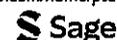# 学位論文

Partial replacement of D-glucose with D-allose

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induced by peritoneal dialysis fluid in rats

香川大学大学院医学系研究科

分子情報制御医学専攻

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Original Article

Partial replacement of D-glucose with D-allose ameliorates peritoneal injury and hyperglycaemia induced by peritoneal dialysis fluid in rats

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Abstract

Background: Peritoneal dialysis (PD) is a crucial dialysis method for treating end-stage kidney disease. However, its use is restricted due to high glucose-induced peritoneal injury and hyperglycaemia, particularly in patients with diabetes mellitus. In this study, we investigated whether partially replacing D-glucose with the rare sugar D-allose could ameliorate peritoneal injury and hyperglycaemia induced by peritoneal dialysis fluid (PDF).

Methods: Rat peritoneal mesothelial cells (RPMCs) were exposed to a medium containing D-glucose or D-glucose partially replaced with different concentrations of D-allose. Cell viability, oxidative stress and cytokine production were evaluated. Sprague–Dawley (SD) rats were administrated saline, a PDF containing 4% D-glucose (PDF-G4.0%) or a PDF containing 3.6% D-glucose and 0.4% D-allose (PDF-G3.6%/A0.4%) once a day for 4 weeks. Peritoneal injury and PD efficiency were assessed using immuno-histological staining and peritoneal equilibration test, respectively. Blood glucose levels were measured over 120 min following a single injection of saline or PDFs to 24-h fasted SD rats.

Results: In RPMCs, the partial replacement of D-glucose with D-allose increased cell viability and decreased oxidative stress and cytokine production compared to D-glucose alone. Despite the PDF-G3.6%/A0.4% having a lower D-glucose concentration compared to PDF-G4.0%, there were no significant changes in osmolality. When administered to SD rats, the PDF-G3.6%/A0.4% suppressed the elevation of peritoneal thickness and blood D-glucose levels induced by PDF-G4.0%, without impacting PD efficiency.

Conclusions: Partial replacement of D-glucose with D-allose ameliorated peritoneal injury and hyperglycaemia induced by high concentration of D-glucose in PDF, indicating that D-allose could be a potential treatment option in PD.

Keywords
D-Allose, peritoneal dialysis, rare sugar

Introduction

In recent years, the number of end-stage kidney disease (ESKD) patients has increased worldwide.[1] Diabetes mellitus (DM) is the most frequent cause of ESKD.[1,2] There are currently three possible therapies for ESKD: renal transplantation, haemodialysis and peritoneal dialysis (PD). Among them, PD is preferable for patients with severe cardiovascular disease and is associated with a higher quality of life (QOL).[3] However, peritoneal injury and hyperglycaemia induced by PD fluid (PDF) limit the application of PD, especially in DM patients with ESKD.[4] PDF contains up to 4% D-glucose to produce high osmolality.

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Exposure to elevated glucose levels and glucose degradation products can lead to peritoneal mesothelial cell loss, as well as the activation of cytokine and angiogenic factor production, ultimately causing progressive fibrosis, angiogenesis and vasculopathy.[5] These peritoneal injuries can greatly enhance peritoneal permeability, thereby restricting the effectiveness and durability of PD.[6,7] In addition, DM patients undergoing PD experience higher increases in blood glucose levels.[8] As a result, maintaining glycaemic control during PD is particularly challenging for patients with DM.[9]

Modifications to PDFs have been made in an attempt to improve the efficiency and sustainability of PD, including the addition of cytoprotective agents and replacement of glucose with other osmotic agents.[7] Rare sugars occur in very small quantities in nature, and approximately 50 types of rare sugars are naturally present.[10,11] D-Allose, a C-3 epimer of D-glucose, is a rare sugar and has 80% sweetness relative to table sugar.[12] D-Allose is considered an ideal alternative to table sugar because it is an ultra-low calorie and nontoxic sugar.[12] Furthermore, as D-allose is a C-3 epimer of D-glucose, D-allose and D-glucose have the same osmolality level. These findings led us to hypothesise that the partial replacement of D-glucose with D-allose could ameliorate peritoneal injury and hyperglycaemia induced by PDF.

Materials and methods

Detailed materials and methods are provided in the Supplemental material.

