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D-Allose has a strong suppressive effect against ischemia/reperfusion injury: a comparative study with allopurinol and superoxide dismutase

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Abstract
Background/Purpose. D-Allose, a rare sugar, is one of the potent inhibitors of ischemia/reperfusion injury of the rat liver. To investigate the potency of this powerful agent we examined its effect against ischemia/reperfusion injury and compared it to that of allopurinol and superoxide dismutase.
Methods. Male Lewis rats were given water ad libitum preoperatively for 12 h and anesthetized by isoflurane inhalation anesthesia. Drugs were administered through a polyethylene catheter inserted into the portal vein for 2 h (D-allose), 10 min (allopurinol), or 5 min (superoxide dismutase) before ischemia, and the livers were then subjected to 70% ischemia, induced by crossclamping the vessels to the lateral and median lobes of the liver for 90 min. Rats were divided into four groups: group 1, pretreated with vehicle (normal saline); group 2, treated with D-allose; group 3, treated with allopurinol; and group 4, treated with superoxide dismutase. The effects of the drugs were evaluated by liver hemodynamics, neutrophil count, myeloperoxidase, liver enzymes, and histological studies.
Results. D-Allose improved liver hemodynamics ($P < 0.001$) and postischemic animal survival ($P < 0.05$) significantly compared with the control group and nonsignificantly compared with the allopurinol and superoxide dismutase groups. Myeloperoxidase activity in the postischemic liver tissue was decreased significantly ($P < 0.05$) by D-allose compared with all other treatment and control groups. Neutrophil count was also significantly ($P < 0.05$) decreased in the D-allose group compared with than that in the control group, as well as the superoxide dismutase group. Only D-allose produced a statistically significant decrease in the level of liver enzymes, compared with levels in the control group.
Conclusions. The moderately protective effect of D-allose, which caused no clinical side effects, is encouraging. D-Allose had the best protective effect against neutrophil-related postischemic injury of the liver tissue, followed by allopurinol and superoxide dismutase. However, a more extensive study is needed to ensure the effects as well as the mechanisms of the effect of this rare sugar.

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Key words D-Allose · Allopurinol · SOD · Liver ischemia · Reperfusion injury

Introduction

Partial or, mostly, total interruption of hepatic blood flow is often necessary when liver surgery is performed. This interruption period is termed "warm ischemia" and during this ischemic period the liver undergoes various injuries. Upon revascularization, when molecular oxygen is reintroduced, the organ undergoes a process termed "reperfusion injury" that causes further deterioration of organ function.

To limit the cause of ischemia/reperfusion (I/R) injury of the liver there have been many reports of the administration of scavengers or inhibitors, such as superoxide dismutase (SOD),[1,2] allopurinol,[3,4] glutathione peroxidase,[5] catalase,[6] facrolimus (FK506),[7] and cyclosporine A,[8] that can interdict oxygen free radicals (OFRs),[9–12] which are said to be responsible for I/R injury, and/or neutrophils. These scavengers have been evaluated in different organs using a variety of experimental models.

In addition D-allose, one of the rare sugars, has been reported to reduce I/R injury.[13] Rare sugars have been defined by the International Society of Rare Sugars (ISRS) as monosaccharides and their derivatives that are rare in nature (The First International Symposium of ISRS, Takamatsu, Japan, 2002). Bhuyan et al.[14] have established a method for the production of D-allose from D-psicose, using immobilized L-rhamnose isomerase. Rare sugars have received increasing attention in recent years for a variety of usages, such as low-calorie carbohydrate sweeteners and bulking agents.[14] However, the biological functions and physiological effects of rare sugars have been little known so far. Nevertheless, D-allose, an aldo-hexose, is one of the

exceptions among rare sugars whose biological function has been suggested. Arnold et al. (US patent no. 5620960; 1997) reported that D-allose substantially inhibited segmented neutrophil production and lowered platelet count, without other detrimental clinical effects. We have also performed a series of experiments using hepatic I/R in a rat model to evaluate the protective effect of D-allose, and found that an ameliorative effect was achieved mainly by reducing the number of neutrophils after reperfusion;[15] as well, an immunosuppressive effect of D-allose was shown in a model of allogenic orthotopic rat liver transplantation,[15] with minimum side effects in comparison to the well-known immunosuppressive agent, FK506.[16] Because neutrophils have been considered to be mostly responsible for the pathophysiological changes occurring after liver transplantation, as well as during hepatic I/R, suppression of neutrophils has been reported to be critical to reduce these injuries. Therefore, in the present study, to investigate the potency of inhibition of I/R injury, we compared the inhibitory effects of D-allose with those of two other well-known inhibitors, allopurinol and SOD.

