读书报告

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SGLT1 activity in lung alveolar cells of diabetic rats modulates airway surface liquid glucose concentration and bacterial proliferation

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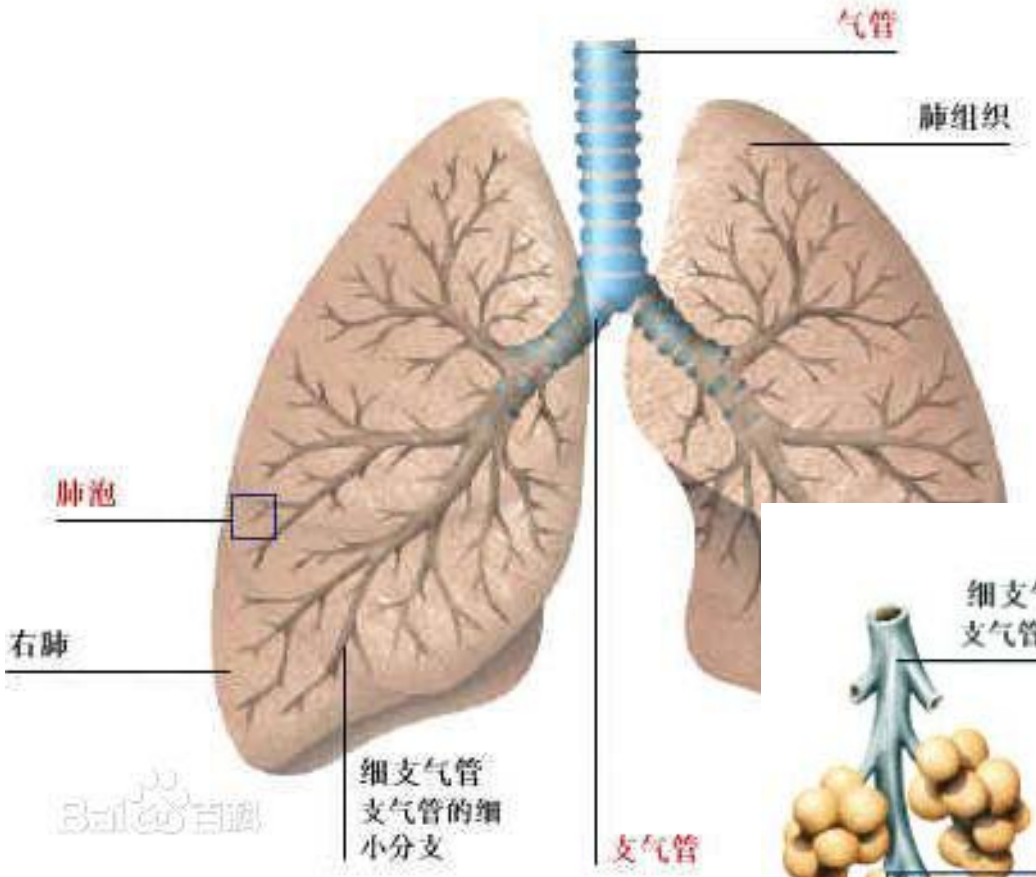
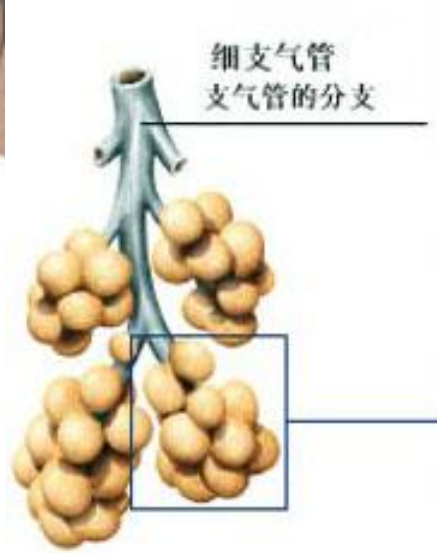
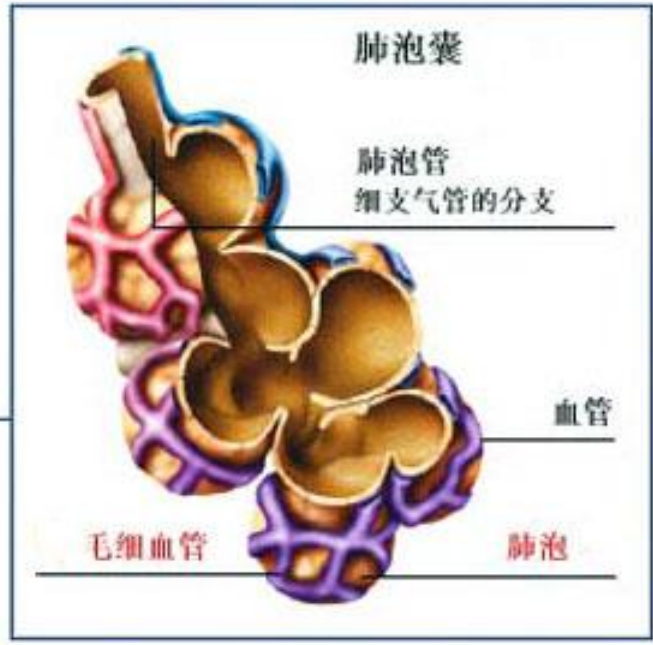
In summary, the results indicate a relationship among SGLT1 activity, ASL glucose concentration and pulmonary bacterial proliferation.

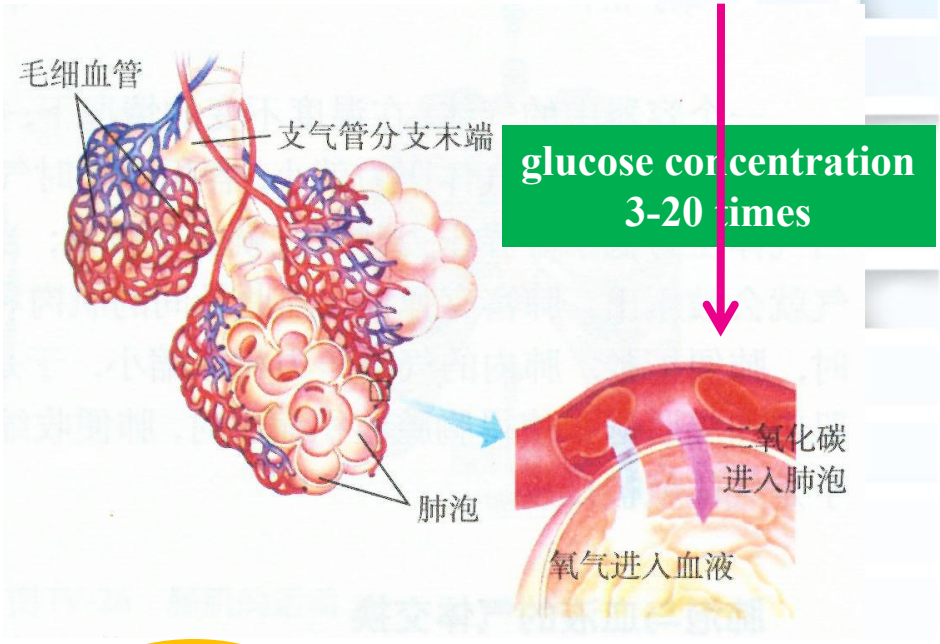
Besides, the study highlights that, in situations of pulmonary infection risk, such as in diabetic subjects, increased SGLT1 activity may prevent bacterial proliferation whereas decreased SGLT1 activity can exacerbate it.


