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Summary

Nitric oxide (NO) neuromodulator is recently known, in addition to regulating neural functions through cyclic GMP, to modulate the metabolic pathway. So, nitric oxide down-regulates the mitochondria activity [1] and the subsequent increase in AMP facilitates the activation of phosphofructokinase enzymatic reaction in the glycolytic pathway [2]. As a consequence, we wanted to better understand the dynamics of neuronal energy metabolism NO regulation.

To do that, we have built a computational model of energy metabolism based on prior works, principally on a model elucidating the control system structures of neuronal metabolism [3]. We took the biochemical pathway model, i.e. glycolysis and mitochondrial activity and the regulation by astrocyte to neuron lactate shuttle, at which we added an activity dependent glutamate cycle [4], drove by the electrophysiological activity [5]. These models take account of their respective modulation by NO.

The calyx of Held

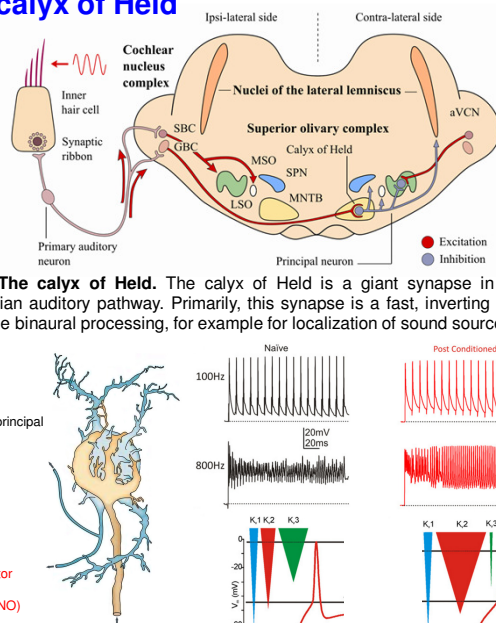


Fig. 1, The calyx of Held. The calyx of Held is a giant synapse in the central mammalian auditory pathway. Primarily, this synapse is a fast, inverting relay, which allows the binaural processing, for example for localization of sound source.

Results

Fig. 5, Metabolic pathway activation in NO conditions without neural modulation. Pyruvate synthesis, by glycolysis and ATP synthesis by mitochondrial activity are shown in both neuron and astrocyte with and without metabolic NO. Compared to the control conditions, the pyruvate synthesis is substantially decreased in both compartments by both glycolysis and mitochondrial NO modulation. The ATP synthesis increases in in neuron but decreases in glial compartment. See the individual effects.

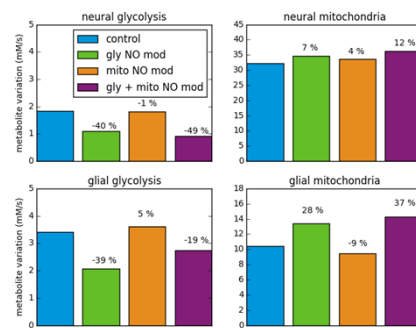
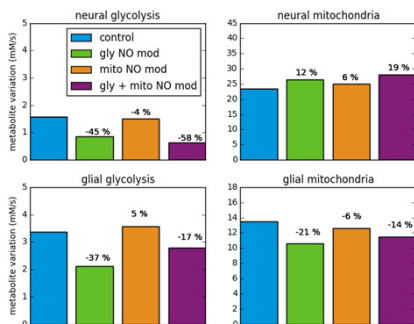


Fig. 6, Metabolic pathway activation in NO conditions with neural modulation. The scheme of metabolite synthesis is roughly the same than the precedent simulation. Except the neural modulation by NO induces a substantial increase in the glial ATP synthesis and a substantial decrease in the neural ATP synthesis. Probably due to the neural ATP consumption during the electrophysiological activity.

Metabolism pathway model

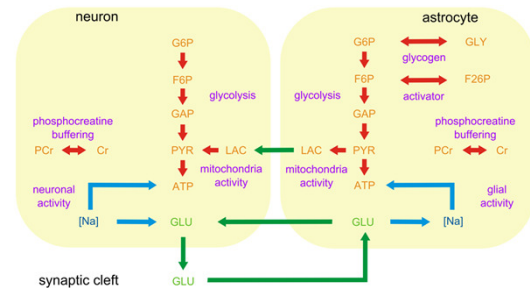


Fig. 3, Neuronal-astrocytic metabolism pathway model. A simple metabolism model (Cloutier, 2010), including glycolysis, mitochondrial activity, and phosphocreatine buffering and F26P dynamics for the astrocyte compartment, and removing the F26P, a neuron compartment. Both are relied by the lactate, following the ANLS hypothesis. To commute the model with the EPSCs, a glutamate cycle model was added. The depolarisation by Na dynamics induces the glutamate release and activates the metabolism by Na-K-ATP pump. In astrocyte glutamate co-transport, with Na, via the EAAT, activates in the same way the metabolic pathway. Finally, the G6P-GLY dynamics were added, in order to follow the experiments.

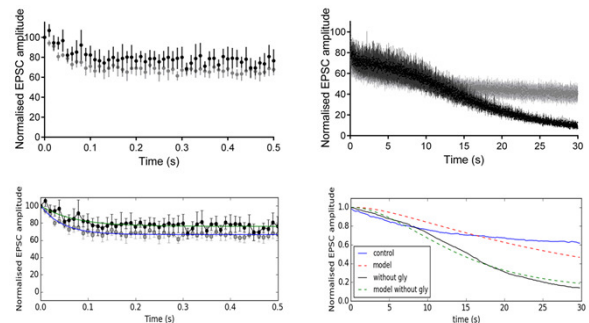


Fig 4. Parameters identification. The glutamate model does not depend of the ATP concentration and there is no relation between the glutamate release and the ATP consumption, left panels (the glutamate model has to be improved, so far it only follows the sodium dynamics). By looking the ATP dynamics it seems the ATP model variation, in control and glycolysis blocked conditions, follow the normalized EPSC amplitudes. To be noted: the variation of the synapse parameters in control conditions or in absence of glycolysis (initial release probability variation).

Conclusions and perspectives

The activity dependent neural and astrocytic metabolic pathway modulation by nitric oxide has been simulated. In conditions where nitric oxide only regulates the metabolic pathway, the results show the neural ATP synthesis occurs principally in the neural compartment. In contrast, when NO also regulates the electrophysiological activity, the ATP synthesis decreases in the neuron and increases in the glial compartment, probably due to the more important ATP consumption during electrophysiological NO modulation.

The model is constructed assuming the ATP synthesis is proportional to the amplitude of the post synaptic currents, that is a strong shortcoming, so a future version will include a model of glutamate cycle tacking account the ATP consumption for glutamate-glutamine conversion, vesicle filling and exocytosis.

References

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