Model of maturation of the respiratory rhythm generator.

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Phrenic motoneurons must receive a stable rhythmic central respiratory command. In rodents, the respiratory rhythm generator is supposed to be located in a small medullary region called the preBotzinger Complex (PBC). At birth (P1) and a few days before (E18), PBC neurons, active in phase with phrenic motoneurons, have been identified as bursting pacemakers as they retain a rhythmic bursting activity while they are pharmacologically isolated from the rest of the network. In an earlier fetal period of development (E16), the density of pacemakers is null or very weak. But phrenic motoneurons are already rhythmically active. Therefore the question arises to understand whether their rhythm comes from network properties or from the presence of pacemaker neurons. In addition, frequency, stability and length of phrenic bursts evolve during the perinatal period. Which factors can explain these evolutions ?

From experimental data[1] and in the continuity of previous model[2] we elaborated a simple model giving a first answer to these questions. Our network is composed of some tens of neurons which consist of a single compartment possessing three Hodgkin-Huxley ionic channels: a potassium, a sodium and a persistent sodium (NaP) one. All neurons are linked together by fast excitatory synapses, the weights of which follow an exponential distribution. A poissonian noise is implemented on each neuron. The network is simulated using the GENESIS program, will be freely accessible, can be widely modified by a non-specialist user and therefore can be used as a demonstration tool. For a statistical use of the simulation, the output can take the form of a kumac file read by the free PAW program[3].

After a short description of the ionic channel roles, we will show that, through NaP conductance heterogeneity, it is possible to solve the pacemaker/network dilemna and to explain the experimental observation of leading pacemaker. The importance of the g(NaP)/g(L) ratio, expected experimentally, will also be emphasized. We will then demonstrate that a purely electrotonic evolution is not able to reproduce the observed changes in rhythm. Then we will study the respective influence of NaP conductance, synaptic weights, noise, heterogeneity, cell number, etc. in order to fit the experimental data from E16 to P1. In a weakly connected network, a particular burst shape has been observed in which the interspike interval becomes bimodal. A particular attention will be given to these bursts as a substructure in the bursts have also been experimentally observed. To conclude, a model will be proposed where the apparition of pacemakers should be mainly driven by epigenetic factors.

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[1] C. A. Del Negro et al., Persistent sodium current, membrane properties ans bursting behavior of the pre-Bötzinger complex inspiratory neurons in vitro, J. Neurophysiol. 88 (2002) 2242 ;
H. Onimaru and J. Homma, Development of the rat respiratory neuron network during the late fetal period, Neurosci. Res. 42 (2002) 209 ;
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[2] J. C. Smith et al., Respiratory rhythm generation in neonatal and adult mammals: the hybrid pacemaker-network model, Respir. Physiol. 122 (2000) 131.

[3] http://paw.web.cern.ch/paw