气管
肺组织
肺泡
右肺
细支气管
支气管的细
小分支
支气管


细支气管
支气管的分支


肺泡囊
肺泡管
细支气管的分支
血管
毛细血管
肺泡

The luminal surface of airway epithelium is covered by a thin layer of fluid, termed the airway surface liquid(ASL).



glucose concentration 3-20 times

interstitium

细胞旁路途径

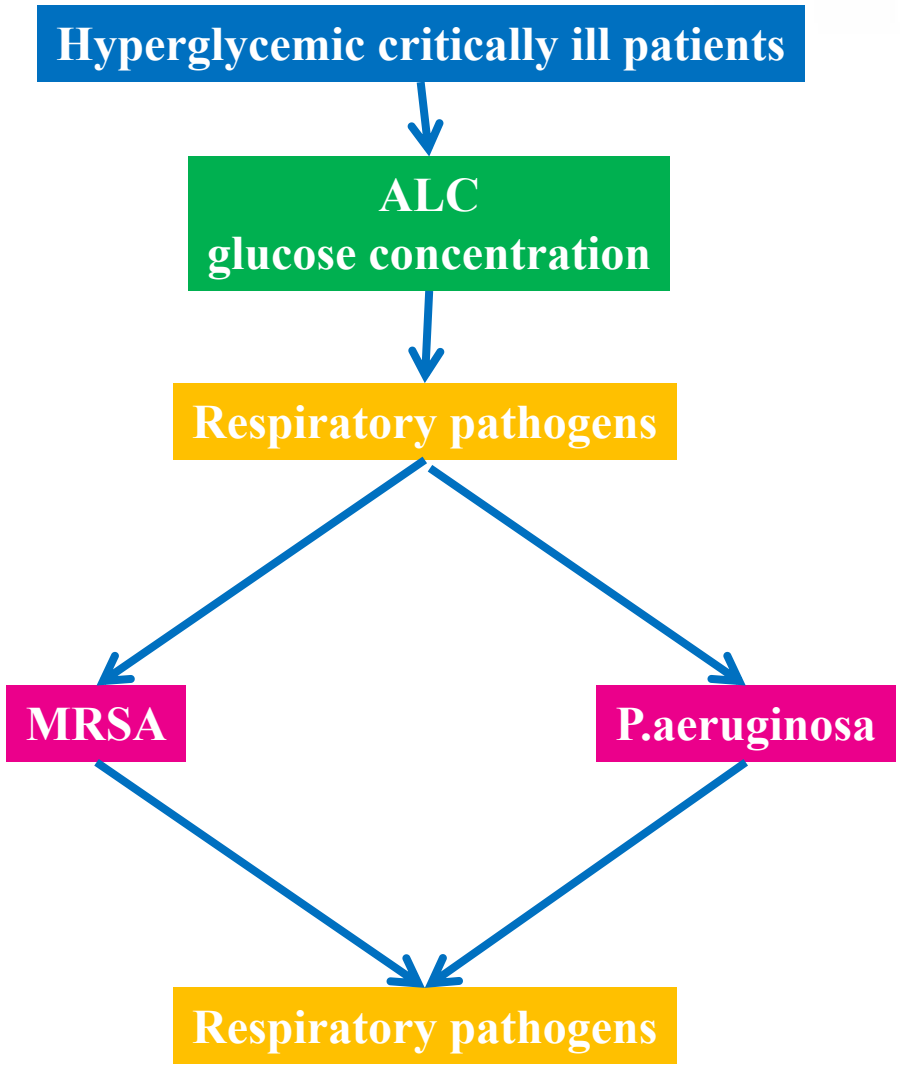
ASL
glucose uptake

GLUT2

proximal airways

SGLT1

distal lung


Hyperglycemic critically ill patients
ALC
glucose concentration
Respiratory pathogens
MRSA
P.aeruginosa
Respiratory pathogens


?
SGLT1

The aims of the present study were to investigate:

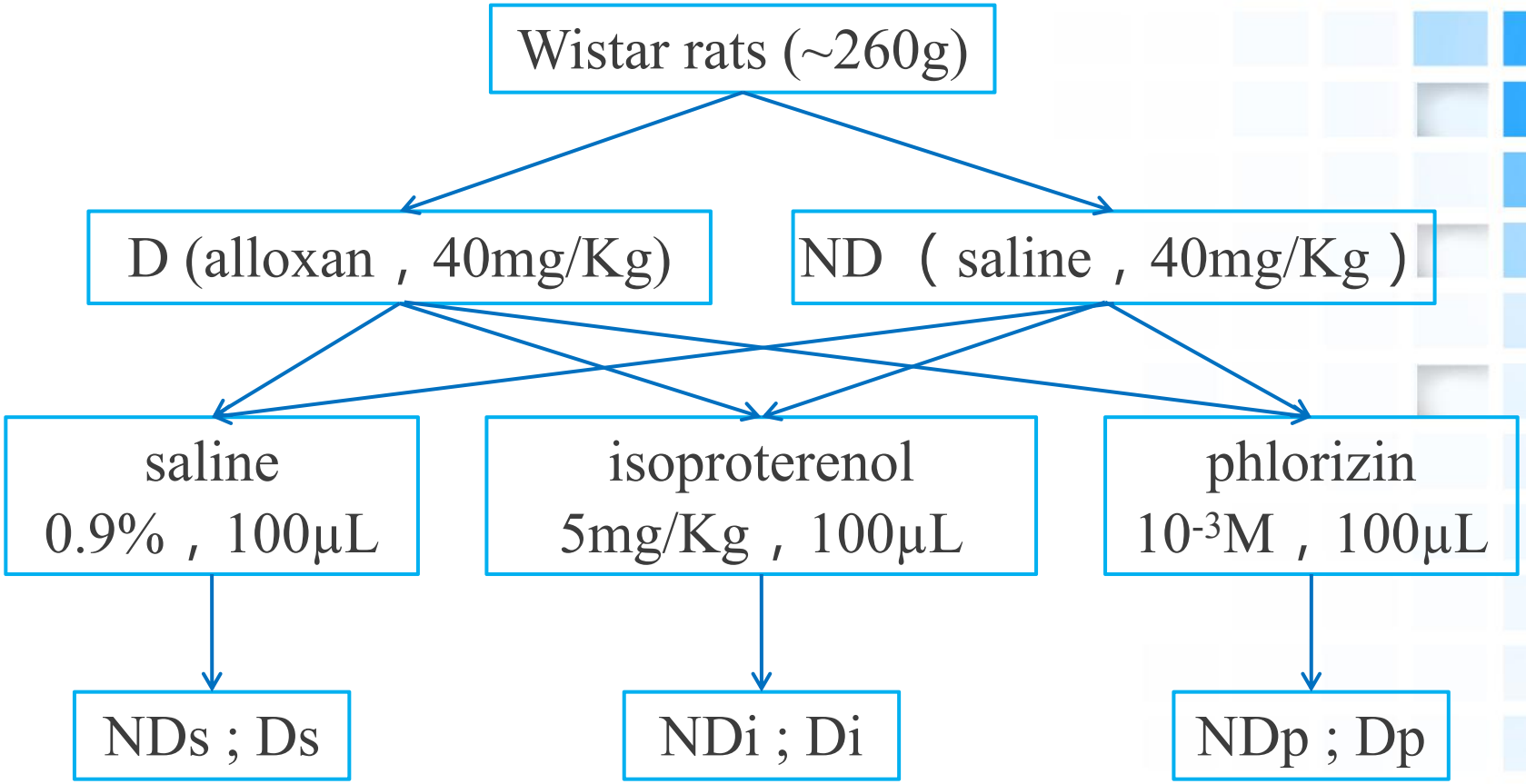
1) the SGLT1 protein subcellular localization in alveolar cells;

2) the glucose concentration on bronchoalveolar lavage (BAL);

3) the proliferation of MRSA and *P. aeruginosa* on BAL, in lung from diabetic rats acutely treated (2 hours after intranasal infusion) with isoproterenol or phlorizin.

Our findings related to the SGLT1 activity in the alveolar epithelium of diabetic rats open new perspectives for the development of drugs that can minimize or maximize respiratory infections, arising from regulation of glucose concentration in ASL.

Methods


Wistar rats (~260g)
D (alloxan，40mg/Kg)