RPMCs culturing

Rat peritoneal mesothelial cells (RPMCs) isolated from tsSV40T Tg rats were a gift from Dr K Kaneko (Keio University, Tokyo, Japan). RPMCs can be passaged and continuously retain the characteristics of primary cultured PMCs when cultured at 33°C or 38°C in a 5% CO_2 incubator with Medium 199.[13,14] In this study, we maintained RPMCs at 33°C in a 5% CO_2 incubator.

Animals

We purchased 46 male Sprague–Dawley (SD) rats (6-week-old) from Clea Japan (Tokyo, Japan). SD rats were used in this study 1 week after acclimation.

The rats were housed in a climate- and humidity-controlled room (temperature 25°C, 12-h light/dark cycle) and allowed free access to standard chow (CRF-1 powder, Oriental Yeast, Tokyo, Japan) and sterilised water. Animal procedures were conducted in accordance with Japanese law and the Guidelines for Proper Conduct of Animal Experiments (1 June 2006, Science Council of Japan). The study was approved by the Animal Care Committee of Kagawa University (A178:4.4.2019).

Animal experiments

One week prior to the start of PD, all rats were anaesthetised with 2.5 mL/kg of a mixed anaesthetic solution (medetomidine–midazolam–butorphanol) administered subcutaneously in the back. Local anaesthetic was applied to the skin of the neck and back, and a small incision was made. An 8 Fr silicone catheter with six or more holes was inserted through the incision and guided through the subcutaneous tissue to the abdomen, with the tip fixed in the bladder side of the abdominal cavity. The other end of the catheter was exposed several centimetres from the back subcutaneously and firmly fixed by suturing the skin. The injection into the peritoneal cavity through the catheter was confirmed. To investigate the role of D-allose on peritoneal protection, saline, PDF containing 4% D-glucose (PDF-G4.0%) or PDF containing 3.6% D-glucose and 0.4% D-allose (PDF-G3.6%/A0.4%) was administrated through the catheter at a dose of 60 mL/kg. The intraperitoneal (i.p.) administration was performed daily under inhalation anaesthesia with isoflurane (Pfizer, New York, USA) for a duration of 4 weeks, following the methodology outlined in a previous study.[15] After 4 weeks of PDF administration, blood samples and dialysates were collected via jugular vein and peritoneal cavity by a syringe at 0, 30, 60 and 120 min of dwell time after i.p. injection of PDF-G4.0% (Figure 1(a)). The peritoneal permeability was evaluated by the dialysate-to-plasma (D/P) ratio of blood creatinine and the absorption of glucose from the dialysate (D/D0). Rats were euthanised by isoflurane overdose, and then the peritoneum was harvested for histological staining. To investigate the effect of D-allose replacement on blood glucose elevation, 24-h fasted rats were i.p. injected by a syringe with saline, PDF-G4.0% or PDF-G3.6%/A0.4%. The blood was collected via jugular vein and the glucose levels were measured at 0, 30, 60 and 120 min following the injection of saline or PDFs (Figure 1(b)).

Statistical analyses

Data were analysed using GraphPad Prism 8.0 (GraphPad Software, San Diego, California, USA) and presented as means $\pm$ SEMs. Two-way analysis of variance (ANOVA) with repeated measurements compared the peritoneal equilibration test (PET) and blood glucose levels, while one-way ANOVA analysed other data. Post hoc Tukey's test was conducted for significant ANOVA results. Statistical significance was defined as $p < 0.05$.

Results

Partial replacement of D-glucose with D-allose attenuated D-glucose-induced RPMCs death, oxidative stress and cytokine production