Materials and methods

Experimental design

Male Lewis rats, weighing 220 to 270 g, obtained from Charles River Japan (Yokohama, Japan) were fasted for 12 h before surgery, but were allowed to drink water ad libitum. The rats were anesthetized by inhalation of isoflurane (Abbott Laboratories, Chicago, IL, USA) and 99% oxygen at a flow rate of 0.2 l/min. The control group received 0.9% normal saline solution as a vehicle, and the treatment groups received SOD (Sigma Chemical, St. Louis, MO, USA), at 6000 IU/kg; allopurinol (Sigma Chemical), at 100 mg/kg; and D-allose (D-allopyranose; Fushimi Pharmaceutical, Tokyo, Japan), at 200 mg/kg. For each of these agents, a single bolus dose was used, which is the most effective dose used for animal experiments. The drugs were administered intravenously into the portal vein through its iliac branch by a catheter.

Surgical procedure

After anesthesia, the abdominal cavity was opened through a transverse incision close to the xyphosternum, extending both sides up to the midaxillary line. During the experiment, the abdomen was covered with a piece of gauze moistened with warm saline to prevent the visceral organs from drying. The liver was exposed, including the hepatoduodenal ligament. A polyethylene catheter (Intramedic PE-50; Clay Adams, Parsippany NJ, USA) was inserted into the cecal branch and the drugs were administered in the portal vein before beginning 90 min of ischemia. The livers were then subjected to 70% ischemia, induced by crossclamping the vessels to the lateral and median lobes of the liver for 90 min. After 90-min total ischemia, the abdominal wall was closed. After the surgery, the animals were housed in separate cages maintained at room temperature, and were allowed access to food and water ad libitum, while follow-up of postoperative survival was done for a period of 7 days.

Measurements

Hemodynamics

The peripheral tissue blood flow (PTBF) of the liver was measured with a laser-Doppler tissue flow meter (Advance, Tokyo, Japan). The probe was fixed on the liver surface. All the flow values were recorded every minute. A transit time flow meter (Transonic Systems, Ithaca, NY, USA) was used to measure the portal venous flow (PVF). A probe (model 45151) was placed on the portal vein and was fixed with ultrasound transmission gel (Parker Laboratories, Orange, NJ, USA). A 15-min stabilization period was allowed to permit all the vascular parameters to stabilize after surgery. The probes were placed on the ischemic lobe and on the portal vein before starting reperfusion, and the flow values were recorded every minute until the end of reperfusion.

Myeloperoxidase

Liver tissues were weighed and homogenized with hexadecyltrimethylammonium bromide (HTAB) buffer (0.5% HTAB in 50 mM potassium phosphate buffer, pH 6.0) with a Polytron homogenizer (Brinkmann, Westbury, NY, USA), and myeloperoxidase (MPO) activity was measured spectophotometrically by the method of Krawisz et al.[17]

Sampling

After 120-min reperfusion, venous blood was collected for biochemical measurements and livers were preserved for histopathology. Blood samples were centrifuged at 2000 rpm for 5 min and the plasma supernatant was stored at −80°C until measurement was done.

Biochemical measurements

Serum lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and total bilirubin (T. Bil) were measured to assess the damage to the hepatic parenchyma. An automatic analyzer (model 7050; Hitachi, Tokyo, Japan) was used to determine the levels of these enzymes.

Histopathological examination

At the end of reperfusion, after the collection of blood for biochemical measurements, the livers were removed, fixed with buffered formaldehyde solution, and stained with hematoxylin-eosin for light microscopic study. Sections were made at 3-μm intervals, and a blind analysis was performed. The extent of sinusoidal congestion, venous congestion, and mitochondrial swelling was graded on a five-point scale, ranging from 0 (intact) to 4 (very severe).

Statistics

Data values are presented as means ± SE. The hemodynamics were analyzed by two-way analysis of variance and post-hoc analysis by Fisher's protected least significant difference (PLSD) test. The Mann-Whitney U-test was used for the comparison of survival and for semiquantitative analysis of tissue injury. Student's *t*-test was used for the intergroup comparisons of MPO and liver function tests. When the *P* value was less than 0.05, the comparison was regarded as significant.

