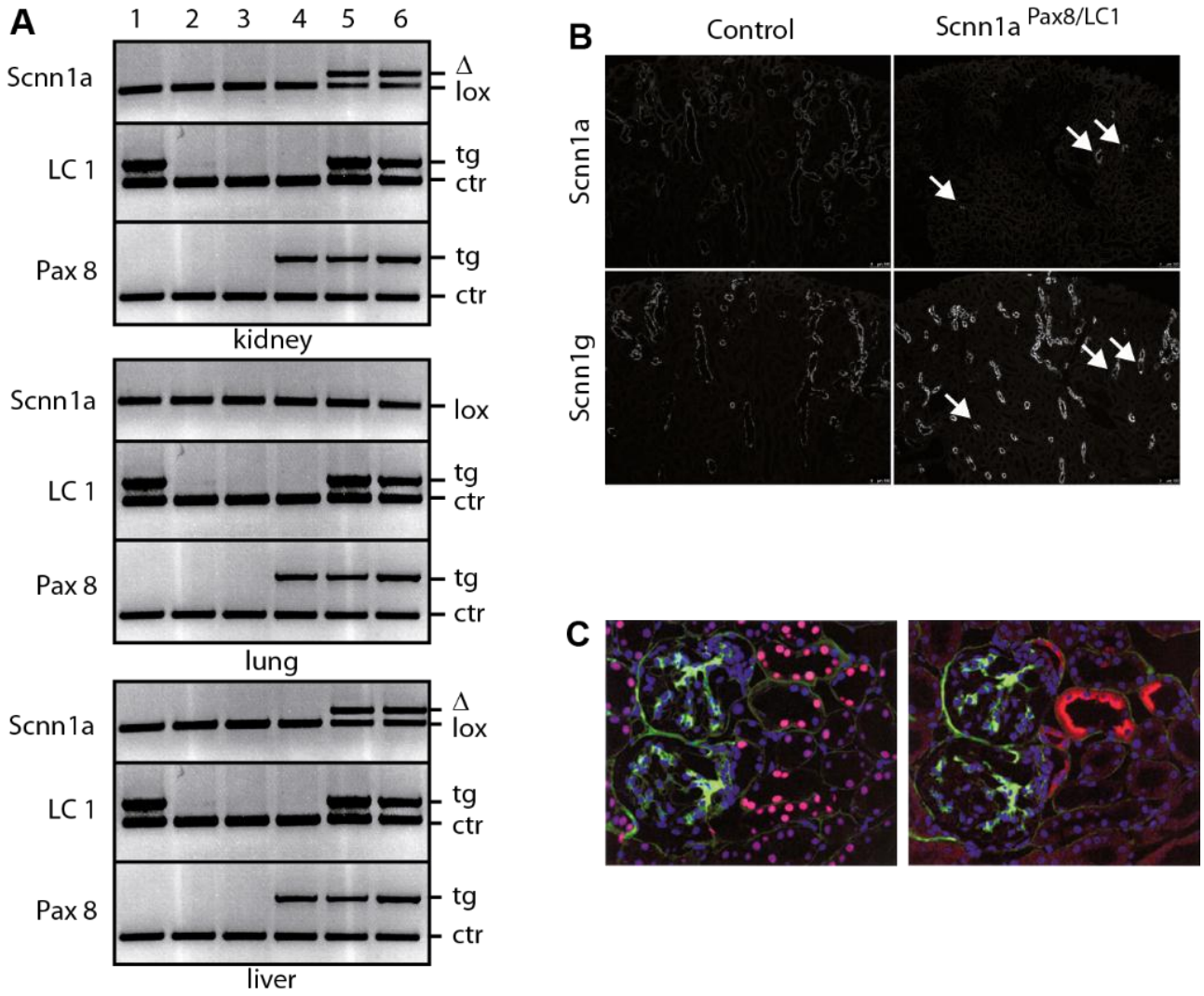
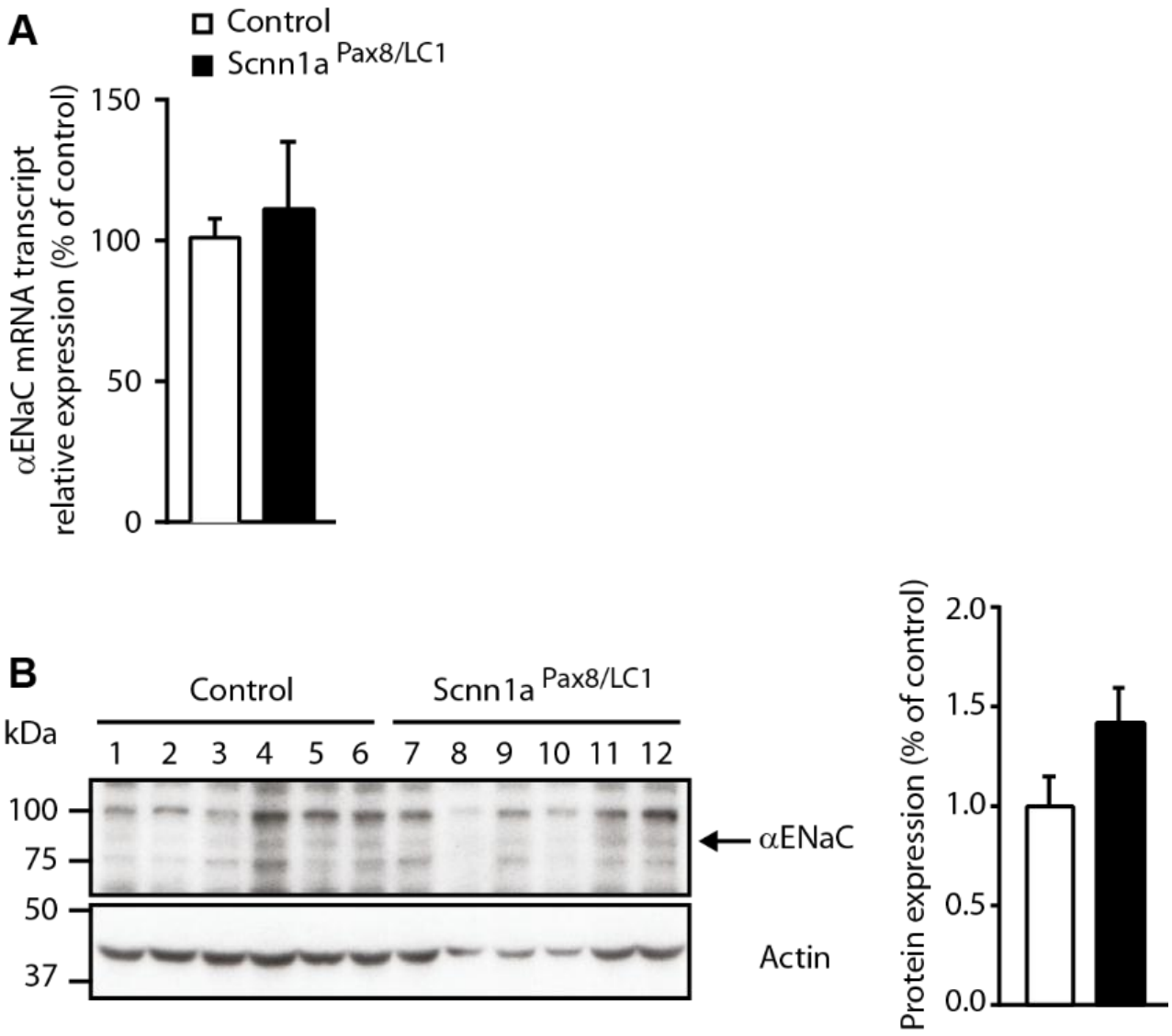


