Supplementary Materials

**Supplementary results**: *Effect of CaSR activity on the medullary thick ascending limb*

While there have been extensive experiments on CaSR activity on Ca2+ permeability in the cortical thick ascending limb, data on the medullary thick ascending limb are relatively sparse. Hence, we conducted additional simulations where medullary thick ascending limb Ca2+ permeability was taken to be constant, independent of the interstitial [Ca2+], which increases along the corticomedullary axis. When medullary thick ascending limb Ca2+ permeability was set to the value corresponding to the spatial average of the outer-medullary interstitial [Ca2+] i.e., 1.875 mM, we observe that calcium reabsorption in the medullary thick ascending limb was 2% and 1% lower in male and female models, respectively, compared to the original simulations. Despite these reductions, the change in calcium transport downstream was negligible (<1%). Meanwhile, urinary calcium excretion increased by 16% and 5% in male and female models, respectively, compared to the original simulations.

**Table S1**: NaPi2, Na+−Pi cotransporter 2; PNa, Na+ permeability; PCl, Cl−permeability; Pf , water permeability; NKCC2, Na+−K+− Cl−cotransporter isoform 2; KCC, K+ − Cl− cotransporter; ENaC, epithelial Na+ channel; PK, K+ permeability; PCT, proximal convoluted tubule; S3, proximal straight tubule; mTAL, medullary thick ascending limb; cTAL, cortical thick ascending limb; DCT, distal convoluted tubule; CNT, connecting tubule; CCD, cortical collecting duct; OMCD, outer medullary collecting duct; IMCD, inner medullary collecting duct; SNGFR, single nephron glomerular filtration rate.

|  |  |  |  |
| --- | --- | --- | --- |
| Parameter | Female-to-Male Ratio | Parameter | Female-to-Male Ratio |
| PCT |  | **S3** |  |
| NHE3 activity | 0.83 |  | 0.83 |
| NaPi2 | 0.75 |  | 0.75 |
| PNa, PCl (paracellular) | 0.4 |  | 0.4 |
| Pf (transcellular) | 0.64 |  | 0.64 |
| mTAL |  | **cTAL** |  |
| NKCC2 activity | 2 |  | 2 |
| KCC activity | 1.5 |  | 1.5 |
| Na+-K+-ATPase activity | 2 |  | 2 |
| Na+ / H+ exchanger | 0.8 |  | 0.8 |
| PNa, PCl (paracellular) | 0.9 |  |  |
| DCT |  | **CNT** |  |
| NCC activity | 1.6 |  |  |
| Na+-K+-ATPase activity | 2 |  | 2 |
| Na+/H+ exchanger | 0.85 |  | 0.9 |
| ENaC activity | 2 |  | 1.3 |
| PNa, PCl (paracellular) | 1.4 |  | 1.4 |
| Pf (transcellular) | 2 |  | 1.5 |
| CCD |  | **OMCD** |  |
| Na+-K+-ATPase activity | 1.5 |  | 1.1 |
| H+-K+-ATPase activity | 1 |  | 1.5 |
| Na+/H+ exchanger | 0.9 |  | 0.9 |
| ENaC activity | 1.5 |  | 1.2 |
| PNa, PCl (paracellular) | 1.4 |  | 1 |
| PK (apical) | 0.7 |  | 1.2 |
| Pf (transcellular) | 2 |  | 2 |
| IMCD |  | **Morphology** |  |
| Na+-K+-ATPase activity | 1.2 | **PCT, S3** |  |
| H+-K+-ATPase activity | 1.5 | Length | 0.8 |
| PNa, PCl (paracellular) | 0.5 | Diameter | 0.8 |
| PK (apical) | 2 | **Distal segments** |  |
| PNa (apical) | 0.5 | Length | 0.85 |
| Pf (transcellular) | 2 | Diameter | 0.85 |
|  |  | Hemodynamics |  |
|  |  | SNGFR | 0.8 |

