACE inhibitory activity in vitro and in vivo.15 There are many varieties of sardine peptide preparation, and many studies have reported a peptide, Val-Tyr (VY), to be an active substance in these peptides.16-18 Generally, foods rather than drugs are preferred for preventing diseases such as hypertension and diabetes. Therefore, in the present study we investigated the effects of this peptide mixture on blood pressure, ACE activity, and blood glucose levels in SHRSPs, a well-characterized model of essential hypertension with high incidence of stroke, cardiac hypertrophy, kidney dysfunction, and hyperglycemia.

Materials and Methods

Materials. The sardine peptide preparation used in this study was made by alkaline protease hydrolysis of sardine muscle followed by fractionation using an ODS column.15 The fraction obtained, the major component of which are peptides of 2–4 amino acid residues, is commercially available from Senmi Ekisu (Ehime, Japan), and is designated sardine peptide (SP) throughout this manuscript. Eighteen

1 Abbreviations: AII, angiotensin II; ACE, angiotensin I-converting enzyme; RAAS, renin-angiotensin-aldosterone system; SHRSP, stroke-prone spontaneously hypertensive rats; WKY, Wistar-Kyoto rats
peptides in SP have so far been identified with ACE inhibitory activity.\(^{19-21}\) SP had an ACE inhibitory concentration 50% of 62.4 μg.ml\(^{-1}\). An ACE inhibitor captopril was purchased from Wako Pure Chemical Industries (Osaka, Japan).

**Treatment of animals.** This study was carried out in accordance with the guidelines of the Experimental Animal Care Committee of the Kinki University Faculty of Agriculture, and management of the rats was conducted in compliance with the “Guidelines for Care and Use of Laboratory Animals.” These guidelines are based on the “Standards Related to the Care and Management of Experimental Animals” and the “Methods for Sacrificing Laboratory Animals.” SHRSPs and the original strain Wistar-Kyoto rats (WKY) were bred in our laboratory. Inbred SHRSPs were obtained from Dr. Hiroyuki Ito (Kinki University, School of Medicine, Osaka, Japan) and were bred in our laboratory for use in this study. The rats were maintained at a room temperature of 23 ± 1°C and, a humidity of 55 ± 5% under a 12-h light-dark cycle (lighting from 0700 to 1900). Ten-week-old male SHRSPs were assigned to an untreated SHRSP group (n = 6), an SP group (n = 7), and a captopril group (n = 6), with captopril as an ACE inhibitor, and were raised for 4 weeks. The untreated SHRSP group and WKY group were fed tap water, while the experimental group and WKY group were orally administered glucose (2 g kg\(^{-1}\)) from 0700 to 1900. Ten-week-old male SHRSPs were carefully stripped of the surrounding fat and connective tissue. The kidneys, aorta, and mesentery were then carefully stripped of the surrounding fat and connective tissue. These organs were homogenized in 0.05m Tris-HCl buffer (pH 7.8) with 0.5% Nonidet P40 and centrifuged at 20,000 g for 20 min at 4°C. The supernatant was used as an enzyme preparation to estimate protein concentration, and stored at −80°C. ACE activity was measured within 3 d of sacrifice.

**ACE activity determination.** Rats at 14 weeks of age were put under anesthesia by intraperitoneal injection of sodium pentobarbital (Nembutal 30 mg kg\(^{-1}\)). Blood was collected from the abdominal aortas into heparinized test tubes. The vessels were placed in individual metabolic cages, and urine was collected during the last 3 d. Urinary albumin concentrations were determined using a commercial assay (Wako). Plasma biochemical parameters, including total cholesterol, triglyceride, and free fatty acid, were determined using a commercial assay (Wako).

**ACE activity determination.** Rats at 14 weeks of age were put under anesthesia by intraperitoneal injection of sodium pentobarbital (Nembutal 30 mg kg\(^{-1}\)), Abbott, North Chicago, IL), and blood was collected from the abdominal aortas into heparinized test tubes. The kidney, aorta, and mesentery were gently flushed with saline containing heparin and extirpated immediately after sacrifice. The vessels were carefully stripped of the surrounding fat and connective tissue. These organs were homogenized in 0.05m Tris-HCl buffer (pH 7.8) with 0.5% Nonidet P40 and centrifuged at 20,000 g for 20 min at 4°C. The supernatant was used as an enzyme preparation to estimate protein concentration, and stored at −80°C. ACE activity was measured within 3 d of sacrifice.