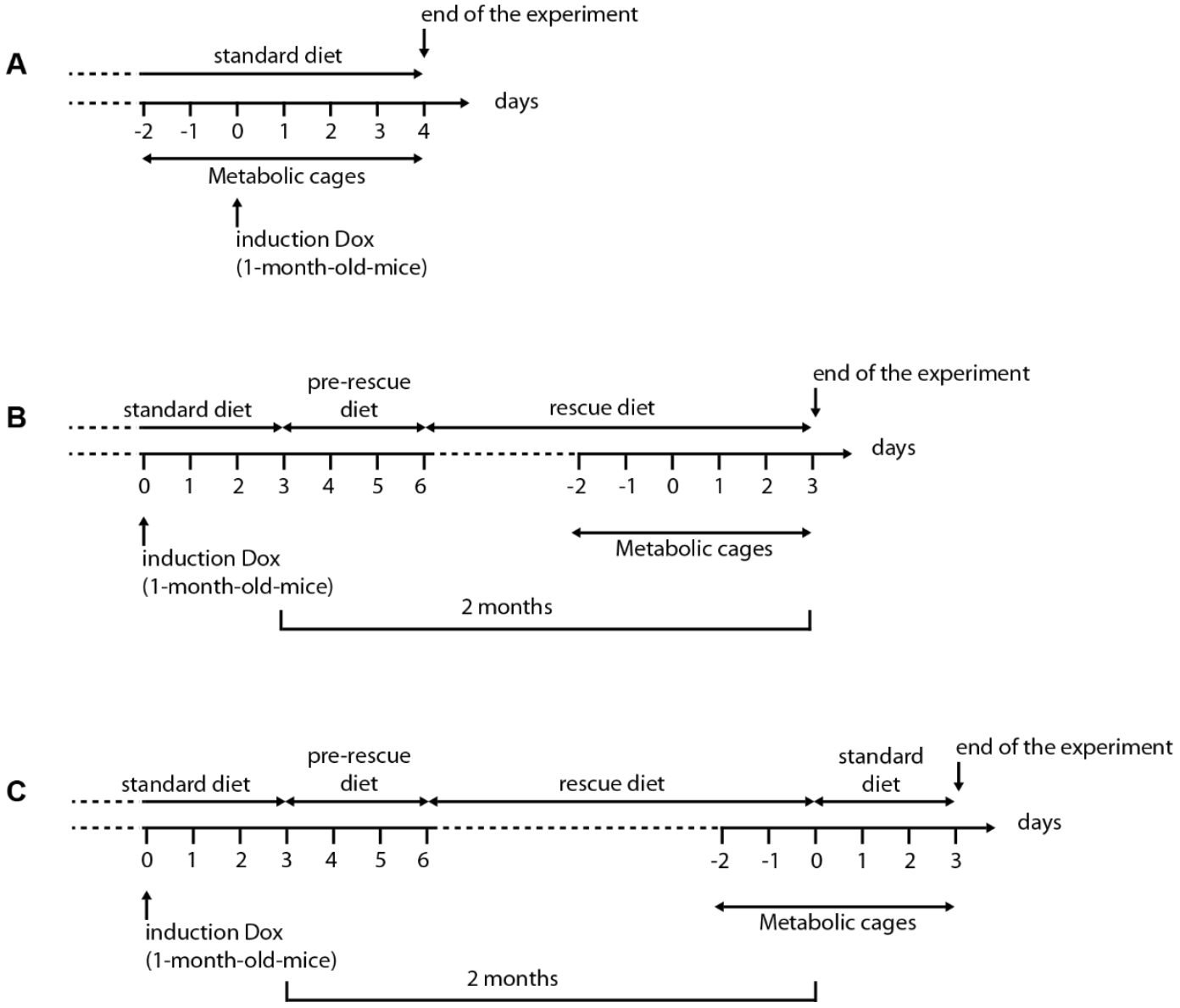
Supplementary Figure 1 Generation of inducible nephron-specific Scnn1a$^{Pax8/LC1}$ mice.

