Risperidone Attenuates Local and Systemic Inflammatory Responses to Ameliorate Diet-Induced Severe Necrotic Pancreatitis in Mice: It May Provide a New Therapy for Acute Pancreatitis

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ABSTRACT

In a previous article, we showed that a potent serotonin-, 5-hydroxytryptamine-2A (5-HT2A) antagonist, risperidone, ameliorated cerulein-induced edematous pancreatitis in mice. In the present article, young female mice were fed a choline-deficient, ethionine-supplemented diet. All of the mice developed severe necrotic pancreatitis, and approximately 50% of them died within 4 days. Serum levels of proinflammatory interleukin (IL)-6 significantly increased on day 3 and returned toward the control on day 4 of choline-deficient ethionine-supplemented (CDE) diet treatment. The time course of IL-6 levels paralleled those of plasma amylase and lipase activities. On the other hand, platelet counts significantly decreased on day 3, and the change became more marked on day 4, coinciding with mortality and histological alterations of the pancreas (edema, inflammatory cell infiltration, necrosis). Preceding these changes, plasma levels of 5-hydroxyindoleacetic acid (5-HIAA) increased on feeding a CDE diet to reach a peak on day 3 and returned toward the control on day 4. Risperidone (0.1–3.2 mg/kg twice a day) hardly affected the 5-HIAA levels but dose-dependently attenuated the serum IL-6 levels, plasma amylase/lipase levels, platelet counts, histological alterations, and mortality of diet-induced pancreatitis mice. These results are discussed in relation to the pathogenesis of acute pancreatitis. Thus, we speculate that acinar cell injury triggers local inflammatory reactions and, if coincided with enhanced IL-6 release, leads to a systemic inflammatory response syndrome, which is responsible for the mortality. In addition, it is suggested that diet-induced 5-HT release and 5-HT2A receptor activation are involved in this whole process of pancreatitis development. Risperidone may provide a new therapy for the disease.

Acute pancreatitis has been considered a multifactorial disease, the severity of which ranges from mild edematous forms to severe necrotizing forms. Mild edematous pancreatitis may resolve spontaneously or after conservative therapy, but severe proinflammatory pancreatitis has a high mortality due to multiple organ failure (Geokas et al., 1985; Pitchumoni et al., 1988). Although it is generally considered that autodigestion by activated pancreatic enzymes is the initial event of acute pancreatitis (Geokas et al., 1972; Becker, 1981; Trapnell, 1981), the degree of hyperenzymemia cannot predict the severity and final outcome of the disease. There is no doubt that additional factor(s) play a part in the progression of acute pancreatitis.

It has been suggested that serotonin (5-HT) is involved in the pathogenesis of acute pancreatitis: the S2-serotonergic (later named 5-HT2) receptor antagonists ketanserin and ritanserin reduced serum amylase concentration in rats (Oguchi et al., 1992): not only 5-HT2 receptor antagonists but also the 5-HT depleter para-chlorophenylalanine reduced the severity of acute pancreatitis in mice (Yoshino and Yamaguchi, 1997). These authors explained that autodigestion by activated pancreatic enzymes is the initial event of acute pancreatitis (Geokas et al., 1972; ABBREVIATIONS: 5-HT, serotonin; 5-HT2 receptor; 5-HIAA, 5-hydroxyindoleacetic acid; CDE, choline-deficient ethionine-supplemented diet; SIRS, systemic inflammatory response syndrome; R-102444, (2R,4R)-4-lauroxyloxy-2-[2-[2-(3-methoxy)phenyl]ethyl]phenoxyl; R96544, (2R,4R)-4-initio-5-hydroxy-1-methylpyrrolidine hydrochloride.
5-HT<sub>2</sub> receptor leads to vasoconstriction and platelet agregation and may enhance autolysis of the pancreas, which is vulnerable to ischemia (Anderson and Schiller, 1968; Schiller and Anderson, 1975; Klar et al., 1990).

The 5-HT<sub>2</sub> receptor has now been classified into 5-HT<sub>2A</sub>, 5-HT<sub>2B</sub>, and 5-HT<sub>2C</sub> subclasses, and Ogawa et al. (2005) have demonstrated recently that R-102444 and its active metabolite R-96544, “selective” 5-HT<sub>2A</sub> receptor antagonists, inhibited the progression of acute pancreatitis. However, R-96544, which has 600- to 2800-fold higher affinity for the 5-HT<sub>2A</sub> (formerly known as 5-HT<sub>2</sub>) receptors than for the 5-HT<sub>2B</sub> and dopamine D<sub>2</sub> receptors, and the α- and β-adrenoceptors, has not been well characterized for the selectivity at three 5-HT<sub>2</sub> receptor subclasses.