ACE activities were measured by a modification of the method of Horiiuchi et al.\(^{22}\) using the synthetic substrate Hip-His-Leu (Peptide Institute, Osaka, Japan), which was specifically designed to measure ACE. Fifty ml of plasma or organ extract was incubated for 30 min at 37°C with 5 μmol Hip-His-Leu in 250 μmol of 0.05 M Hippuric acid from Hip-His-Leu (Nacalai Tesque, Kyoto, Japan) at ambient temperature with a mobile phase of methanol-10 mM KH₂PO₄ (1:1) adjusted to pH 3.0 with phosphoric acid at a flow rate of 0.5 ml.min\(^{-1}\). One unit of enzyme activity was defined as the amount of enzyme catalyzing the release of 1 μm of hippuric acid from Hip-His-Leu per min at 37°C.

**Glucose tolerance test.** The oral glucose tolerance test (OGTT) was performed at 14 weeks of age. After 15 h of overnight fasting, the rats were orally administered glucose (2 g kg\(^{-1}\)). Blood was collected from the tail vein in ethylenediaminetetraacetic acid (1.5% EDTA-2Na/physiological saline)-treated tubes chilled on ice. Blood glucose levels were measured using a commercial kit (Wako), and insulin was measured using an insulin measurement kit (Morinaga Institute of Biological Science, Tokyo).

**Statistical analysis.** The data are presented as means ± SD. Data were analysed statistically with a statistical software package (Statview J-4.5, Abacus Concepts, Berkeley, CA) by one-way analysis of variance (ANOVA) with the Bonferroni/Dunn post hoc test. A probability value of p < 0.05 was considered statistically significant.

**Results.** There were no differences in body weight among the SP group, the captopril group, and the untreated SHRSP group. Blood pressure in the SHRSPs increased with age, but normotensive the WKYs (data not shown) showed no age-related increase in blood pressure. Four weeks after the onset of administration, blood pressure was significantly lower in the SP group and the captopril group than in the untreated SHRSP group, and the lower pressure levels in both treatment groups were maintained until the end of treatment (Fig. 1B). At the end of the experimental period, blood pressure was 223 ± 6, 210 ± 6, and 207 ± 6 mmHg in the untreated SHRSP group, the SP group, and the captopril group respectively (Table 1). No differences were observed in the food intake among the untreated SHRSP group, the captopril group, and the SP group (Table 2). There were no differences in total cholesterol, triglyceride, or free fatty acid among the three groups.

Figure 2 shows the results for ACE activity in the serum, aorta, mesentery, and kidney. In the study tissue, aorta, and mesentery, the SHRSPs showed higher ACE activity than the normotensive WKYs. In the kidney, no significant difference was observed in ACE activity between the SHRSPs and the WKYs. Treatment with sardine peptide and captopril significantly reduced ACE activity in the aorta, mesentery, and kidney as compared to the untreated SHRSP group. The serum ACE activity of the untreated SHRSP was markedly lower than that of the WKYs. SP treatment did not affect serum ACE activity. The ACE activity of the captopril group, however, was markedly higher than that of the untreated SHRSP group.

Figure 3 shows the results of the oral glucose tolerance test (OGTT) in 14-week-old SHRSPs and WKYs. The plasma glucose levels of the SHRSPs were significantly higher than those of the WKYs under the fasting condition and after glucose loading (Fig. 3A). The plasma insulin levels the fasting condition were significantly lower in the SHRSPs than in the WKYs (Fig. 3B). In the WKYs, the plasma insulin increased by 3.0 ng.ml\(^{-1}\) in response to glucose loading, and reached its peak at 15 min after glucose loading. Only a slight increase was observed (0.5 ng.ml\(^{-1}\)) in plasma insulin levels in the SHRSPs at 30 min after glucose loading.

Fasting glucose levels were not affected by treatment with SP or captopril in the SHRSPs, whereas peak glucose levels at 30 min after glucose loading was significantly lower in the SP and captopril groups. At this time, the plasma glucose concentrations of the untreated SHRSP group, the SP group, and the captopril group were 181.4 ± 18.4 mg.dl\(^{-1}\), 157.4 ± 13.1 mg.dl\(^{-1}\), and 156.0 ± 18.0 mg.dl\(^{-1}\) respectively. There was no difference in plasma insulin levels among the SP group, the captopril group, and the untreated SHRSP group.

