Model equations and parameters

The model used in this study builds on our previous work and uses the following equations [1]. K^+ concentration in the ECS ($[K^+]_o$) depends upon the fluxes through Na^+/K^+–ATPase (J_{NKA}), K^+ channels (J_K), $Na^+/K^+/Cl^-$ co-transporter (J_{NKCC1}) , K^+/Cl^- co-transporter (J_{KCC1}) , as well as K^+ exchange with the bath solution (J_{Kdiff}). The rate equation for $[K^+]_o$ is

$$\frac{d[K^+]_o}{dt} = \frac{1}{VR_{sa}} (J_K - 2J_{NKA} - J_{NKCC1} - J_{KCC1}) + J_{Kdiff} \tag{1}$$

where VR_{sa} is the ratio of the ECS to the astrocytic volume. The flux through the K^+ channels (*μM s⁻¹*) is

$$J_K = G_K (v_i - E_K) \tag{2}$$

where G_K is whole-cell conductance of K^+ channels, v_i is the membrane potential, and E_K is the reversal potential of K^+ channels given by the Nernst equation (*mV*).

$$E_K = \frac{V_T}{z_K} \ln\left(\frac{[K^+]_o}{[K^+]_i}\right) \tag{3}$$

z_K is the valency of K^+. J_{NKA} exports 3 Na^+ and imports 2 K^+. J_{NKA} ($\mu M\ s^{-1}$) is given as

$$\begin{aligned} J_{NKA} = J_{NKA_{max}} (&-I_1 (a_1, b_1, t, t_0, c_1)\, I_2 (a_2, b_2, t, t_0, c_2) \\ &+ d)\, H_{1.5}([Na^+]_i, K_{Na_i})\, H([K^+]_o, K_{K_o}) \end{aligned} \tag{4}$$

where J_{NKAmax} is the maximum flux through Na^+/K^+–ATPase and $H_n(x,K)$ is of the from $\frac{x^n}{x^n + K^n}$, where n is the Hill coefficient, x is the concentration of Na^+ or K^+, and K in the function $H_n(x,K)$ is the dissociation constant of the respective ion to the pump.

$$I(a, b, t, t_0, c) = \frac{a}{1 + a exp(b(t - t_0)\ + c)} \tag{5}$$

where a, b, c, and d are constants, t represents time during the simulation, and t_0 represents the time at which ischemia is initiated. The sigmoidal forms are used to mimic the scenario where local ischemia near the cell settles in slowly or normal oxygen and glucose supply restore slowly after the solution is switched to ischemic condition and back to normal, respectively.

K^+ diffusion between the ECS and bath solution ($\mu M\ s^{-1}$) is given as

$$J_{Kdiff} = diff([K^+]_{bath} - [K^+]_o) \tag{6}$$

where *diff* is the diffusion constant. One Na^+, one K^+, and 2 Cl^- ions move in inward direction through NKCC1. The flux through NKCC1 ($\mu M\ s^{-1}$) is

$$J_{NKCC1} = G_{NKCC1} \emptyset\ \ln\left(\frac{[Na^+]_o [K^+]_o [Cl^-]_o^2}{[Na^+]_o [K^+]_i [Cl^-]_i^2}\right) \tag{7}$$

G_{NKCC} is the whole-cell conductance of NKCC1. Cl^- and K^+ flux through KCC1 channels ($\mu M\ s^{-1}$) is

$$J_{KCC1} = G_{KCC1} \emptyset\ \ln\left(\frac{[K^+]_o [Cl^-]_o}{[K^+]_i [Cl^-]_i}\right), \tag{8}$$

where G_{KCC1} is the whole-cell conductance of KCC1.

The rate equation for $[Na^+]_o$ depends on the flux through Na^+ channels (J_{Na}), NKA, NBCe1, Na^+/H^+ exchanger, and Na^+ exchange with the bath solution (J_{Nadiff}).

$$\frac{d[Na^+]_o}{dt} = \frac{1}{VR_{sa}} (J_{Na} + 3J_{NKA} - J_{NKCC1} - J_{NBCe1} + J_{NHE}) + J_{Nadiff}, \tag{9}$$

Na^+ flux through Na^+ channels ($\mu M\ s^{-1}$) is

$$J_{Na} = G_{Na} (v_i - E_{Na}) \tag{10}$$

where G_{Na} is the whole-cell conductance of Na^+ channels and E_{Na} is the reversal potential for Na^+.

$$E_{Na} = \frac{V_T}{z_{Na}} \ln\left(\frac{[Na^+]_o}{[Na^+]_i}\right) \tag{11}$$

Fluxes through NBCe1 and NHE (*μM s⁻¹*) are given in Section 2.6.

Na^+ exchange with the bath solution ($\mu M\ s^{-1}$) is given as

$$J_{Nadiff} = diff([Na^+]_{bath} - [Na^+]_o) \tag{12}$$

where *diff* is the diffusion constant of Na^+.

