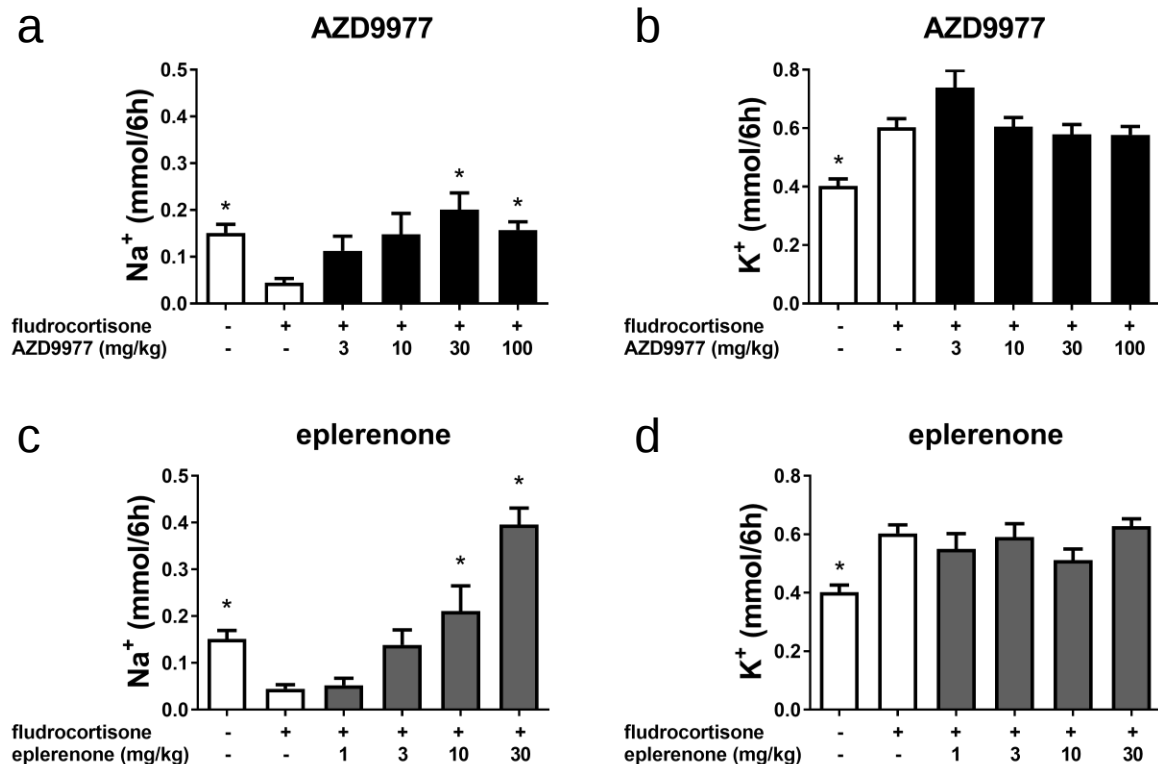
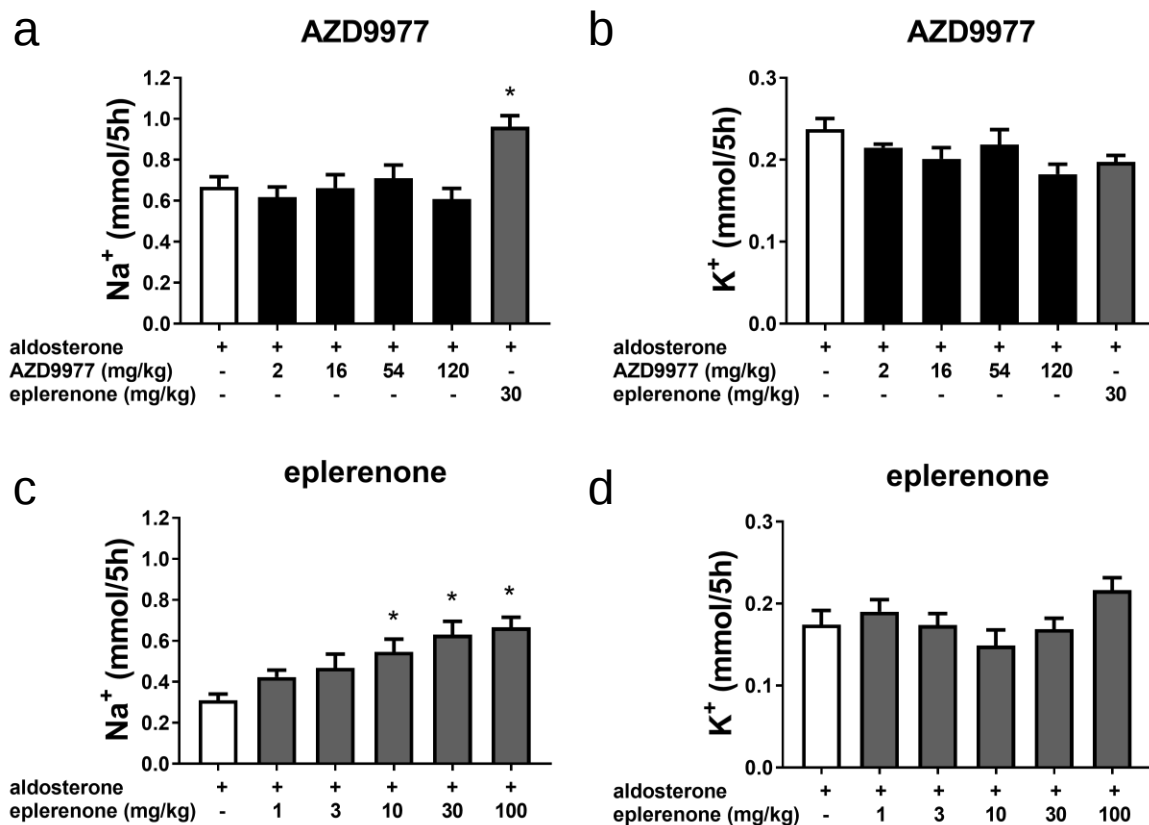