The molecule structures of D-glucose and its C3-epimer D-allose are shown in Figure 2(a). As exposure to high
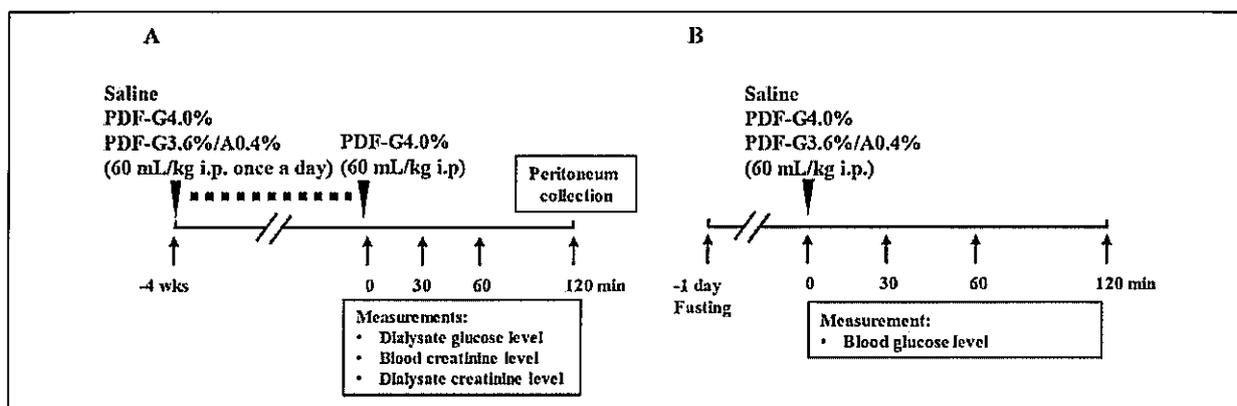
Figure 1. Protocols for animal experiments. (a) Rats were i.p. administered once a day with saline, PDF containing 4.0% D-glucose (PDF-G4.0%) or PDF containing 3.6% D-glucose and 0.4% D-allose (PDF-G3.6%/A0.4%) using a catheter at a dose of 60 mL/kg·day for 4 weeks. On the final day, PDF-G4.0% was administered using a syringe at a dose of 60 mL/kg. Peritoneal equilibration tests were conducted by measuring glucose levels in drained dialysates and creatinine levels in both blood and drained dialysates at 0, 30, 60 and 120 min. After scarification, the rat peritoneum was collected. (b) Saline, PDF-G4.0% or PDF-G3.6%/A0.4% was i.p. administered using a syringe to rats at a dose of 60 mL/kg. Blood glucose levels were measured at 0, 30, 60 and 120 min after the administration of saline, PDF-G4.0% or PDF-G3.6%/A0.4%.

i.p.: intraperitoneal; PDF: peritoneal dialysis fluid.

concentrations of D-glucose can impair human PMCs,[16] we investigated the morphological changes of RPMCs after incubation with 4% D-glucose. As shown in Supplemental Figure 1, cell shrinkage and nuclear fragmentation were observed 24 h after incubation in a medium containing 4.0% D-glucose. Moreover, the viability of RPMCs was significantly reduced after incubation in a medium containing 4.0% D-glucose, compared to the normal culture group (G4%: 0.666 ± 0.022, $p < 0.05$ vs. control group). The viability of RPMCs was significantly improved when 10% of D-glucose was replaced with D-allose (G3.6%/A0.4%: 0.777 ± 0.026, $p < 0.05$ vs. G4.0% group) and when 20% of D-glucose was replaced with D-allose (G3.2%/A0.8%: 0.778 ± 0.018, $p < 0.05$ vs. G4.0% group), respectively. However, there was no significant improvement in viability when 5% of D-glucose was replaced with D-allose (G3.8%/A0.2%: 0.722 ± 0.019, $p = 0.338$ vs. G4.0% group) (Figure 2(b)). Additionally, the viability of RPMCs was also significantly improved when 10% of D-glucose was replaced with D-allose in the medium containing 1.5% or 2.3% D-glucose, which are commonly used in clinical PD settings (Supplemental Figure 2). Furthermore, the level of dihydroethidium (DHE) staining, which serves as an indicator of oxidative stress, was significantly increased in RPMCs incubated in medium containing 4.0% D-glucose (G4.0%: 1.846 ± 0.066, $p < 0.05$ vs. control group). The level of DHE staining was significantly reduced when 10% of D-glucose was replaced with D-allose (G3.6%/A0.4%: 1.410 ± 0.031, $p < 0.05$ vs. G4.0% group) and when 20% of D-glucose was replaced with D-allose (G3.2%/A0.8%: 1.331 ± 0.101, $p < 0.05$ vs. G4.0% group). However, there was no significant reduction when 5% of D-glucose was replaced (G3.8%/A0.2%: 1.818 ± 0.130, $p = 0.718$ vs. G4.0% group) (Figure 2(c)). The production of cytokines,

such as transforming growth factor beta (TGFβ) and vascular endothelial growth factor (VEGF), was observed to increase in RPMCs cultured in a medium containing 4% D-glucose, but not in those cultured in a medium containing 3.6% D-glucose and 0.4% D-allose, compared to the normal culture group (Supplemental Figure 3A). The replacement of 5%, 10% and 20% of D-glucose with D-allose did not affect the osmolality of these media (Supplemental Table 1).