(**A**) Genotyping using Scnn1a, Pax8 and LC1 specific primers from the whole kidney (upper), lung (middle) and liver (lower panel) from control (lanes 1-4) and experimental animals (lanes 5 and 6); lane 1: Scnn1a$^{lox/lox;+/LC1}$; lanes 2 and 3: Snn1a$^{lox/lox}$; lane 4: Scnn1a$^{lox/lox;+/Pax8-rtTA}$); and experimental mice: lanes 5 and 6: Scnn1a$^{\Delta/lox,+/Pax8-rtTA;+/LC1}$. (**B**) Immunofluorescent detection of α and γ ENaC in consecutive kidney sections from either a control or a Scnn1a$^{Pax8/LC1}$ mouse on a regular salt diet following two months of rescue diet. Arrows point to the very few renal tubules with remaining α ENaC abundance in the Scnn1a$^{Pax8/LC1}$ mouse. (**C**) Immunofluorescent detection of Cre (purple) and αENaC (red staining) on consecutive kidney sections from Scnn1a$^{Pax8/LC1}$ mice on a regular diet following two months of rescue diet. The green fluorescence is related to binding of a FITC-conjugated anti-mouse IgG to deposits of endogenous immunoglobulin in the glomerular mesangium and kidney interstitium. Cell nuclei were counterstained with DAPI (blue).