Results

Hemodynamics

Peripheral tissue blood flow

The allopurinol and SOD groups showed an average postischemic peripheral liver tissue blood flow of 69.4 ± 26.8% and 66.2 ± 21.6% of the preischemic value, respectively (Fig. 1a), which was significantly different ($P < 0.002$) from that of the control (55.1 ± 19.3%) D-allose showed much greater improvement, with an average value of 82.7 ± 32.1%, which was significantly different from that of the control ($P < 0.001$), as well as that of allopurinol and SOD ($P < 0.05$; Fig. 1a).

Portal venous flow

D-Allose, allopurinol, and SOD showed average portal venous flows of 75.8 ± 21.5%, 72.6 ± 25.1%, and 70.0 ± 23.3% of the preischemic value, respectively (Fig. 1b). D-Allose and allopurinol had a significant difference ($P < 0.002$) from the control value, while SOD showed an improved value compared with that of the control group, but this difference failed to reach statistical significance.

Animal survival rate

Figure 2 shows the 1-week survival of the animals after 90-min ischemia followed by 120-min reperfusion. On the first day after the procedure, a significant difference ($P < 0.05$) in survival was observed in the D-allose (56%) and allopurinol (66%) groups when compared to the control (33%) group. There was also a significant difference ($P < 0.05$) for the allopurinol group compared to the SOD (45%) group. However, on the second day, this difference between allopurinol and SOD was not demonstrated, but a significant difference in all treatment groups was observed when compared to control. Furthermore, no deaths were observed in the groups from the third day on. At 7 days of observation, the total survival rate obtained in the D-allose, allopurinol, SOD, and control groups was 56%, 45%, 45%, and 17%, respectively. However, pretreatment the D-allose exerted a nonsignificant beneficial effect over allopurinol and SOD.

Neutrophils in whole blood

Figure 3a,b shows the percentages and total numbers of neutrophils in the venous blood at the end of 2-h reperfusion after 90-min ischemia. The percentage of neutrophils decreased significantly ($P < 0.05$) in the D-allose and allopurinol groups compared to the control group, but SOD failed to reach a significant difference from the control. There was a significant ($P < 0.05$) and nonsignificant decrease in the D-allose group compared to the SOD and allopurinol groups, respectively. The total number of neutrophils also showed the same tendency, without a significant difference between the D-allose and SOD groups.

MPO activity

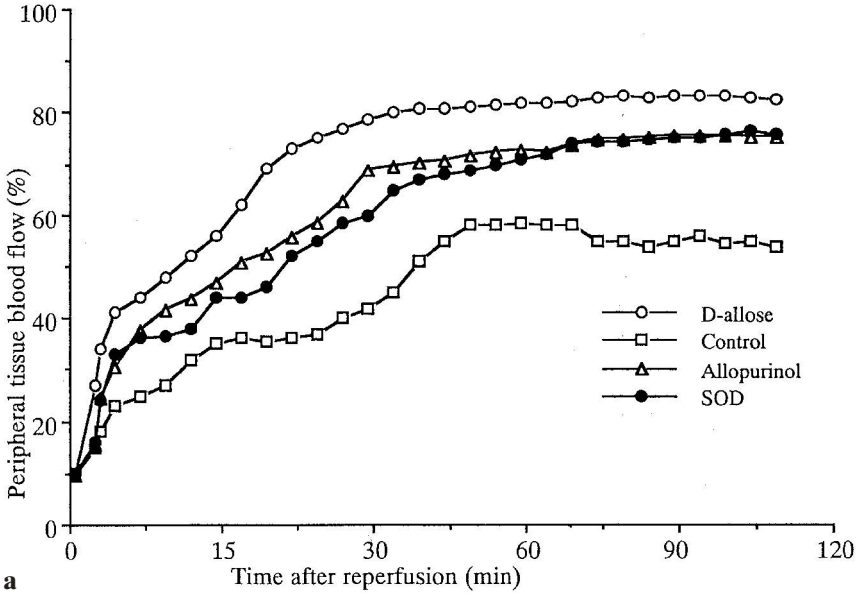
The MPO activity in the liver tissue in all the treatment groups was significantly decreased ($P < 0.05$) when compared with the control group at the end of 2-h reperfusion following 90 min of hepatic ischemia. The activity in the D-allose group was also significantly decreased ($P < 0.05$) compared with that in the allopurinol and SOD groups (Fig. 4). There was no significant difference between the allopurinol and SOD groups.