Partial replacement of D-glucose with D-allose ameliorated D-glucose-induced peritoneal injury in rats

To assess the potential protective effects of D-allose on peritoneal injury induced by high concentration of D-glucose in a rat model, we administrated saline, PDF-G4.0% or PDF-G3.6%/A0.4% to SD rats. The blood glucose level in the PDF-G3.6%/A0.4% was significantly lower than that in the PDF-G4.0%, while there was no significant difference in osmolality between them (Supplemental Table 2). Compared to the saline group (29.144 ± 1.385 μm), the thickness of the peritoneum was significantly increased in the PDF-G4.0% group (115.344 ± 13.430 μm, $p < 0.05$ vs. saline group), but was attenuated in the PDF-G3.6%/A0.4% group (81.226 ± 4.148 μm, $p < 0.05$ vs. PDF-G4.0% group) (Figure 3(a) and (b)). Rats administered PDF-G4.0% showed significantly higher expression levels of TGFβ and VEGF in their peritoneum compared to those administered saline. However, there were no significant differences in the expression levels of TGFβ and VEGF between PDF-G3.6%/A0.4% and the saline groups (Supplemental Figure 3B).
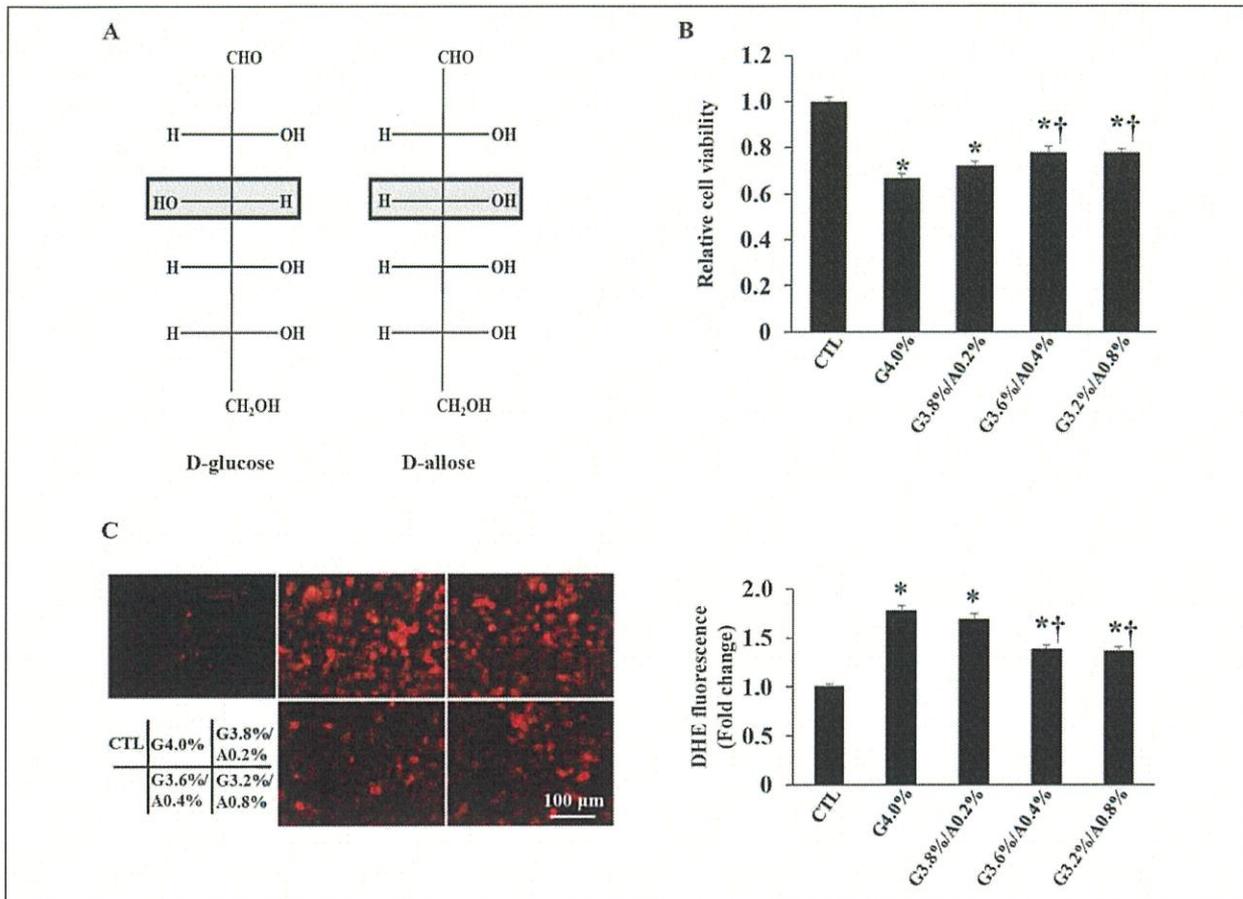
Figure 2. Partial replacement of D-glucose with D-allose attenuated RPMCs death, oxidative stress and cytokine production. (a) Molecule structures of D-glucose and D-allose. (b) RPMC viability were assessed after 24-h incubation in the normal culture medium (Control), medium containing 4% D-glucose (G4.0%), 3.8% D-glucose/0.2% D-allose (G3.8%/A0.2%), 3.6% D-glucose/0.4% D-allose (G3.6%/A0.4%) or 3.2% D-glucose/0.8% D-allose (G3.2%/A0.8%). Data are means ± SEMs ($n = 6$ in each group, obtained from three independent experiments). (c) DHE staining was performed after 24-h incubation in control, G4.0%, G3.8%/A0.2%, G3.6%/A0.4% or G3.2%/A0.8% medium. Scale bar in (c) was 100 μm. The quantitative data are means ± SEMs ($n = 5$ in each group, obtained from three independent experiments). *: $p < 0.05$ versus control group; †: $p < 0.05$ versus G4.0% group.
RPMC: rat peritoneal mesothelial cell; DHE: dihydroethidium.

