

Ryohei Kawasaki, Yoshihito Tashiro, Michinori Hirata
Product Research Department, Chugai Pharmaceutical Co., Ltd., Kamakura, Japan

Introduction

- Erythropoiesis-stimulating agents (ESAs) are widely used to treat renal anemia, and epoetin beta pegol (continuous erythropoietin receptor activator; C.E.R.A.) has a longer half-life than any other ESA.
- Elevated levels of intact fibroblast growth factor 23 (iFGF23) are associated with an increase in cardiovascular disease with CKD progression.¹
- Hematopoiesis induced by ESAs causes functional iron deficiency.²
- It has been demonstrated that iron deficiency promotes production of iFGF23.³

References
1. Jessica Kendrick et al., J Am Soc Nephrol 2011; 22: 1913–1922. 2. Yusuke Sasaki et al., Int J Hematol 2014; 99: 561–569. 3. Valentin David et al., Kidney Int 2016; 89: 135–146.

Aim

To investigate whether the reduction of serum iron levels by C.E.R.A. affects the levels of iFGF23 in both normal and chronic glomerulonephritis (cGN) rats.

Methods

CKD model: chronic glomerulonephritis (cGN) rats

cGN was established by intravenous injection of anti-Thy1.1-antibody (OX-7, 0.6 mg/kg) into uninephrectomized rats (F344, male, 7 weeks old) on Day 0.

Treatment

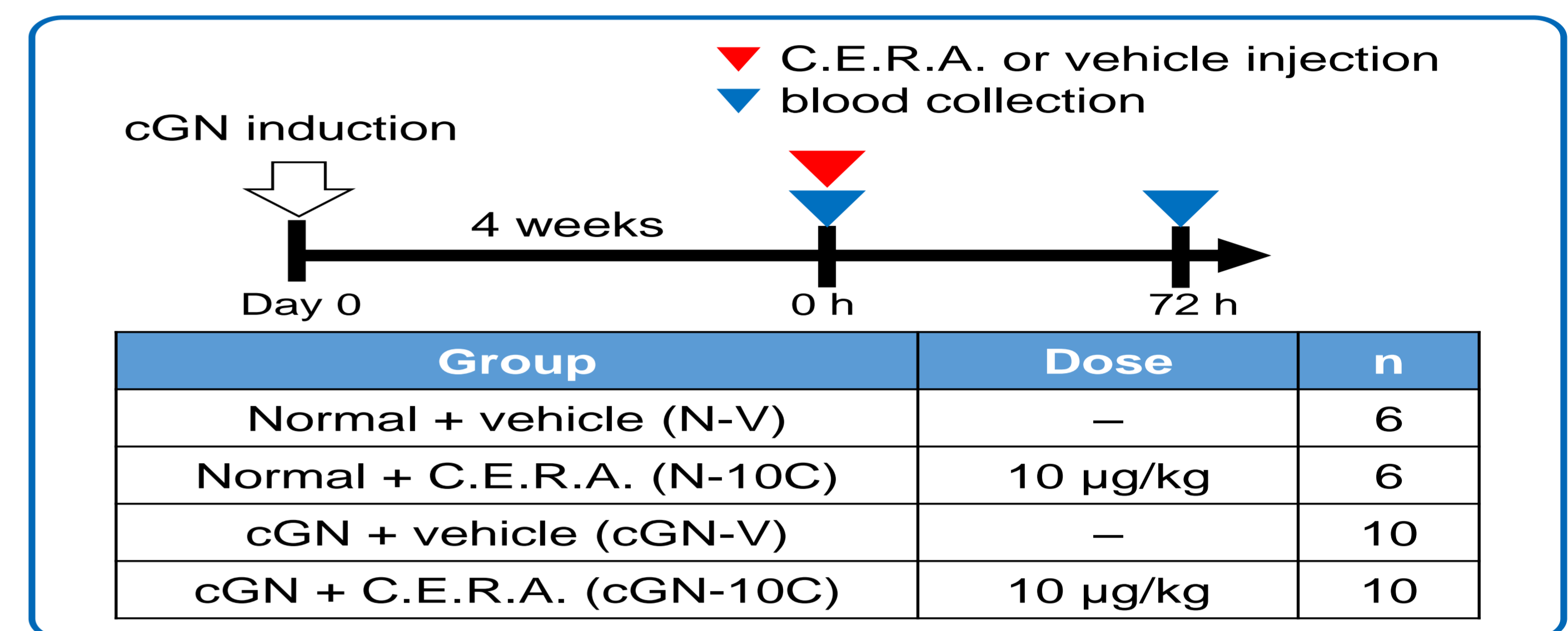
Four weeks after induction of cGN, C.E.R.A. (10 µg/kg) or vehicle was intravenously injected once into normal and cGN rats.