Enzymatic assays

As shown in Fig. 5a,b, serum levels of LDH, AST, and ALP after 2-h reperfusion following 90 min of ischemia were significantly higher ($P < 0.05$) in the control group when compared to the D-allose group, whereas in the other treatment groups, the values were nonsignificantly lower than that of the control group. However, there was no significant difference among the treatment groups.

Histological assessment of liver tissue

The scores for semiquantitative assessment of tissue injury are shown in Fig. 6. Sinusoidal congestion was



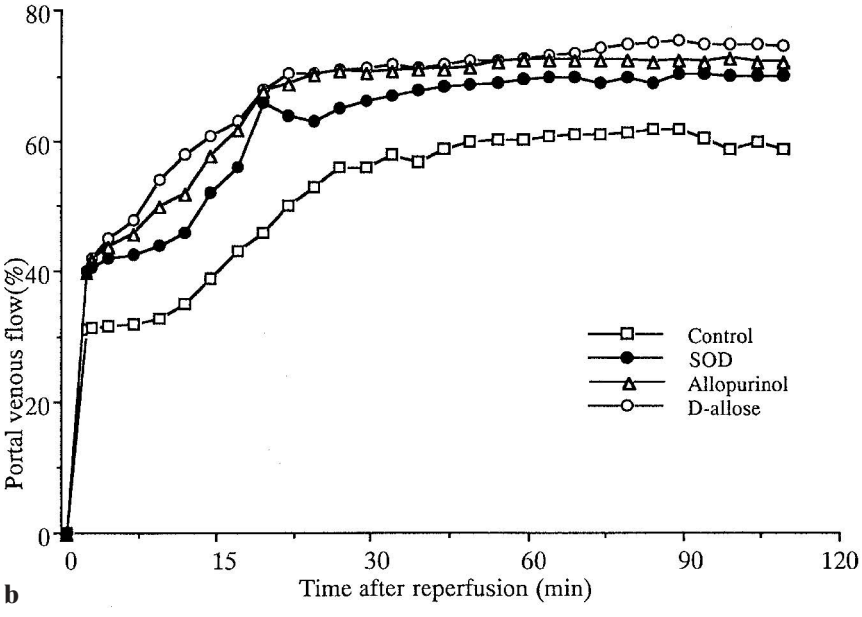


Fig. 1. a Effect of various drugs on postischemic peripheral liver tissue blood flow in the rat after 90-min partial ischemia followed by 2-h reperfusion. Flow was measured during reperfusion. D-Allose vs control, $P < 0.001$; allopurinol vs control, $P < 0.002$; superoxide dismutase (*SOD*) vs control, $P < 0.002$; D-allose vs allopurinol, $P < 0.05$; D-allose vs SOD, $P < 0.05$. **b** Effect of various drugs on postischemic portal venous flow in the rat after 90-min partial ischemia followed by 2-h reperfusion. Flow was measured during reperfusion. D-Allose vs control, $P < 0.002$; allopurinol vs control, $P < 0.002$