**Table S2**: Baseline and inhibition excretion values for Na+ and Ca2+. Transport and excretion values are given in pmol/min. Percentage changes from baseline values are shown in parentheses. Co-inhibition refers to the simultaneous inhibition of TRPV5, NCX1, and PMCA.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | PT transport | | TAL transport | | DCT transport | | CNT transport | | Urinary excretion | |
|  | Na+ | Ca2+ | Na+ | Ca2+ | Na+ | Ca2+ | Na+ | Ca2+ | Na+ | Ca2+ |
| Base case | | | | | | | | | | |
| Male | 3085 | 26 | 1180 | 7.7 | 154 | 1.8 | 117 | 1.3 | 53 | 1.2 |
| Female | 1869 | 19 | 1438 | 5.2 | 168 | 2.9 | 13 | 2.0 | 42 | 1.0 |
| Ca2+ Specific Inhibitions | | | | | | | | | | |
| Co-inhibition 100 (male) | 3085 (0%) | 26 (0%) | 1180 (0%) | 7.7 (0%) | 153 (0%) | 0.0  (-99%) | 119 (+2%) | 0.0 (-99%) | 51 (-2%) | 4.6 (+269%) |
| Co-inhibition 100 (female) | 1869 (0%) | 19 (0%) | 1438 (0%) | 5.2 (0%) | 170 (+1%) | 0.0  (-99%) | 13 (+2%) | 0.0 (-99%) | 37  (-12%) | 6.1 (+499%) |
| NCX1-100 (male) | 3085 (0%) | 26 (0%) | 1180 (0%) | 7.7 (0%) | 154 (0%) | 1.7  (-8%) | 117 (0%) | 0.81 (-35%) | 52  (-1%) | 1.8 (+47%) |
| NCX1-100 (female) | 1869 (0%) | 19 (0%) | 1438 (0%) | 5.2 (0%) | 170 (+1%) | 1.7  (-40%) | 13 (0%) | 0.78 (-60%) | 39  (-7%) | 3.4 (+232%) |
| PT-50 (male) | 3085 (0%) | 24 (-7%) | 1180 (0%) | 9.4 (+22%) | 154 (0%) | 1.8 (0%) | 118 (+1%) | 1.3 (0%) | 54 (+2%) | 1.5 (+17%) |
| PT-50 (female) | 1869 (0%) | 19 (-1%) | 1437 (0%) | 5.0 (+5%) | 168 (0%) | 2.9 (0%) | 13 (0%) | 2.0 (0%) | 42 (0%) | 1.1 (+5%) |
| TAL-50 (male) | 3085 (0%) | 26 (0%) | 1182 (0%) | 5.8 (-25%) | 154 (0%) | 1.8 (+2%) | 117 (0%) | 1.3 (+4%) | 51  (-3%) | 3.0 (+146%) |
| TAL-50 (female) | 1869 (0%) | 19 (0%) | 1439 (0%) | 3.6 (-31%) | 168 (0%) | 3.0 (+1%) | 13 (-1%) | 2.0 (+4%) | 40  (-4%) | 2.5 (+144%) |
| Na+ Specific Inhibitions | | | | | | | | | | |
| NHE3-50 (male) | 2529 (-18%) | 22 (-18%) | 1203 (+2%) | 7.8 (+1%) | 168 (+9%) | 1.7 (-4%) | 156 (+33%) | 1.2  (-5%) | 98 (+87%) | 2.2 (+78%) |
| NHE3-50 (female) | 1534 (-17%) | 16 (-16%) | 1312  (-8%) | 6.1 (+15%) | 220 (+31%) | 2.3 (-21%) | 66 (+410%) | 1.8  (-7%) | 69 (+66%) | 1.2 (+20%) |
| NHE3-80 (male) | 1708 (-44%) | 15 (-44%) | 1153  (-2%) | 7.3 (-4%) | 198 (+29%) | 1.8 (0%) | 194 (+66%) | 1.2  (-7%) | 177 (+236%) | 3.0 (+133%) |
