Protective effects of rhubarb on experimental severe acute pancreatitis

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INTRODUCTION
Acute pancreatitis is a commonly occurring disease with self-limited course and uneventful recovery. But it can present as a severe form with significant morbidity and mortality. Up to now, the pathogenesis of acute pancreatitis still remains poorly understood and the treatment still remains nonspecific and primarily supportive. Rhubarb, a traditional Chinese herbal medicine, has been widely used in China for the treatment of many diseases. It has also been shown to have a good curative effect on acute pancreatitis in recent years[1,2]. However, fewer experimental data are available to reveal its possible mechanisms. In the present study, we investigated the effects of rhubarb on severe acute pancreatitis (SAP) in rats, and tried to elucidate the possible mechanisms of its clinically well-known therapeutic effect.

MATERIALS AND METHODS

Materials
Cerulein was purchased from BACHEM Co., Ltd. (Switzerland). The tablets of rhubarb were kindly provided by professor Dong-Hai Jiao (Shanghai Xiangshan Chinese Medicine Hospital), which is the ethanol extract from crude rhubarb. The main chemical constituents of rhubarb tablets include emodin, aloe-emodin, rhein, d-catechin, and gallic acid. Sandostatin (somatostatin) is purchased from Novartis Pharma (Switzerland) and Secretin from Eisai Co., Ltd. (Japan). Male Sprague-Dawley rats (provided by the animal center of PUMC Hospital) weighing 350–450 g were used in these studies. They were fed standard laboratory chow and tap water ad libitum and housed in cages in a temperature-(22±2 °C) and humidity-(55±5%) controlled room, with a 12-h light cycle before experimentation.

Protocol I: effects of rhubarb on SAP

Animal models and experimental design SAP was induced by two intraperitoneal injections (ip) of cerulein (40 µg/kg body weight) at 1-hr interval and then the rats were immersed in 22 °C water to the level of the xiphoid in restraint cages for 5 h (stress). Rhubarb (75 or 150 mg/kg body weight) was orally administered (po) twice, 2 and 15 h before the first cerulein injection. The doses of rhubarb were selected according to our preliminary study. Experiments were performed 5 h after the first cerulein injection because previous data had shown that at that time cerulein-induced pancreatitis in the pancreas were the most severe[4]. The time course of cerulein-induced pancreatitis had been confirmed in our early study[5].

Thirty-four rats were randomly divided into five groups and treated as shown below: Control group: normal saline (NS) po+ip, without stress (n=6); Rhubarb group: rhubarb (150 mg/kg) po+NS ip, without stress (n=6); Cerulein+Stress group: NS po+cerulein ip, with stress (n=9); Cerulein+Stress+Rhubarb 75 mg group: rhubarb 75 mg/kg po+cerulein ip, with stress (n=6); Cerulein+Stress+Rhubarb 150 mg group: rhubarb 150 mg/kg po+cerulein ip, with stress (n=7).

Microcirculation in pancreas Local Pancreatic blood flow (PBF) was measured with a hydrogen gas clearance technique prior to sacrifice[6,7]. All animals were anesthetized with an
intrapерitoneal pentobarbital injection (40 mg/kg body weight). Body temperature was monitored by a rectal thermometer and kept at 36–37 °C with a heating lamp over the abdomen. The pancreas was exposed by laparotomy and then a urethane-coated platinum electrode, 80 µm in diameter with a 0.5 mm portion uncoated at its tip, was inserted into the pancreatic duct through an opening at proximal end of the duct and its tip was kept at 2.5 cm away from the duodenum. The incision was covered with a piece of wet gauze to avoid the loss of body warmth and fluid. The rats were then ventilated with 10% hydrogen in air through a nasal tube. Platinum catalyzes the oxidation of gaseous hydrogen to hydrogen ions. The process is accompanied by a release of electrons, which can be measured as current. For measuring the changing rate of the tissue hydrogen concentration, the blood flow can be determined and calculated by using the following formula: blood flow (mL/min/100 g pancreas)=100 (E.) /0.693/T1/2. PBF value was directly provided using a MHG-D1 (Unique Medical Co., Tokyo, Japan) with a built-in computer.

