

PBI-4050 Protects Against Renal and Pancreatic Fibrosis in Type II Diabetes



PROMETIC

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INTRODUCTION

PBI-4050, a novel first-in-class orally active compound which is currently in clinical phase Ib/II in CKD patients, displays antifibrotic activities via a novel mechanism of action. In a double-blind single ascending dose (400 to 2400 mg) in healthy volunteers, PBI-4050 was found to be safe and well tolerated up to 2400 mg without any significant adverse effects (SAEs). Similarly, PBI-4050 was well tolerated in CKD patients with no SAEs observed at 800 mg. In the present study, we examined whether PBI-4050 affected hyperglycemia, insulin resistance and the development of renal and pancreatic fibrosis in two models of type II diabetes (db/db and eNOS^{-/-} db/db).

STUDY DESIGN

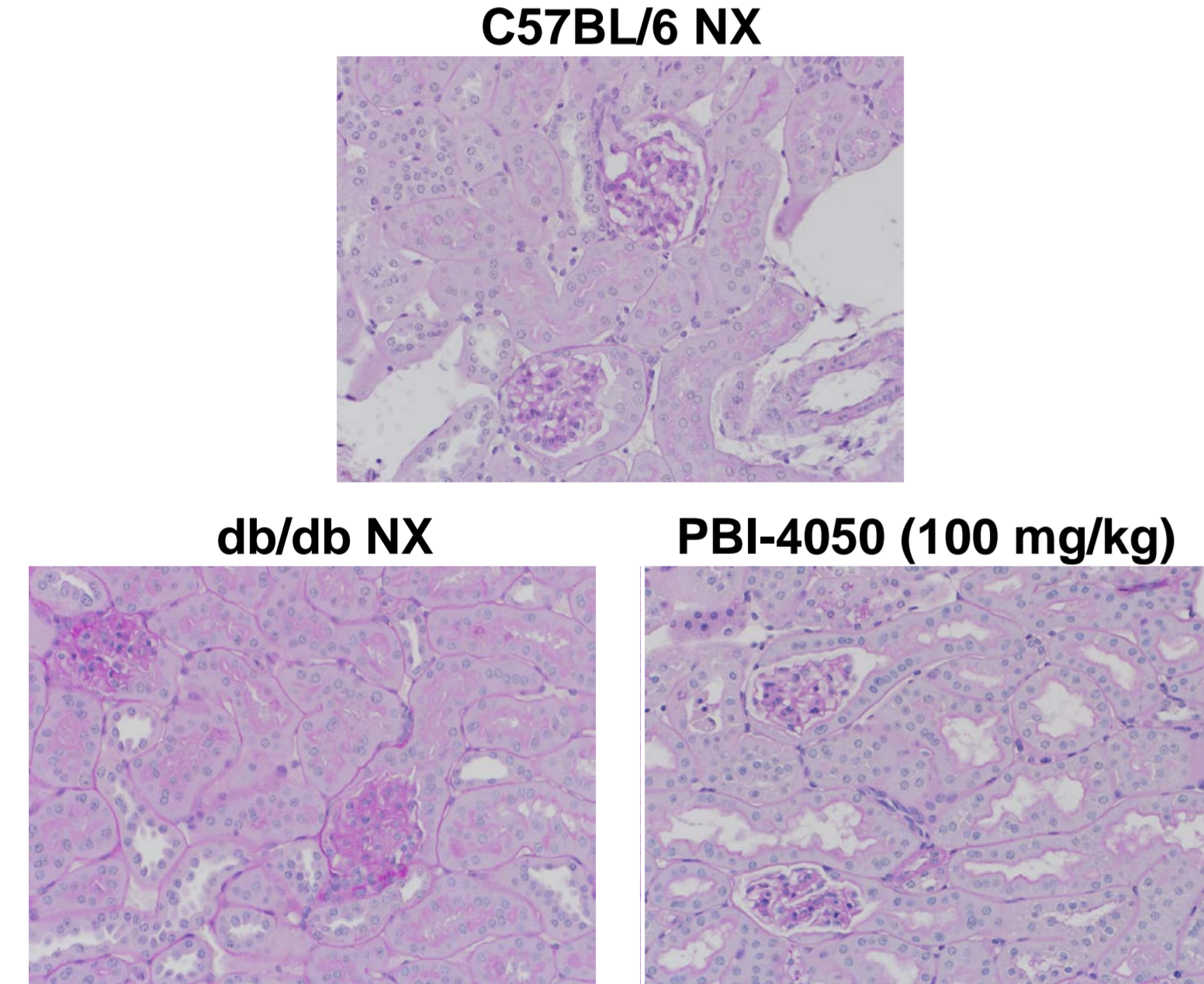
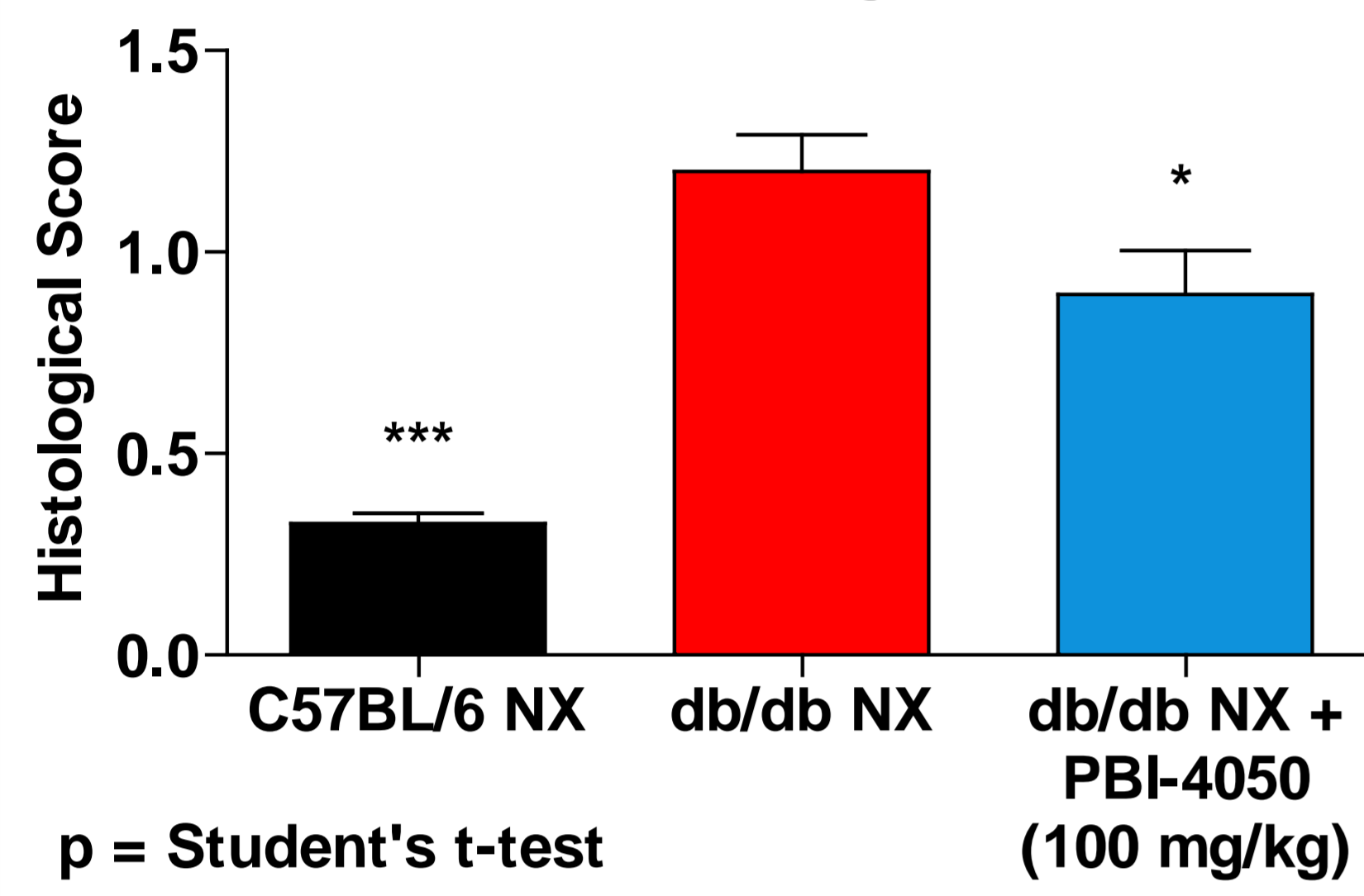
Six-week old db/db or C57BL/6 mice were subjected to uninephrectomy (NX) or sham operations. Sham operated mice underwent exposition of the kidney and removal of the perirenal fat. NX animals were treated by gastric gavage with vehicle or PBI-4050 administered once daily at 100 mg/kg. Animals were treated from day 1 to 130. BKS db/db with eNOS knockout (eNOS^{-/-} db/db) mice received vehicle (water) or PBI-4050 (200 mg/kg/day) by daily gastric gavage either from 8 to 20 weeks of age (early treatment) or from 16-24 weeks of age (late treatment). A subset of mice with late treatment was kept until death to achieve a survival curve.

