BMC Neuroscience

Oral presentation

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Modeling of the receptor, G-protein and effector reactions in vertebrate olfactory receptor neurons

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from Seventeenth Annual Computational Neuroscience Meeting: CNS*2008
Portland, OR, USA. 19–24 July 2008

Published: 11 July 2008

BMC Neuroscience 2008, **9**(Suppl 1):O10 doi:10.1186/1471-2202-9-S1-O10

This abstract is available from: http://www.biomedcentral.com/1471-2202/9/S1/O10

A biochemical model is developed for the receptor, G-protein and effector (RGE) steps of olfactory signal transduction in the cilia of the vertebrate olfactory receptor neurons (ORNs). It describes the steps from odorant binding to activation of the effector enzyme, which catalyzes the conversion of ATP to cAMP. In the cilia of the olfactory receptor neurons (ORNs), cAMP regulates cyclic nucleotide gated channels, which in turn control Ca influx and Ca dependent activation of chloride conductances. As a result the cilia potential becomes depolarized.

The first part of the model structure is a modified version of the RGE-part in a previously developed model for insect olfaction [1]. Since our aim was to develop a model for vertebrate ORNs, certain parts of the previous model were reinterpreted. Biologically realistic values for the rate parameters and initial densities of reacting species were estimated by calibrating the model to empirical data for vertebrates [2,3]. The new RGE-model was integrated- and linked to a previous model of receptor potential generation in vertebrate ORNs. [2], which had a specific emphasis on biochemical reactions *following* the effector enzyme. The models were made compatible by minimizing the difference in cAMP production rate when ignoring post effector inhibitory mechanisms. When our RGE model replaced the RGE-part of [2] (through the cAMP synthesis equation), the output from the combined model closely reproduced the output from the original model [2] at six different (pulse) stimulus intensities. Our model complements and extends the previous model [2] with a more elaborate treatment of the initial RGE-processes.

A variance decomposition sensitivity analysis was performed on the RGE part of the model. Time-dependent sensitivity indices [4] were computed, so that the effect of the parameter uncertainties (rate constants and initial conditions) on the model output could be monitored over time. The model output was found to be sensitive to only a few, dominant parameters, and more robust to changes in other parameters. During odor input, the level of activated effector was mainly governed by the initial density of G-protein and the catalytic constant. After the pulse has ended, the rate constant that governs the activation of the effector becomes the dominating parameter.

Acknowledgements

This work was supported by the European Network of Excellence GOSPEL (General Olfaction and Sensing Projects on a European Level).

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