| NHE3-80 (female) | 1091 (-41%) | 12 (-37%) | 1265  (-12%) | 5.9 (+13%) | 247 (+47%) | 3.0 (+1%) | 154 (+1086%) | 1.8  (-6%) | 196 (+370%) | 2.3 (+126%) |
| NKCC2-70 (male) | 3066 (0%) | 26 (0%) | 961  (-18%) | 6.1 (-21%) | 163 (+6%) | 1.7 (-7%) | 154 (+32%) | 1.2  (-3%) | 120 (+128%) | 3.2 (+156%) |
| NKCC2-70 (female) | 1808 (-3%) | 18 (-4%) | 1267  (-11%) | 4.2 (-20%) | 204 (+21%) | 2.7 (-9%) | 63 (+384%) | 1.9  (-2%) | 103 (+148%) | 3.3 (+220%) |
| NKCC2-100 (male) | 3049 (-1%) | 26.1 (-1%) | 240 (-79%) | -1.0 (backleak) | 184 (+19%) | 1.4 (-19%) | 229 (+95%) | 0.89 (-29%) | 609 (+1057%) | 11.0 (+785%) |
| NKCC2-100 (female) | 1774 (-5%) | 17 (-8%) | 287 (-80%) | -2.9 (backleak) | 241 (+43%) | 2.2 (-26%) | 204 (+1469%) | 1.5 (-22%) | 838 (+1914%) | 12 (+1068%) |
| NCC-70 (male) | 3085 (0%) | 26 (0%) | 1180 (0%) | 7.7 (0%) | 107 (-30%) | 1.9 (+3%) | 145 (+23%) | 1.1 (-10%) | 64 (+21%) | 1.3 (+5%) |
| NCC-70 (female) | 1845 (-1%) | 19 (-1%) | 1446 (0%) | 5.2 (0%) | 130 (-22%) | 2.7 (-8%) | 45 (+247%) | 1.8 (-6%) | 53 (+27%) | 1.4 (+37%) |
| NCC-100 (male) | 3085 (0%) | 26 (0%) | 1180 (0%) | 7.7 (0%) | 49 (-68%) | 1.8 (-2%) | 172 (+46%) | 0.98 (-21%) | 83 (+58%) | 1.6 (+25%) |
| NCC-100 (female) | 1845 (0%) | 19 (0%) | 1446 (0%) | 5.2 (0%) | 31 (-81%) | 2.0 (-30%) | 106 (+716%) | 1.6 (-18%) | 79 (+90%) | 2.3 (+123%) |
| NCC-100 (male-chronic) | 3148 (+2%) | 27 (+2%) | 1155 (-2%) | 7.5 (-1%) | 45 (-71%) | 1.9 (+3%) | 164 (+40%) | 1.0 (-17%) | 62 (+17%) | 0.9 (-23%) |
| NCC-100 (female-chronic) | 1951 (+4%) | 20 (+3%) | 1396 (-2%) | 5.0 (-5%) | 26 (-84%) | 2.3 (-22%) | 87 (+570%) | 2.1 (4%) | 51 (+23%) | 0.8 (-21%) |
| ENaC-70 (male) | 3085 (0%) | 26 (0%) | 1180 (0%) | 7.7 (0%) | 150 (-2%) | 2.3 (+28%) | 54 (-53%) | 1.6 (+30%) | 93 (+76%) | 0.35 (-71%) |
| ENaC-70 (female) | 1869 (0%) | 19 (0%) | 1446 (0%) | 5.2 (0%) | 171 (+1%) | 3.5 (+19%) | -7.8 (backleak) | 2.1 (+8%) | 69 (+66%) | 0.28 (-73%) |
| ENaC-100 (male) | 3085 (0%) | 26 (0%) | 1180 (0%) | 7.7 (0%) | 147 (-4%) | 2.4 (+34%) | -24 (backleak) | 1.8 (+46%) | 173 (+228%) | 0.02 (-98%) |
| ENaC-100 (female) | 1869 (0%) | 19 (0%) | 1446 (0%) | 5.2 (0%) | 168 (0%) | 3.8 (+26%) | -37 (backleak) | 2.2 (+11%) | 115 (+176%) | 0.01 (-99%) |