RESULTS

PBI-4050 protects against renal fibrosis

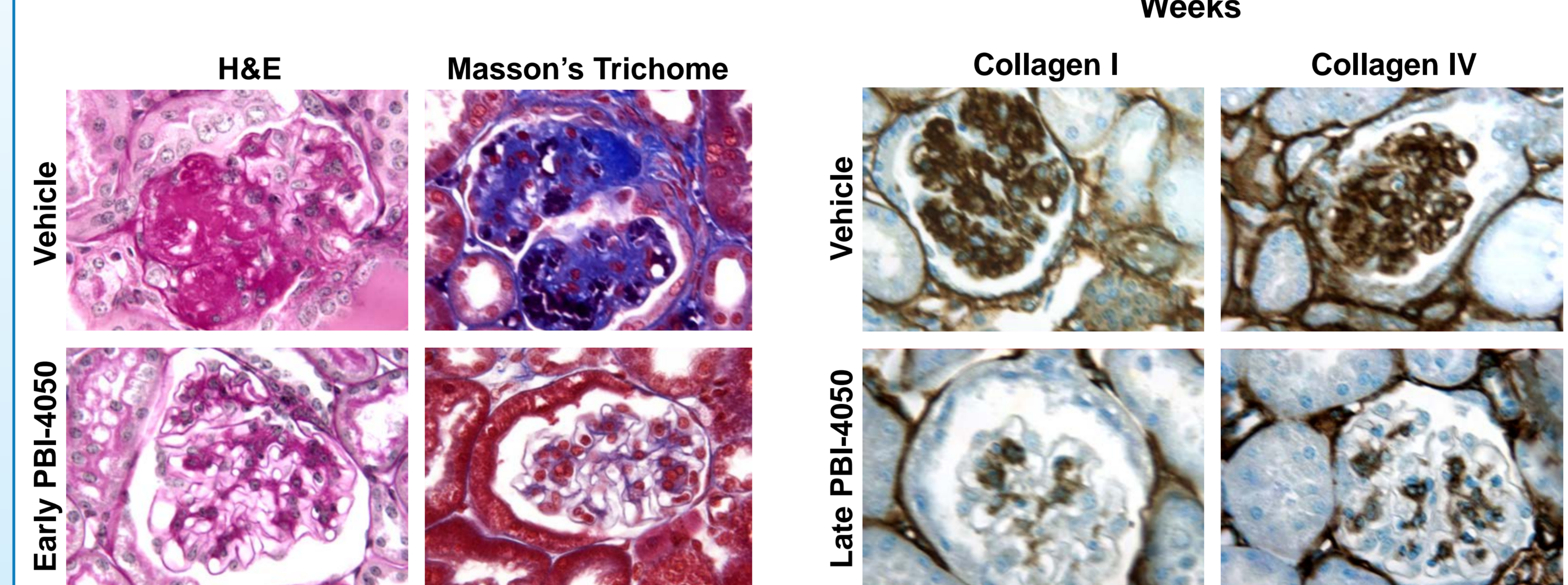
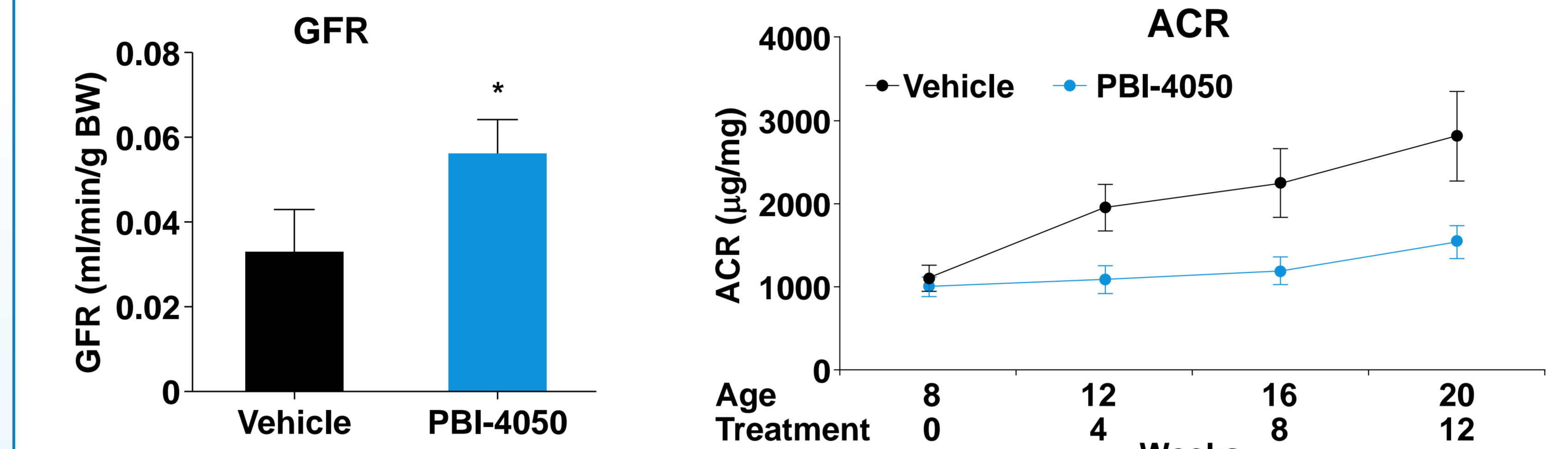
Uninephrectomized db/db mice

PBI-4050 reduces mesangial expansion.

