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- 1995** Dr. rer. nat., University of Kassel, Germany
- 1995–1999** Postdoctoral training, Department of Pharmacology, Toxicology, and Pharmacy; School of Veterinary Medicine, Hannover, Germany
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Objects of Research

Our research focuses on the physiology and pathophysiology of basal ganglia and associated brain structures in neurological diseases. Neurological movement disorders like dystonia and other hyperkinetic syndromes are typically attributed to defects or biochemical imbalances within basal ganglia structures. During the last years, we have obtained several new data on disturbed neuronal function and activity of basal ganglia structures mainly by means of electrophysiological investigations in an animal model of idiopathic paroxysmal dystonia.

More recent studies focus on basal ganglia function and dysfunction in temporal lobe epilepsy, in which a remote control of epileptic activity originating within the limbic system is hypothesized for basal ganglia structures. Furthermore, new therapeutic strategies are explored experimentally by manipulation of the basal ganglia function.

1. Pathophysiology of basal ganglia neurons in epilepsy and movement disorders

Numerous studies suggest that the substantia nigra pars reticulata (SNr), a basal ganglia output structure, acts as a seizure-manipulating gate in different epilepsy models including the amygdala kindling model of temporal lobe epilepsy. However, the exact mechanisms underlying the seizure-modulating effects of the SNr are not well understood. By means of electrophysiological in vivo single unit recordings in anesthetized amygdala kindled rats, we aim to gather more information about the role of the SNr and related structures for the propagation and manipulation of seizure activity. One feature of the basal ganglia is their serial GABAergic connectivity. According to basal ganglia functional models, an increased activity of SNr neurons is reflecting a proconvulsant state, a decreased SNr activity mirrors an anticonvulsant state. Recent data of our group indeed revealed site-specific increases in the discharge rate and an altered discharge pattern of GABAergic SNr neurons in amygdala kindled rats. According to the scheme shown in Figure 1, the obtained changes are attributable at least in part to activity changes in the subthalamic nucleus, an excitatory (glutamatergic) basal ganglia structure monosynaptically connected to the SNr. The functional relevance of these data is examined currently by investigations of a target structure of the SNr, i.e., the pedunculoopontine nucleus.

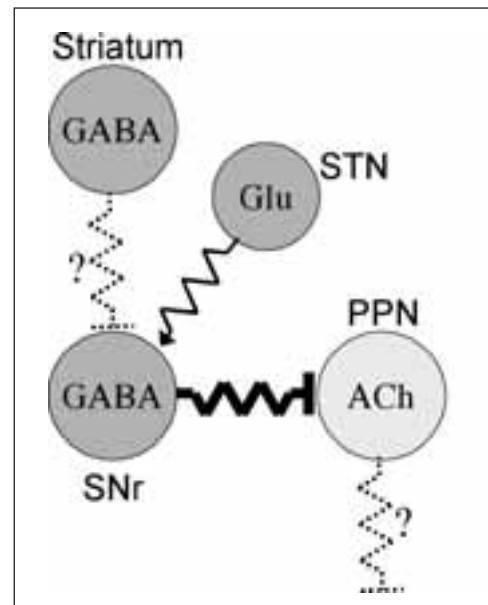


Figure 1. Simplified basal ganglia scheme showing the hypothesized (?) or observed kindled activity state of the striatum, the subthalamic nucleus (STN), the substantia nigra pars reticulata (SNr), and the pedunculoopontine nucleus (PPN). The involved neurotransmitters are GABA, glutamate (Glu), and acetylcholine (ACh). Bold line, increased firing rate; dotted lines, decreased firing rates; curved lines, changes in firing pattern.

Apart from experimental epilepsy, we investigate the basal ganglia function and dysfunction in animal models of movement disorders like dystonia and in hyperkinetic rats characterized by several features including side-preferred circling behavior.

2. Experimental therapeutic manipulations in epilepsy models

We recently observed a reduced responsiveness of SNr neurons to the antiepileptic drug valproate in the amygdala kindling model of temporal lobe epilepsy. In this difficult-to-treat type of epilepsy, plastic network changes as described above might contribute to the high rate of pharmacoresistance found in human patients suffering from temporal lobe epilepsy. Apart from conventional pharmacological treatment options, we investigate new therapeutic strategies that are under experimental or clinical development.

2.1. Local drug delivery by microinjection

By means of stereotaxically guided microinjections of drugs in freely behaving animals, we manipulate basal ganglia function in order to establish suitable brain targets for a therapeutic remote control of seizure activity. Subregions of the SNr and the subthalamic nucleus might be interesting locations for further treatment options as follows.

2.2. Neuronal transplantation

An imbalance between inhibitory and excitatory neurotransmission in specific brain regions is assumed for different types of epilepsy. In pharmacoresistant and inoperable cases of epilepsies, new treatment options are highly needed. One experimental possibility is the transplantation of inhibitory neurons into appropriate brain regions, for which a proof of principle has been shown for example by local drug manipulations. We use cell lines which are genetically manipulated to produce high amounts of the inhibitory transmitter GABA. Several groups including ours have demonstrated anticonvulsant effects of transplantation of those cells into suitable brain sites including basal ganglia subregions in epilepsy models. However, the ameliorating effects are typically transient and we aim at improving the transplantation parameters.

2.3. High frequency deep brain stimulation

High frequency deep brain stimulation of the subthalamic nucleus, assumed to inhibit the subthalamic and SNr activity, has been reported to reduce seizure frequency in some patients suffering from medically intractable seizures and considered unsuitable for resective surgery. These clinical studies have been encouraged by the suppressive effects of pharmacological or electrical inhibition of the SNr or the subthalamic nucleus on different types of seizures in animal models of epilepsy and by the clinical experience with using high frequency stimulation of basal ganglia structures in patients suffering from movement disorders like Parkinson's disease. The obtained effects in epileptic patients so far are typically marginal and the mechanisms of action are not well understood. Our research here is aimed at gathering more information

about the mechanisms of action and the appropriate stimulation parameters for deep brain stimulation in animal models of epilepsies.

Future Aims

Major goals of research are to investigate basal ganglia function and dysfunction in epilepsies and movement disorders and to define common grounds and differences between different neurological disorders. This shall enable new rational treatment approaches for epilepsies and other neurological disorders.

Selected Publications

- [1] Gernert M., Hamann M., Bennay M., Löscher W., Richter A. (2000) Deficit of striatal parvalbumin-reactive GABAergic interneurons and decreased basal ganglia output in a genetic rodent model of idiopathic paroxysmal dystonia. **J. Neurosci.** 20: 7052-7058.
- [2] Gernert M. and Löscher W. (2001) Lack of robust anticonvulsant effects of muscimol microinfusions in the anterior substantia nigra of kindled rats. **Eur. J. Pharmacol.** 432: 35-41.
- [3] Gernert M., Bennay M., Fedrowitz M., Rehders J.H., Richter A. (2002) Altered discharge pattern of basal ganglia output neurons in an animal model of idiopathic dystonia. **J. Neurosci.** 22: 7244-7253.
- [4] Gernert M., Thompson K., Löscher W., Tobin A.J. (2002) Genetically engineered GABA-producing cells demonstrate anticonvulsant effects and longterm transgene expression when transplanted into the central piriform cortex of rats. **Exp. Neurol.** 176: 183-192.
- [5] Fedrowitz M., Lindemann S., Löscher W., Gernert M. (2003) Altered spontaneous discharge rate and pattern of basal ganglia output neurons in the circling (*ci2*) rat mutant. **Neurosci.** 118: 867-878.

Group Structure

Group leader:	Manuela Gernert
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