**Serum amylase level and pancreatic wet weight** After measuring PBF, a blood sample was collected from the vena cava to determine serum amylase level by Phadebas amylase test[10]. After decapitation, the pancreas was quickly removed, trimmed of fat and lymph nodes, and weighed to determine the severity of pancreatic edema, expressed as grams pancreatic wet weight per kilogram body weight.

**Histologic examination** A portion of the pancreatic tail from each rat was fixed in 40 g/L neutral-buffered formaldehyde, embedded in paraffin, and stained with hematoxylin and eosin. A blinded pathologist evaluated morphologic changes microscopically. Interstitial edema was scored as 0=absent, 1=expanded interlobular septa, 2=expanded intralobular septa, and 3=separated individual acini. Hemorrhage was evaluated as percentage involvement of the total pancreas: 0=absent, 1=1–10%, 2=11–50%, 3=more than 50%. Vacuolization and parenchymal necrosis were scored as percentage involvement of the examined area: 0=absent, 1=1–10%, 2=11–25%, 3=26–50%, and 4=more than 50%. Polymorphonuclear neutrophil (PMN) infiltration was scored as 0=absent, 1=less than 20 PMNs per intermediate-power field (IPF) (at×200 magnification), 2=20–50 PMNs per IPF, 3=more than 50 PMNs per IPF.

**Protocol II: effects of rhubarb on pancreatic exocrine secretion in rats with SAP**

**Animal models and experimental design** SAP was induced as mentioned in protocol I. Rhubarb (150 mg/kg) was orally administered twice at 2 and 15 h before the first cerulein injection. Sandostatin was subcutaneous injected (sc) from the tail vein. A laparotomy was then performed through a midline incision, and the duodenal loop was identified. The main pancreatic duct was ligated proximal to the duodenal, and polyethylene tube (PE10) was inserted into the duct for draining pancreatic juice[10]. Pancreatic juice was collected for 30 min. The protein content of pancreatic juice was quantitated by Follin’s method. Amylase was assessed by Phadebas test and bicarbonate concentration by blood gas analyzer (ABL510, Denmark).

**Statistics** All data were expressed as mean±SD. For continuous data, statistical analysis of data was accomplished by Student’s t-test and analysis of variance (ANOVA). Histologic data were expressed as percentage of the scores and mean±SD and compared by means of nonparametric tests: the Mann-Whitney for two groups and the Kruskal-Wallis for multiple groups. P<0.05 was considered statistically significant.

**RESULTS**

**Part I: protective effects of rhubarb on cerulein+stress -induced SAP in rats**

Severe edema and diffused hemorrhage in the pancreas were observed macroscopically in the Cerulein+Stress group. Upon microscopic examination, edema, hemorrhage, focal acinar necrosis, conspicuous vacuolization, and PMN infiltration in the pancreas were observed also in the Cerulein+Stress group. In the Cerulein+Stress+Rhubarb group, the severities of pancreatitis were alleviated with reduced scores of histology (P<0.01, P<0.05). There was no significant change in edema between the groups (Table 1).

The data of pancreatic wet weight, serum amylase level, and PBF were shown in Table 2. There were no significant changes in the rats treated with rhubarb alone compared with the controls. The pancreatic wet weight and serum amylase level markedly increased in the Cerulein+Stress group. With the addition of rhubarb (150 mg/kg) to SAP model, a slight decrease in pancreatic wet weight from 11.60±0.61 g/kg to 10.65±0.77 g/kg (P<0.05) and an obvious reduction of 50% in serum amylase (P<0.01) was observed. PBF was 242±17 mL/min/100 g before the treatment. In the Cerulein+Stress+Rhubarb group, it dropped to 93±5 mL/min/100 g (38% of the normal value) and partially recovered in the Cerulein+Stress+Rhubarb 150 mg group (135±12 mL/min per 100 g, 60% of the normal value, P<0.01 vs the SAP group).