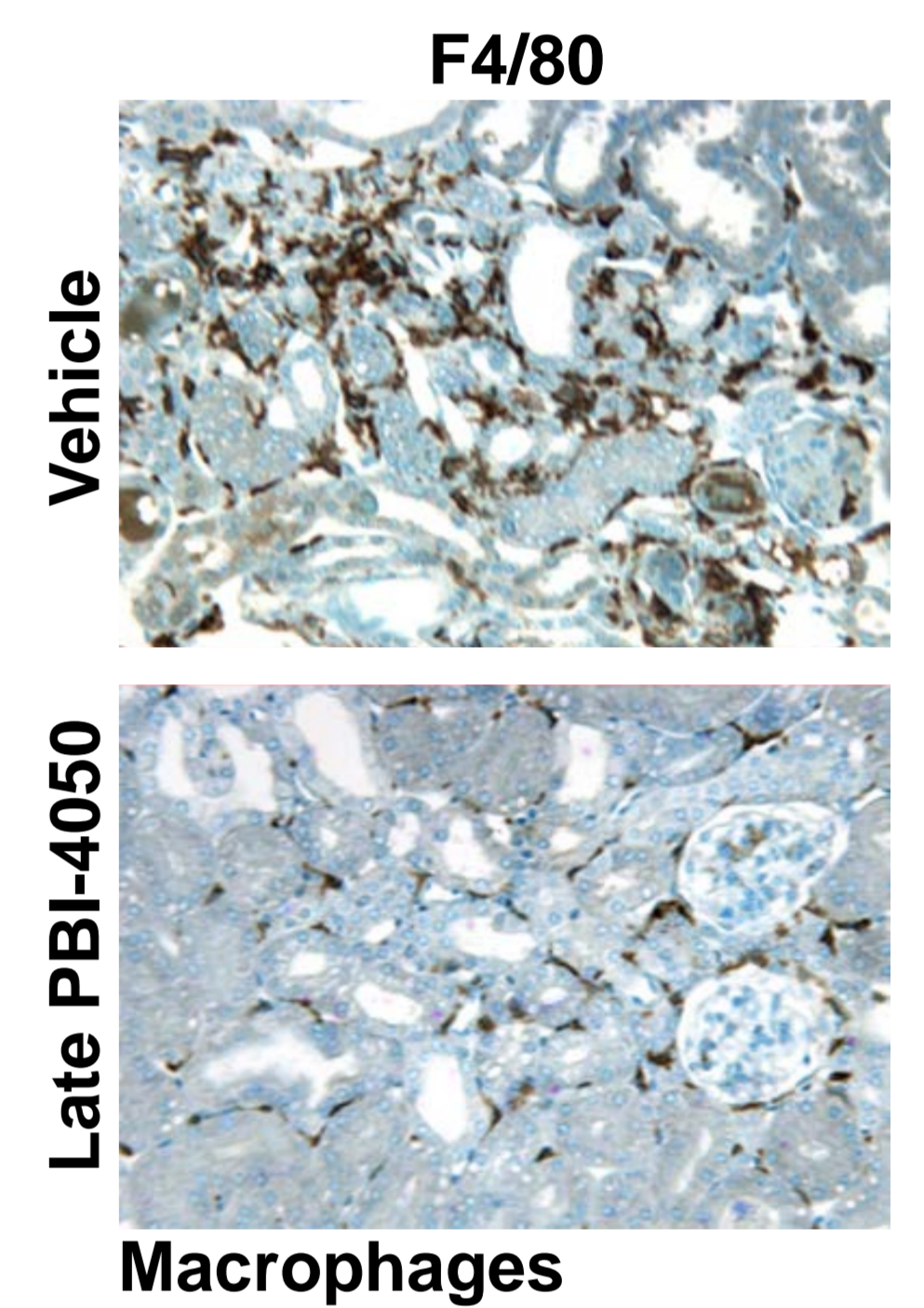


db/db eNOS^{-/-} mice

Early PBI-4050 treatment preserves glomerular filtration rate (GFR) and decreases albumin/creatinin ratio (ACR) in db/db eNOS^{-/-} mice.



PBI-4050 prevents macrophage infiltration in kidney

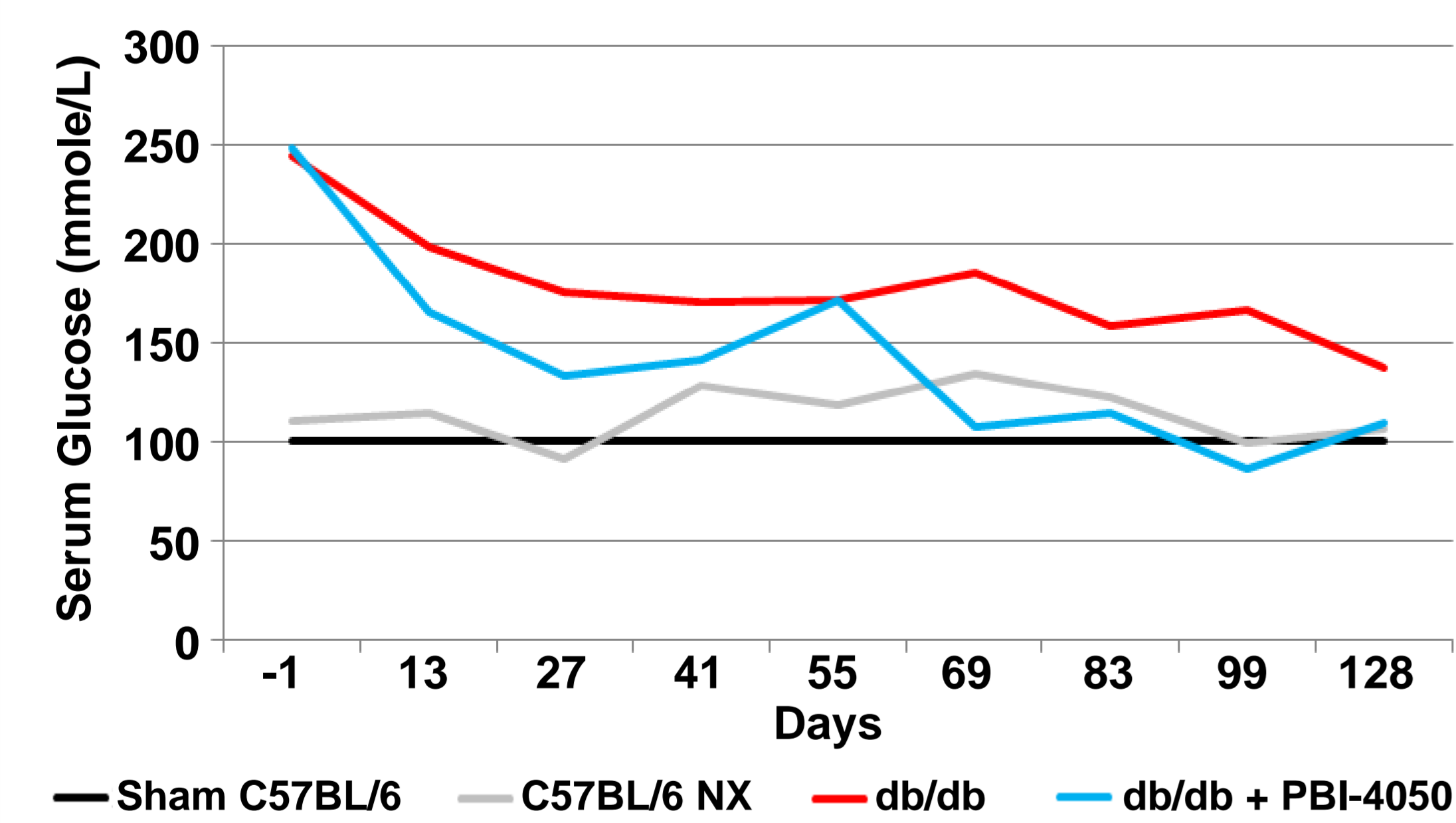


Statistics:
*p < 0.05; **p < 0.01; ***p < 0.001.