Blood collection

Blood was collected from the jugular vein at 0 h and 72 h after the injection of C.E.R.A. or vehicle.

Measurement

- The number of reticulocytes in blood was evaluated by automated hematology analyzer (XT-2000iV; Sysmex).
- Serum iron and plasma creatinine levels were evaluated by autoanalyzer (TBA-2000FR; Toshiba Medical Systems)
- Plasma iFGF23 levels were evaluated by ELISA (KAINOS Laboratories).



Results

Figure 1

C.E.R.A. significantly increased the number of reticulocytes in blood (Ret) 72 h after the injection in (a) normal and cGN (b) rats.

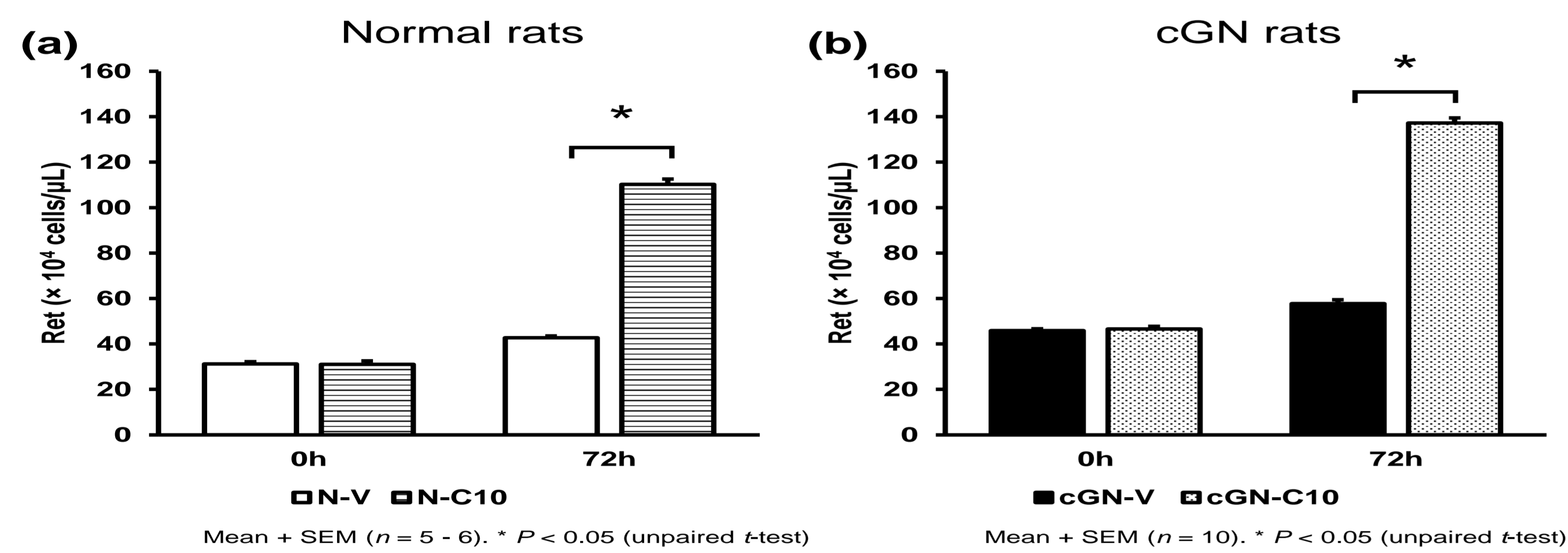


Figure 2

C.E.R.A. significantly decreased serum iron (Fe) levels 72 h after the injection in (a) normal and (b) cGN rats.