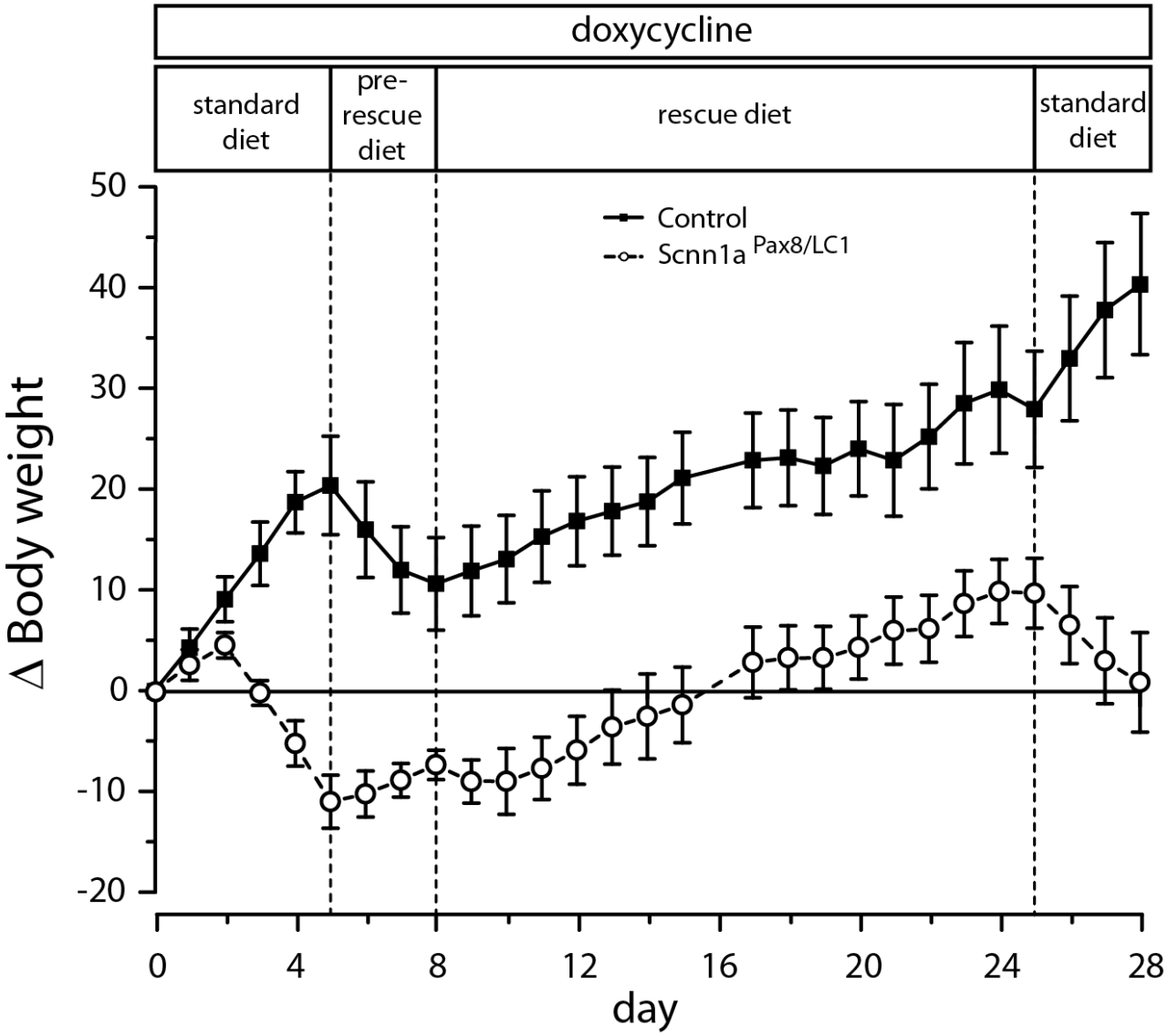
Supplementary Figure 2 αENaC detection in whole liver extracts.

(**A**) Scnn1a (αENaC) mRNA transcript expression in whole liver using quantitative real-time PCR normalized to β-actin. (**B**) Western blot analysis and protein expression quantification relative to β actin for αENaC on whole liver extracts of control (n=6) and Scnn1a$^{Pax8/LC1}$ knockout mice (n=6) under standard salt diet.