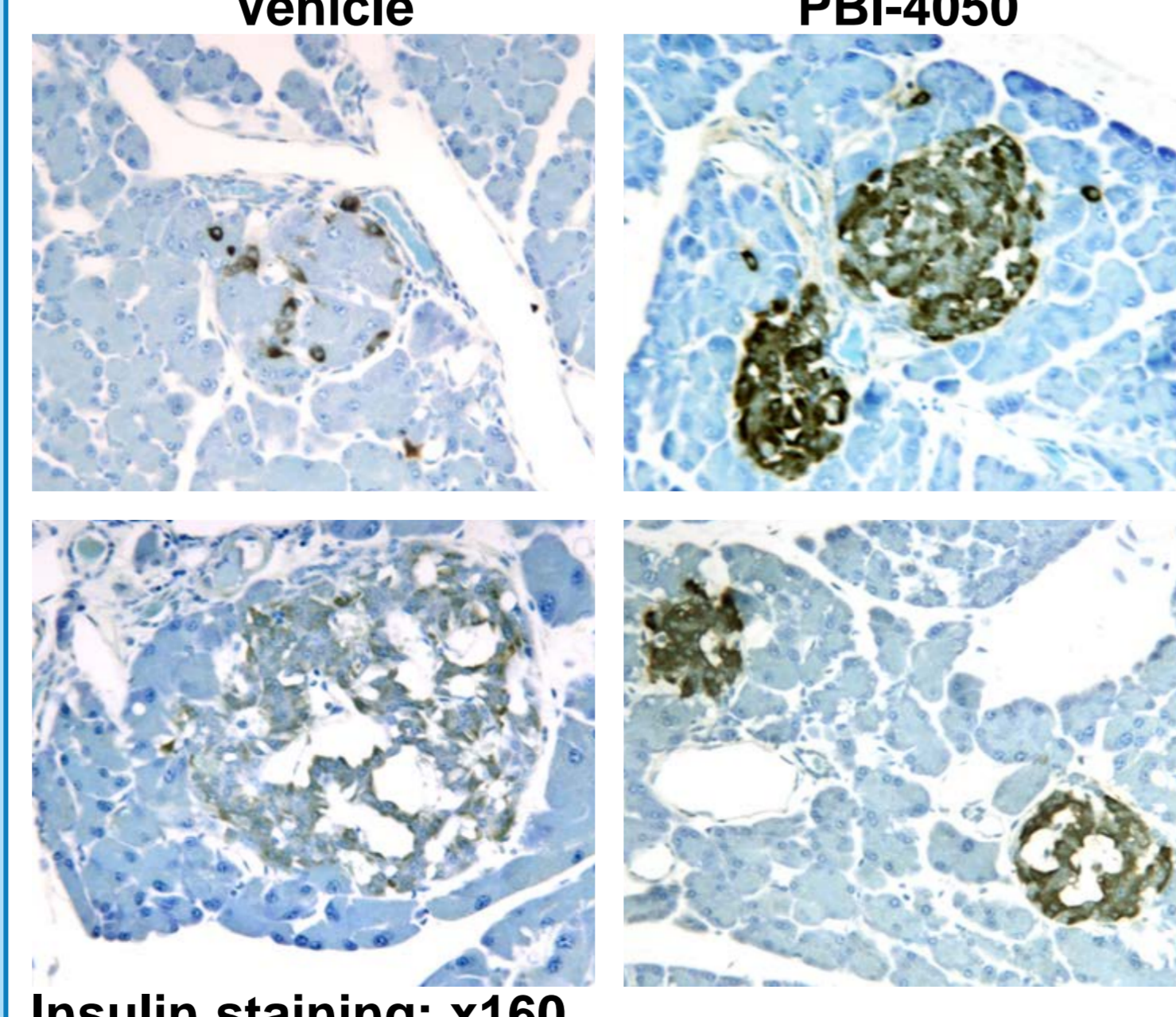
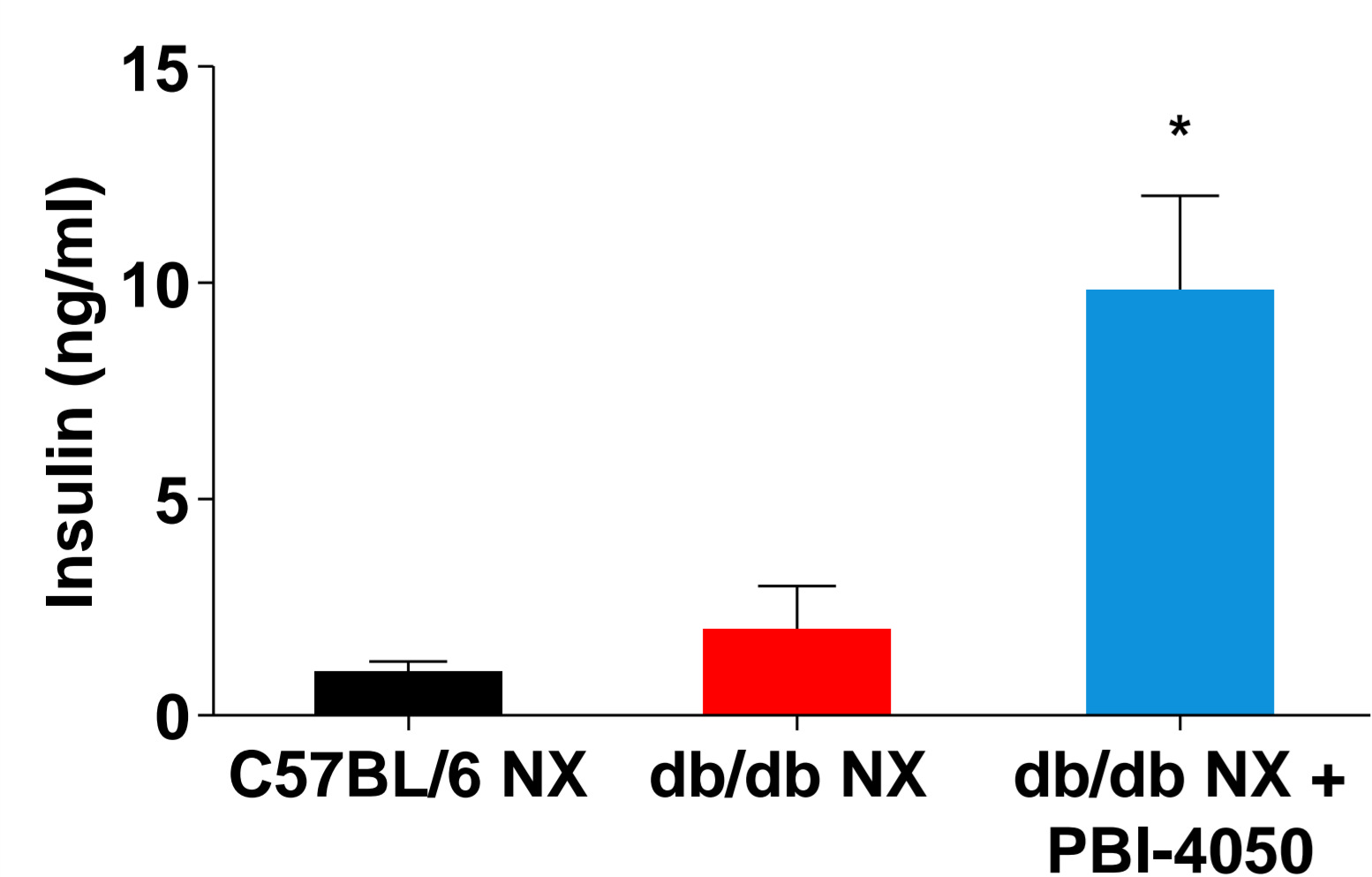
PBI-4050 protects against pancreatic fibrosis