Partial replacement of D-glucose with D-allose did not alert the PD efficiency

Compared to the saline group, both the administration of PDF-G4.0% and PDF-G3.6%/A0.4% led to a decrease in 2-h glucose D/D0 levels and an increase in creatinine D/P levels. However, there was no significant difference observed between the PDF-G4.0% and PDF-G3.6%/A0.4% groups (Figure 4).

Partial replacement of D-glucose with D-allose ameliorated D-glucose-induced hyperglycaemia in rats

In 24-h fasted rats, blood glucose levels were increased at 30, 60, and 120 min in the PDF-G4.0% group compared to those in the saline group. However, these increases were significantly reduced when PDF-G3.6%/A0.4% was administrated (Figure 5(a)). Compared to the saline group (168.750 ± 4.127 mg·h/dL), the area under the curve (AUC) of blood glucose was increased in the PDF-G4.0% group (345.425 ± 9.465 mg·h/dL, $p < 0.0001$ vs. saline group) but significantly reduced in the PDF-G3.6%/A0.4% group (298.156 ± 10.490 mg·h/dL, $p = 0.002$ vs. PDF-G4.0% group) (Figure 5(b)).

Discussion

The number of patients with kidney failure is growing worldwide. Currently, 3.8 million people receive dialysis to treat ESKD.[17] Among those, approximately 11% of patients are treated with PD.[18] PD offers several advantages
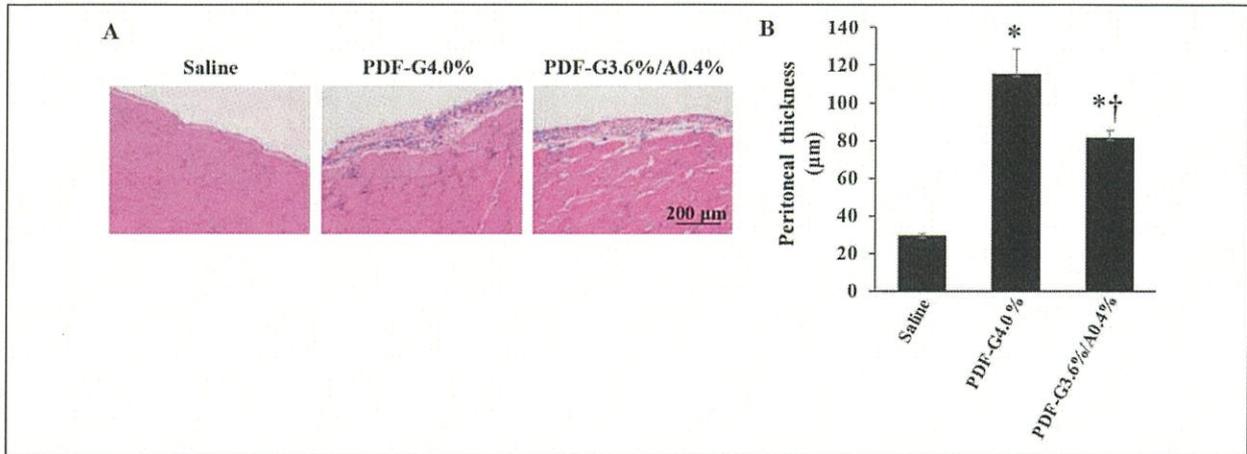
