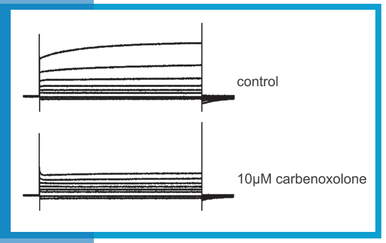
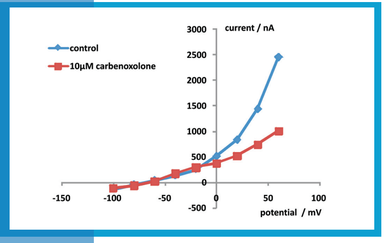
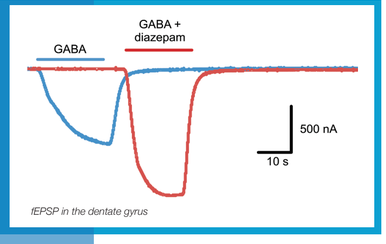
Xenopus Oocytes







fEPSP in the dentate gyrus

Heterologous expression

In order to study the physiological and pharmacological properties of membrane proteins, like ion channels or transporters, these proteins can be expressed in heterologous expression systems. We routinely use oocytes from the African clawed frog Xenopus laevis as an expression system. Because we have our own Xenopus colony, a continuously high quality of our oocytes is assured.

Xenopus oocytes allow to record reliable and reproducible membrane currents elicited after activation of voltage-gated or ligand-gated ion channels as well as membrane transporters by two electrode voltage clamp (TEVC) techniques. Expression rates can as high as 90% depending on the contruct used for injection. Because we use an automated system for both cDNA or cRNA injection and for TEVC recording large numbers of cells can be tested within a short period of time.

For voltage gated ion channels, like for example Panx1 hemichannels, almost every necessary voltage protocol can be used. In addition, specific pharmacologically active compounds can be applied that block or facilitate ion channel activity.

For ligand gate ion channels, like for example the GABAA receptor, a fast application system assures proper activation, facilitation or inactivation of the ion channel of interest.

Injected oocytes can also be used for a number of other experimental assays in which expression of membrane proteins must be analysed, including studies of ion channel mutants. We therefore also provide oocytes injected with cDNA or cRNA for studies that do not require electrophysiological recordings.

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Drug effects are investigated with respect to their convulsive activity, channel specificity, interaction with learning and memory mechanisms (LTP/LTD) or concerning to their effects on heart activity (QT prolongation, heart rhythms, intracardial propagation, etc.).

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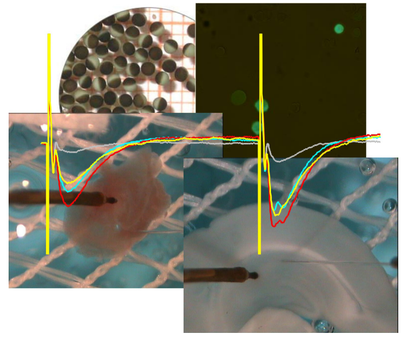

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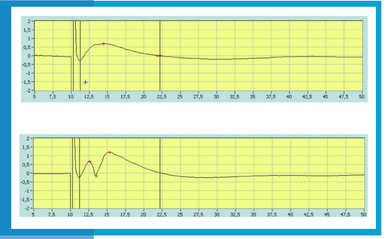
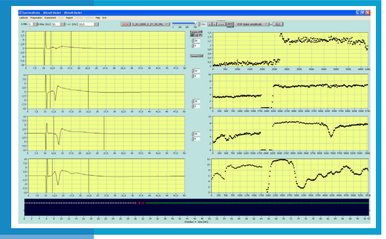
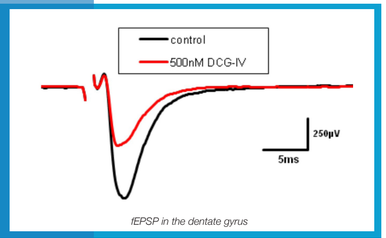
Brain Slices







fEPSP in the dentate gyrus

Long-term potentiation in the hippocampus

The hippocampus is a key structure in learning and memory. Memory formation is accompanied by long-term changes in synaptic transmission in hippocampal neurons. At the cellular level, long-term synaptic plasticity can be observed as an increased efficacy in synaptic transmission leading to enhanced postsynaptic responses. Because it is stable over many hours even in various in vitro preparations, his phenomenon has been termed long-term potentiation (LTP). Experimentally, LTP can be easily induced in hippocampal neurons by applying specific stimulation patterns to intrinsic afferent fibers. Since LTP is regarded as a cellular analogue to memory formation drugs that influence LTP are regarded as potentially interfering with normal CNS function. Thus, drug effects on induction and maintenance of hippocampal LTP are widely used for screening purposes in neuropharmacology.

The most frequently used model for LTP is the hippocampal CA3 to CA1 projection that can be easily accessed by extracellular recording techniques. In this model, electrical stimulation of CA3 afferents to CA1 pyramidal cells, the Schaffer collaterals, by various temporal patterns robustly induces LTP.

Metabotropic glutamate receptors

Metabotropic glutamate receptors (mGluRs) are expressed in many different structures of the mammalian CNS, they are involved in many different functions, including motor control, spatial memory, olfactory priming, anxiety, and the perception of pain. A loss of mGluR expression can result in CNS malfunctions, like ataxia and learning deficits, and pathological activations of mGluRs have been reported to be linked to neurological disorders, like Chorea Huntington, Alzheimer's disease, stroke, and epilepsy. Also, mGluRs may be involved in cognitive disorders and schizophrenia.

