ATP and astrocytes are involved in the lamprey respiratory control

Ludovica Iovino, E. Cinelli, D. Mutolo, F. Bongianni
Dipartimento di Medicina Sperimentale e Clinica, Sezione Scienze Fisiologiche, Università degli Studi di Firenze, Viale G.B. Morgagni 63, 50134 Firenze, Italy

The paratrigeminal respiratory group (pTRG) is a brainstem region responsible for the respiratory rhythm generation in the lamprey, a lower vertebrate that has proved to be highly useful to demonstrate that the basic features of rhythmogenic networks have been conserved throughout vertebrate evolution. It is well known that ATP is involved in the control of respiration and that astrocytes contribute to the purinergic modulation.
Since no information is available on the role of ATP and astrocytes within the lamprey respiratory network, experiments were performed on isolated brainstems of lampreys. The vagal motor output was used to monitor respiratory activity. Bilateral microinjections (30-50 nl) of 1 mM ATP into the pTRG caused marked increases in respiratory frequency followed by decreases in respiratory motor output due to the ATP metabolite adenosine.
Increases in respiratory frequency were mimicked by similar microinjections of 1 mM ATP-γ-S, a nonhydrolyzable ATP agonist, while decreases were induced by microinjections of 0.5 mM adenosine. Bath applications and microinjections of selective agonists and antagonists of purinergic receptors showed that ATP increased respiratory activity by acting on pTRG P2X receptors.
To disclose the respiratory role of astrocytes, bath application of the gliotoxin aminoadipic acid (1 mM) was employed. This manouvre dramatically depressed the respiratory motor output. Interestingly, under these conditions, the responses to ATP-γ-S microinjected into the pTRG were abolished, indicating that pTRG astrocytes play a key respiratory role. Consistently with the glial function of providing glutamine to neurons for glutamate synthesis, bath application of 5 mM glutamine caused a rapid recovery of baseline respiration.
The results show for the first time that ATP and astrocytes strongly contribute to the modulation of the lamprey respiratory pattern. Their function in rhythmic networks appears to be phylogenetically conserved.

A REST/NRSF- dependent transcriptional pathway governs synaptic homeostasis induced by chronic hyperactivity

Cosimo Prestigio[1,2], G. Lignani[1,2], P. Baldelli[1,2], F. Benfenati[1,2]
[1]Center for Synaptic Neuroscience (NSYN) IIT, Genova, Italy
[2]Departement of experimental medicine, Genova, Italy

Homeostatic plasticity is a regulatory feedback response in which either synaptic strength or intrinsic excitability can be adjusted up or down to offset sustained changes in neuronal activity. Although a growing number of evidences constantly provide new insights into these two apparently distinct homeostatic processes, a unified molecular model remains unknown. REST is a zinc-finger transcription factor initially identified as a gene repressor central for neuronal differentiation. During neuronal development a progressive downregulation of REST de-represses the expression of many neuronal genes involved in a variety of processes crucial for the morphological and functional differentiation of neurons. Besides this physiological role, a late REST increment in adult is involved in pathological states such as ischemia and epileptic seizures.
We have recently demonstrated that REST is up-regulated in neurons exposed to chronic hyperactivity. Such increase leads to the down-regulation of voltage-gated sodium channels, which enabled the recovery of a physiological firing activity. Although sodium channels represent one of the main REST-target genes, some excitatory presynaptic genes were found to be regulated by REST. Here we report that REST is also able to participate in synaptic scaling during sustained neuronal activity by reducing the strength of excitatory presynaptic contacts without altering the post-synaptic site. Indeed chronic hyperactivity triggers a REST-dependent decrease of the size of synaptic vesicle pools through the transcriptional repression of several REST-target presynaptic genes.
These data identify REST as a common molecular player able to downscale simultaneously both intrinsic excitability and pre-synaptic properties in response to elevated neuronal activity.