Using drugs of known selectivity at 5-HT<sub>2</sub> receptor subclasses, we have demonstrated that risperidone, spiperone, and ketanserin, which strongly block the 5-HT<sub>2A</sub> receptors (Bonhaus et al., 1995; Knight et al., 2004) dose-dependently ameliorated cerulein-induced pancreatitis, and their potency order paralleled their reported p<sub>K<sub>i</sub></sub> values at the 5-HT<sub>2A</sub> receptors but not those at the 5-HT<sub>2B</sub> and 5-HT<sub>2C</sub> receptors (Hamada et al., 2007). It is interesting that metagline, ritalinser and methysergide, which act evenly on 5-HT<sub>2A/2B/2C</sub> receptors (Knight et al., 2004) were less potent compared with their high p<sub>K<sub>i</sub></sub> values at 5-HT<sub>2A</sub> receptors. Thus, we speculated that an activation of 5-HT<sub>2A</sub> receptor in the smooth muscle cells reduces blood flow and aggravates cerulein-induced acute pancreatitis, whereas an activation of 5-HT<sub>2B</sub> and/or 5-HT<sub>2C</sub> receptor in the endothelial cells increases blood flow and attenuates the pancreatitis. We also proposed that the most potent 5-HT<sub>2A</sub> antagonist risperidone, which actually blocks 5-HT<sub>2A</sub>-mediated vasoconstriction but not 5-HT<sub>2B/C</sub>-mediated vasodilation, may provide a new therapy for acute pancreatitis.

Our proposal, however, is based on the cerulein-induced edematous pancreatitis (CIEP), which resolves spontaneously. Thus, the present paper aimed to examine the effect of risperidone on the diet-induced necrotic pancreatitis (DINP) in mice. In addition to the conventional biomarkers of acute pancreatitis, serum IL-6 levels were determined because there is increasing evidence that IL-6 predicts the severity of acute pancreatitis better than other cytokines, including transforming growth factor-α (Panek et al., 2006; Stimac et al., 2006).

**Materials and Methods**

**Drugs.** Commercially available risperidone (Risperdal oral solution; Janssen Pharmaceuticals, Antwerp, Belgium) was diluted in saline and administered in a volume of 20 ml/kg. The control mice were given only saline.

**Animals.** Female 4-week-old ICR mice weighing approximately 14 to 20 g were purchased from Japan SLC (Shizuoka, Japan). The animals were kept in our laboratory for 3 days under conditions of 22 ± 1°C and 12-h light/dark cycles with lights on at 8:00 AM and then were used for the acute pancreatitis studies. All experimental procedures described were approved by the Experimental Animal Research Committee of Kyoto Pharmaceutical University.

**Diet-Induced Acute Pancreatitis.** Acute pancreatitis was induced by feeding the mice a choline-deficient, 0.5% DL-ethionine-supplemented diet (CLEA Japan, Tokyo, Japan) ad libitum, starting at 10:00 AM. Under ether anesthesia, blood was taken from the orbital sinus into tubes with or without heparinization and centrifuged at 5000 rpm. Obtained plasma was subjected to the analysis of amylase, lipase, and 5-HIAA levels, whereas serum was used for the analysis of IL-6 levels. For the determination of platelet counts, blood samples were collected into EDTA-containing tubes, which were provided by SRL Inc. (Kyoto, Japan).

**Time Course Study.** Mice were randomly assigned to five groups (n = 10) and given a choline-deficient ethionine-supplemented (CDE) diet. Blood was taken before (day 0) or 1, 2, 3, or 4 days after the beginning of the experiment (10:00 AM–12:00 PM). The plasma amylase and lipase levels were determined simultaneously in one set of experiments, and 5-HIAA levels were determined in another set of experiments. Serum IL-6 and blood platelet count were determined in each set of experiments. Some of the CDE diet mice died during the experiment and are excluded from the data. The results of survived mice were expressed as the mean ± S.E.M.

