## Modulation and Plasticity of Rhythm-Generating Networks

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**Summary**

The research presented in this thesis focuses on the understanding of plasticity and flexibility of brain cells, which are organized in rhythm generating networks. Rhythmic brain activity is a hallmark of many functions of physiological (normal) and pathological (abnormal) states of the central nervous system. The normal activity range from rather complex oscilations in the neocortex, which are thought to be involved in memory storage and information prosessing, to rhythmic discharging networks of the brainstem and the spinal cord, which participe in the control of movements.
Many rhythmic networks contain central pattern generators (CPG) to produce rhythmic activites that create a basis for motor outputs. These include, for example, well investigated networks in insects, which coordinate the alternating movements of the limbs. In mammels such CPG are a part of the control of rhythmic motor output, including the central control of breathing. An essential part of the respiratory network and is called PreBötzinger Complex (PreBötC). Breathing is essential for survival and is therefore highly preserved and tightly regulated. On the other hand, respiration is highly flexible and can rapidly adapt to changes of the metabolic demand ($O_2$, $CO_2$ and pH) and to voluntary behaviour (i.e. singing or speech). The PreBötC is essential for the generation of breathing activities in mammals, and has recently been also identified in humans. Located within the ventrolateral medulla, a kernel of several hundred neurons forms the PreBötC. It is composed of excitatory glutamatergic neurons that express the neurokinin type1 receptor and somatostatin as well as several populations of inhibitory neurons.
In chapter 1 of this thesis, I explain the detailed knowledge of the components of the respiratory network (here called building blocks). It summarizes a wide spectrum of information, rooting from research over the last decades, in order to give the reader the background for the experimental chapters 2 and 3. The chapter emphasizes the concept that combinations of synaptic connectivity and intrinsic properties of the cells need to be considered as essential building blocks of these neuronal networks to enable the stability and flexibility needed. It also highlights the data indicating, that the PreBötC in isolation can generate three distinct discharge pattern, which are termed "fictive eupnea" (normal breathing activity), "fictive sighs" (augmented breaths) and "fictive gasping".
In chapter 2, I present the data of a study, in which we investigated if distinct voltage gated calcium channels are necessary to generate eupnea, sighs and gasping using *in vivo* and *in vitro* experiments in mice with a functional null mutation of the α-1 subunit of the P/Q -type calcium channels (*Cacn1A*). We found that the mice show severe breathing deficits, with a highly reduced number of sighs and lower respiratory frequency. The effects became more pronounced with the postnatal development of the animals, leading to early mortality. In detailed *in vitro* experiments using the brainstem slice preparation, we studied the mechanisms underlying the deficits and found a reduced excitatory synaptic transmission between PreBötC neurons. Furthermore, we show in part a compensation by other calcium channels to sustain the network activity in these mice. The deficits of the PreBötC described might partly explain the breathing disturbances in the mice.
In chapter 3 and 4, we investigated the effects of the inflammation molecule prostaglanin $E_2$ ($PGE_2$) on respiratory and cortical activities. $PGE_2$ is one of the major metabolic products of the enzyme cyclooxygenase-2 (COX-2), an inducible enzyme, which is regulated by neuronal activity and increased after an inflammation or hypoxia.
In the experiments presented in chapter 3, we show that injections of $PGE_2$ into the PreBötC area changed the breathing activity of the animals. Low concentration of $PGE_2$ lead to the generation of more sighs (augmented breaths), while eupnea (normal breathing) remained unaltered. Only injections of high concentration of $PGE_2$ changed also the frequency of eupnea. In detailed pharmacological experiments *in vitro* using the brainstem slice preparation which contained the isolated PreBötC, we found that this effect could be mediated by the activation of distinct currents in PreBötC neurons with intrinsic bursting properties.
In chapter 4, we investigated short and long term consequences of $PGE_2$ exposure in organotypic slice cultures of the neocortex. A short exposure to $PGE_2$ caused an inhibition of network activity mediated by a reduction of post-synaptic excitatory synaptic transmission. Long term exposure (48 hours) led, in contrast, to a hyper-excitable network state caused by an increase of pre-synaptic excitatory synaptic transmission. Furthermore, we could show that this homeostatic mechanism is distinct from other homeostatic plasticity described in cortical neurons (upscaling of postsynaptic glutamate receptors). Chronic or repeated activation of homeostatic plasticity in cortical networks might play an important role in the development of post-traumatic epilepsy.
Taken together, I investigated in the presented thesis the plasticity, reconfiguration and modulation of rhythm-generating networks. The data of the experimental chapters of this thesis show the diversity of mechanisms that might enable networks to produce a stable function, but still adpapt to challenges. In chapter 5, I provide additional examples of neuronal networks in invertebrates and vertebrates, that illustrate several concepts and rules that might be universal for such networks.