K^+ concentration in the astrocyte ($[K^+]_i$) depends on the fluxes due to K^+ channels, NKA, NKCC1, and KCC1. That is,

$$\frac{d[K^+]_i}{dt} = -J_K + 2J_{NKA} + J_{NKCC1} + J_{KCC1}. \tag{13}$$

$[Na^+]_i$ depends on the fluxes through Na^+ channels, NKA, NBCe1, and NHE. These fluxes are already described above.

$$\frac{d[Na^+]_i}{dt} = -J_{Na} - 3J_{NKA} + J_{NKCC1} + J_{NBCe1} - J_{NHE} \tag{14}$$

Cl^- concentration in the astrocyte ($[Cl^-]_i$) and ECS ($[Cl^-]_o$) is given by electroneutrality (μM).

$$\frac{d[Cl^-]_i}{dt} = \frac{d[Na^+]_i}{dt} + \frac{d[K^+]_i}{dt} - J_{NBCe1} \tag{15}$$

$$[Cl^-]_o = [Na^+]_o + [K^+]_o - [HCO_3^-]_o \tag{16}$$

Membrane potential of the astrocyte (*mV*) is given as

$$\frac{dv_i}{dt} = \gamma_v(-J_K - J_{Na} - J_{Cl} - J_{NKA} + J_{NBCe1} - J_{NHE}) \tag{17}$$

where γ_v converts flux from concentration unit to current unit. Cl^- flux through leak channels ($\mu M\ s^{-1}$) is

$$J_{Cl} = G_{Cl}(v_i - E_{Cl}) \tag{18}$$

where G_{Cl} is the maximum conductance of Cl^- channels. E_{Cl} is the reversal potential of Cl^- and is given by

$$E_{Cl} = \frac{v_T}{z_{Cl}} \ln\left(\frac{[Cl^-]_o}{[Cl^-]_i}\right) \tag{19}$$

where z_{Cl} is the valence of Cl^-.

The rate equations for extracellular pH(pHo) and the intracellular pH(pH_i)

$$\frac{dpH_o}{dt} = \frac{1}{VR_{sa}\beta_{tot}}(-J_{NHE} - J_{NBCe1}) + diff(pH_{bath} - pH_o). \tag{20}$$

$$\frac{dpH_i}{dt} = \frac{J_{NHE}+J_{NBCe1}}{\beta_{tot}}, \tag{21}$$

The equations for J_{NBCe1} and J_{NHE} are similar to those used in [47]. That is,

$$J_{NBCe1} = G_{NBCe1}(v_i - E_{NBCe1}), \tag{22}$$

where E_{NBCe1}, v_i, and G_{NBCe1} are the reversal potential for Na^+ and HCO_3^- flux through NBCe1, the membrane potential of astrocyte, and the whole-cell conductance of NBCe1, respectively. E_{NBCe1} is calculated using the Nernst equation

$$\mathrm{E_{NBCe1}} = \frac{\mathrm{V_T}}{\mathrm{z_{NBCe1}}} \ln\left(\frac{[Na^+]_o}{[HCO_3^-]_i^2}\frac{[HCO_3^-]_o^2}{[Na^+]_i}\right). \tag{23}$$

$V_T = \frac{RT}{F}$ where R, T, and F represent the gas constant, temperature, and Faraday's constant and Z_{NBCe1} represents the net charge transported. $[HCO_3^-]_i$ is the intracellular bicarbonate concentration. J_{NHE} is given as

$$J_{NHE} = G_{NHE}\,(v_i - E_{NHE}), \tag{24}$$

where G_{NHE} is the whole-cell conductance of NHE and E_{NHE} is its reversal potential.

$$E_{NHE} = \frac{V_T}{z_{NHE}}\ \ln\left(\frac{[Na^+]_i\ [H^+]_o}{[Na^+]_o\ [H^+]_i}\right). \tag{25}$$

$[H^+]_o$ and $[H^+]_i$ represent extra- and intracellular hydrogen concentrations, respectively. Z_{NBCe1} is the net charge transported by NHE.

$[HCO_3^-]_o$ is given by the Henderson-Hasselbalch equation [48],

$$[HCO_3^-]_o = 10^{(pH_o - pK_a)}[CO_{2(\mathrm{aq})}], \tag{26}$$

where pK_a is the negative logarithm (base=10) of the acid dissociation constant of carbonic acid, and $[CO_{2(aq)}]$ is the product of solubility (s) in aqueous solution or water and partial pressure of carbon dioxide (P_{CO2}). Similarly, $[HCO_3^-]_i$ is given as

$$[HCO_3^-]_i = 10^{(pH_o - pH_i)}[HCO_3^-]_o. \tag{27}$$

$[H^+]_o$ and $[H^+]_i$ is calculated by using the Kassirer–Bleich approximation [48],

$$[H^+]_{i/o} = \frac{sK_hP_{CO_2}}{[HCO_3^-]_{i/o}}, \tag{28}$$

where K_h is the dissociation constant of carbonic acid.