**Drug Effect.** Mice were randomly assigned to five groups of 10 each. Risperidone (0.1, 0.32, 1, or 3.2 mg/kg) was given subcutaneously twice a day (9:00 AM and 5:00 PM) for 3 days, starting with the introduction of the CDE diet. The results of one or two series of experiments were combined and expressed as the mean of survived animals. In the case of histological examination, mice were randomly assigned to five groups of five each, and the results of three series of experiments were combined and expressed as the mean of survived animals.

**Biochemical Analysis of Blood.** Blood parameters were analyzed by SRL Inc., according to the following methods. Serum IL-6 levels were measured by a two-step sandwich chemiluminescent enzyme immunoassay method using alkaline phosphatase-labeled anti-human IL-6 monoclonal antibody and 3-[2′-spirodiamantane]-4-methoxy-4-(3′-sphloropyloxy)phenyl-1.2-dioxetane disodium salt as a substrate. The lower and upper limits of detection of IL-6 were 51 and 10,000 pg/ml, respectively.

Plasma amylase activity was measured with an enzymatic calorimetric test, using 2-chloro-4-nitrophenyl-beta-maltose as a substrate. The colored product absorbance was measured at 405 to 660 nm with a Hitachi 7170 AutoAnalyzer (Hitachi, Tokyo, Japan).

Plasma lipase activity was measured with an enzymatic calorimetric test, using 1,2-O-dilauryl-rac-glycer-3-glutaric acid-(6 methyl-resorufin)-ester as a substrate. The colored product absorbance was measured at 570 to 700 nm with a Hitachi 7170 AutoAnalyzer. Blood platelet counts were measured by a fully automated hematology analyzer (Sysmex SE-9000; Sysmex America, Inc., Mundelein, IL). Plasma levels of 5-HIAA, a metabolite of 5-HT, were measured using a high-performance liquid chromatography (L-6000; Hitachi) and an electrochemical detector (ECD-300; Eicom, San Diego, CA).

**Examination of Pancreas.** At a predetermined time, the pancreas was taken through an incision of the abdominal wall under ether anesthesia. The excised pancreas was fixed in a formalin solution, embedded in paraffin, and sectioned at 5-μm thickness. Each sample was examined blindly for the extent of edema, inflammatory cell infiltration, and acinar cell necrosis and scored according to the criteria: 0, no change; 1, slight change; 2, moderate change; 3, severe change; and 4, very severe change. The results of two series of experiments were combined and expressed as the mean of 10 animals.

**Statistical Analysis.** Results are expressed as mean ± S.E.M. A one-tailed paired Student’s t test was used to study the statistical significance of the time course changes in plasma parameters. Dunnett’s multiple comparison test was used to study the statistical significance of the drug effect on the plasma parameters. Dunn’s multiple comparison test was used for the analyses of histological scores. Steel’s multiple comparison test was used to study the statistical significance of the drug effect on the mortality.

**Results**

**Time Course of Changes in CDE-Fed Mice.** Feeding the mice with a CDE diet caused severe necrotic pancreatitis.
Values on days 3 (0.82 \times 10^{6}/mm^3) and 50.0\% (25/50) died on days 3 and 4, respectively (Fig. 1, left), none of the mice died on days 1 and 2, but 22.0\% died on day 4. When the data of all the time course studies were combined (Table 1). Each value represents the mean \pm S.E. of survivors in a group of 10. The number of survivors is shown in parentheses.

**Table 1**

<table>
<thead>
<tr>
<th>Days after CDE</th>
<th>IL-6 (pg/ml)</th>
<th>Amylase (U/l)</th>
<th>Lipase (U/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0</td>
<td>51.0 (10)</td>
<td>744.0 \pm 32.8 (10)</td>
<td>29.4 \pm 1.8 (10)</td>
</tr>
<tr>
<td>Day 1</td>
<td>63.2 \pm 5.2 (10)</td>
<td>534.0 \pm 35.9 (10)</td>
<td>24.0 \pm 1.6 (10)</td>
</tr>
<tr>
<td>Day 2</td>
<td>421.7 \pm 60 (10)</td>
<td>1880.0 \pm 287 (10)</td>
<td>326.5 \pm 51.2 (10)</td>
</tr>
<tr>
<td>Day 3</td>
<td>5670.1 \pm 1406.4** (9)</td>
<td>28617.1 \pm 6305.1** (7)</td>
<td>4230.7 \pm 1128.7** (7)</td>
</tr>
<tr>
<td>Day 4</td>
<td>110.7 \pm 35.5 (6)</td>
<td>2514.3 \pm 518.3 (7)</td>
<td>272.9 \pm 63.9 (7)</td>
</tr>
</tbody>
</table>

**p < 0.01; Statistically significant compared with the control (day 0).**

When the data of all the time course studies were combined (Fig. 1, left), none of the mice died on days 1 and 2, but 22.0\% (11/50) and 50.0\% (25/50) died on days 3 and 4, respectively.

