

Supplementary Figure 1. Effects of chronic treatment with empagliflozin on systolic blood pressure,

blood ketone, blood glucose and body weight in cytoATP-Tg mice. a-b Graph of the blood glucose before

treatment with empagliflozin (**a**) (+/+ [control]: $n = 10$, db/db [control]: $n = 8$, db/db [EMPA]: $n = 10$; EMPA:

empagliflozin) and after 8-week treatment with empagliflozin (**b**) (+/+ [control]: $n = 10$, db/db [control]: $n = 8$,

db/db [EMPA]: $n = 10$). * $p = 0.000$. **c-d** Graph of the blood ketone before treatment with empagliflozin (**c**)

(+/+ [control]: $n = 10$, db/db [control]: $n = 8$, db/db [EMPA]: $n = 10$) and after 8-week treatment with

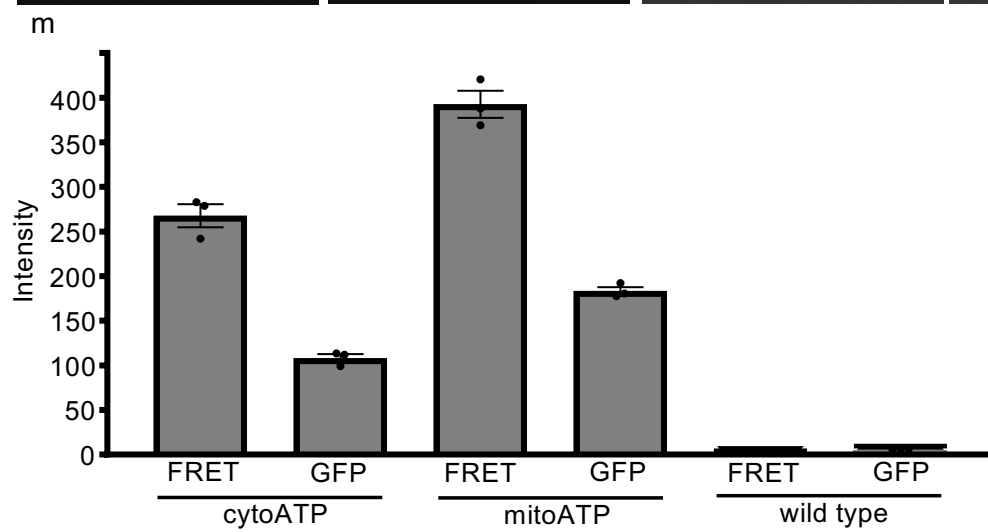
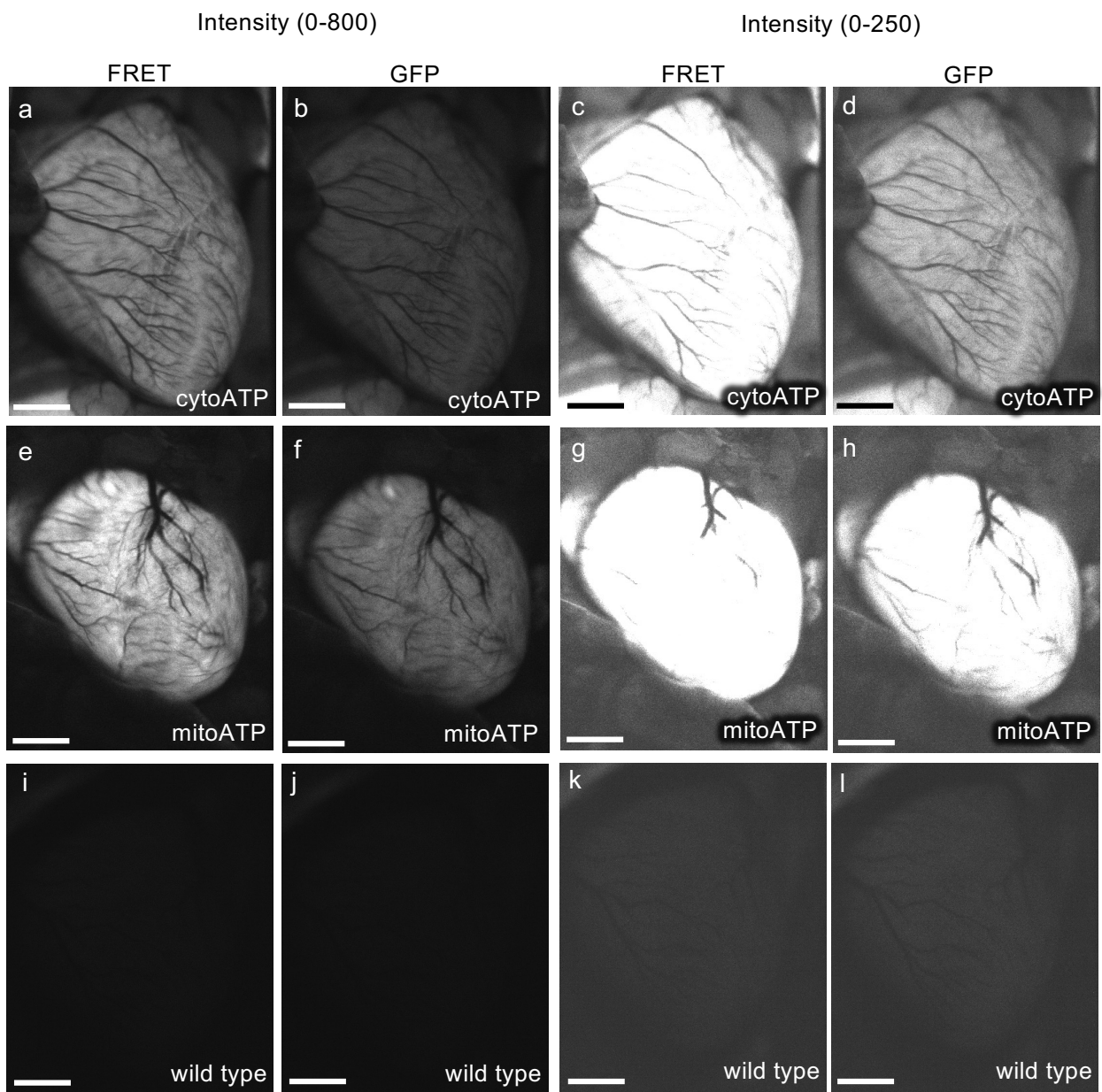
empagliflozin (**d**) (+/+ [control]: $n = 10$, db/db [control]: $n = 8$, db/db [EMPA]: $n = 10$). * $p = 0.005$, 0.004