Uninephrectomized db/db mice

PBI-4050 reduces serum glucose measured on 5-hour starved mice.

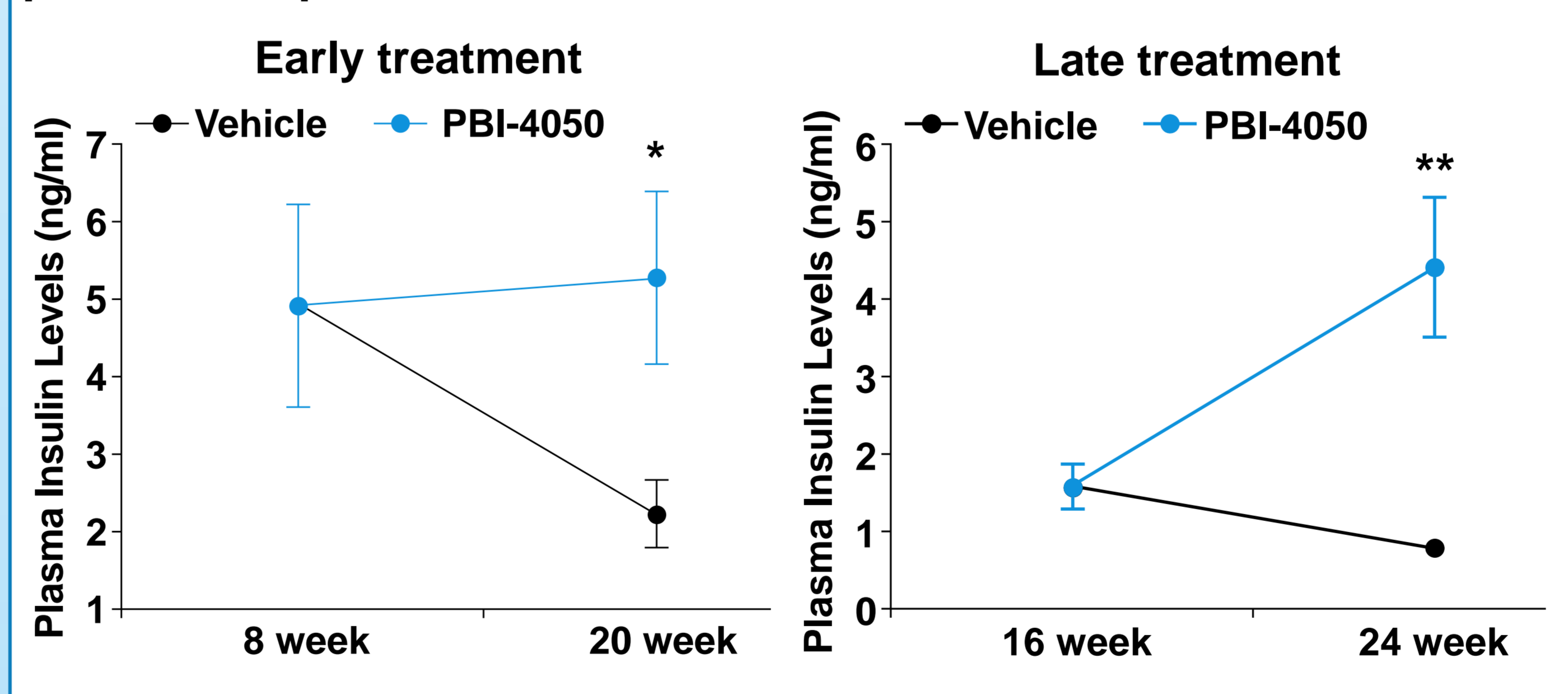


PBI-4050 increases serum insulin level in NX db/db.