Figure 3. Partial replacement of D-glucose with D-allose ameliorated glucose-induced peritoneal injury. (a) HE staining of the peritoneum. Scale bar, 200 μm. (b) Quantitative evaluation of peritoneal thickness measured at five locations in each sample using ImageJ (Version 1.8.0, NIH). The data are presented as means $\pm$ SEMs, with a sample size (n) of four in the saline group and seven in both the PDF containing 4.0% D-glucose (PDF-G4.0%) and PDF containing 3.6% D-glucose and 0.4% D-allose (PDF-G3.6%/A0.4%) groups. *: $p < 0.05$ versus saline group; †: $p < 0.05$ versus PDF-G4.0% group.
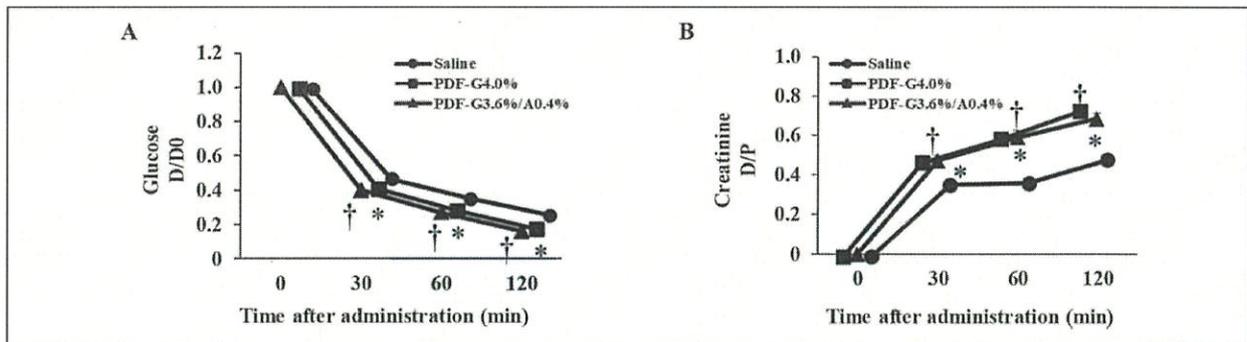HE: haematoxylin and eosin; PDF: peritoneal dialysis fluid.

Figure 4. D-Allose did not alert the peritoneal equilibration test parameters. (a) The 120- to 0-min dialysate glucose ratio (D/D0) and (b) D/P ratio of creatinine. The data are presented as means $\pm$ SEMs, with a sample size (n) of four in the saline group and seven in both the PDF containing 4.0% D-glucose (PDF-G4.0%) and PDF containing 3.6% D-glucose and 0.4% D-allose (PDF-G3.6%/A0.4%) groups. *: $p < 0.05$, PDF-G4.0% group versus saline group; †: $p < 0.05$, PDF-G3.6%/A0.4% group versus saline group. No significant difference between groups PDF-G4.0% and PDF-G3.6%/A0.4%.
D/P: dialysate-to-plasma; PDF: peritoneal dialysis fluid.