**Table 1** Effect of rhubarb on morphologic alterations in pancreas in rats with severe acute pancreatitis

| Group                  | n | Edema | Hemorrhage | Vacuolization | Necrosis | PMN infiltration |
|------------------------|---|-------|------------|---------------|----------|-----------------|
| Control                | 6 | 0     | 0          | 0             | 0        | 0               |
| Rhubarb                | 6 | 0     | 0          | 0             | 0        | 0               |
| Cerulein+Stress        | 9 | 2-3   | 2-3        | 2-3           | 2-3      | 2-3             |
| Cerulein+Stress+Rhubarb 75 mg | 6 | 3    | 1 (0.0)    | 2-3           | 1-2      | 1-2             |
| Cerulein+Stress+Rhubarb 150 mg | 7 | 2-3   | 1-2 (1.0)  | 1-3           | 1-2      | 1-2             |

Values are expressed as the range of the scores, with the mean±SD. The nonparametric test (Kruskal-Wallis method) showed aP<0.05, bP<0.01 vs Cn+St group; and no significant difference in edema.
Table 2 Effect of rhubarb on the changes of pancreatic wet weight, serum amylase activity, pancreatic blood flow

| Group          | n | Pancreatic wet weight (g/ kg) | Serum amylase activity (U/ L) | Pancreatic blood flow (mL/ min/ 100 g) |
|----------------|---|-------------------------------|-------------------------------|-------------------------------------|
| Control        | 6 | 3.29±0.12                     | 81 360±2 200                  | 242±17                              |
| Rhubarb        | 6 | 3.34±0.14                     | 85 370±2 910                  | 238±18                              |
| Cerulein+Stress| 9 | 11.60±0.61                   | 458 490±43 100                | 93±5                               |
| Cerulein+Stress+Rhubarb 75 mg | 6 | 10.99±0.91                   | 321 710±89 800                | 113±12                             |
| Cerulein+Stress+Rhubarb 150 mg | 7 | 10.65±0.77                   | 298 650±36 450               | 135±12                             |

\*P <0.05, \*\*P <0.01 vs control group; \*P <0.05, \*\*P <0.01 vs Cn+St group.

Table 3 Effect of rhubarb and Sandostatin on the exocrine function of pancreatitis in rats

| Group          | n | Volume (µL/ 30 min) | Bicarbonate (mmol/ L) | Protein (mg/ mL) | Amylase (U/ L) |
|----------------|---|---------------------|-----------------------|-----------------|---------------|
| Control        | 6 | 697.30±22.13        | 139.50±38.98          | 12.33±1.65      | 157 580±14 038|
| Rhubarb        | 6 | 704.58±29.52        | 108.00±38.31          | 12.87±2.52      | 154 000±18 717|
| Sandostatin    | 6 | 685.90±36.49        | 123.00±35.04          | 13.21±0.92      | 156 916±8 540 |
| Cerulein +Stress| 6 | 192.22±28.83        | 130.67±41.69          | 3.64±0.98       | 69 440±13 449 |
| Rhubarb+Cerulein+Stress | 6 | 177.33±46.70        | 403.00±68.59         | 2.62±0.65       | 3 768±990     |
| Sandostatin+Cerulein+Stress | 6 | 216.60±19.08        | 134.83±59.69         | 3.18±0.75       | 4 285±3 148   |

\*P <0.05, \*\*P <0.01 vs control group; \*P <0.05, \*\*P <0.01 vs Cn+St group.

**Part II: the effects of rhubarb on pancreatic exocrine function in cerulein-stress-induced SAP**

After pretreatment with rhubarb or somatostatin, total volume, amylase activity, protein content, and bicarbonate concentration of pancreatic juice in both Rhubarb group and Sandostatin group did not differ significantly from the controls (Table 3). Amylase activity in Cerulein+Stress group declined to 44%. In addition, the volume and protein output reduced significantly compared with that of the control group. No significant improvement was found in the volume and protein content of pancreatic juice in the Cerulein+Stress+Rhubarb group and the Cerulein+Stress+Sandostatin group compared with Cerulein+Stress group, whereas the amylase activity of pancreatic juice in the Cerulein+Stress+Rhubarb group and the Cerulein+Stress+Sandostatin group significantly decreased than that of the Cerulein+Stress group (P<0.01), and were 2.4% and 2.7% of the control respectively. Interestingly, the bicarbonate concentration of Cerulein+Stress+Rhubarb group increased to 403±69 mmol/ L, which was three times of the control. This phenomenon could not be seen in Cerulein+Stress+Sandostatin group.