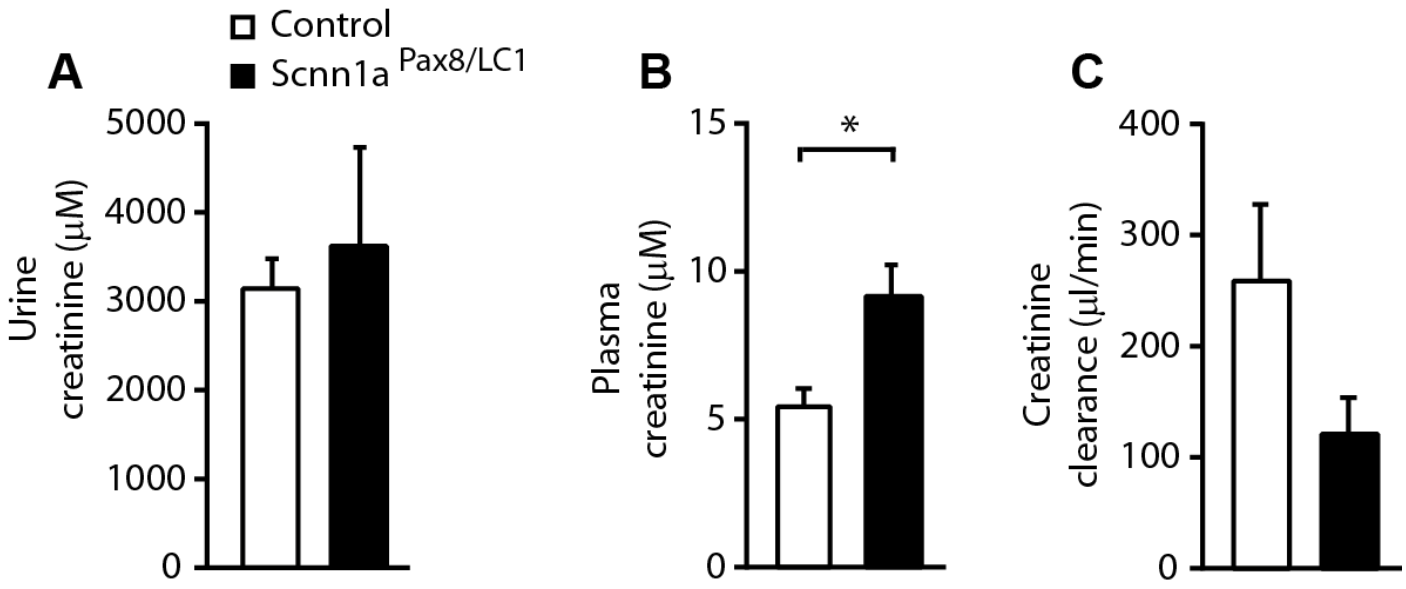
Supplementary Figure 3 Schematic representation of the experimental protocols

Experimental setup to determine metabolic parameters in control and knockout animals induced by doxycycline (Dox) and kept under a (**A**) standard salt diet, a (**B**) high sodium / reduced potassium diet and (**C**) back to the standard diet following two months of high sodium / reduced potassium treatment.