ND（saline，40mg/Kg）
saline
0.9%，100μL
isoproterenol
5mg/Kg，100μL
phlorizin
10-3M，100μL
NDs ; Ds
NDi ; Di
NDp ; Dp

Methods

1、Measurement of isoproterenol effects on the cardiovascular system.

2、Volume measurement of pulmonary water content.

3、Collection of bronchoalveolar lavage (BAL) and tissue sampling.

4、Hematoxylin-eosin and periodic acid-Schiff staining of lung samples.

5、Immunohistochemistry analysis.

6、In vitro bacterial proliferation.

7、In vivo P. aeruginosa proliferation.

8、Analytical Procedures.

9、Statistical analysis.

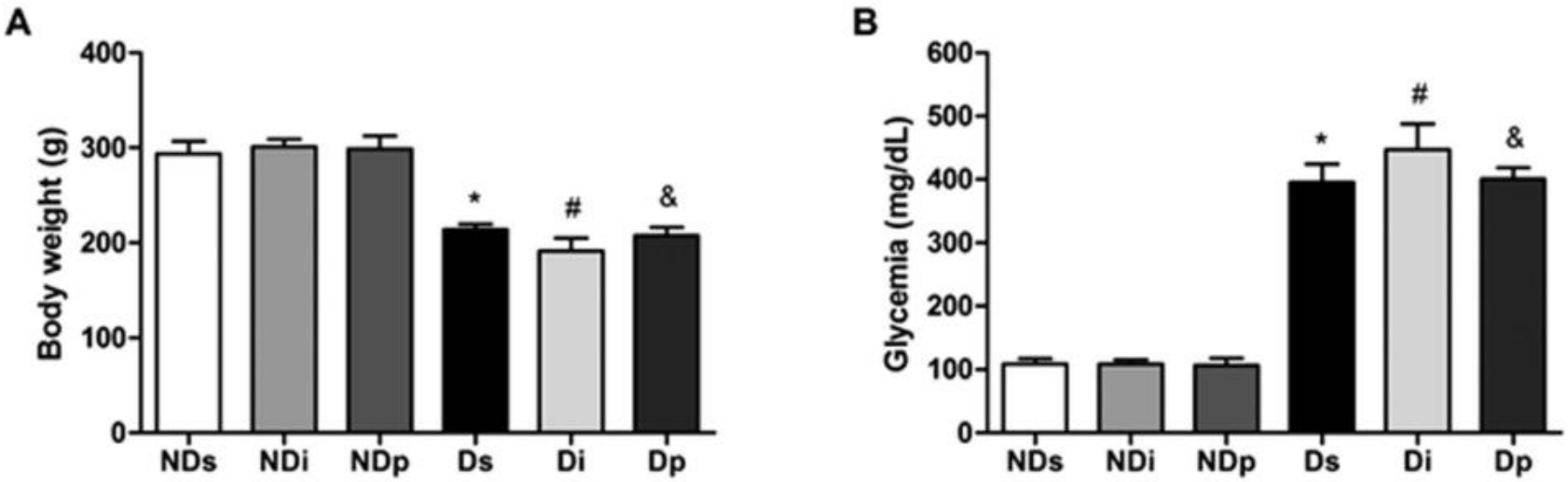
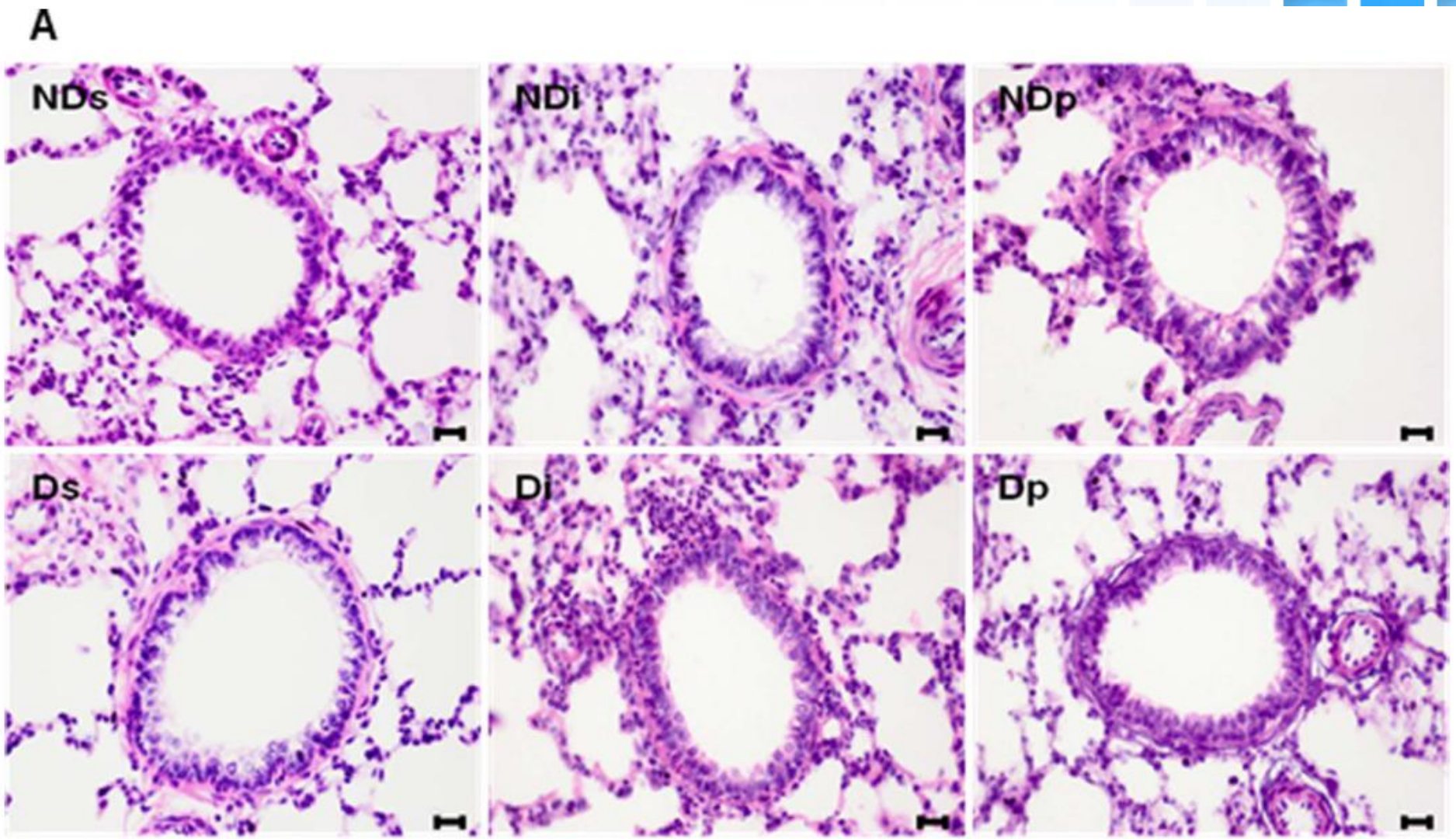