Platelet counts hardly changed on days 1 and 2 of CDE diet feeding but then decreased on days 3 and 4 (Fig. 1, right). The values on days 3 (0.82 \pm 0.09 \times 10^{6}/mm^3) and 4 (0.68 \pm 0.21 \times 10^{6}/mm^3) were significantly different from the prefeeding value (1.04 \pm 0.04 \times 10^{6}/mm^3).

Serum IL-6 levels did not reach a detection limit (51.0 pg/ml) before feeding the CDE diet (day 0) but then gradually increased to peak on day 3 (Table 1). The peak value (5670.1 \pm 1406.4 pg/ml) was significantly different from the prefeeding value (day 0).

Plasma amylase levels tended to decrease on day 1 but then increased to peak on day 3 (Table 1). The peak value (28617.1 \pm 6305.1 pg/ml) was significantly different from the prefeeding value (day 0).

Plasma lipase levels also tended to decrease on day 1 but then increased to peak on day 3. The peak value (4230.7 \pm 1128.7 pg/ml) was significantly different compared with the prefeeding value (29.4 \pm 1.8).

The edema, inflammatory cell infiltration, and necrosis were graded according to the degree of alterations as described under Materials and Methods. The edema, inflammatory cell infiltration, and necrosis developed on day 3, and their histological scores (1.75 \pm 0.11, 1.13 \pm 0.09, and 2.75 \pm 0.21, respectively) were significantly different from the prefeeding value, respectively (Table 2). Similar or even more histological alterations were observed on day 4.

Plasma 5-HIAA levels increased to reach 101.8 \pm 34.0, 106.9 \pm 9.0, 137.8 \pm 49.0, and 64.0 \pm 13.4 ng/ml on days 1 to 4, respectively (Fig. 2). Although these values were not significantly different from the prefeeding value (day 0), this could be ascribed to the large variation among mice.

**Table 2**

<table>
<thead>
<tr>
<th>Days after CDE</th>
<th>Histologic Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0 (10)</td>
<td>Edema 0</td>
</tr>
<tr>
<td>Day 1 (10)</td>
<td>Infiltration 0</td>
</tr>
<tr>
<td>Day 2 (10)</td>
<td>Necrosis 0.05 \pm 0.05</td>
</tr>
<tr>
<td>Day 3 (7)</td>
<td>Edema 1.75 \pm 0.11**</td>
</tr>
<tr>
<td>Day 4 (7)</td>
<td>Infiltration 2.14 \pm 0.23**</td>
</tr>
</tbody>
</table>

**p < 0.01; Statistically significant compared with the control (day 0).**
Effect of Risperidone on the Serum Levels of IL-6. As shown in Fig. 3, the CDE-fed control mice (risperidone 0) revealed increased serum IL-6 levels (4545.7 ± 1932.6 pg/ml), which was dose-dependently reduced by risperidone (0.1–3.2 mg/kg, twice a day). The value at 3.2 mg/kg (75.4 ± 18.9 pg/ml) was significantly different compared with the control. As shown in Fig. 5, the CDE-fed control mice (risperidone 0) revealed decreased platelet count (0.78 ± 0.06 × 10^6/mm^3), which was significantly different from the value (1.06 ± 0.04 × 10^6/mm^3) in normal mice that were fed standard chow. The thrombocytopenia in CDE-fed mice was dose-dependently attenuated by risperidone. Although the value at 0.1 mg/kg (0.84 ± 0.08 × 10^6/mm^3) was not significantly different from the CDE-fed control (0.78 ± 0.06 × 10^6/mm^3), those at 0.32 (1.12 ± 0.05 × 10^6/mm^3), 1.0 (1.11 ± 0.03 × 10^6/mm^3), and 3.2 (1.24 ± 0.08 × 10^6/mm^3) mg/kg were significantly different from the CDE-fed control.

Effect of Risperidone on the Mortality. The data of all the mice that were subjected to study risperidone effects were combined. Although 28.0% (16/56) of the control mice died on day 3, the mortality rates of mice treated with 0.1, 0.32, 1, and 3.2 mg/kg risperidone were 3.1 (2 of 65), 1.5 (1 of 65), 4.6 (3 of 65), and 0% (0 of 65), respectively. These values in risperidone-treated mice were significantly different from the control (p < 0.01).