Because they are becoming an increasingly interesting target for pharmacological compounds, reliable and easy-to-handle models for mGluR functions are needed. One model system to study mGluR function in vitro is the medial perforant path-dentate gyrus (MPP-DG) synapse in the hippocampus. In this system, application of the group-II mGluR agonist DCG-IV reduces postsynaptic responses in DG neurons to MPP stimulation.

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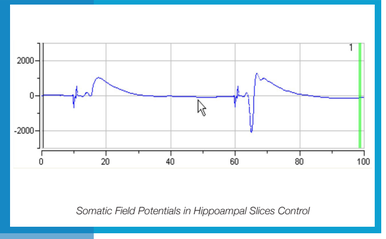
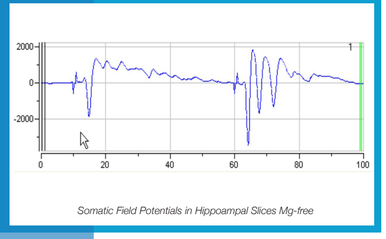
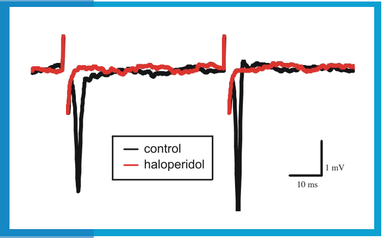
Brain Slices



Somatic Field Potentials in Hippoampal Slices Control



Somatic Field Potentials in Hippoampal Slices Mg-free



Experimental models for epilepsy research

The development of antiepileptic drugs critically depends on experimental models that allow testing anti¬convulsant effects. Epileptiform activity can be experimentally induced by a variety of methods both in vivo and in vitro, usually by either a reduction of postsynaptic inhibition or by a general increase of spontaneous activity. In vitro, the induction of epileptiform activity in hippocampal or neocortical brain slices can be achieved by an overactivation of postsynaptic NMDA receptors. Usually, NMDA receptors are blocked by Mg2+ ions and this Mg block is only released when postsynaptic neurons are activated through non-NMDA receptors. By reducing the concentration of extracellular Mg2+ ions, epileptiform activity can be easily and reproducibly evoked and antivonvulsant effects of bath-applied compounds can be recorded with minimum experimental effort. Because the hippocampal slice preparation is a well-defined experimental model and the application of Mg2+-free extracellular solutions is easy, this is perfectly suited for pharmacological studies of anti-convulsant compounds on a routinely basis.

Dopamine release in the striatum

Basal ganglia neurons, particularly in the striatum, integrate glutamatergic neocortical and thalamic input and dopaminergic input from the substantia nigra. Functionally, the striatum is involved in planning and modulation of motor command pathways. However, the execution of a variety of other, cognitive functions also critically depends on undisturbed striatal signal integration. Thus, stimuli that are associated with reward, but also novel, unexpected or intense stimuli, and cues associated with such events, also activate striatal neurons. Imbalanced glutamatergic and dopaminergic input can be related to the pathophysiology of neurological and psychological disorders, like Parkinson's desease, schizophrenia or addictive behaviors.

The release of dopamine in the striatum has therefore become a standard target in pharmaceutical compound evaluation and electrophysiological assays to monitor dopamine release have gained increasing interest. Acute brain slices from the mammalian striatum are a valuable model system to study compound effects on the release and postsynaptic actions of dopamine.

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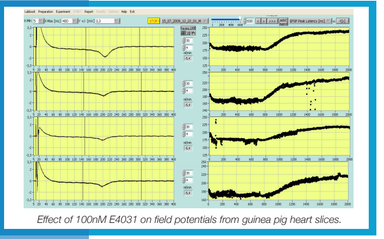
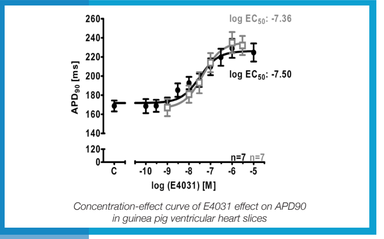
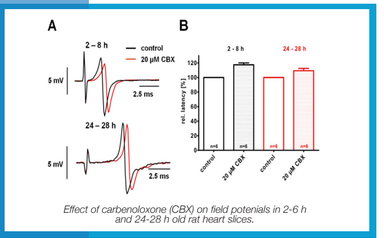
Heart Slices



Effect of 100nM E4031 on field potentials from guinea pig heart slices.



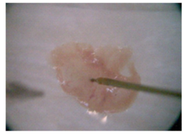
Concentration-effect curve of E4031 effect on APD90 in guinea pig ventricular heart slices



Effect of carbenoloxone (CBX) on field potenials in 2-6 h and 24-28 h old rat heart slices.

Heart slice Model

The long QT syndrome (LQTS) is characterized by the appearance of long QT intervals in the electrocardiogram. It is accomplished by atypical ventricular tachycardia like torsade de pointes and thus results in a high risk of sudden cardiac death. Therefore, the evaluation of a QT prolongation due to the action of new compounds plays an essential role in pharmacological development of new drugs and in safety pharmacology. Beside the common in vivo measurements of animal ECG and in vitro assays like the Langendorff heart model or the patch clamp analysis of herg channels expressed in mammalian cell lines the new technique of isolated living heart slices was developed during the last years in our lab. Standardized heart slices with normal physiology and pharmacology can be prepared from nearly any adult laboratory animal (mouse, rat, guinea pig, etc.) and even from human biopsy material.



Physiological parameters including action potential duration (APD) can be measured over up to 30 hours with the Synchroslice multiple slice evaluation system in up to 4 heart slices simultaneously. Different test procedures can be performed including extracellular recording of stimulus induced cardiac field potentials or intracellular recordings from single cardiac myocytes. Many different parameters, e.g. action potentials duration, amplitude, latency, transmural differences, refractory periods, etc. are analyzed automatically.

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