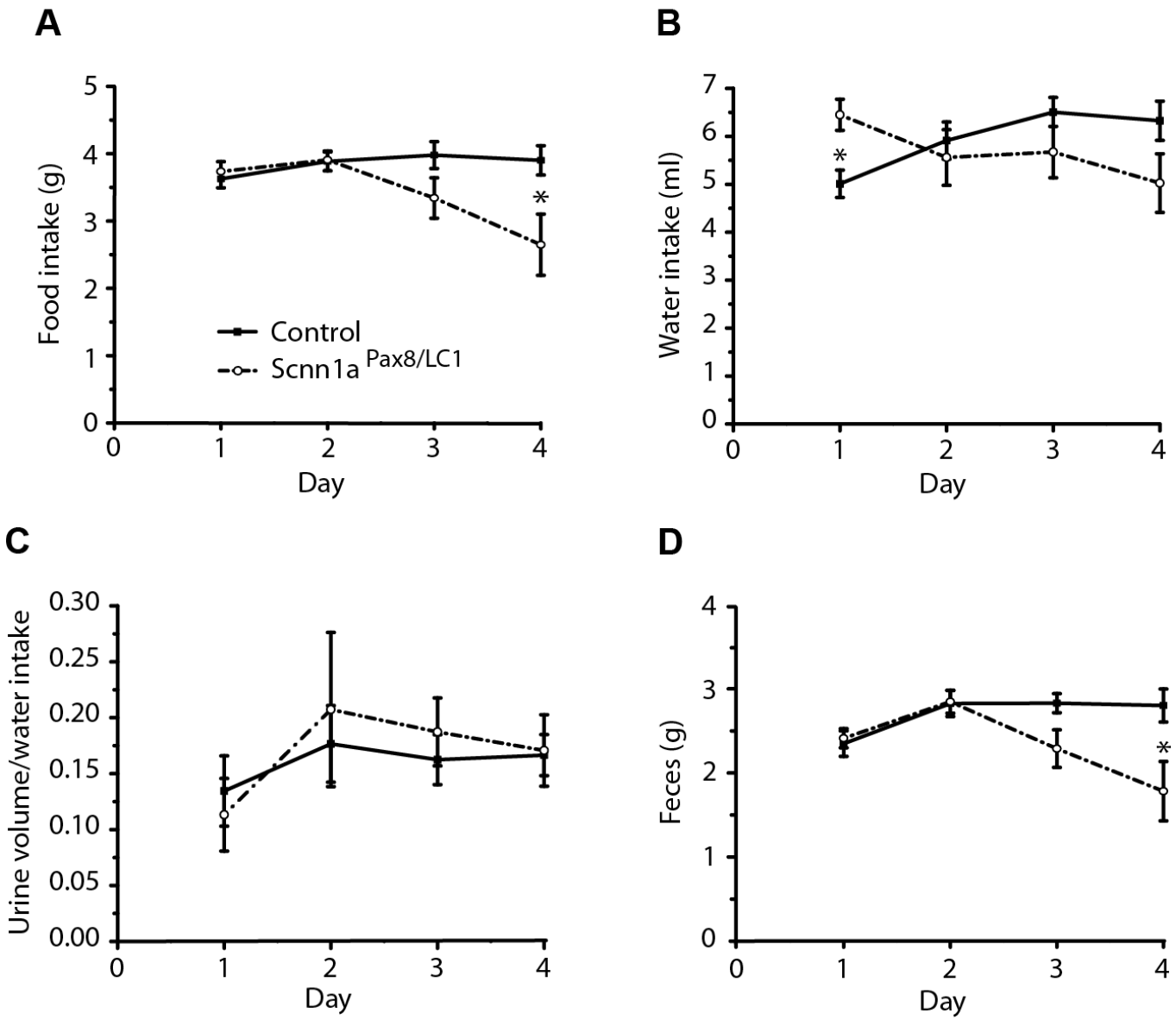
Supplementary Figure 4 Diet-dependent body weight change in doxycycline-induced Scnn1a$^{Pax8/LC1}$ knockout mice

Body weight changes (Δ body weight) in percentage of initial body weight in control (n=8) and Scnn1a$^{Pax8/LC1}$ knockout (n=9) mice following doxycycline-induction and subjected to different diet conditions as indicated. Standard diet: 0.17% Na^+ / 0.97% K^+, (Day 0-5 and Day 25-28), pre-rescue diet: 3.5% Na^+ / 0% K^+, (Day 5-8), rescue diet: 3.5% Na^+ / 0.2% K^+, (Day 8-25).