The total area under the curve (AUC) for glucose is presented in Fig. 3C. No comparison of the WKY with...
Fig. 1. Effects of SP and Captopril on the Body Weight (A) and Blood Pressure (B) of the SHRSPs. SHRSPs were fed tap water, water containing SP (1 g kg\(^{-1}\) d\(^{-1}\)), or captopril (8 mg kg\(^{-1}\) d\(^{-1}\)). Systolic blood pressure was measured by the tail-cuff method. The rats in each group were fed commercial diets (Funabashi-SP, Funabashi Farm, Chiba, Japan). The values are expressed as means ± SD. Significant difference from the untreated SHRSP group (\(p < 0.05\)) is indicated.

Table 1. Organ Weights of SHRSPs and WKYs at 14 Weeks of Age

<table>
<thead>
<tr>
<th></th>
<th>WKY</th>
<th>SHRSP</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Un-treated</td>
</tr>
<tr>
<td>n</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td>126 ± 10(^a)</td>
<td>223 ± 6(^a)</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>332 ± 17(^b)</td>
<td>231 ± 10(^b)</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dl)</td>
<td>77.2 ± 6.2(^b)</td>
<td>141.4 ± 3.9(^b)</td>
</tr>
<tr>
<td>Brain weight (g)</td>
<td>2.26 ± 0.01(^b)</td>
<td>1.76 ± 0.07(^a)</td>
</tr>
<tr>
<td>Heart weight (g)</td>
<td>1.05 ± 0.04(^a)</td>
<td>1.07 ± 0.07(^a)</td>
</tr>
<tr>
<td>Pancreas weight (g)</td>
<td>1.91 ± 0.10(^b)</td>
<td>0.86 ± 0.09(^a)</td>
</tr>
<tr>
<td>Kidney weight (g)</td>
<td>1.29 ± 0.09(^b)</td>
<td>1.01 ± 0.11(^a)</td>
</tr>
<tr>
<td>Brain/body wt (%)</td>
<td>0.68 ± 0.04(^a)</td>
<td>0.76 ± 0.03(^a)</td>
</tr>
<tr>
<td>Heart/body wt (%)</td>
<td>0.32 ± 0.02(^a)</td>
<td>0.46 ± 0.03(^a)</td>
</tr>
<tr>
<td>Pancreas/body wt (%)</td>
<td>0.58 ± 0.04(^a)</td>
<td>0.38 ± 0.04(^a)</td>
</tr>
<tr>
<td>Kidney/body wt (%)</td>
<td>0.39 ± 0.02(^a)</td>
<td>0.42 ± 0.03(^a)</td>
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</table>

The data represent mean ± SD. Different superscript letters denote significant differences.

Table 2. Effects of SP and Captopril on Plasma Biochemical Parameters

<table>
<thead>
<tr>
<th></th>
<th>SHRSP</th>
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<tbody>
<tr>
<td></td>
<td>Un-treated</td>
</tr>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Food intake (g/d)</td>
<td>17 ± 2</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>50.0 ± 6.5</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>73.4 ± 10.7</td>
</tr>
<tr>
<td>Free fatty acid (mEq/l)</td>
<td>0.29 ± 0.06</td>
</tr>
</tbody>
</table>

The data represent mean ± SD.

SHRSP was conducted the since fasting blood glucose levels in the WKYs was different from the SHRSPs. Glucose AUC was significantly reduced in the SP group in comparison to the untreated SHRSP group, but no significant difference was observed in AUC between the SP and the captopril group.

The organ weights of the SHRSPs are shown in Table 1. The pancreas weight of the SHRSPs was markedly lower than that of the WKYs. No difference was observed in the pancreas weight or the ratio of pancreas weight to body weight among the untreated SHRSP group, the SP group, and the captopril group. The heart weight and the ratio of heart weight to body weight were significantly higher in the SHRSPs than in the WKYs. The heart weight and the ratio of heart weight to body weight were significantly lower in the captopril group than in the untreated SHRSP group. These two measurements were lower in the SP group too. No differences were observed in the weights of other organs among the untreated SHRSP group, the captopril group, and the SP group.

Urinary albumin excretion at 14 weeks of age was 1.5 ± 2.2 mg d\(^{-1}\) and 0.4 ± 1.1 mg d\(^{-1}\) in the untreated SHRSP group and the SP group respectively. Albumin excretion in the urine was not observed in the captopril group (Fig. 4).