**DISCUSSION**

Severe acute pancreatitis still has a comparatively high mortality due to the systemic inflammatory response syndrome leading to multiple organ failure. Molecular and pathophysiologic investigations have allowed us to get more information about the events in the initiation and the natural course of acute pancreatitis, and subsequently to know more about how to deal with it. Despite considerable experimental efforts, the complexity in the evolution of acute pancreatitis is still far from being completely understood.

Since studies of acute human pancreatitis has many limitations due to its rapid and severe clinical course, so innovative therapeutic concepts should first be clarified in animal experiments. The cerulein model of experimental acute pancreatitis has become popular for the analysis of intracellular events in the early phase of pancreatitis. The major limitation of this non-invasive model is that it can only produce a mild, self-limited disorder. In order to establish a non-traumatic, easy to induce and reproducible experimental model of clinical relevance, some researchers have modified the animal treatment protocols. It was revealed that early microcirculatory changes, included the increased permeability of endothelial lining and an accumulation of extravasated fluid in the periblobular space, would be more severe if cold stress was added to cerulein induced pancreatitis[10]. Recently, Ding et al[11] had established a mouse model of severe acute pancreatitis by co-injection of cerulein and lipopolysaccharide, which could produce the same pathological characteristics as those of severe acute pancreatitis in human. In our work, we have used a rat model, in which cerulein-induced mild acute pancreatitis could develop into severe acute pancreatitis under water-immersion stress[12]. Cerulein can cause blocking of zymogen secretion, co-localization of zymogens and lysosome, and digestive enzyme activation. Water-immersion stress can stimulate sympathetic nerve system. In this model, multiple vasoconstrictive factors are released, which contribute to a reduction of pancreatic blood perfusion and tissue hypoxia or anoxia with the consequence of damages of microvascular endothelium. Moreover, an enhanced release of cytokines in turn precipitates the microcirculatory disorders. Our study had shown that cerulein plus water-immersion model evolved a highly reproducible form of pancreatitis that was characterized by hyperamylasemia, pancreatic hemorrhage and reduction of pancreatic blood flow.

The significance of disorders of the microcirculation with the consequence of tissue hypoxia or anoxia has been under consideration in the pathogenesis of acute pancreatitis for several decades[13-15]. The hypothesis that the pathogenesis of acute pancreatitis involves ischemia - reperfusion-associated events has attracted new attention[16,17]. The decreased pancreatic capillary blood flow, reduced functional capillary density, and irregular intermittent perfusion were observed in the specimens of cerulein-induced experimental acute pancreatitis[18]. In addition, experimental studies have indicated that synthesis and release of pro-inflammatory cytokines such as TNFα, IL-1[19], and platelet activating factor (PAF)[20,21], were responsible for local injury and systemic dispersion of the inflammation in the development of pancreatitis. There also had strong evidence that oxygen free radicals were closely associated with the severity of acute pancreatitis[22,23]. Elucidation
of these mechanisms may lead to the possibility of specific therapies aimed at reducing microcirculatory disorders, interrupting the inflammatory process, and therefore preventing tissue injury in acute pancreatitis. Unfortunately, there is still no specific compound for treatment of severe acute pancreatitis other than supportive critical care today.

Rhubarb, a Chinese herbal medicine, has a very broad spectrum of biological activities and pharmacological functions. Rhubarb is used as a laxative, anti-inflammatory, and-homeostatic in the treatment of constipation, diarrhea, jaundice, and gastrointestinal hemorrhage, etc. Clinical studies have shown that rubarb could improve the prognosis of patients with systemic inflammatory reaction syndrome (SIRS) by its antagonizing effect against inflammatory cytokines and complement[21]. As reported by Chen et al., rubarb could reduce the leakage of oxygen radicals from the mitochondria of intestinal mucosa, exert protective effect on barrier of intestinal mucosa, and improve the gastrointestinal blood perfusion in shocked rats[22-28]. It has also been shown that rubarb was effective in alleviating the severity of early phase of acute pancreatitis, and preventing further complications at later stages[29]. The sites of action could be related to its inhibition of pancreatic enzymic activities[29]. In experimental pancreatitis the therapy of Tong Xia purgative method, in which rubarb was the main compound, could alleviate the degree of lung injury mediated by TNF[30]. Taken together, Chinese herbs have many pharmacological substances and therefore have multiple therapeutic effects on acute pancreatitis. This study has shown that administration of rubarb resulted in a marked reduction of serum amylase activity, significant amelioration in the severity of SAP, and improvement of microcirculatory disturbances in pancreas. Rhubarb may play an important role in the regulation of local blood flow of pancreas by eliminating the oxygen free radicals, as well as inhibiting the release of cytokines.