each. **e** Graph of the body weight change ratio after 8 weeks (+/+ [control]: $n = 10$, db/db [control]: $n = 8$,

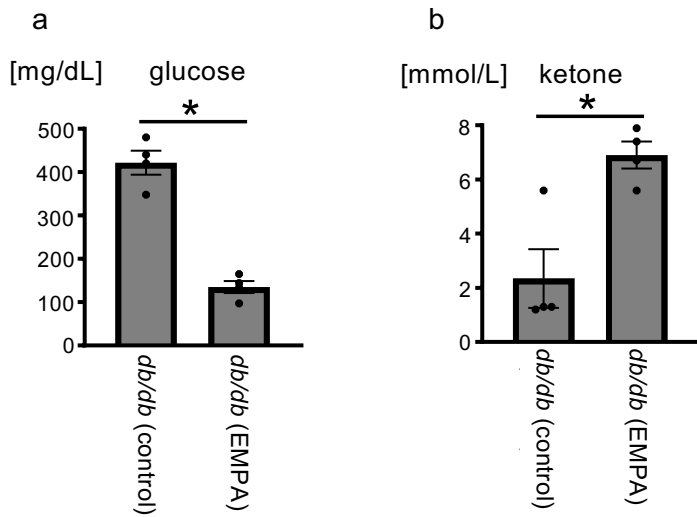
db/db [EMPA]: $n = 10$). **f-g** Graph of the systolic blood pressure before treatment with empagliflozin (**f**) (+/+

[control]: $n = 10$, db/db [control]: $n = 8$, db/db [EMPA]: $n = 10$) and after 8-week treatment with

empagliflozin (**g**) (+/+ [control]: $n = 10$, db/db [control]: $n = 8$, db/db [EMPA]: $n = 10$).



Supplementary Figure 2. Autofluorescence in the hearts did not have a significant effect on measurement of FRET and GFP. **a-d** Fluorescence intensity of FRET (**a, c**) and GFP (**b, d**) in a live heart of a cytoATP-Tg mouse (FRET, Fluorescence Resonance Energy Transfer). Higher brightness indicates stronger intensity. Scale bar: 2 mm. **e-h** Fluorescence intensity of FRET (**e, g**) and GFP (**f, h**) in a live heart of a mitoATP-Tg mouse. Higher brightness indicates stronger intensity. Scale bar: 2 mm. **i-l** Autofluorescence intensity of FRET (**i, k**) and GFP (**j, l**) in a live heart of a wild-type mouse. Higher brightness indicates stronger intensity. Scale bar: 2 mm. **m** Graph of the intensity of FRET and GFP in each mouse (cytoATP: $n = 3$, mitoATP: $n = 3$, wild type: $n = 3$).



Supplementary Figure 3. Effects of single treatment with empagliflozin on blood glucose and blood ketone in *db/db*; mitoATP-Tg mice. a-b Graph of the blood glucose (a) and ketone (b) levels in *db/db*; mitoATP-Tg mice after 4 h of fasting followed by 3 h of control or empagliflozin (30 mg/kg b.w., EMPA) treatment (*db/db* [control]: $n = 4$, *db/db* [EMPA]: $n = 4$; EMPA: empagliflozin). * $p = 0.000, 0.009$ each.