Figure 1. General parameters. Body weight **(A)** and blood glucose concentration **(B)** of non-diabetic saline (NDs), non-diabetic isoproterenol (NDi), non-diabetic phlorizin (NDp), diabetic saline (Ds), diabetic isoproterenol (Di) and diabetic phlorizin (Dp) treated rats. Results are mean ± SEM of 6–8 animals; $^{*}P < 0.05$ vs NDs, $\#P < 0.05$ vs NDi, and $\&P < 0.05$ vs NDp; one-way ANOVA followed by Student Newman Keuls post-test.

Diabetes, isoproterenol and phlorizin do not change alveolar structures in rats.

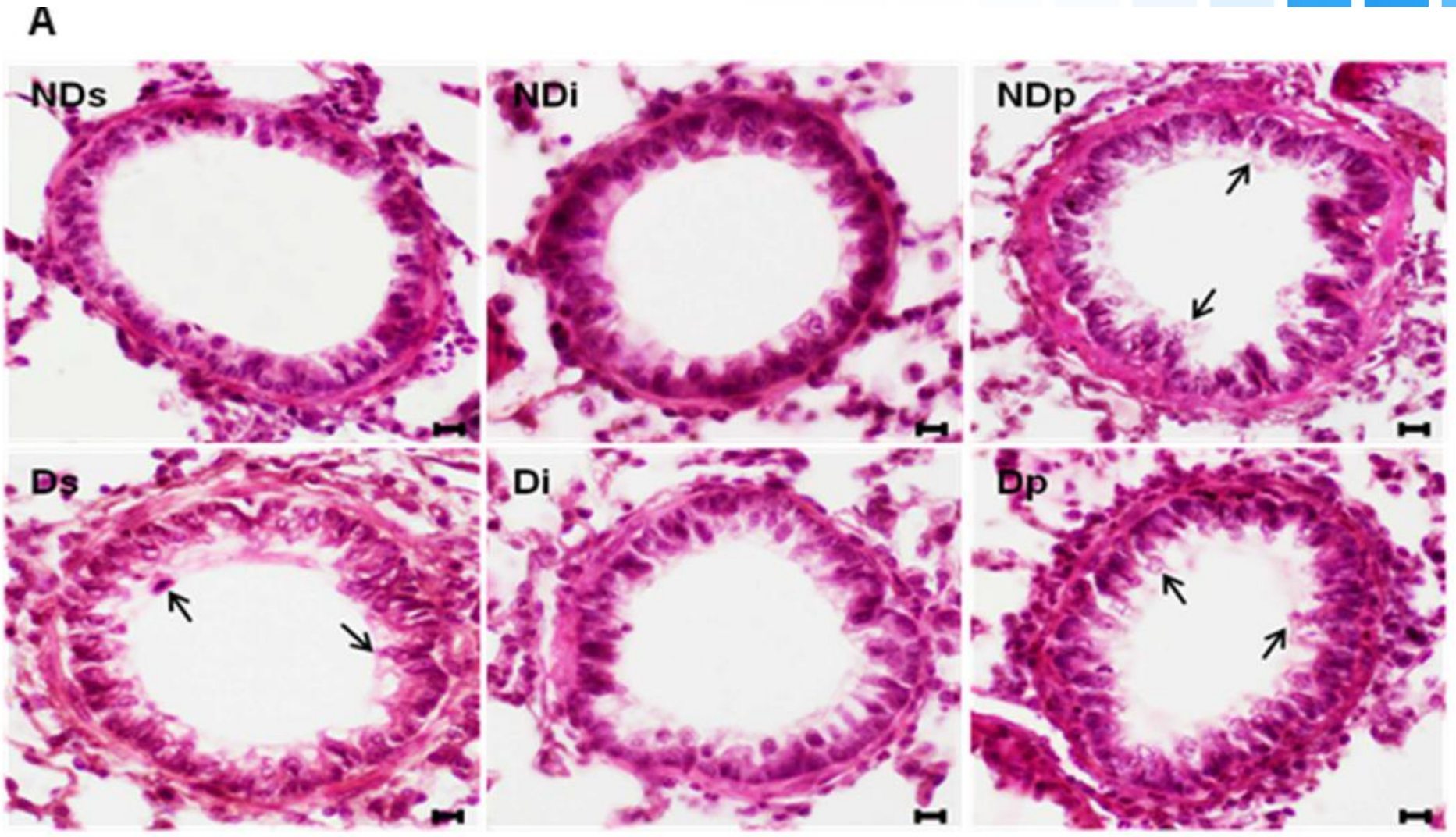


B

Histopathological changes	NDs	NDi	NDp	Ds	Di	Dp
Inflammatory infiltrate	-	-	-	-	-	-
Cell desquamation lumen	-	-	-	-	-	-
Epithelial thickening	-	-	-	-	-	-
Interstitial fibrosis	-	-	-	-	-	-

Figure 2. Hematoxylin-eosin stained of lung tissue. Alveolar and bronchiolar structures in lung from non-diabetic saline (NDs), non-diabetic isoproterenol (NDi), non-diabetic phlorizin (NDp), diabetic saline (Ds), diabetic isoproterenol (Di) and diabetic phlorizin (Dp) treated rats. Hematoxylin-eosin stained sections (**A**), magnification, x400, scale bar, 20 μm, and potential histopathological alterations **(B)**; present (+) and absent (−). Images are representative of 4–6 animals in each group.

Diabetes, isoproterenol and phlorizin modulate mucus secretion.



