Energy costs of neuronal synaptic transmission

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Summary

We developed a three component model (pre-synaptic, post-synaptic and axon initial segment) of the calyx of Held synapse and its target, the principal neurons in the MNTB to estimate the metabolic efficiency in this brainstem auditory system. Model parameters are fit such that data from whole cell recordings is reproduced, and models are compared between a baseline condition with low levels of nitric oxide (NO), and following conditioning with evoked activity that increases NO levels. Energy consumption by each component is estimated during low and high frequency activity.

Energy budget

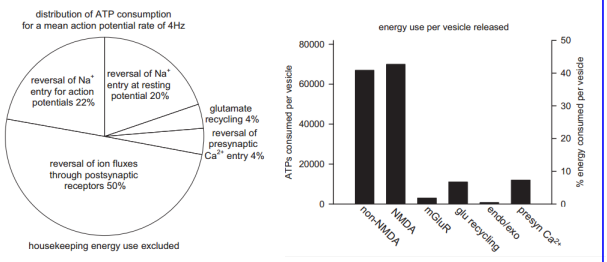


Fig. 2, Metabolic cost of neurotransmission. Energy useage of the pre-synapse, post synapse, and action potential (AP) firing were calculated from the number of ATP molecules consumed by each component following neurotransmitter release (Attwell, 2001). Coefficients were identified to evaluate the absolute and relative energy consumption of the pre-synapse, the post synapse and the AP firing site from the amount of transmitter release, the post-synaptic current (EPSC) integral, and the AP sodium current integral, respectively.

Nitric Oxide modulation

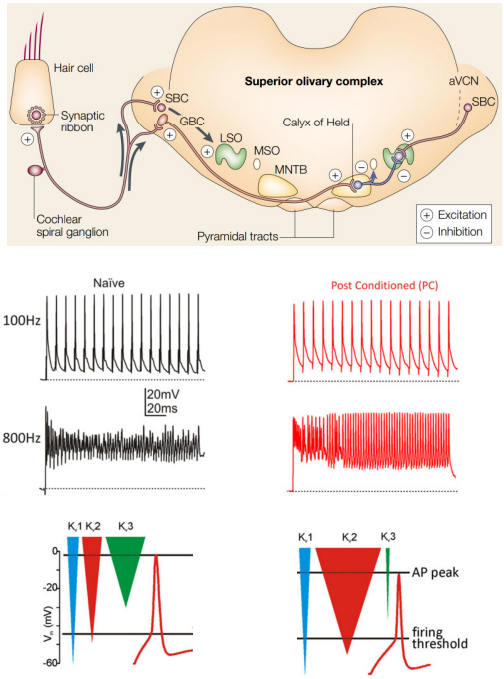
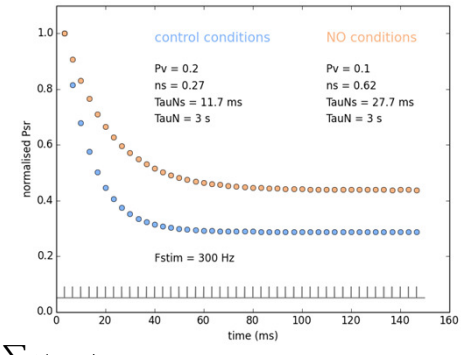


Fig. 1, Nitric oxide enhances maximal firing frequency. After conditioning, NO causes a rebalancing of potassium channels in the MNTB principal cells that allows a higher firing rate to be transmitted through the calyx of Held (Steinert, 2011).