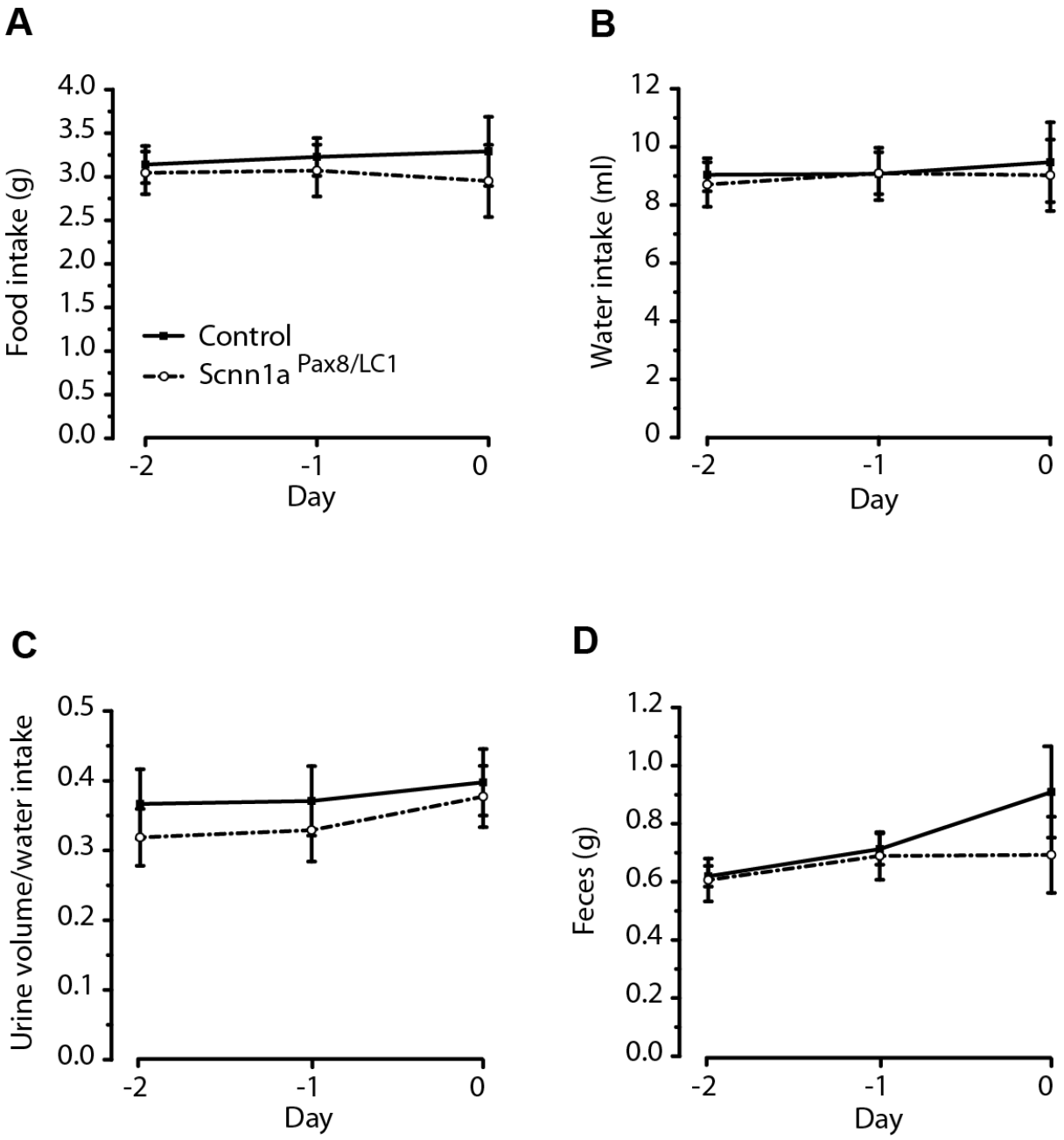
Supplementary Figure 5 Creatinine concentration and creatinine clearance in the Scnn1a$^{Pax8/LC1}$ knockout mice

(**A**) Urinary and (**B**) plasmatic creatinine concentrations in control (n=6) and knockout mice (n=5). (**C**) Creatinine clearance in control (n=6) and knockout mice (n=5).