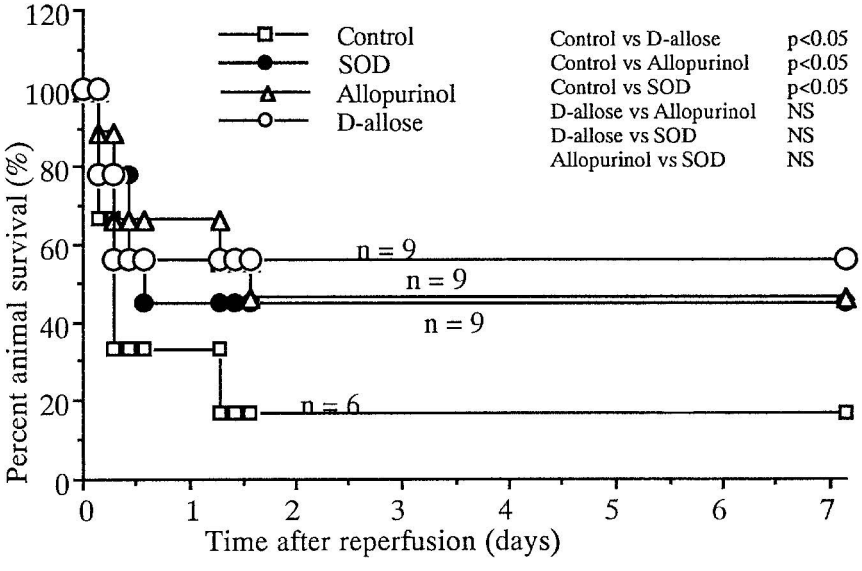
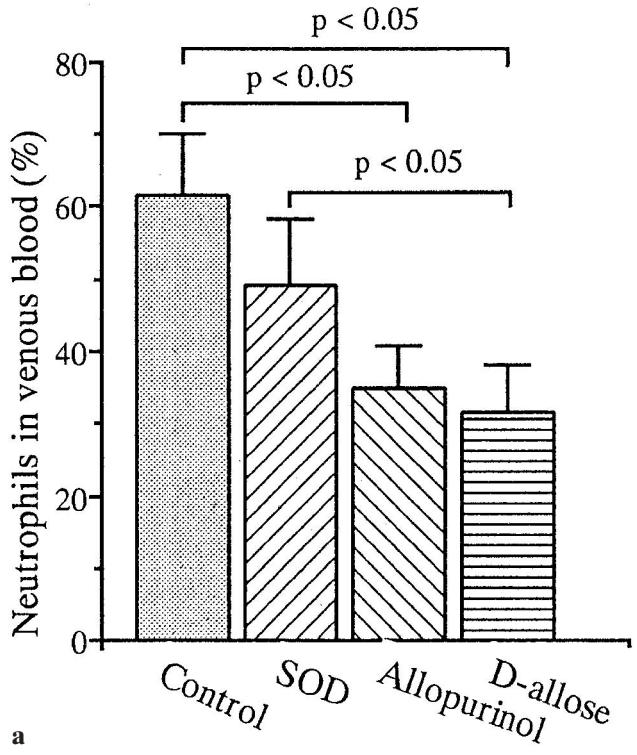
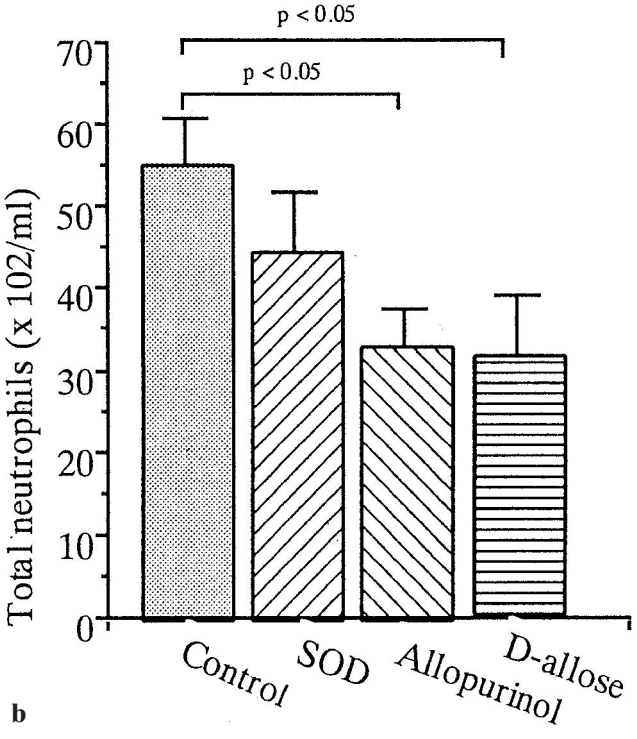


Fig. 2. Percent animal survival for 1 week after 90-min partial liver ischemia followed by 2-h reperfusion. On the seventh postoperative day, the control group showed poor survival. D-Allose showed improved survival compared with the control group. *NS*, not significant



a



b

Fig. 3a,b. Effect of the drugs on **a** percentage of blood neutrophils and **b** total number of neutrophils. Neutrophils were counted in venous blood taken at the end of 2-h reperfusion