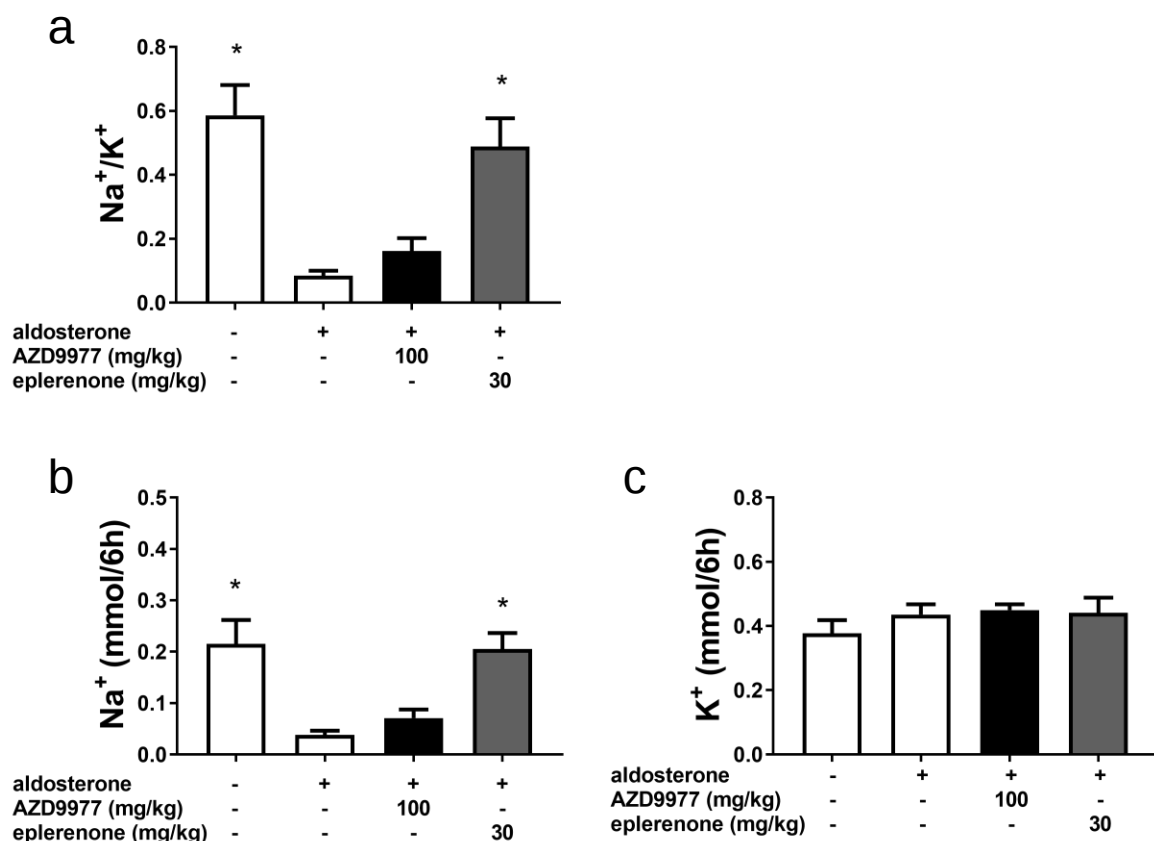
S1 Figure. Na⁺ and K⁺ excretion values, fludrocortisone testing.