Few studies have characterized the alteration in pancreatic exocrine function after the induction of experimental pancreatitis. Niederau et al.[31] evaluated basal and stimulated pancreatic secretion in vivo and in vitro in four different models of acute pancreatitis. They found that a secretory blockade during pancreatitis was strikingly similar in all models, in particular the pancreatic secretory response to CCK. This secretory blockade might at least partly explain the failure to treat acute pancreatitis effectively by inhibition of secretion. Our preliminary experiment also showed a nearly complete blockade of pancreatic exocrine secretion in rats with SAP (data was not shown). We successfully obtained the pancreatic juice sample by co-injection with CCK analog and secretin at physiological dosage. This study demonstrated a significant reduction of the volume, amylase activity, and protein content of pancreatic juice in rats with SAP. After treatment with rubarb, bicarbonate output was distinctly increased, which has yet unknown significance. Like secretin, rubarb might stimulate flow of bicarbonate- and electrolyte-rich ductular secretion via cAMP, and then exert a protective effect on acute pancreatitis[32], which requires further study.

Our present study showed that rubarb with its natural complexity and typical prescription in combination exerted protective effects on SAP in rats, probably through improvement of pancreatic microcirculation, amelioration of inflammation, inhibition of pancreatic enzyme, and partial alteration of pancreatic exocrine.

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REFERENCES

1. Zheng XL, Wu XZ. A report of 100 cases of acute pancreatitis treated with Chinese and West medicine. Zhongxiyi jiie Jifu Zhongtongxun 1979; 1: 14-17
2. Jiao DH, Shen XM, Jing BW. Clinical study of acute pancreatitis treated with a single recipe of rubarb during the past 17 years. Zhongji Zahi 1994; 35: 172-173
3. Yamaguchi H, Kimura T, Nawata H. Dose stress play a role in the development of severe pancreatitis in rats? Gastroenterol 1990; 98: 1682-1688
4. Yamaguchi H, Kimura T, Mizuma K, Nawata H. Activation of proteases in cerulein-induced pancreatitis. Pancreas 1989; 4: 565-571
5. Liu X, Nakano I, Yamaguchi H, Ito T, Goto M, Koyanagi S, Kinjo M, Nawata H. Protective effect of nitric oxide on the development of acute pancreatitis in rats. Dig D Sci 1995; 40: 2162-2169
6. Furukawa M, Kimura T, Sumii T, Yamaguchi H, Nawata H. Role of local pancreatic blood flow in development of hemorrhagic pancreatitis induced by stress in rats. Pancreas 1993; 8: 499-505
7. Reber HA, Karonjia ND, Alvarez C, Widdison AL, Leung FW, Ashley SW, Lutrin FJ. Pancreatic blood flow in cats with chronic pancreatitis. Gastroenterology 1992; 103: 652-659
8. Ceska M, Birath K, Brown B. A new and rapid method for the clinical determination of α-amylase activities in human serum and urine. Optimal Conditions. Clin Chim Acta 1969; 26: 437-444
9. Tian R, Zhu L. The effect of secretin, CCK-8 and insulin on pancreatic exocrine secretion in isolated rat pancreas. Basic Medical Science Clinics 1997; 17: 353-357
10. Chen HM, Sunamura M, Shibuya K, Yamauchi JI, Sakai Y, Fukuyama S, Mikiyama T, Takeida K, Matsuosu S. Early microcirculatory derangement in mild and severe pancreatitis models in mice. Surg Today 2001; 31: 634-642
11. Ding SP, Li JC, Jin C. A mouse model of severe acute pancreatitis induced with caerulein and lipopolysaccharide. World J Gastroenterol 2003; 9: 584-589
12. Bockman DE. Microvascularature of the pancreas. Relation to pancreatitis. Int J Pancreatol 1992; 12: 11-21
13. Broe PJ, Zuidema GD, Cameron JL. The role of ischemia in acute pancreatitis: studies with an isolated perfused canine pancreas. Surgery 1982; 91: 377-382
14. Pfefeer RB, Lazzarini-Robertson A Jr, Safdidi D, Mixture G Jr, Secoy CF, Hinton JW. Gradations of pancreatitis, edematous, and hemorrhagic, experimentally produced by controlled injection of microspheres into blood vessels in dogs. Surgery 1962; 51: 764-769
15. Slater DN, Bardsley D, Mangnall Y, Smythe A, Fox M. Pancreatic ischaemia: sensitivity and reversibility of the changes. Br J Exp Pathol 1975; 56: 530-536
16. Menger MD, Bonkhoff H, Vollmar B. Ischemia-reperfusion-induced pancreatic microvascular injury. An intravital fluorescence microscopic study rats. Dig Dis Sci 1996; 41: 823-830
17. Toyama MT, Lewis MP, Kuske AM, Reber PU, Ashley SW, Reber HA. Ischemia-reperfusion mechanisms in acute pancreatitis. Scand J Gastroenterol Suppl 1996; 31: 20-23
18. Zhou ZG, Chen YD, Sun W, Chen Z. Pancreatic microcirculatory impairment in experimental acute pancreatitis in rats. World J Gastroenterol 2002; 8: 933-936
19. Gomez-Cambronero LG, Sabater L, Pereda J, Cassinello N, Cams B, Vina J, Sastre J. Role of cytokines and oxidative stress in the pathophysiology of acute pancreatitis: pathological implications. Curr Drug Targets Inflamm Allergy 2002; 1: 393-403
20. Zhao H, Chen JW, Zou YK, Zou XF, Li PY. Influence of platelet activating factor on expression of adhesion molecules in experimental pancreatitis. World J Gastroenterol 2003; 9: 338-341
21. Konturek SJ, Dembinski A, Konturek PJ, Warzecha Z, Jawork J, Gustaw P, Tomaszewska R, Stachura J. Role of platelet activating factor in pathogenesis of acute pancreatitis in rats. Gut
Sanfey H, Bulkley GB, Cameron JL. The role of oxygen-derived free radicals in the pathogenesis of acute pancreatitis. Ann Surg 1984; 200: 405-413