Discussion

Hypertension and diabetes coexist frequently in that elevation of blood pressure and blood glucose levels are common aggravating factors.\(^1,3\) In the present study, we used SHRSPs that have a genetic predisposition to hypertension and stroke. There is growing evidence that
SHRSPs have impaired glucose tolerance and insulin resistance. The SHRSPs bred in our laboratory showed increased blood glucose levels after glucose loading as compared to the WKYs. In addition, we found impaired insulin secretion in response to glucose load in SHRSPs, insulin response to glucose loading is known to be lower in Japanese population as than in other ethnic populations. Matsumoto et al. demonstrated that Japanese have a higher tendency to develop glucose intolerance by impaired early-phase insulin secretion. Considering the high prevalence of hypertension in Japanese and the fact that the incidence of newly developed diabetes is much higher in hypertensives than in normotensives, the SHRSPs is a very useful model for the study of the insulin resistance of many Japanese, as SHRSPs is a non-obese, hypertensive strain.

In the present study, SP known to have ACE inhibitory activity was administered to SHRSPs, and its effect on blood pressure and blood glucose level was investigated. The following two findings were obtained: (i) Chronic administration of SP to SHRSPs elicited decreased blood pressure and ACE activity in local tissues such as the aorta, mesentery, and kidney. (ii) SP administration to SHRSPs elicited a reduction in glucose levels after glucose loading, but it had no effect on insulin secretion. These results lead us to speculate that SP administration improves insulin resistance in SHRSPs. Thus, the decrease in the blood glucose level after glucose loading may be associated with inhibition of the RAAS in SP-treated SHRSPs. These data are very interesting in that the suppression of RAAS by SP brought about not only decreased blood pressure but also an improvement of glucose tolerance in the SHRSPs.

RAAS components exist in circulation and in local tissues such as the kidney, aorta, mesentery, brain, and pancreatic islets. The function of RAAS in the circulation is to regulate short-term homeostatic reactions in response to acute effects, whereas RAAS in local tissues is involved in the long-term control of blood pressure. In the case of acute administration of an ACE inhibitor, serum ACE activity decreases in normal rats and various hypertensive model rats. On the one hand, in chronic administration of an inhibitor, no reduction in ACE activity is observed in the serum, but one is observed in the aorta, mesentery, and kidney. In addition, SHRSPs show a high level of tissue ACE activity and a high AII concentration, but serum ACE activity and AII concentrations in SHRSPs are considerably lower than those of WKYs. The SHRSPs bred in our laboratory showed upregulation of ACE activity in the aorta and mesentery, which is

![Graph showing effects of SP and Captopril on ACE Activity in the Serum, Kidney, Aorta, and Mesentery of the SHRSPs.](image-url)
consistent with our previous data. Thus, ACE activity in local tissue plays an important role in the development of hypertension.

In the present study, blood pressure decreased moderately in the SP group as compared to the untreated SHRSP group. SP contains a wide variety of peptides, among which VY is a predominant ACE inhibitory peptide. It has also been confirmed that VY is resistant to gastrointestinal proteases. Matsui et al. demonstrated that VY treatment induced a reduction in blood pressure in SHRs and that the target site of VY was the abdominal aorta and kidney. Consistently with VY dosing in the SHRs, ACE activity in the kidney, aorta, and mesentery decreased in the SP group. The same levels of reduction in blood pressure and decreased ACE activity in the tissues were observed in the captopril-treatment SHRSPs at a dosage of 8 mg·kg⁻¹·d⁻¹. These results indicate that reduction of tissue ACE activity in the SP group led to amelioration of hypertension.

Fig. 3. Effects of SP and Captopril Treatment of the SHRSPs on Glucose and Insulin Levels after Glucose Loading.

SHRSPs were fed tap water, water containing SP (1 g·kg⁻¹·d⁻¹), or captopril (8 mg·kg⁻¹·d⁻¹) from 10 weeks of age. Normotensive WKYs were given tap water. The oral glucose tolerance test was done at 14 weeks of age. After 15 h of overnight fasting, 2 g·kg⁻¹·d⁻¹ glucose was orally administered. A small amount of blood from the tail vein was collected at 0, 15, 30, and 60 min after glucose administration. Plasma glucose (A), insulin concentrations (B), and glucose area under the curve (C) are shown. The values are expressed as means ± SD. Significant difference from the untreated SHRSP group (p < 0.05, "p < 0.01) is indicated. Different superscript letters denote significant differences between groups (p < 0.05).