Model identification

Fig. 3, Synapse model. A 'vesicle state' model with activity dependent vesicle release (see equations). n is the proportion of vesicles from a readily releasable vesicle pool of maximal size n0 (which is replenished with two different time constants). Vesicles release with probability Pv on presynaptic stimulation, resulting in a postsynaptic response, Psr.
The parameters of this model were identified in control and NO conditions.



$$\frac{dn}{dt} = (1 - n_s)\left(\frac{n_0 - n}{\tau_n}\right) + n_s\left(\frac{n_0 - n}{\tau_{ns}}\right) - \sum \delta(t - t_s).n.P_v$$

$$Psr = n.P_v$$

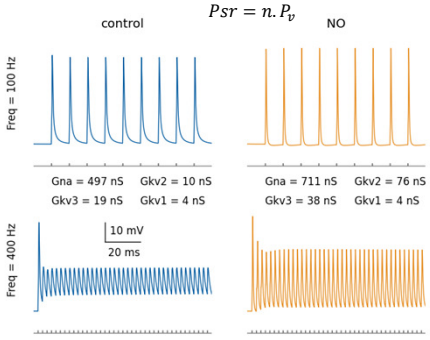
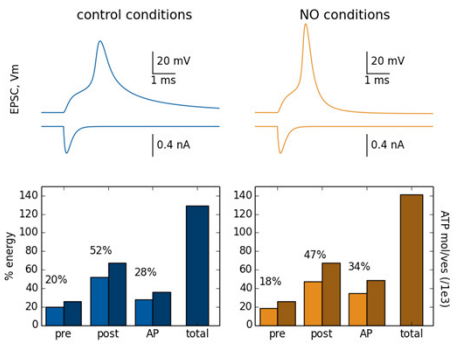


Fig. 4, MNTB ion channel conductance identification. The Na conductance model comes from hippocampal neurons, Kv3, Kv1 conductances from the cochlear nucleus (Rothman, 2003), and the Kv2 conductance from MNTB neurons (Johnston, 2008).
The channel densities were identified with a error minimization algorithm between the data and the response of the model in 100 Hz control conditions and 400 Hz NO conditions. Different firing thresholds and the relative dominance of Kv3/Kv2 potassium channels were taken into account.

Results

Fig. 5, Low frequency firing rate energy consumption is slightly higher in NO conditions. Relative contributions are shown in light colors, absolute contributions (ATP molecules) in dark colors.



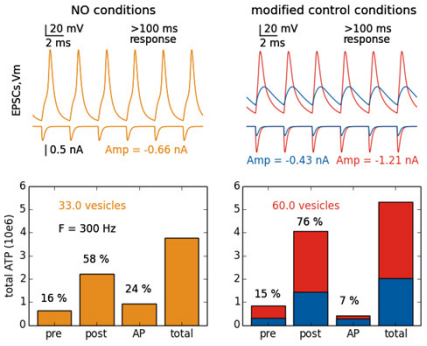


Fig. 6, High frequency firing rate energy consumption is significantly lower in NO conditions. NO model is compared to the control model (red: artificially increased EPSCs in order to force AP firing in control).

Sensitivity analysis

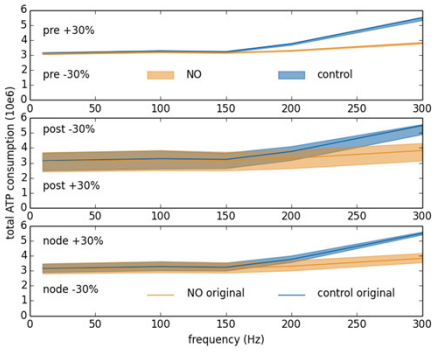


Fig. 7, Parameter sensitivity. 30% variation in component costs does not alter the relative frequency dependent metabolic cost between NO and control. Highest sensitivity for the post synapse is directly related to the highest enegy consumption here.

References
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Attwell D, Laughlin SB. An energy budget for signaling in the grey matter of the brain. J Cereb Blood Flow Metab. 2001 Oct;21(10):1133-45.
Johnston J *et al.* Initial segment Kv2.2 channels mediate a slow delayed rectifier and maintain high frequency action potential firing in medial nucleus of the trapezoid body neurons. J Physiol. 2008 Jul 15;586(14):3493-509. doi: 10.1113/jphysiol.2008.153734. Epub 2008 May 29.
Rothman JS, Manis PB. The roles potassium currents play in regulating the electrical activity of ventral cochlear nucleus neurons. J Neurophysiol. 2003 Jun;89(6):3097-113.