Discussion

Acute pancreatitis was induced in 4-week-old mice by feeding with a CDE diet. All the mice revealed DINP, and approximately 50% of them died within 4 days. Although the mortality is less compared with the previous studies (Lombardi et al., 1975; Yoshino and Yamaguchi, 1997), this could be ascribed to the use of older mice in the present study. When Lombardi et al. (1975) first introduced the DINP model, they considered that a CDE diet inhibited the biosynthesis of lecithins, a major membrane constituent, and caused a blockage of exocytosis of zymogen granules, which in turn leads to intracellular enzyme accumulation, acinar
cell injury, and enzyme leakage into the interstitium/blood, resulting in autodigestion of the pancreas by activated enzymes. However, there was no explanation for necrosis suddenly ensuing despite the remarkable overall preservation of cellular structures during the first 24 to 48 h of CDE treatment. Also in the present study, little histological alterations were found on days 1 and 2. The following discussion may afford an explanation for this issue.

It is a novel finding that serum IL-6 levels significantly increased on day 3 and returned toward the control on day 4 of CDE treatment. The time course change paralleled those of plasma amylase and lipase activities. In contrast, platelet counts significantly decreased on day 3, and the change became more marked on day 4, coinciding with the mortality and histologic alterations of the pancreas (edema, inflammatory cell infiltration, and necrosis). These results are compatible with the hypothesis that acinar cell injury causes local inflammatory response, and, if this response is very strong, it results in a systemic inflammatory response syndrome (SIRS), which could be responsible for the morbidity and mortality (Bhatia, 2005). Although the edema and inflammatory cell infiltration in the present study reflect local inflammatory reaction, the depressed platelet counts no doubt reflect SIRS-related hypercoagulopathy. Furthermore, there is evidence that plasma IL-6 concentration is predictive for severity and mortality in SIRS (Oda et al., 2005; Rau et al., 2007) and in acute pancreatitis (Panek et al., 2006; Stimac et al., 2006). In addition, Takács et al. (1996) noted that maximal IL-6 levels correspond to the severity of acute pancreatitis in rats, and we found that the peak serum IL-6 level was higher in the DINP than CIEP model (K. Hamada and I. Yamaguchi, unpublished observation). Taken together, we speculate that IL-6 plays an important role in the transformation of local inflammation (mild edematous pancreatitis) to SIRS (severe necrotic pancreatitis) via its broad proinflammatory actions. Our speculation may explain why necrosis suddenly ensued on day 3 despite the remarkable overall preservation of cellular structures during the first 24 to 48 h of CDE treatment. However, the present study does not exclude the possible involvement of other inflammatory cytokines in the pancreatitis development (Bhatia et al., 2000; Sakorafas and Tsiotou, 2000; Granger and Remick, 2005), and further studies are needed to clarify this point.