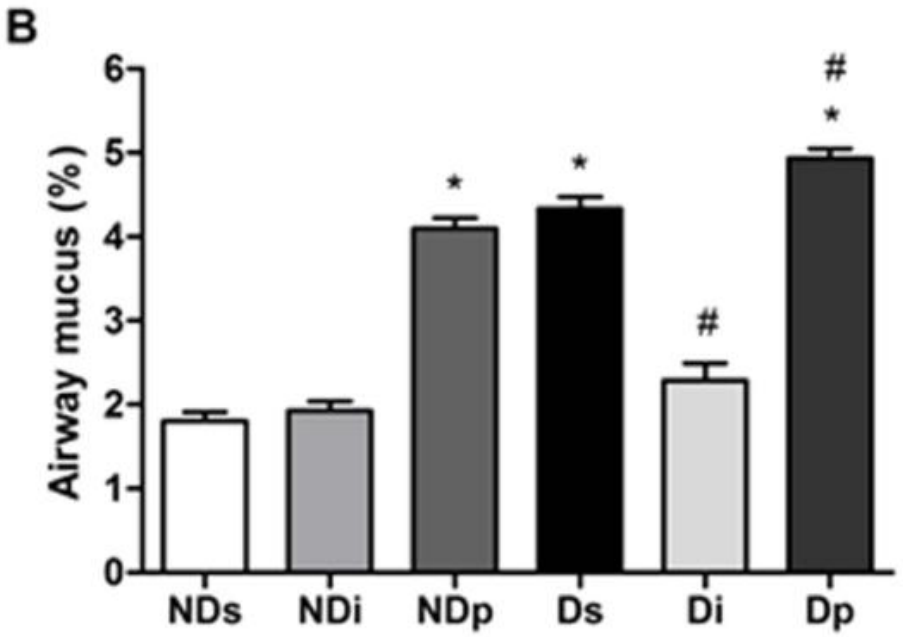
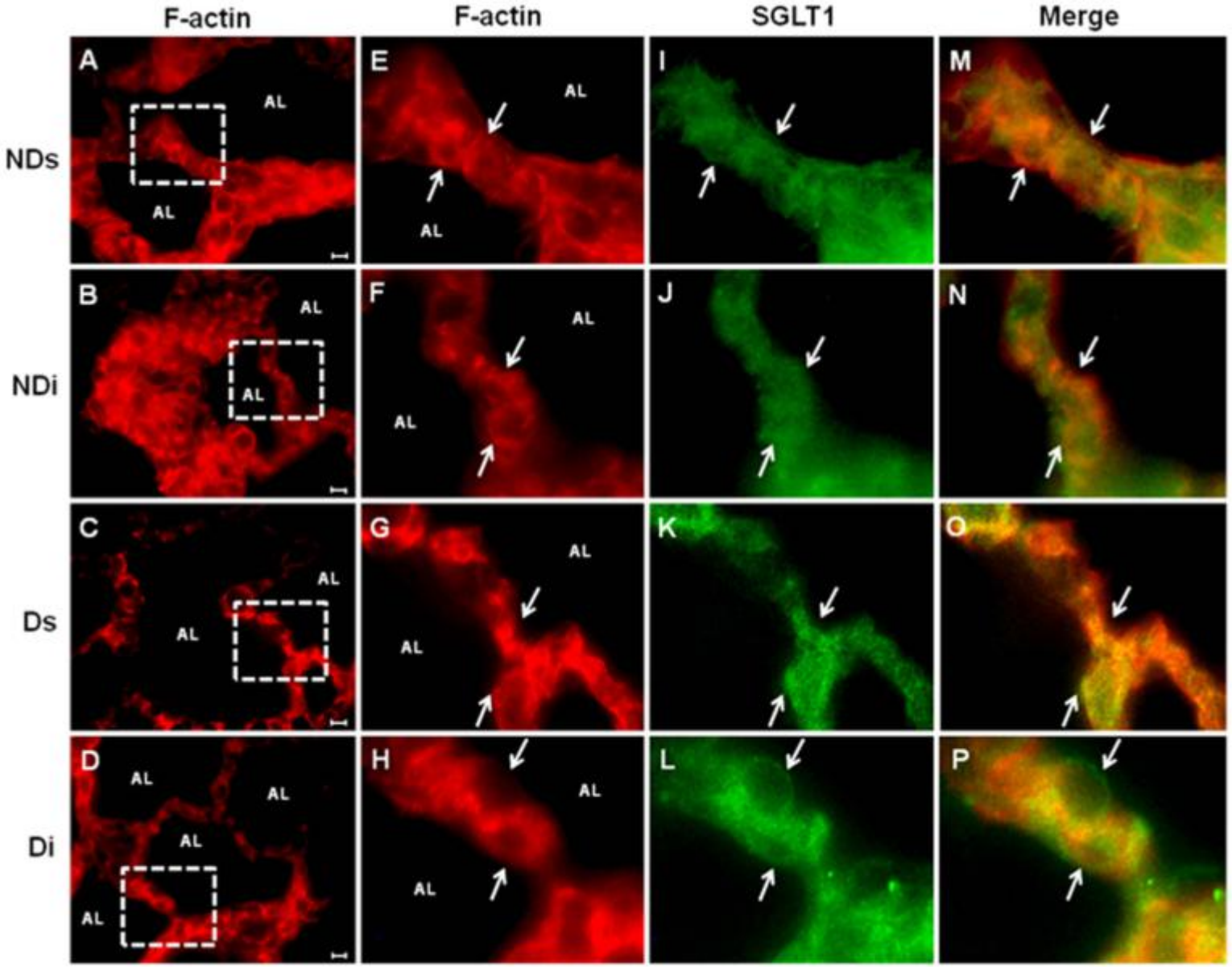
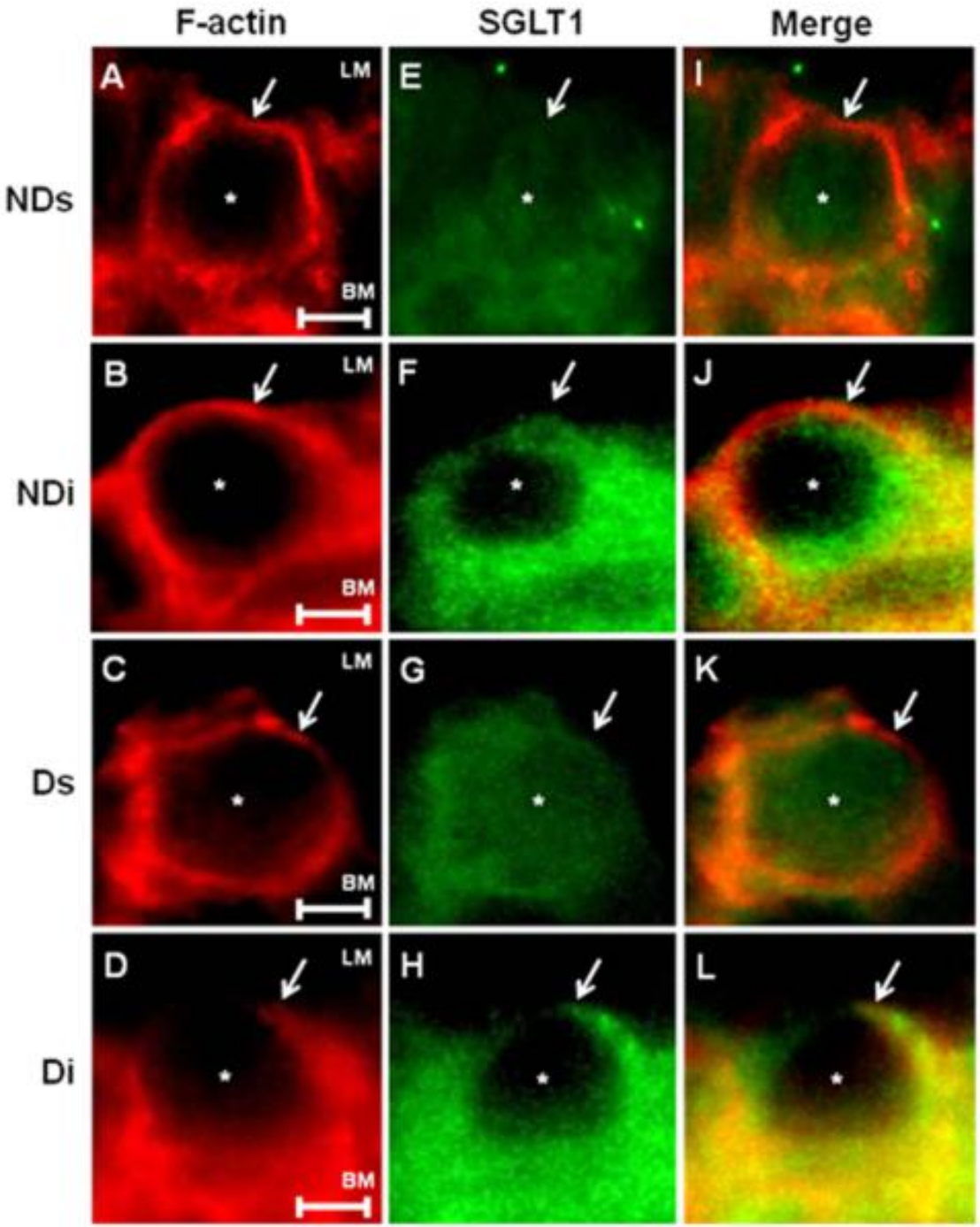


Figure 3. Periodic acid–Schiff (PAS) staining of lung tissue. Bronchiolar PAS stained sections of non-diabetic saline (NDs), non-diabetic isoproterenol (NDi), non-diabetic phlorizin (NDp), diabetic saline (Ds), diabetic isoproterenol (Di) and diabetic phlorizin (Dp) treated rats. (**A**) Photomicrographs of PAS stained lung; black arrows indicate the pink-magenta stained mucus in bronchiolar lumen; magnification, ×400, scale bar, 20 μm. (**B**) Quantitative mucus production, expressed as mucus filled area related to total airway lumen area. Results are mean ± SEM of 4–6 animals; $^{*}P < 0.05$ vs NDs; and $^{\#}P < 0.05$ vs Ds. One-way ANOVA followed by Student Newman Keuls post-test for mean comparisons.

Subcellular distribution of SGLT1 protein in alveolar cells.




F-actin
SGLT1
Merge
NDs
NDi
Ds
Di
A
B
C
D
E
F
G
H
I
J
K
L
LM
BM

Effect of isoproterenol and phlorizin on BAL glucose concentration of diabetic rats.