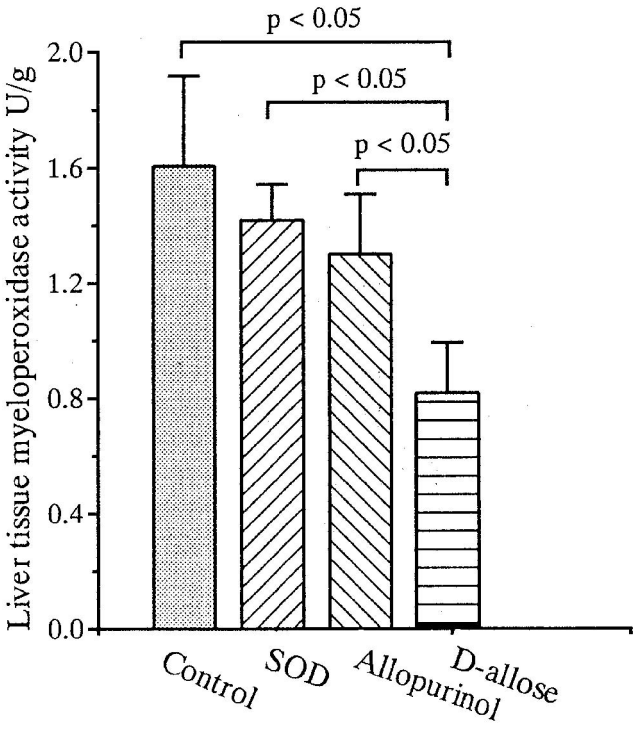


Fig. 4. Changes in liver tissue myeloperoxidase (MPO) activity in the groups after 2-h reperfusion following 90-min partial liver ischemia. D-Allose significantly reduced the activity of MPO compared with that in the control as well as the other treatment groups. $*P < 0.05$ versus corresponding values in the D-allose group

observed, at moderate to severe levels in three rats and at a very severe level in three rats in the control group; and at moderate to severe levels in four rats each in the SOD and allopurinol groups, whereas it was mild to moderate in four rats in the D-allose group. Venous congestion was moderate to very severe in five rats in the control group and moderate in all the treatment groups, excepting for one rat which showed severe congestion in the SOD group. Possible mitochondrial swelling was moderate to very severe in all the six rats in the control group; a similar tendency was shown in all the treatment groups, excepting for the D-allose group, which showed less severe swelling than the allopurinol and SOD groups.

Discussion

Reperfusion injury is integrally and intimately related to the inflammatory response which results, initially, in microcirculatory failure and is afterwards followed by necrosis and cell death. Mechanisms of microcirculation failure-related injury are complex. However, several drugs have been reported to prevent I/R injury, such as allopurinol, SOD, glutathione peroxidase, catalase,

