5. DISCOVERY RESEARCH IN NEUROBIOLOGY

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RESEARCH ACTIVITY

Cellular and Network Neurobiology Group

Research in the group aims to identify the cellular and network mechanisms of the generation of characteristic cortical (mainly hippocampal) activity patterns using *in vitro* electrophysiology and computer simulations.

1. A hippocampal slice preparation, which exhibits spontaneous repetitive sharp waves under control conditions, and which can be induced to generate gamma oscillations by the application of cholinergic drugs, has been developed. In parallel, a large-scale network model of the CA3 area based on experimentally determined cellular and network parameters has been constructed, which consists of interacting pyramidal cell and interneuron populations, and exhibits repetitive sharp waves (including accompanying high-frequency ripple oscillations) very similar to their experimental counterparts. (Figure 1) (*Káli et al., 2012*). The model also made explicit predictions concerning the mechanisms which contribute to the generation of sharp waves: it suggested that the initiation of sharp waves relies on random fluctuations of population activity, while the termination of sharp waves probably requires some novel form of slow negative feedback.

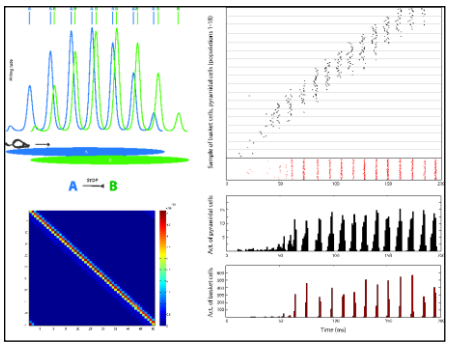

Fig. 1 *(top left) activity during exploration of two CA3 pyramidal cells with overlapping place fields, showing theta phase precession; (bottom left) matrix of synaptic weights between pre- and postsynaptic populations, ordered by place field location, which formed during exploration as a result of spike-timing-dependent plasticity; (right) spontaneous replay of learned sequences of activity during sharp-wave-associated ripple oscillation.*

2. The effects of neuronal morphology and voltage-gated conductances on the frequency-dependent impedance of neurons are also investigated.

Endocrine Neurobiology Group

A major long-term goal of the group is the elucidation of neuronal and hormonal mechanisms acting centrally in the neuroendocrine control of reproduction. One particular focus is on central actions of estrogen on estrogen-receptive neuronal systems throughout the brain. Further, hormonal and afferent neuronal control of gonadotropin-releasing hormone (GnRH) neurons is studied, with special regard to negative and positive estrogen feedback to

these cells which underlies reproductive cyclicity in the female. In addition to rodents, neuronal networks innervating human GnRH neurons are also in the scope of studies using post-mortem human brain samples. The impact of diminishing estradiol signaling on diverse brain functions during menopause is also under exploration in rodent models of menopause by means of gene expression profiling. This translational research supports drug discovery targeting the safe and novel way of hormone replacement therapy for menopausal women.

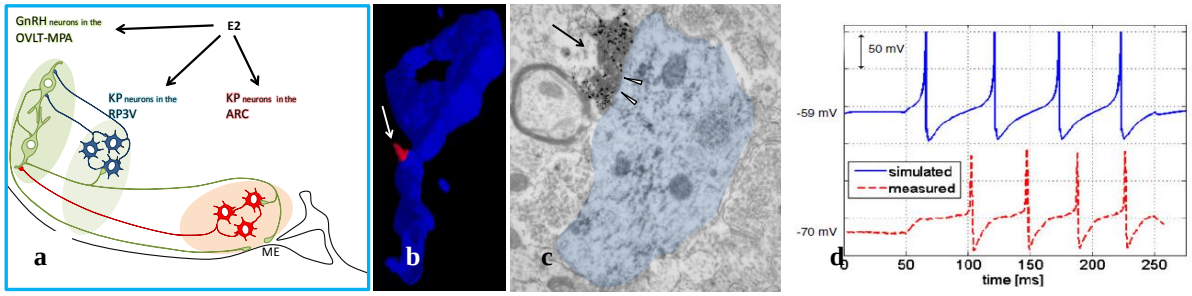

Fig. 2 *Interaction of key neuronal elements of the hypothalamic regulatory center for reproduction. (a) Network model of kisspeptin (KP) and gonadotropin-releasing hormone (GnRH) neurons. Traditional synaptic (b,c), as well as, non-synaptic mechanisms (direct hormonal, volume and retrograde transmission) act within the network, which ultimately determine the firing (d) and secretory activity of the GnRH neurons.*

Another line of discovery research is dedicated to obtain integrated knowledge from structural, functional and molecular aspects of the complex hypothalamic mechanisms that regulate stress, adaptation and metabolism. A special emphasis is placed on the neuronal circuitry involved in the central regulation of the hypothalamic-pituitary-adrenal and thyroid axes, and the crucial role of type-2 deiodinase in thyroid hormone actions in the brain. These studies use cutting-edge light and electron microscopic techniques, a wide repertoire of molecular biological techniques and slice electrophysiology. The translational value of these efforts is manifested in the better understanding of the role of the brain in development of obesity and addiction, and the dissection of molecular mechanisms of thyroid hormone actions.

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