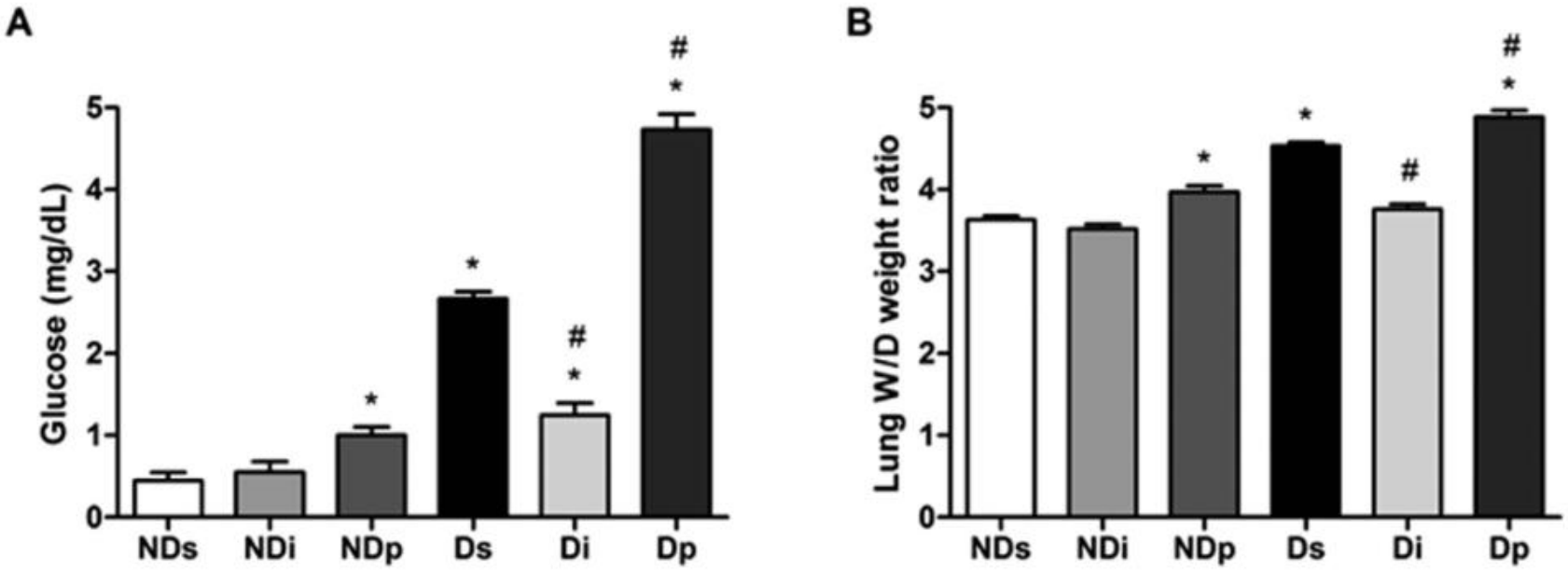
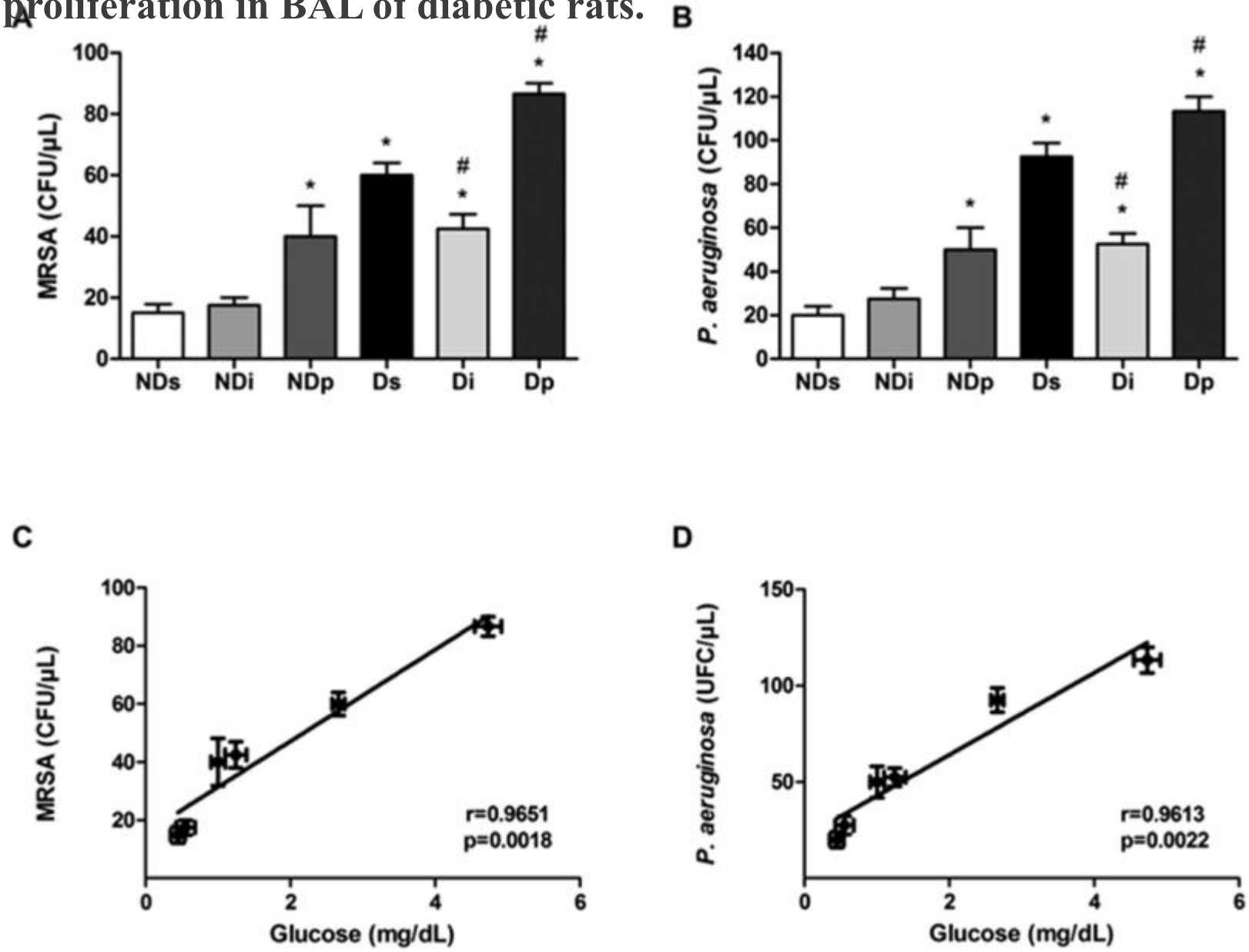


Figure 6. Bronchoalveolar lavage glucose concentration and lung water content. Bronchoalveolar lavage glucose concentration **(A)** and lung water content **(B)** were analyzed in samples from non-diabetic saline (NDs), non-diabetic isoproterenol (NDi), non-diabetic phlorizin (NDp), diabetic saline (Ds), diabetic isoproterenol (Di) and diabetic phlorizin (Dp) treated rats. Lung water content was estimated from the wet (W)/dry (D) tissue weight ratio. Results are mean ± SEM of 4–7 animals; $^{*}P < 0.05$ vs NDs; $^{\#}P < 0.05$ vs Ds. One-way ANOVA followed by Student Newman Keuls post-test.