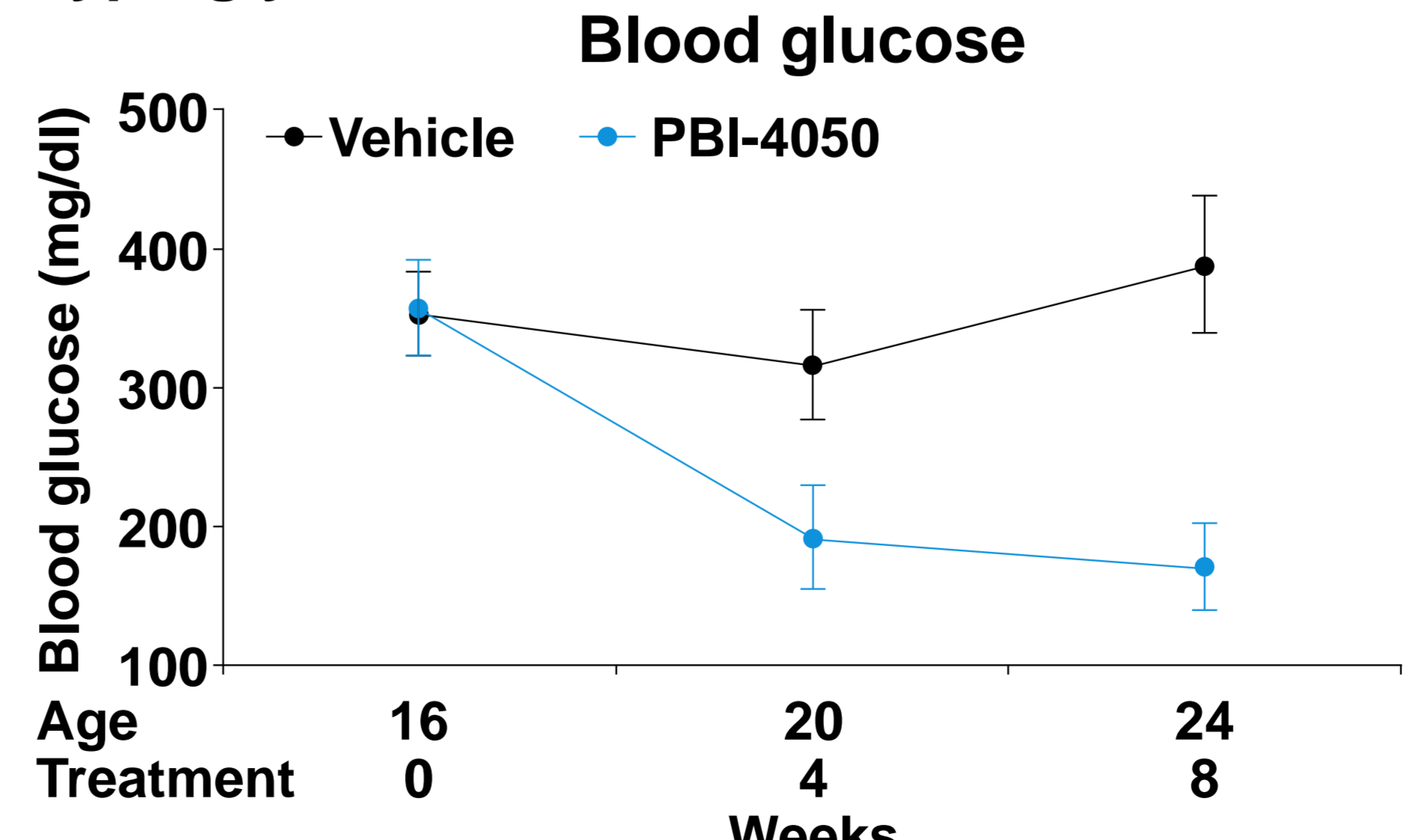


db/db eNOS^{-/-} mice

Early PBI-4050 treatment preserves and late treatment restores plasma and pancreatic islet insulin levels in db/db eNOS^{-/-} mice.