Repeated doses of fludrocortisone reduce the Na⁺ (a, c) and elevate the K⁺ (b, d) excretion in urine collected 2-8 hours after the initial dose (white bars). Single doses of AZD9977 (a, b, black bars) or eplerenone (c, d, grey bars) reverse the effect on Na⁺ excretion (a, c) but not on K⁺ excretion (b, d). Doses in mg/kg are indicated below each bar. The groups dosed with fludrocortisone are indicated. Mean $\pm$ SEM, n=7-31 per group, *p<0.05 vs fludrocortisone alone. Data is assembled from four experiments.



S2 Figure. Na⁺ and K⁺ excretion values, aldosterone testing.

AZD9977 (a) does not affect the urinary Na⁺ excretion after administration of a NaCl bolus and a single dose of aldosterone whereas eplerenone (c) dose dependently elevates the urinary Na⁺ excretion. Neither compound has effect on urinary K⁺ excretion over the time period studied (b, d). Eplerenone at 30 mg/kg was used in the AZD9977 experiment as a positive control for Na⁺ excretion. Doses in mg/kg are indicated below each bar. Mean $\pm$ SEM, n=7-8 per group, *p<0.05 vs aldosterone alone. Data is assembled from two experiments.



S3 Figure. Repeated aldosterone administration in absence of 2.7% NaCl load.

Repeated dosing of aldosterone reduces the urinary Na⁺/K⁺ ratio (a) primarily by reducing Na⁺ excretion (b) without measurably elevating the K⁺ excretion (c) in urine collected 2-8 hours after the initial dose (white bars). AZD9977 (black bars) does not affect the urinary Na⁺/K⁺ ratio when tested with repeated doses of aldosterone whereas eplerenone (grey bars) elevates the urinary Na⁺/K⁺ ratio (a). The described effects are driven by the effects on urine Na⁺ excretion since K⁺ excretion is not measurably altered by either treatment (b, c). Mean ± SEM, n=7-8 per group, *p<0.05 vs aldosterone alone.

Method

10 weeks old rats were dosed with vehicle or 10 µg/kg aldosterone by subcutaneous injection and placed in metabolic cages for urine collection. Vehicle and mineralocorticoid dosing was repeated after 2 hours when 100 mg/kg AZD9977 or 30 mg/kg eplerenone was administered by oral gavage. Urine was collected for 6 hours after compound administration. AZD9977 and eplerenone doses were chosen to yield similar exposures in relation to rat MR potencies.