over haemodialysis, including low cost and improved QOL with home-based treatment.[19] However, the use of PD is limited by complications such as peritonitis and hyperglycaemia.[20] In particular, high glucose levels that create an osmotic gradient and glucose degradation products can lead to peritoneal injury and fibrosis, resulting in increased membrane permeability.[21] Furthermore, absorbed glucose can raise blood glucose levels and worsen diabetes. Therefore, alternative agents have been investigated.[7]

The peritoneum, acting as a semipermeable membrane, plays a crucial role in the exchange capacity of PD and is directly susceptible to damage caused by PDFs. In recent decades, PDF-induced oxidative stress has emerged as an important risk factor for peritoneal damage in PD.[22] Factors in PDF, including glucose and its degradation products, are associated with the induction of oxidative stress through multiple pathways.[23] Therefore, finding D-glucose alternatives with other safe osmotic agents remains a challenge in reducing oxidative stress. Previous studies have reported that D-allose has protective properties in skin flap ischaemia/reperfusion injury by suppressing oxidative stress.[24] Indeed, the improved cell viability in this study, achieved by replacing D-glucose with D-allose, could be attributed to reduced oxidative stress induced by high concentration of D-glucose in RPMCs.
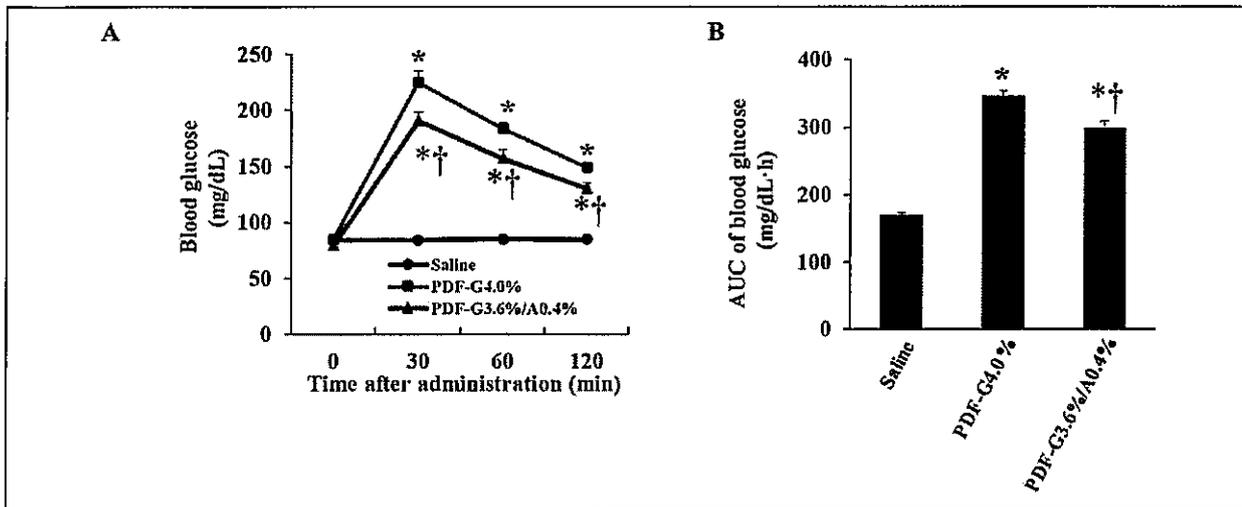
Figure 5. Partial replacement of D-glucose with D-allose suppressed the increase in blood glucose levels. (a) Blood glucose levels over 120 min after i.p. administration of saline, PDF containing 4.0% D-glucose (PDF-G4.0%) or PDF containing 3.6% D-glucose and 0.4% D-allose (PDF-G3.6%/A0.4%) groups. (b) AUC of blood glucose for 120 min following i.p. administration of saline, PDF-G4.0% or PDF-G3.6%/A0.4%. The data are presented as means ± SEMs, with a sample size (n) of 10 in the saline group, 10 in the PDF-G4.0% group and 8 in the PDF-G3.6%/A0.4% group. *: $p < 0.05$ versus saline group; †: $p < 0.05$ versus PDF-G4.0% group. i.p.: intraperitoneal; PDF: peritoneal dialysis fluid; AUC: area under the curve.