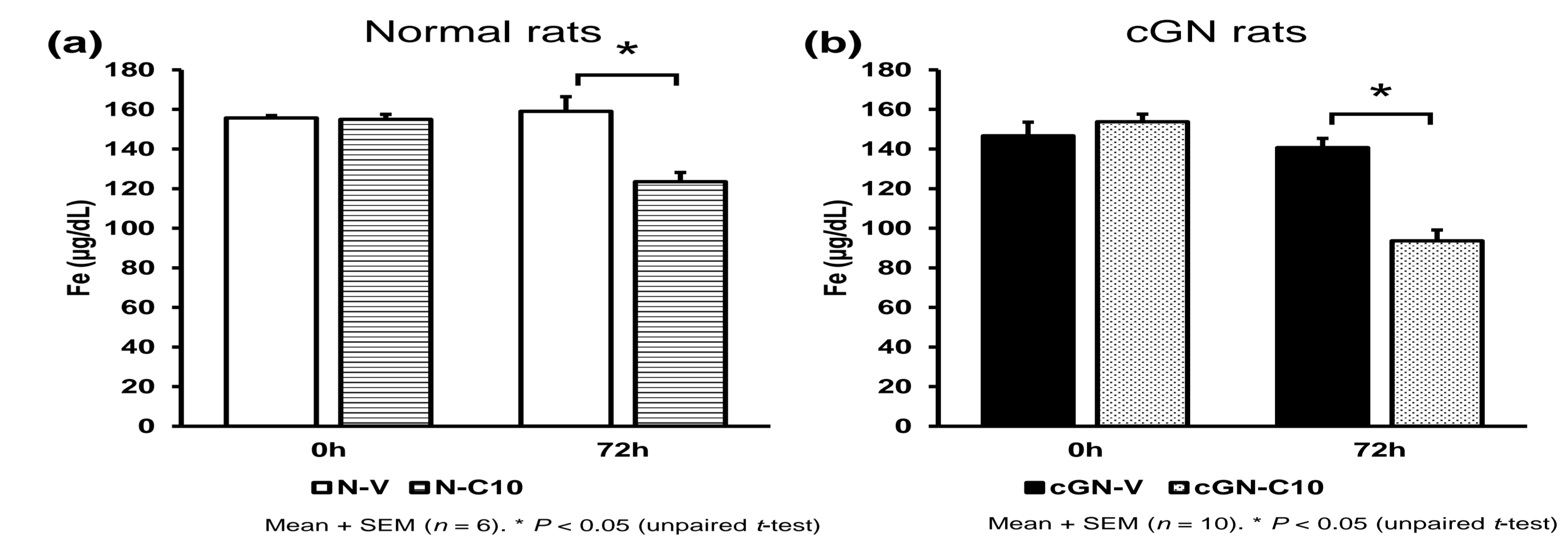


Figure 3

There was no significant difference in plasma iFGF23 levels between the C.E.R.A.-injected group and the vehicle-injected group in (a) normal and (b) cGN rats.

