The EC/SMC/IP_3 Pathway and Parameter Values in Code version 2.0

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Todo list

Chapter 1

Notes for reading

This report provides the basic equations and parameters for the IP_3 pathway in the EC and SMC for NVU 2.0 The following notes, definitions and equations provide the reader with a comprehensive guide to version 1.2 of NVU. The document is set out in sections where each section contains the equations for each compartment, namely neuron, synaptic cleft, astrocyte, perivascular space, smooth muscle cell, endothelial cell, extracellular space and finally the lumen. The reader will find multiple definitions and equations but by dividing the document into sections corresponding to compartments it is hoped that a more clear understanding is obtained. Concentrations as written on the left-hand-side of the o.d.e. are given by the notation of N_j where j can be any specii such as $Na^+$of Ca^{2+}. True concentrations are written with square brackets as in $[Ca^{2+}]_n$. In point of fact they are equivalent. Subscripts on variable such as concentrations denote the compartment, n=neuron, k=astrocyte, s=synaptic cleft, i=smooth muscle cell, j=endothelial cell, e = extracellular space. Concentrations with "hats" denote those in the ER/SR stores.

1.0.1 Version 1.2 /2.0 difference

The basic difference between version 1.2 and version 2.0 is the new neuron model. This is based on the work of Chang et al [1] and that of Kager et al [2]. For this version the neuron model has 4 compartments; i) soma/axon, ii) dendrite , iii) post synaptic terminal and extracellular space (ECS). Ion channels for Na^+, and K^+efflux into the ECS. $K^+$is buffered in the ECS and a portion of the K^+flux is passed into the synaptic cleft compartment. On reaching a certain concentration of K^+in the synaptic cleft glutamate is pumped into the synaptic cleft . This glutamate is taken up by both the post-synaptic neuron and the astrocyte. The neuron is stimulated by injection of a current of specified value into the soma/axon compartment.

Chapter 2

Basic Equations

2.1 Global Constants

F	Faraday's constant	96500 C mole^{-1}
T	Temperature	300 K
R_{gas}	Gas constant	8.315 J mole K^{-1}

2.2 Smooth Muscle Cell

IP_3 concentration om the SMC (in µM):

$$\frac{\mathrm{d}[IP_3]_i}{\mathrm{d}t} = J^{SMC-EC}_{IP_3-coupling_i} - J_{degrad_i} \tag{2.2.1}$$

IP_3 degradation (in µM s^{-1}):

$$J_{degrad_i} = k_{di} I_i \tag{2.2.2}$$

Heterocellular IP_3 coupling between SMCs and ECs (in µM s^{-1}):

$$J^{SMC-EC}_{IP_3-coupling_i} = -P_{IP_3}([IP_3]_i - [IP_3]_j) \tag{2.2.3}$$

Code description

```
du(idx.I_i, :) = J_IP3_coup_i - J_degrad_i;
J_IP3_coup_i = -p.P_IP3 * (I_i - I_j);
  J_degrad_i = p.k_d{_i} * I_i;
```

Release of calcium from IP_3 sensitive stores in the SMC (in µM s^{-1}):

$$J_{IP_{3i}} = F_i \frac{[IP_3]_i^2}{K_{ri}^2 + [IP_3]_i^2} \tag{2.2.4}$$

Code description

```
J_IP3_i = p.F_i * I_i.^2 ./ (p.K_r_i^2 + I_i.^2);
```

F_i	Maximal rate of activation-dependent calcium influx	0.23 µM s^{-1}	[3]
K_{ri}	Half-saturation constant for agonist-dependent calcium entry	1 µM	[3]
$R_{K,i}$	scaling parameter for membrane voltage regulatory effect on K_{act_i}	??? mV	ME
k_{di}	Rate constant of IP_3 degradation	0.1 s^{-1}	[3]
P_{IP_3}	Heterocellular IP_3 coupling coefficient	0.05 s^{-1}	[3]

2.3 Endothelial Cell

Endothelial cell

IP_3 concentration of the EC (in µM):

$$\frac{\mathrm{d}[IP_3]_j}{\mathrm{d}t} = J_{EC,IP_3} - J_{degrad_j} - J^{SMC-EC}_{IP_3-coupling_j} \tag{2.3.1}$$

IP_3 degradation (in µM s^{-1}):

$$J_{degrad_j} = k_{dj}[IP_3]_j \tag{2.3.2}$$

Code Description

```
du(idx.I_j, :) = p.J_PLC - J_degrad_j - J_IP3_coup_i;
J_degrad_j = p.k_d_j * I_j;
J_IP3_coup_i = -p.P_IP3 * (I_i - I_j);
```

Coupling

Heterocellular electrical coupling between SMCs en ECs (in mV s^{-1}):

$$V^{SMC-EC}_{coupling_i} = -G_{coup}(v_i - v_j) \tag{2.3.3}$$

Heterocellular IP_3 coupling between SMCs and ECs (in µM s^{-1}):

$$J^{SMC-EC}_{IP_3-coupling_i} = -P_{IP_3}([IP_3]_i - [IP_3]_j) \tag{2.3.4}$$

Calcium coupling with EC (in µM s^{-1}):

$$J^{SMC-EC}_{Ca^{2+}-coupling_i} = -P_{Ca^{2+}}([Ca^{2+}]_i - [Ca^{2+}]_j) \tag{2.3.5}$$

Release of calcium from IP_3-sensitive stores in the EC (in µM s^{-1}):

$$J_{IP_{3j}} = F_j \frac{[IP_3]_j^2}{K_{rj}^2 + [IP_3]_j^2} \tag{2.3.6}$$

Code Description

G_{coup}	Heterocellular electrical coupling coefficient	0.5 s^{-1}	ME
P_{IP_3}	Heterocellular IP_3 coupling coefficient	0.05 s^{-1}	[3]
$P_{Ca^{2+}}$	Heterocellular $P_{Ca^{2+}}$ coupling coefficient	0.05 s^{-1}	[3]

C_{m_j}	Membrane capacitance	25.8 pF	[3]
J_{EC,IP_3}	IP_3 production rate	µM s^{-1}	[3]

```
J_IP3_j = p.F_j * I_j.^2 ./ (p.K_r_j^2 + I_j.^2);
J_degrad_j = p.k_d_j * I_j;
```

F_j	Maximal rate of activation-dependent calcium influx	0.23 µM s^{-1}	[3]
K_{rj}	Half-saturation constant for agonist-dependent calcium entry	1 µM	[3]
k_{dj}	Rate constant of IP_3 degradation	0.1 s^{-1}	[3]

Bibliography

[1] **Chang, J. C.; Brennan, K. C.; He, D.; Huang, H.; Miura, R. M.; Wilson, P. L. and Wylie, J. J.** (**2013**): A Mathematical Model of the Metabolic and Perfusion Effects on Cortical Spreading Depression, PloS one, Vol. 8, No. 8 p. e70469.

[2] **Kager, H.; Wadman, W. J. and Somjen, G. G.** (**2000**): Simulated seizures and spreading depression in a neuron model incorporating interstitial space and ion concentrations., Journal of neurophysiology, Vol. 84, No. 1 pp. 495–512.

[3] **Koenigsberger, M.; Sauser, R.; Bény, J.-L. and Meister, J.-J.** (**2006**): Effects of arterial wall stress on vasomotion., Biophysical journal, Vol. 91, No. 5 pp. 1663–1674.