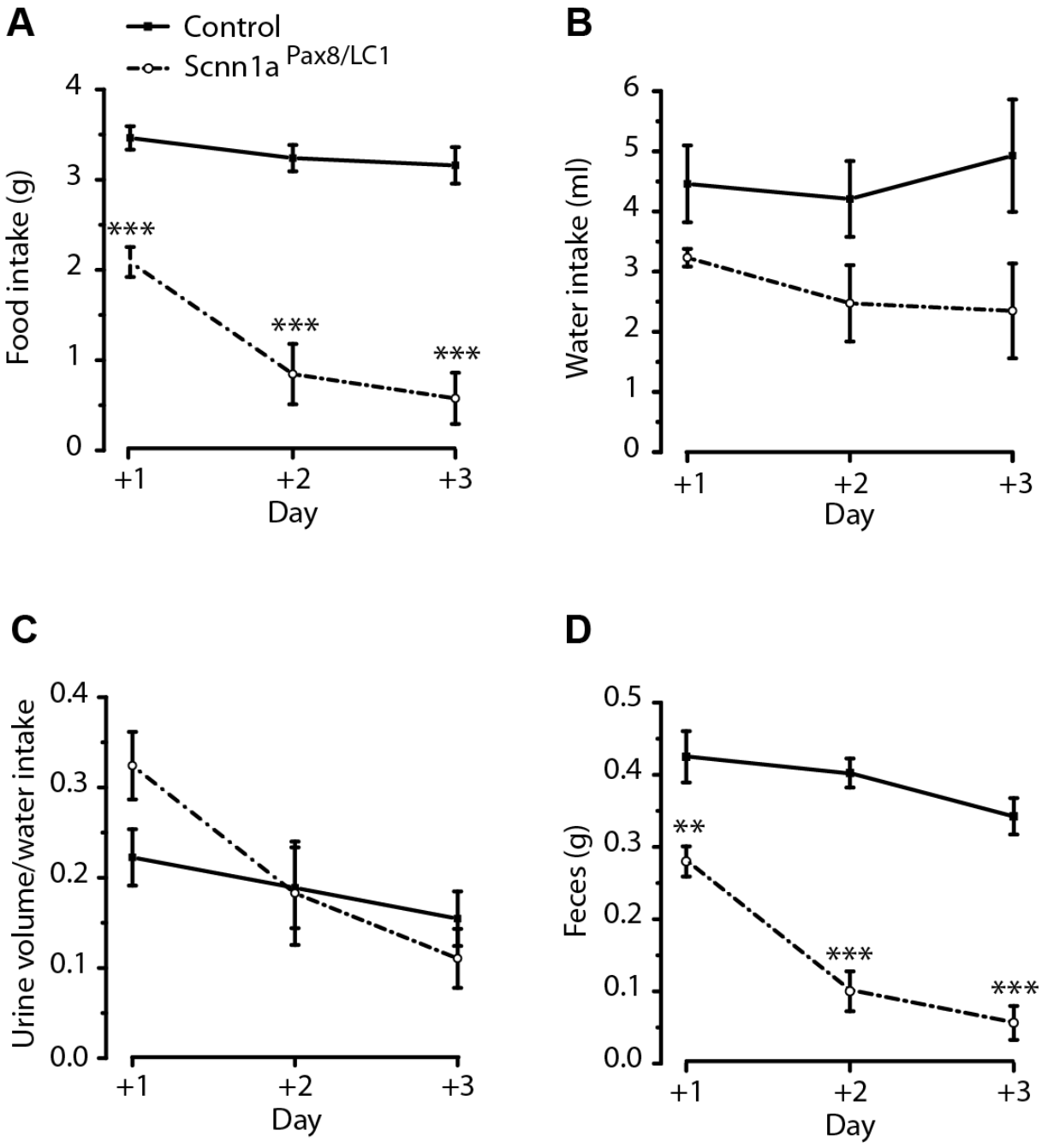
Supplementary Figure 6 Measurement of physiological parameters following doxycycline induction under regular (standard) diet.

(A) Food intake (g), **(B)** water intake (ml), **(C)** urine volume to water intake ratio and **(D)** amount of feces (g) daily measured in 4-week-old control (n=12) and Scnn1a$^{Pax8/LC1}$ knockout mice (n=10) under a standard salt diet.



Supplementary Figure 7 High Na^+ and reduced K^+ diet restores food and water intake and sodium and potassium excretion in αENaC knockout mice.

(A) Food intake (g) **(B)** water intake (ml) **(C)** urine volume to water intake ratio and **(D)** feces amount (g) daily measured in control (n=11) and $Scnn1a^{Pax8/LC1}$ knockout mice (n=11) at the end of two months of high Na^+ and reduced K^+ diet.



Supplementary Figure 8 Reversible establishment of PHA1 following switch to standard diet in diet-rescued Scnn1a$^{Pax8/LC1}$ mice.

(**A**) Food (g) and (**B**) water (ml) intake, (**C**) urine volume to water intake ratio and (**D**) feces amount (g) daily measured in control (n=8) and Scnn1a$^{Pax8/LC1}$ knockout mice (n=8) during three days of standard diet following two months of high Na^+ and reduced K^+ diet.