The equations for NKA are modified to simulate 2-minute chemical ischemia as explained in Appendix A

Table S1. Parameters used in the equations for ion dynamics in the astrocyte and ECS, and membrane potential of the astrocyte.

Parameter	Description	Value
γ_v	Scaling factor for membrane potential	1970 $mV\ \mu M^{-1}$
VR_{sa}	Volume ratio between the ECS and astrocyte	3
V_T	Voltage constant in Nernst equation	26.7 mV
G_K	Peak conductance of K^+ channels	2072.3 $\mu M\ mV^{-1}\ s^{-1}$
G_{Na}	Peak conductance of Na^+ channels	68.08 $\mu M\ mV^{-1}\ s^{-1}$
G_{NBCe1}	Peak conductance of NBCe1	392.22 $\mu M\ mV^{-1}\ s^{-1}$
G_{NHE}	Peak conductance of NHE	$\frac{1}{3}G_{NBCe1}$
J_{NaKmax}	Maximum flux through NKA	4.26 x 10^4 $\mu M\ s^{-1}$
K_{Na}	Association constant for Na^+ to NKA	10 x 10^3 μM
K_{Ko}	Association constant for K^+ to NKA	1.5 x 10^3 μM
diff	Diffusion constant of Na^+, K^+, and pH	0.5 s^{-1}
β_0	Buffering capacity due to CO_2/HCO_3	25 mM / pH unit
pK_a	Negative logarithm of the acid dissociation constant of carbonic acid	6.1
s	Solubility of CO_2	2.25 x 10^{-4} $mM\ Pa^{-1}$

P_{CO2}	Partial pressure of CO_2	5332.9 *Pa*
K_h	Dissociation constant of CO_2	800 *nmol* L^{-1}

Table S2. The initial values of state variables.

Parameter	Description	Value
$[Na^+]_o$	Extracellular Na^+ concentration	157 *mM*
$[Na^+]_i$	Intracellular Na^+ concentration	12 *mM*
$[K^+]_o$	Extracellular K^+ concentration	2.5 *mM*
$[K^+]_i$	Intracellular K^+ concentration	146 *mM*
V_i	Intracellular membrane potential	-83 *mV*
pH_o	Extracellular pH value	7.35
pH_i	Intracellular pH value	7.32

Table S3. Parameters used in functional forms of ions in the bath.

Parameter	Description	Value
$[K^+]'_{bath}$	Baseline value of $[K^+]_{bath}$	2.5 *mM*
	k_1	-0.002675 s^{-1}
	k_2	-2
	k_3	-0.0052 s^{-1}
	k_4	1.350
	k_5	0.73
	k_6	-0.00169
	k_7	7.6
	k_8	-1.02
$[Na^+]'_{bath}$	Baseline value of $[Na^+]_{bath}$	157 *mM*
	p_1	-1.1906 x 10^{-26} s^{-1}
	p_2	5.045 x 10^{-23} s^{-1}
	p_3	-8.122 x 10^{-20} s^{-1}
	p_4	5.6637 x 10^{-17} s^{-1}
	p_5	-7.006 x 10^{-15} s^{-1}
	p_6	-1.3156 x 10^{-11} s^{-1}
	p_7	7.521 x 10^{-9} s^{-1}
	p_8	-1.326 x 10^{-6} s^{-1}
	p_9	3.51 x 10^{-6} s^{-1}
	p_{10}	1.0005
pH'_{bath}	Baseline value of pH_{bath}	7.35 -5.4275 x 10^{-19} s^{-1}
	p_1	-4.7273 x 10^{-26} s^{-1}
	p_2	2.47264 x 10^{-22} s^{-1}
	p_3	-5.4275 x 10^{-19} s^{-1}
	p_4	6.4515 x 10^{-16} s^{-1}
	p_5	-4.4486 x 10^{-13} s^{-1}
	p_6	1/7487 s^{-10}

p_7	-3.4571 s^{-8}
p_8	2.0687 x 10^{-6} s^{-1}
p_9	1.0069 x 10^{-4} s^{-1}
p_{10}	0.9999

Table S4. Parameters used in the NKA flux.

Parameter	Description	Value
a_1	Parameter in sigmoidal function	1000
b_1	Parameter in sigmoidal function	0.0022134 s^{-1}
c_1	Parameter in sigmoidal function	0
t_0	Beginning of pump inhibition	300 s
a_2	Parameter in sigmoidal function	1.52
b_2	Parameter in sigmoidal function	-0.02014 s^{-1}
c_2	Parameter in sigmoidal function	5.738
d	Intercept parameter in sigmoidal functions	1.13

Some Abbreviations used in the poster.
MEM: minimum essential medium
NBCe1 Ko: Nbce1-deficient mice
SEX: both
BCECF:2’,7’-bis-(Carboxyethyl)-5-(and-6)-carboxyfluorescein