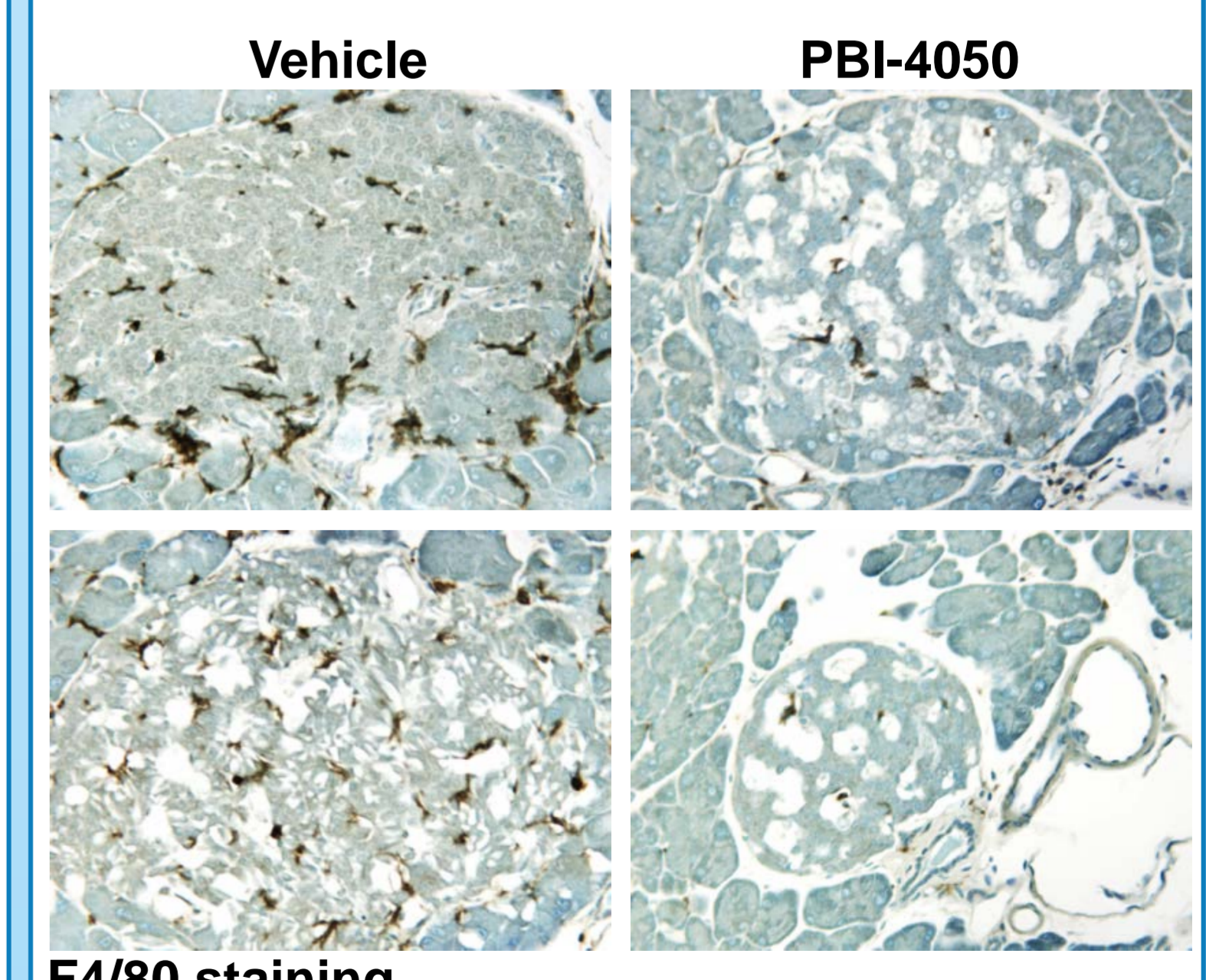
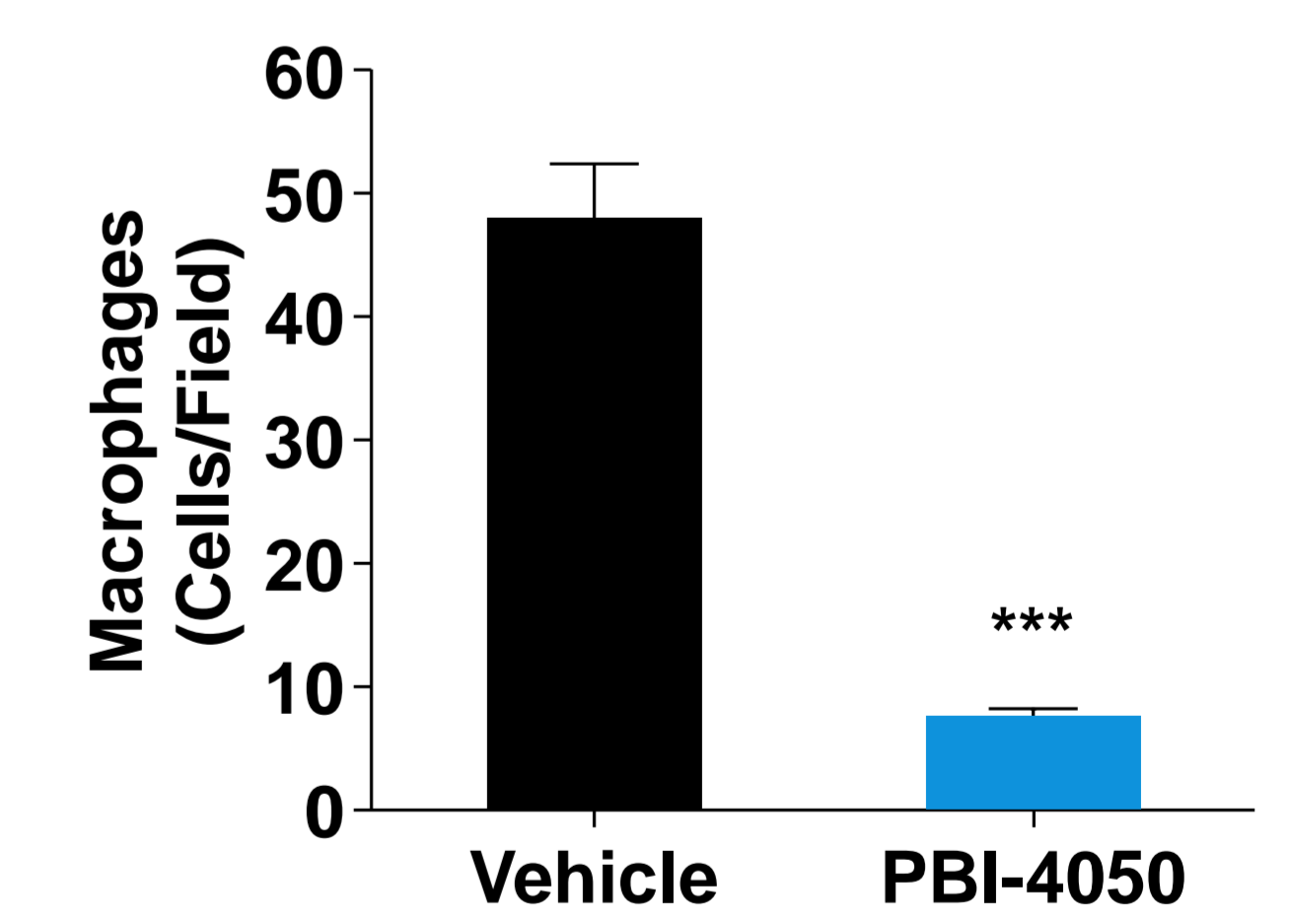


Late PBI-4050 treatment decreases fasting hyperglycemia.



PBI-4050 prevents macrophage infiltration in pancreas

Late PBI-4050 treatment decreases islet leukocyte infiltration in db/db eNOS^{-/-} mice.



CONCLUSION

These studies suggest that PBI-4050 improves hyperglycemia, preserves insulin production, and prevents both pancreas islet and renal fibrosis in association with decreased macrophage infiltration.