The present study confirmed our previous finding that the plasma levels of 5-HIAA increased on feeding a CDE diet, gradually reached a peak on day 3, and returned toward the control on day 4 (Yoshino and Yamaguchi, 1997). The increase in 5-HIAA levels apparently preceded the above-mentioned blood parameter changes and the histological alterations that first appeared on day 3. These results suggest that a CDE diet causes 5-HT release and triggers DINP. Regarding the pathogenic role of 5-HT, it is interesting to note that a “hyperstimulation concept” has been employed repeatedly to explain the pathogenesis of experimental acute pancreatitis; peptide and cholinergic secretagogues cause edematous pancreatitis in a supramaximal dose, which induces submaximal secretory responses (Saluja et al., 1989;
Previous pharmacological studies have also suggested the possible involvement of endogenous 5-HT in the initiation/progression of acute pancreatitis; not only the 5-HT depleter para-chlorophenylalanine but also 5-HT2 receptor antagonists reduced the severity of DINP and/or CIEP models (Oguchi et al., 1992; Yoshino and Yamaguchi, 1997). Although the 5-HT2 receptor has now been classified into 5-HT2A, 5-HT2B, and 5-HT2C subclasses, we have demonstrated recently that risperidone, spiperone, and ketanserin, which strongly block 5-HT2A receptors (Bonhaus et al., 1995; Knight et al., 2004), attenuated the hyperenzymemia and histological alterations in the CIEP model, and their potency order paralleled their reported pK\textsubscript{i} values at the 5-HT2A receptors but not those at 5-HT2B and 5-HT2C receptors (Hamada et al., 2007). Although risperidone dose-dependently attenuated the serum IL-6 levels, plasma amylase/lipase levels, platelet counts, mortality, and histological alterations (edema, inflammatory cell infiltration, and necrosis) in the DINP model. Thus, it is tempting to speculate that risperidone attenuates the initiation and progression of acute pancreatitis through its actions on 5-HT2A receptors. Bonhaus et al. (1995) have demonstrated the existence of 5-HT2A receptors in the pancreas by RT-PCR and Northern blot analysis. However, risperidone also blocks dopamine D\textsubscript{2} receptors and \(\alpha\)-adrenoceptors, which could possibly be involved in the mechanism of risperidone action. Although further studies are needed to clarify this point, it should be noted that R-96544, which has 600 to 2800-fold higher affinity for the 5-HT2 receptor has now been classified into 5-HT2A, 5-HT2B, and 5-HT2C subclasses, we have demonstrated recently that risperidone, spiperone, and ketanserin, which strongly block 5-HT2A receptors (Bonhaus et al., 1995; Knight et al., 2004), attenuated the hyperenzymemia and histological alterations in the CIEP model, and their potency order paralleled their reported pK\textsubscript{i} values at the 5-HT2A receptors but not those at 5-HT2B and 5-HT2C receptors (Hamada et al., 2007). Also in the present study, risperidone dose-dependently attenuated the serum IL-6 levels, plasma amylase/lipase levels, platelet counts, mortality, and histological alterations (edema, inflammatory cell infiltration, and necrosis) in the DINP model. Thus, it is tempting to speculate that risperidone attenuates the initiation and progression of acute pancreatitis through its actions on 5-HT2A receptors. Bonhaus et al. (1995) have demonstrated the existence of 5-HT2A receptors in the pancreas by RT-PCR and Northern blot analysis. However, risperidone also blocks dopamine D\textsubscript{2} receptors and \(\alpha\)-adrenoceptors, which could possibly be involved in the mechanism of risperidone action. Although further studies are needed to clarify this point, it should be noted that R-96544, which has 600 to 2800-fold higher affinity for the 5-HT2A receptors than for the 5-HT3 and dopamine D\textsubscript{2} receptors, and the \(\alpha\)- and \(\beta\)-adrenoceptors attenuate hyperenzymemia and histological alteration in the DINP and CIEP models (Ogawa et al., 2003).

Regarding the mechanism of risperidone action, it is noteworthy that 5-HTP, a precursor of 5-HT, decreased the protein concentration of pancreatic juice, and the change (possibly a blockage of exocytosis) was reversed by cyproheptadine, a nonselective 5-HT2A antagonist (Mori et al., 1979). Furthermore, 5-HT enhances vascular permeability (Fujii et al., 1994) and neutrophil chemoattractant production by the endothelial cells (Charles et al., 1991), and the changes are attenuated by 5-HT2A antagonists. Thus, we speculate that risperidone attenuates not only the 5-HT-induced blockage of exocytosis but also resultant local inflammatory responses.

Another possibility is that risperidone inhibits IL-6 release to attenuate the development of SIRS, which is associated...
with shock, hypercoagulopathy, and mortality. This possibility is supported by that 5-HT induces IL-6 production by smooth muscle cells (Ito et al., 2000) or macrophages/lymphocytes (Kubera et al., 2005) in a manner blocked by 5-HT₂₅A antagonists. It has also been reported that 5-HT₂₅A antagonists attenuate 5-HT-induced vasoconstriction (Centurión et al., 2001; Calama et al., 2002) and that risperidone and its active metabolite 9-OH-risperidone reduced 5-HT-induced platelet aggregation (De Clerck et al., 2004). These results, when put under the light of above discussion, suggest that risperidone inhibits the progression of local inflammation (edematous pancreaticitis) to systemic inflammation (necrotic pancreatitis) through its actions on 5-HT₂₅A receptors in the platelets, vascular smooth muscle cells, and macrophages/lymphocytes.

In conclusion, the present study clearly demonstrated that a potent 5-HT₂₅A antagonist, risperidone, ameliorated DINF. Because we have already shown that risperidone attenuates CIEP (Hamada et al., 2007), it may be reasonable to assume that risperidone ameliorates not only mild but also severe pancreatitis and that risperidone provides a new therapy for acute pancreatitis.

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References