Fox and Andras *BMC Neuroscience* 2010, **11**(Suppl 1):P189
http://www.biomedcentral.com/1471-2202/11/S1/P189

BMC Neuroscience

POSTER PRESENTATION Open Access

A model of endocannabinoid 2-AG-mediated depolarization-induced suppression of inhibition

David Fox*, Peter Andras

From Nineteenth Annual Computational Neuroscience Meeting: CNS*2010
San Antonio, TX, USA. 24-30 July 2010

Depolarization-induced suppression of inhibition (DSI) is known to be mediated by the endocannabinoid 2-arachidonoylglycerol (2-AG). It's calcium-dependent production and subsequent retrograde diffusion from postsynaptic pyramidal cells to presynaptic cannabinoid receptors (CB_1) located on the preterminal axon and the perisynapse of CCK-containing basket cells in the CA1 region of the hippocampus transiently suppresses GABA transmitter release [1,3]. This endocannabinoid signaling system has many physiological implications for memory-related synaptic plasticity and gamma oscillations; exogenous application of synthetic cannabinoids has a dramatic impact on the functioning of this system, more precisely the loss of synchronized cell assemblies by modification of inhibitory feedback loops in the CA1 region of the hippocampus [4,5], thus altering outcome of spatial memory-related tasks in animals and learning in humans.

This study uses computational modeling methods to understand the modes of production and action of the endocannabinoid 2-AG in monosynaptically suppressing transmitter release. Using the NEURON simulation environment [2], we developed an isopotential model cell with an L-type Ca^{2+} channel being the sole pathway for Ca^{2+} entry required for synthesis of 2-AG. The observed time courses for 2-AG passive diffusion (between adjacent shell compartments), and uptake and intracellular hydrolysis can be observed with successive depolarizing current pulses delivered by a single-electrode voltage clamp. These changes in concentration levels in the compartment representing the perisynapse and preterminal axon (the CCK-positive basket area covering the pyramidal cell expressing CB_1) are directly proportional to the GABA synaptic depression due to inhibition of presynaptic calcium channels. The amount of CB_1 activation is described by the Langmuir equation and, together with the Ca^{2+} ion cooperativity for transmitter release, affects the synaptic conductance profile described by the solution of two coupled linear ODEs. It is shown that in the model, $[Ca^{2+}]_i$ had to rise to 0.1μM in order to sufficiently activate the kinetic model describing the Phospholipase C-Diacylglycerol pathway (PLC-DAG) for 2-AG production [1,3]. We also show highly simplified dynamics of PLC after stimulation by $[Ca^{2+}]_i$, DAG production, and the spatial gradient in 2-AG across compartments (discretization of Fick's second law for diffusion). Uptake and intracellular hydrolysis is driven by the concentration gradient and the association rate constant for the irreversible reaction hydrolysing 2-AG. The end result observed is the recovery of biexponential postsynaptic conductance time course, which can vary depending on as yet unknown parameter values. The suppression can be effective over a much smaller timescale due to summation of high-frequency inputs by the synapse.

Acknowledgements
We would like to thank Ted Carnevale for helpful comments and suggestions during the development of the model.

Published: 20 July 2010

References

1. Kano M, Ohno Shosaku, Hashimotodani Y, Uchigashima M: **Endocannabinoid-mediated Control of Synaptic Transmission.** *Physiol Rev* 2009, **89**:309-380.
2. Carnevale NT, Hines ML: **The NEURON book.** *Cambridge* 2006.
3. Piomelli D: **The Molecular Logic of Endocannabinoid-signaling.** *Nature rev* 2003, **4**:873-844.
4. Glickfeld LL, Scanziani M: **Distinct Timing in the Activity of cannabinoid-sensitive and cannabinoid-insensitive Basket Cells.** *Nature Neurosci* 2006, **9**:807-815.

* Correspondence: david.fox1@ncl.ac.uk
School of Computing Science, Newcastle University, Tyne and Wear, NE1 7RU, UK

5. Robbe D, Montgomery SM, Thorne A, Rueda-Orozco PE, McNaughton BL, Buzsaki G: **cannabinoids reveal importance of spike timing coordination in Hippocampal Function.** *Nature Neurosci* 2006, **9(12)**:1526-1533.
6. Foldy C, Neu A, Jones MV, Soltesz I: **Presynaptic, Activity-dependent Modulation of cannabinoid Type 1 receptor-mediated inhibition of GABA Release.** *J Neurosci* 2006, **26(5)**:1465-1469.

doi:10.1186/1471-2202-11-S1-P189
Cite this article as: Fox and Andras: **A model of endocannabinoid 2-AG-mediated depolarization-induced suppression of inhibition.** *BMC Neuroscience* 2010 **11**(Suppl 1):P189.