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Control/Tracking Number: 2011-S-9353-SfN
Activity: Scientific Abstract
Current Date/Time: 5/11/2011 12:43:42 PM

Modeling and analysis of rhythm generation mechanisms in excitatory networks of brain stem and spinal cord

AUTHOR BLOCK: *Y. I. MOLKOV¹, P. E. JASINSKI¹, N. A. SHEVTSOVA¹, J. C. SMITH², I. A. RYBAK¹;
¹Dept. of Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA; ²Cell. & Systems Neurobio. Section, NINDS, NIH, Bethesda, MD

Abstract:

The mechanisms generating neural oscillations in the brain stem (pre-Böttinger Complex, pre-BötC) and spinal cord that persist after blockade of synaptic inhibition remain poorly understood. Experimental studies in thick medullary slices (~700 μm) from neonatal mice containing the pre-BötC identified two types of pacemakers and proposed two intrinsic neuronal bursting mechanisms that may contribute to rhythm generation in the pre-BötC: one with rhythmic bursting activity based on the persistent sodium current (I_{NaP}), and the other involving calcium (I_{Ca}) and calcium-activated, nonspecific cationic (I_{CAN}) currents (Thoby-Brisson M, Ramirez JM. J Neurophysiol 2001, 86:104-112). Interestingly, only the I_{NaP} -dependent bursting mechanism has been found in the pre-BötC within thin (~350 μm) slices from neonatal rats (Koizumi H, Smith JC. J Neurosci 2008, 28:1773-1785). Both these mechanisms were also suggested to contribute to the generation of rhythmic activity in the isolated spinal cord. However, an involvement and relative roles of these mechanisms in the operation of rhythmogenic excitatory networks within the brain stem respiratory and spinal cord locomotor central pattern generators are still under debate. Studies of the effects of pharmacological blockers of I_{NaP} and/or I_{CAN} on the network bursting activity and its characteristics (burst frequency, amplitude, and duration) have shown inconsistent results. Therefore, in this theoretical/modeling study we have investigated rhythmogenic mechanisms in a population of excitatory neurons with I_{NaP} , I_{Ca} and I_{CAN} conductances randomly distributed within the population. In addition, we incorporated in the model and investigated the possible roles of Na^+/K^+ pump, IP_3 -dependent intracellular calcium release, and mutually excitatory synaptic interactions within the population in generation of population bursting activity. We have demonstrated that such population can operate in several regimes of oscillatory bursting activity, which can be dependent on I_{NaP} and/or I_{CAN} , or independent of both. The particular oscillatory regime also depends on several external and internal parameters, such as those defining general neuronal excitability, mutual neuronal interactions including the number of neurons involved (which may vary for example with the size of the slices studied experimentally) and the state of particular ionic conductances. The existence of multiple oscillatory regimes and the transitions between them may provide explanations for the different rhythmogenic mechanisms inferred to operate under various experimental conditions in vitro.

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Presentation Preference (Complete): Poster Only

Linking Group (Complete): None selected

Nanosymposium Information (Complete):

Theme and Topic (Complete): E.04.c. Respiratory regulation: Respiratory rhythm and pattern generation ; D.11.f. Models

Keyword (Complete): RESPIRATION ; LOCOMOTOR ACTIVITY ; MODELING

Support (Complete):

Support: Yes

Grant/Other Support: : NIH Grant R01 NS057815

Grant/Other Support: : NIH Grant R01 NS069220

Grant/Other Support: : Intramural NIH/NINDS

Special Requests (Complete):

Is the first (presenting) author of this abstract a high school or undergraduate student?: None

Religious Conflict?: No Religious Conflict

Additional Conflict?: No

Status: Finalized

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