Mathematical modeling of neuronal response to neuropeptides: Angiotensin II signaling via G-protein coupled receptor

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ABSTRACT

We have developed a mathematical model of the AT1 mediated pathways including activation of PLC, PKC, IP3, and channel mediated variation of the cytosolic Ca2+ level after Angiotensin II stimulation. Different Ca2+ responses and the respective time courses of activated PKC and Ca2+ dependent proteins, e.g. CaMKII are described in the model. The obtained simulation results are in good agreement with the measurement data found in literature. For example, the model describes the state-dependent exposure to AngII: increase in Ca2+ at low baseline Ca2+ levels as well as the decrease in Ca2+ at high (chronic activated) baseline. Additionally, simulation studies revealed that variations in the Na-Ca-exchanger transport characteristics could account for the observed cell-to-cell variability. Additional pathways were included in the model, e.g. MAPK, thus enabling the description of relevant transcription factor patterns. Also a Hodgkin-Huxley model approach is used to investigate the function of cell signaling in altering the firing behavior of NTS neurons in response to various baroreceptor stimuli.

SUMMARY and RESULTS

G-protein coupled (GPCRs) and other receptors modulate cell physiology, in particular by influences on transcriptional output, to produce adaptive change in the state of the cell. In neurons GPCRs are involved in the alteration of neuronal activity (neuromodulation) via cascades of interacting proteins. Mathematical modeling and analysis provides appropriate tools to decipher this complex integration of signals. Angiotensin II and AT1 receptor dependent signaling was investigated as examples that use GPCR signaling pathways (Gq).

The octapeptide Angiotensin II is a multifunctional hormone and elicits profound physiological and behavioural effects by acting within the brain. It is involved in stimulation of water and sodium uptake, vasopressin secretion, increased blood pressure and modulation of baroreflexes. Most of the effects are mediated by the activation of receptor type I (AT1). AT1 signals via a wide variety of intracellular signaling molecules: (1) G-protein mediated stimulation of phospholipase C (PLC) and phosphoinositide (PI) hydrolysis, with subsequent $Ca2+$ mobilisation and activation of Ca dependent enyzmes (like PKC, CaMKII); (2) Jak/STAT pathway; (3) transactivation of tyrosine kinase pathways via downstream components of the G-protein stimulated pathways. Relevant signalling outputs modify gene expression patterns and thus modulate long-term neuronal activity via changes in membrane ionic currents and firing.

We have developed an ODE model of the AT1 mediated pathways including activation of PLC, PKC, IP3, and channel mediated variation of the cytosolic $Ca2+$ level after Angiotensin II stimulation. Different $Ca2+$ responses and the respective time courses of activated PKC and $Ca2+$ dependent proteins, e.g. CaMKII are described in the model (adapted from [Mishra and Bhalla, Biophys. J., 83:1298-1316, 2002]). The obtained simulation results are in good agreement with the measurement data found in literature [Fernandez et al., Hypertension Jan.2003:56-63]. For example, the model describes the state-dependent exposure to AngII: increase in $Ca2+$ at low baseline $Ca2+$ levels as well as the decrease in $Ca2+$ at high (chronic activated) baseline. Additionally, simulation studies revealed that variations in the Na-Ca-exchanger transport characteristics could account for the observed cell-to-cell variability. Additional pathways were included in the model, e.g. MAPK, thus enabling the description of relevant transcription factor patterns. Also a Hodgkin-Huxley model approach is used to investigate the function of cell signaling in altering the firing behavior of NTS neurons in response to various baroreceptor stimuli.