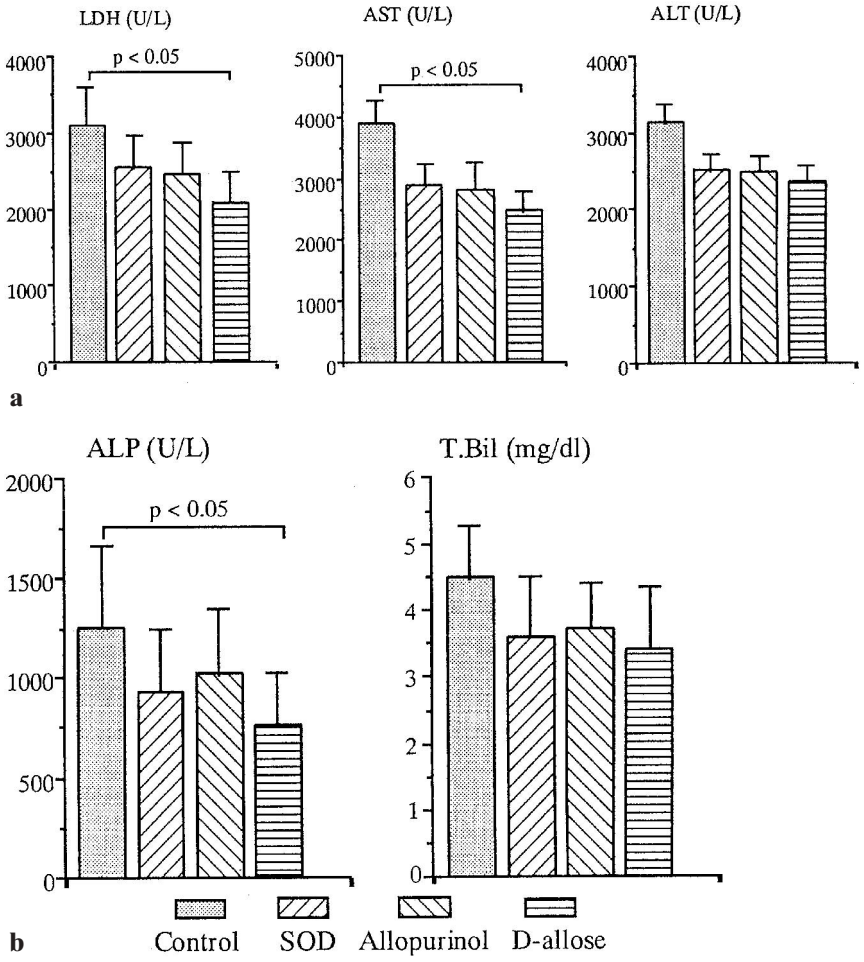


Fig. 5a,b. Serum levels of liver enzymes and total bilirubin (*T. Bil*) after 2-h reperfusion following 90-min partial liver ischemia. Levels of lactate dehydrogenase (*LDH*), aspartate aminotransferase (*AST*), and alkaline phosphatase (*ALP*), were significantly different in the D-allose group compared with those in the control group

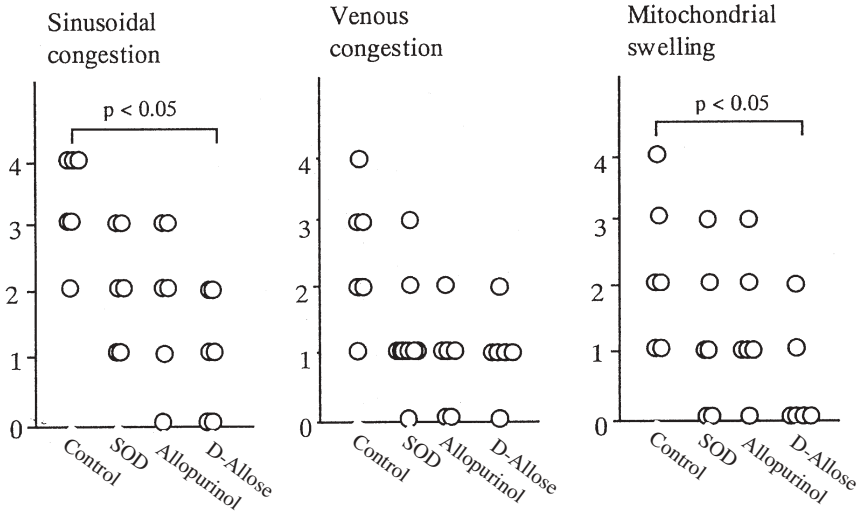


Fig. 6. Semiquantitative assessment of the liver tissue after 2-h reperfusion following 90-min partial liver ischemia. The extent of sinusoidal congestion, venous congestion, and mitochondrial swelling was graded on a five-point scale, ranging from 0 (intact) to 4 (very severe)

adenosine,[18] FK506, and cyclosporine A. Of these, we selected two of the well-known scavengers or antioxidants, allopurinol and SOD, to compare their protective effects to that of D-allose in a rat model of I/R injury.

In the present study, a significant ($P < 0.05$) decrease in LDH, AST, and ALP levels was noted only in the D-allose group compared with levels in the control group. Allopurinol and SOD also decreased these levels, but nonsignificantly, compared with the

control group (Fig. 5a, b). Histological changes of the liver tissue corresponded to liver enzyme levels in decreasing the extent of sinusoidal congestion and mitochondrial swelling (Fig. 6). These results suggest that D-allose, is the most potent inhibitor of I/R injury.