Effects of isoproterenol and phlorizin on MRSA and P. aeruginosa proliferation in BAL of diabetic rats.



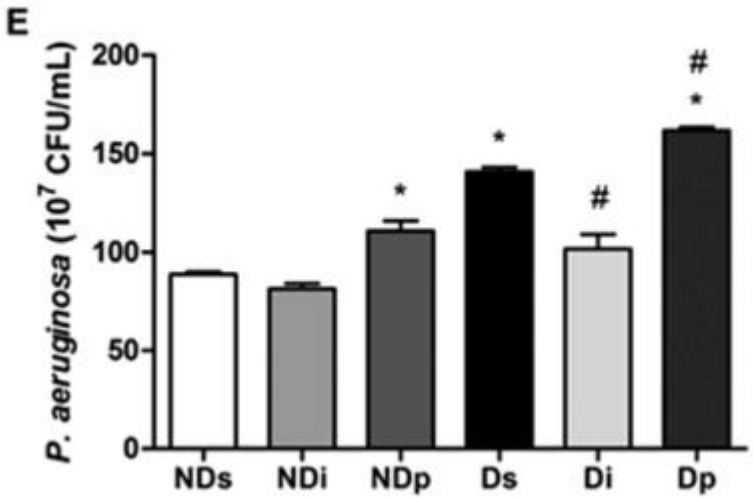
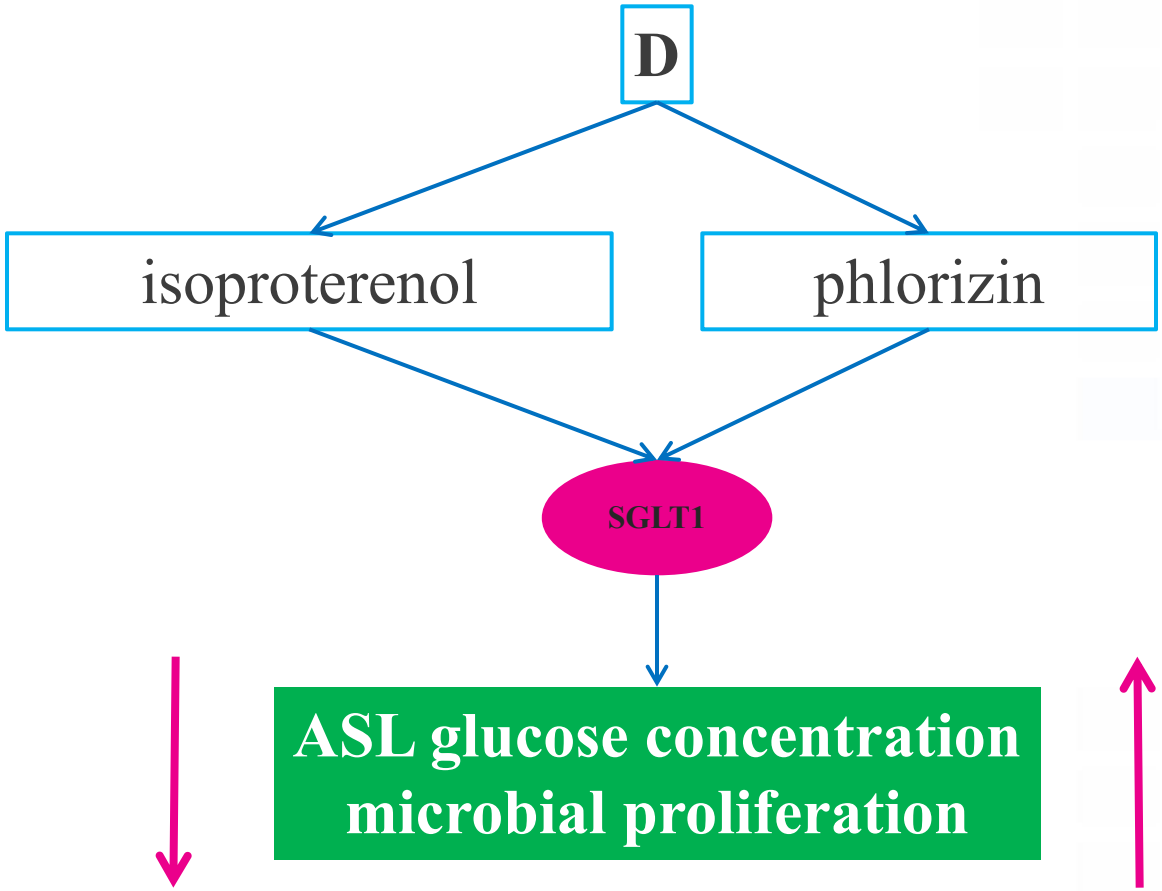


Figure 7. Bacterial proliferation analysis in bronchoalveolar lavage and lung tissue. Bacterial proliferation was analyzed in samples from non-diabetic saline (NDs), non-diabetic isoproterenol (NDi), non-diabetic phlorizin (NDp), diabetic saline (Ds), diabetic isoproterenol (Di) and diabetic phlorizin (Dp) rats. *In vitro* proliferation of methicillin-resistant *Staphylococcus aureus* (MRSA, panel **A**) and *Pseudomonas aeruginosa* (*P. aeruginosa*, panel **B**) were analyzed in bronchoalveolar lavage samples (BAL). Mean values of BAL glucose concentration (from Fig. 6) and of bacterial proliferation rate were analyzed by Pearson correlation test (panels **C** and **D**). *In vivo P. aeruginosa* proliferation was analyzed in lung tissue samples collected 6 hours after bacterial inoculation (panel **E**). Results are mean ± SEM of 4–6 animals; $^{*}P < 0.05$ vs NDs, $^{\#}P < 0.05$ vs Ds; one-way ANOVA followed by Student Newman Keuls post-test.

Discussion


D
isoproterenol
phlorizin
SGLT1
ASL glucose concentration
microbial proliferation

This is the first report to reveal that SGLT1 protein activity of the lung alveolar cells regulates the glucose concentration in the airway surface liquid and, consequently, the pulmonary bacterial proliferation risk, in diabetic state. Furthermore, the study unravels effects of β -adrenergic stimulation, which paves the way for new therapies able to prevent or fight pulmonary bacterial infection in diabetic patients. Finally, the study contributes to revealing that in-hospital diabetic patients taking the dual SGLTs inhibitors are at very high risk of pulmonary infection, and drug withdrawal should be considered.

思考

SGLT1

方法


THANK