Fibrotic changes in the peritoneum are another mechanism involved in PDF-induced peritoneal injury. Two cooperative processes, the fibrosis process itself and the inflammation, are implicated in peritoneal fibrosis.[6,25] Among these processes, the elevated production of TGFβ is a significant early event that mediates fibrogenesis triggered by glucose and its degradation products.[26] In addition to fibrosis, angiogenesis is particularly important because it plays a crucial role in the function of peritoneal transport.[27] VEGF triggers vasodilation, which causes increased permeability of capillary walls and enhances the rapid transportation of solutes. Simultaneously, it contributes to peritoneal fibrosis.[28] Although the direct impact of D-allose on tissue fibrosis has not been previously documented, our findings indicate that replacing D-glucose with D-allose resulted in a reduction in the expression of TGFβ and VEGF, as well as peritoneal thickness. The observed protective effects of D-allose could be attributed to its ability to suppress the production of TGFβ and VEGF.[29]

In this study, it was surprising that the partial replacement of D-glucose with D-allose did not demonstrate any impact on PET results, despite its ability to attenuate the increase in peritoneal thickness. However, it is possible that conducting longer term experiments, extending beyond 4 weeks, could potentially reveal improvements. This is an aspect that should be further investigated in future studies.

DM is the leading cause of chronic kidney disease (CKD) worldwide.[30] The use of PD as a treatment option for CKD patients with DM is constrained due to the occurrence of hyperglycaemia resulting from the high concentrations of glucose in PDF.[8] Therefore, reducing the glucose content in PDF presents a challenge for the management of PD in patients with DM. In this study, replacing D-glucose with D-allose resulted in decreased blood glucose levels while maintaining the osmolality of the PDF. These findings suggest that the use of D-allose-replaced PDF holds promise as a beneficial treatment option for patients with DM.

In the field of PD treatment, various osmotic agents have been developed in addition to D-glucose. Two commercially available agents, icodextrin and amino acids, have the capacity to replace up to 50% of D-glucose in the PDF.[31] The utilisation of icodextrin-containing PDF has shown potential for prolonging the duration of PD treatment. However, the effects of icodextrin on long-term PD treatment and patient survival remain uncertain and require further investigation.[32] On the other hand, amino acid-containing PDF can improve the nutritional status of certain patients but may also lead to acidosis and azotemia.[33] Hence, there is an urgent need for the development of novel PD agents.

D-Allose is naturally occurring in very small quantities in the environment, but we have developed a new manufacturing method in our facility, allowing for large-scale production.[34] However, there are still many unknowns regarding the physiological behaviour of D-allose, and it is currently being researched. Previous studies have shown that monosaccharides, including D-glucose, D-fructose and D-allulose, can degrade at high pH and temperature.[35,36] D-Allose may also degrade in such environments. Therefore, it is important to investigate the potential

degradation of D-allose, especially during sterilisation processes involving heat. Further studies are needed to examine the characteristics of degradation products generated in such conditions.

Limitations

This study utilised RPMCs and a rat model, thus the effects of D-allose on human PMCs were not investigated. Further research is required to understand the impact of D-allose on human PMCs. Additionally, it has been reported that D-allose is mainly excreted through the kidneys.[37] Therefore, testing D-allose in a rat model with kidney failure would provide insights into the influence of kidney failure on D-allose excretion. Although D-allose did not exhibit toxicity in animal experiments,[38] its uptake and metabolism in cells, particularly mammalian cells, remain unclear. Hence, clinical trials are necessary to evaluate the clinical application of D-allose in humans.

Conclusions

Our results suggest that D-allose may be a promising therapeutic option for reducing the adverse effects of high glucose in PD. Further studies are warranted to explore the effects of D-allose on human PMCs and to evaluate its clinical application in humans.

Authors' note

TO and HYF contributed equally to this work.

Author contributions

TM and KA designed this study. HYF, AT and SY collected and analysed the experimental data from the cultured RPMCs. TO, HYF and TF collected and analysed the data from SD rats. HYF, TO, TS and KO drafted the manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Animal Care Committee of Kagawa University (A178:4.4.2019).

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Informed consent

Informed consent was not sought for the present study, because only cultured cells and rats were used.

Supplemental material

Supplemental material for this article is available online.

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