Park BK, Chung JB, Lee JH, Suh JH, Park SW, Song SY, Kim H, Kim KH, Kang JK. Role of oxygen free radicals in patients with acute pancreatitis. World J Gastroenterol 2003; 9: 2266-2269

Peng SM, Wang SZ, Zhao JP. Effect of rhubarb on inflammatory cytokines and complements in patients with systemic inflammation reaction syndrome and its significance. Zhongguo Zhongxiyi Jiehe Zazhi 2002; 22: 264-266

Chen D, Qiao L, Jing B. Effect of rhubarb on oxygen radicals leakage from mitochondria of intestinal mucosa in burned rats. Zhongguo Zhongxiyi Jiehe Zazhi 2000; 20: 849-852

Chen D, Yang X, Jiang X. Clinical and experimental study on effect of rhubarb on gastrointestinal blood flow perfusion. Zhongguo Zhongxiyi Jiehe Zazhi 2000; 20: 515-518

Chen DC, Jin BW, Zhang XY. Therapeutic effects of rhubarb on gastrointestinal failure. China Natl J New Gastroenterol 1996; 2: 206-208

Chen DC, Yang XY, Zhang XY, Chen XY. Protective effect of rhubarb on barrier of intestinal mucosa. China Natl J New Gastroenterol 1997; 3: 81-83

Sun G, Chen MZ, Pan GZ. An vitro study of Qing-yi decoction NO.1 on pancreatic enzyme activity and release. Acta Academiae Medicinae Sinicae 1985; 7: 337-340

Xia Q, Jiang JM, Gong X, Chen GY, Li L, Huang ZW. Experimental study of Tong Xia purgative method in ameliorating lung injury in acute necrotizing pancreatitis. World J Gastroenterol 2000; 6: 115-118

Niederau C, Niederau M, Luthen R, Strohmeyer G, Ferrell LD, Grendell JH. Pancreatic exocrine secretion in acute experimental pancreatitis. Gastroenterology 1990; 99: 1120-1127

Renner IG, Wisner JR Jr, Lavigne BC. Partial restoration of pancreatic function by exogenous secretin in rats with ceruleotide-induced acute pancreatitis. Dig Dis Sci 1986; 31: 305-313

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