To explain the mechanisms, we examined blood flow, because circulatory disorders of the liver can develop after any kind of mechanical stress and/or occlusion of the hepatic hilum during experimental or clinical manipulation. Studies showed that an increase of the blood flow in the liver can contribute to a good prognosis in liver disease, when the liver has been injured ischemically.[19,20] Therefore, it is important to control the hepatic microcirculatory state after an ischemic insult induced during the treatment of liver diseases. In our study, liver hemodynamics were significantly improved in all the treatment groups compared with the ischemic control (Fig. 1a, b). Among the treatment groups, D-allose improved the blood flow most strongly after reperfusion. Two theories of the mechanism of action have been advanced, one being vasodilation, caused by agents such as prostaglandin E1,[21,22] and the other being the prevention of neutrophil adhesion, or neutrophil suppression in the reperfused tissues. Our result suggests that the mechanism is the prevention of neutrophil adhesion to the vascular endothelium or the suppression of neutrophils. Of the mechanisms of neutrophil adhesion, the endothelial cells damaged by I/R injury may release chemotactic factors that, in turn, stimulate neutrophil activation and adhesion to the endothelium, and the subsequent production of oxygen free radicals (OFRs)[23,24] and, finally, endothelial cell death.[25] According to other studies, neutrophil-endothelium adherence is, in part, a response to reactive oxygen radicals, as well as being a response to cytokines with chemotactic properties.[26,27] Oxygen free radicals are generated by activated neutrophils, and the subsequent adherence to endothelium results in microvascular failure, frequently called the "no-reflow phenomenon," and tissue injury.[28] However, whether neutrophils adhere to the endothelium through the generation of OFRs or whether OFRs are generated by the activated neutrophils and then cause adhesion to the endothelium, neutrophils play a central part in the injury. The cause of neutrophil suppression by D-allose, i.e., whether D-allose suppresses the production of neutrophils or whether it blocks the cascade of neutrophil activities that is involved in I/R injury, is unknown. However, in either case, neutrophils are central to the mediation of the endothelial damage in I/R.

In order to clarify the role of D-allose as an antioxidant, a research group at Kagawa Medical University and at the National Agricultural Research Center for Western Region, Kagawa, have been examining the scavenging activity of D-allose, together with that of other sugars, using electron spin resonance. They found scavenging activities in rare sugars, although the activities were weaker than those in the other common scavengers, SOD and carotinoids.[29] The same group also analyzed the effect of D-allose and other sugars on the production of reactive oxygen species (ROS) from rat blood neutrophils stimulated by the addition of opsonized zymosan. Significant inhibition of ROS production was detected only when D-allose was added, although the inhibition was found to be dose-dependent.

Activated neutrophils can secrete several enzymes, such as MPO and elastase, which are indirectly involved in tissue injury.[30,31] The MPO assay is a widely used method to quantify the neutrophils as an index of inflammation, because MPO is an enzyme released mainly from neutrophils. In an attempt to determine the relationship between neutrophil accumulation and MPO activity, we used MPO as an index of the accumulation of activated neutrophils in the venous blood, because this activity is directly proportional to the neutrophil count in the blood and the tissue injury caused by I/R.[19]

In the control group, we found that MPO activity in liver tissue increased four- to five fold after reperfusion, and, concomitantly, liver damage was significantly worse, with a marked elevation of neutrophils in the blood (Fig. 3a, b). Pretreatment with the drugs reduced the increase of MPO activity in the blood and finally decreased liver tissue injury by several-fold compared ($P < 0.05$) to the control group; D-allose had the best effect against this increase of neutrophils. Allopurinol had the second best effect, but was close to that of D-allose. The effect of SOD was less pronounced. These findings also suggest that D-allose prevented the accumulation of neutrophils in the postischemic liver.

Allopurinol is a xanthine oxidase (XO) inhibitor.[32] The basis of the protective effect of allopurinol against ischemic damage was previously considered to be the preservation of purine metabolites from irreversible breakdown by the inhibition of XO.[33] The other agent that we used in the present study, SOD, is a free radical scavenger, which dismutes the superoxide anion to hydrogen peroxide, providing partial protection of the tissue against free radicals.[9] Studies have mentioned that good results were obtained in preventing the harmful effects of severe liver ischemia with drugs that do not have any direct effect on neutrophil number and activation, such as SOD[9] and allopurinol[10] whereas we obtained significant amelioration of the effects of I/R injury with the agent D-allose, which has a direct effect on neutrophil number and activation, in contrast to the effect of the agents, allopurinol and SOD. We think that an agent like D-allose, which has a direct effect on neutrophils, is of much greater importance than other agents to minimize the injury caused by I/R. However,

the underlying mechanisms of this protective action remain to be elucidated.

Conclusions

This study evaluated the important role of neutrophils in the production of liver I/R injury. Decrease of liver tissue MPO is suggested to be a good marker of better function and survival of I/R-injured livers. The use of drugs such as D-allose, allopurinol and SOD shows a modulatory effect in improving the liver function after I/R, with the superiority of D-allose being shown. This improvement in turn, induces better organ condition and better animal survival. However, further studies are required to elucidate the mechanism by which D-allose exerts its beneficial effect, as well as to investigate whether it improves functions in the I/R-injured liver other than those studied in the present report.

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