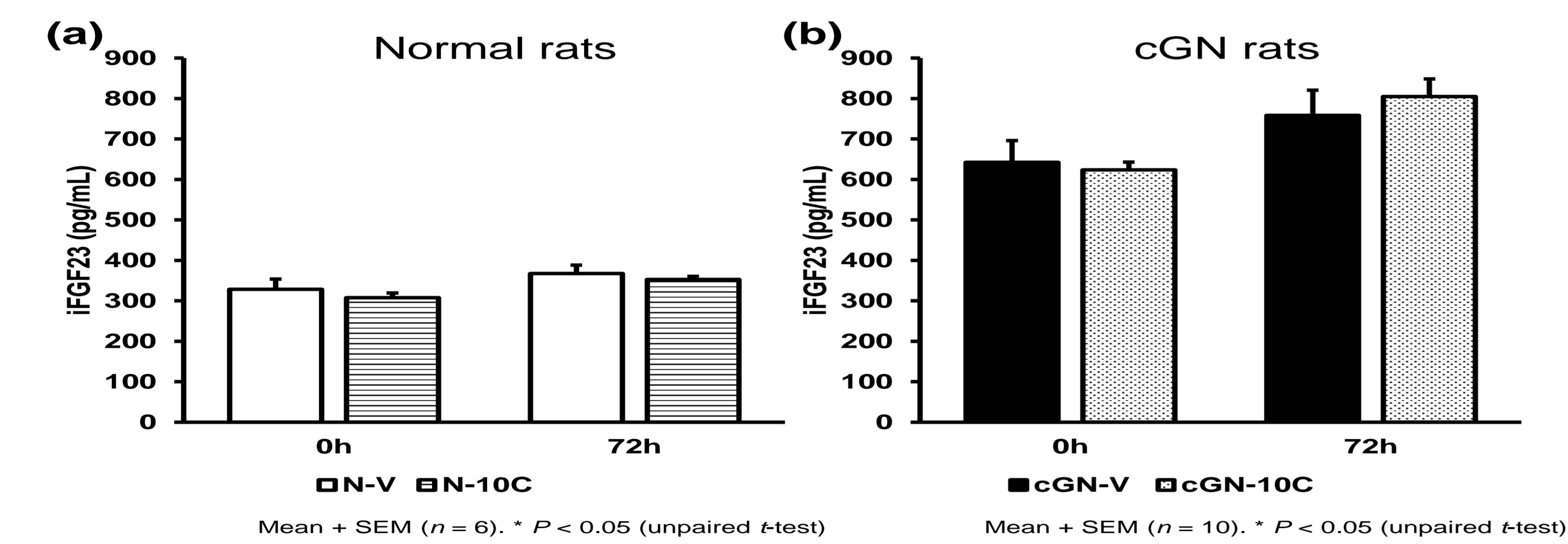
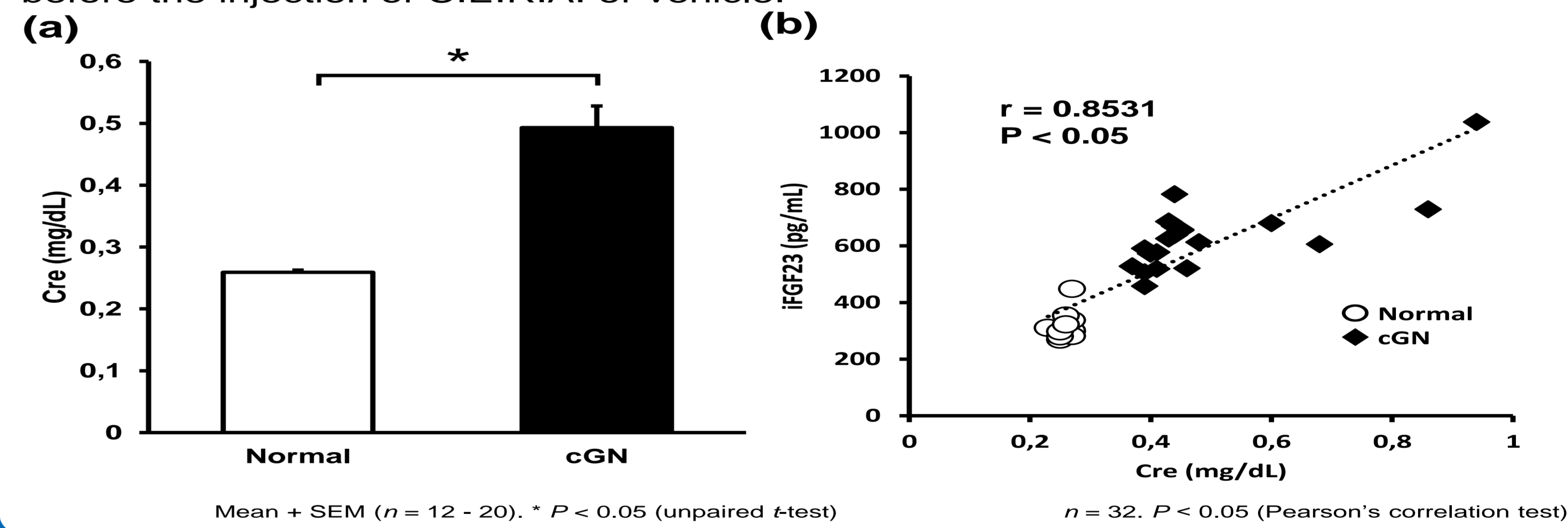


Figure 4

(a) Plasma creatinine (Cre) levels in cGN rats were significantly higher than those in normal rats. (b) There was a positive correlation between plasma Cre levels and iFGF23 levels before the injection of C.E.R.A. or vehicle.



Discussion and Conclusion

- C.E.R.A. increased the number of reticulocytes in blood and decreased serum iron levels 72 h after the injection of C.E.R.A. (Figure 1, Figure 2).
 - The decrease in serum iron levels was caused by hematopoiesis.
- There was no significant difference in plasma iFGF23 levels between the vehicle-injected group and the C.E.R.A.-injected group despite the decreased levels of serum iron in the C.E.R.A.-injected group (Figure 3).
- There was a positive correlation between plasma creatinine and iFGF23 levels (Figure 4).
 - Similarly to the previous reports, plasma iFGF23 levels increased in cGN rats. This cGN model is a CKD model with increasing levels of iFGF23 accompanied with the reduction of renal function.

✓ This study indicated that serum iron levels decreased by a single injection of C.E.R.A. does not affect plasma iFGF23 levels in normal and cGN rats. However, further study is needed to evaluate the impact of repeated injection of C.E.R.A. on plasma iFGF23 levels.