Fig. 4. Effects of SP and Captopril on Urinary Albumin Excretion.

SHRSPs were fed tap water, water containing SP (1 g·kg⁻¹·d⁻¹), or captopril (8 mg·kg⁻¹·d⁻¹) from 10 weeks of age. Urinary albumin was measured at 14 weeks of age. The black line represents the average for each group.
the captopril group, whereas insulin secretion was not affected by sardine or captopril treatment. In clinical studies, treatment with ACE inhibitors or angiotensin receptor blockers appears to help reduce the onset of new cases of diabetes.\(^{35,36}\) There is a large body of evidence to indicate that inhibition of the RAAS in various diabetic animal models improves glucose tolerance in various models of insulin resistance and obesity.\(^{37–39}\) On the other hand, chronic hydralazine as a vasodilator treatment for obese animals of SHR genetic background did not improve glucose disposal or insulin resistance, indicating that glucose uptake is independent of blood flow.\(^{40}\) Hence, we suspect that upregulation of RAAS was involved in the hyperglycemia in the SHRSPs and that reduced glucose levels after glucose loading in the sardine peptide and captopril treatment groups was independent of hemodynamic effects. Acute treatment with captopril at a therapeutic dosage of 5 mg·kg\(^{-1}\) had no significant effect on insulin signaling in rats with insulin resistance or diabetes.\(^{35,36,37,39}\) However, chronic treatment with a therapeutic dosage of captopril on cardiac metabolism improved the ability to increase glycolysis by increasing insulin signaling in obese and insulin resistant mice.\(^{41}\)

All has been found to reduce insulin receptor substrate-1 (IRS-1) tyrosine phosphorylation and phosphatidylinositol-3-kinase (PI-3 kinase) activity via the AT 1 receptor and to inhibit the translocation of a glucose transporter (GLUT4) to the cell membrane.\(^{38}\) Suppression of angiotensin receptor signaling with ACE inhibitor or angiotensin receptor antagonist can also enhance insulin signaling and glucose transport.\(^{37,39}\) However, in the present study, we did not examine the effects of SP on the insulin signal pathway in the SHRSPs. Considering that augmentation of insulin resistance in muscle and adipose tissue in SHRSPs has been reported, further studies are needed to elucidate the underlying mechanism of the decreased blood glucose in SP-treated SHRSPs.

It was reported recently that a local rennin-angiotensin-system (RAS) exists in the pancreatic islets, and it is implicated in the pathogenesis of \(\beta\)-cell dysfunction.\(^{37,42}\) Moreover, RAS inhibitors prevent pathological islet changes in rodent models of type-2 diabetes mellitus.\(^{43,44}\) However, insulin secretion was not influenced by chronic captopril or SP treatment in the SHRSPs in the present study. Since the pancreas size in the SHRSPs was very small compared with that in WKYs, we speculate that the SHRSPs experienced abnormal morphological development in the pancreas cells.

SHRSPs have been observed to exhibit progressed end-organ damage and renal failure and increased cerebral injury as a result of hypertension.\(^{45}\) Four weeks of treatment of captopril beginning at 10 weeks of age suppressed urinary albumin excretion and increases in heart weight. SP administration had similar effects, although they were not statistically significant as compared with the untreated SHRSP group. There is increasing evidence that elevated AII plays a role in the primary consequences of chronic hypertension, \(\nu\)–\(\nu\), end-organ damage such as stroke, renal failure, and myocardial infarction.\(^{46,47}\) ACE inhibitors and angiotensin receptor antagonists have cardiovascular, cerebrovascular, and renal protective effects. It may be hypothesized that administration of sardine peptide, having ACE inhibitory activity, to SHRSPs has a protective effect against end-organ damage.

In conclusion, inhibition of ACE activity in SHRSPs is considered to have a preventive effect on the hyperglycemia and end-organ damage sequela of genetic hypertension. SP, having ACE inhibitor activity, contribute to improving not only hypertension but also hyperglycemia. In the present study, we did not confirm the effect of sardine peptide on insulin sensitivity in SHRSPs, and thus further studies are required to elucidate the effects of SP on glucose uptake in skeletal muscles and the activity of the insulin signaling machinery.

References

Sardine Peptide Improves Glucose Tolerance in SHRSPs

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