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Rescue of cGMP kinase I and the cause of premature death

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Background

50% of mice with a classical deletion of the cGK Iá and Iβ gene (cGKI$^{-/-}$) die at 6 weeks [1] whereas 50% of cGK Iα and Iβ rescue mice (RM) survive until one year [2]. Here, we investigated the reason(s) for the premature death of the different gene-targeted cGKI animals.

Results

cGKI$^{-/-}$ and the RM have a severe anemia and splenomegalie which is associated with a strongly reduced iron content and expression of the ferritin light chain in the spleen. Furthermore, the mRNA levels of transferrin receptor (TfRc) and divalent metal ion transporter (DMT1) are increased in the spleen. Oral or i.m. administration of iron restores partially the iron levels in the spleen of gene-targeted cGKI mice, but affects the anemia only moderately. Examination of the intestinal tract showed a massive ulceration in the duodenum that caused intestinal bleeding in cGKI$^{-/-}$ and at the later age in the RM as well.

The cGKI protein was expressed in smooth muscle cells of all intestinal sections including the duodenum of RM. However, H^+ induced duodenal HCO_3^- secretion was severely reduced in the cGKI$^{-/-}$ and RM. HCO_3^- secretion was measured as described in [3]. Interestingly, the duodenal HCO_3^- secretion was not affected by targeted deletion of the cGKI gene in the secretory epithel or in Cajal cells. In line with this result, we did not detect the cGKI protein by extensive immuno-cytochemical analysis in the secretory epithel or Cajal cells.

Conclusion

These results confirm previous observations that cGKI confers antiapoptotic/prosurvival function to erythrocytes [4]. In addition, we propose that cGKI$^{-/-}$ and RM die because of the massive intestinal bleedings caused by an ulceration of the duodenum. We conclude that the cGMP/cGKI pathway it is essential for H^+ induced secretion of HCO_3^- thereby protecting the small intestine from gastric acid injury.

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