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- 1974** DVM, Free University of Berlin, Germany
- 1975** Doctoral thesis in pharmacology, Free University of Berlin, Germany

Postdoctoral work at Free University of Berlin, National Institutes of Health (NIH) Bethesda/USA, and Leo Pharmaceutical Products Ballerup/Denmark
- 1981** Habilitation (Pharmacology), Free University of Berlin, Germany
- 1986** Research Fellow at Schering, Berlin
- Since 1987** Professor and Chair of Pharmacology, Toxicology, and Pharmacy at the School of Veterinary Medicine Hannover

Current Research

The research of our group is directed to the pathophysiology of common brain diseases such as epilepsy with the aim to develop new targets for pharmacological prevention or treatment of these disorders. This also includes the investigation of mechanisms underlying the drug refractoriness of epilepsy and other CNS disorders.

1. Epilepsy research

Epilepsy, a common neurological disorder characterized by recurrent spontaneous seizures, is a major, worldwide, health problem which affects about 1-2% of the population. Despite progress in understanding the pathogenesis of seizures and epilepsy, the cellular basis of human epilepsy remains a mystery. In the absence of a specific etiological understanding, approaches to drug therapy of epilepsy must necessarily be directed at the control of symptoms, i.e., the suppression of seizures. Chronic administration of antiepileptic (anti-convulsant) drugs is the treatment of first choice in epilepsy. The 20th century has witnessed considerable progress in the pharmacotherapy of epilepsy.

However, despite the development of various antiepileptic drugs, about one third of patients with epilepsy is resistant to current pharmacotherapies. Even in patients in whom pharmacotherapy is efficacious, current antiepileptic drugs do not seem to affect the progression or underlying natural history of epilepsy. Furthermore, there is currently no drug available which prevents the development of epilepsy, e.g., after head trauma or stroke. The rapidly expanding information about the cellular, molecular and genetic mechanisms of epilepsy is expected to lead to more effective therapies, prevention, or even a cure of different types of epilepsy. In our group, a number of innovative approaches for future therapies are assessed, using animal models of different types of epilepsy. These approaches include the use of molecular, cellular, neurophysiological, neurochemical, neuropathological, neurobehavioral, and neuropharmacological techniques with the aim to enhance our understanding of the mechanisms involved in development and progression of epilepsy and to develop new targets for pharmacological prevention or treatment of this disorder. Furthermore, we study the mechanisms underlying resistance to medical treatment, including the role of multi-drug transporters and genetic polymorphisms.

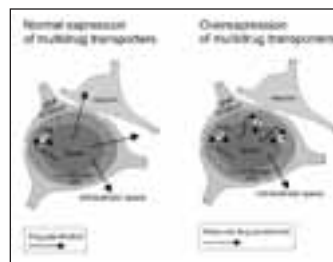


Fig. 1: The role of multidrug transporters (mdts) in limitation of drug penetration through the blood-brain barrier (BBB) into extracellular space, neurons or other target cells in the brain (from Löscher, Trends Pharmacol. Sci. 23:113-8, 2002).

The figure shows a schematic illustration of a brain capillary with three endothelial cells which, unlike endothelial cells in most other tissues, are joined by tight junctions and lack intercellular pores and pinocytotic vesicles. Processes from pericapillary astrocytes ("glial endfeet")

terminate on the capillary and contribute to the barrier function. The BBB passively excludes strongly ionized (polar), hydrophilic drugs, but nonpolar, highly lipid-soluble drugs (like most antiepileptic drugs) penetrate easily into the brain by simple diffusion (dashed arrows). As an active defence mechanism of the BBB, ATP-dependent multidrug transporters, which are located in the apical (luminal) cell membrane of capillary endothelial cells of the BBB, act as outwardly directed active efflux pumps, transferring drugs back into blood after they have entered endothelial cells from blood, thus limiting penetration of many lipophilic drugs into brain parenchyma. Overexpression of these transporters, including P-glycoprotein and members of the multidrug resistance-associated protein (MRP) family, as shown in epileptogenic brain tissue, is therefore likely to result in reduced drug penetration into brain parenchyma. This overexpression not only occurs in endothelial cells of the BBB as illustrated in the figure, but also in glial foot processes extending onto capillaries (not illustrated), suggesting that glial overexpression of multidrug transporters represents a "second barrier" that limits drug penetration, resulting in the simultaneous expression of resistance to a variety of unrelated lipophilic antiepileptic drugs.

2. Movement disorders

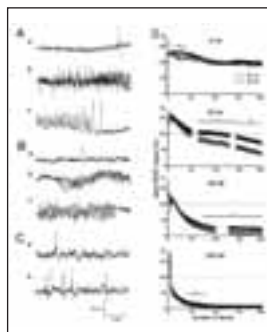
By cooperating with breeders of laboratory animals throughout the world, we have identified and subsequently characterized a number of interesting rodent models of different movement disorders, including a hamster model of paroxysmal dystonia and two rat mutants with abnormal circling behavior. In addition to rotational behavior, one of these rat mutants (*ci2*) also exhibits other neurological abnormalities, vestibular and auditory dysfunctions, and

a progressive retinopathia, resembling the Usher syndrome in humans. Together with several groups of the ZSN and other centers, including the NIH, we currently characterize the genetics and genetically-mediated cellular and biochemical abnormalities of this interesting rat mutant. Genetic animal models such as the *ci2* circling rat mutant are of essential practical importance for the development of effective research approaches to understanding genetically based human afflictions and may help to define new therapeutic strategies.

3. Phenotyping of rat and mouse mutants with neurological abnormalities

The evaluation of neurological and neurobehavioral dysfunctions is an important component for the phenotypic characterization of spontaneously occurring or induced gene mutations in rats and mice. Transgenic and knockout technology provides a powerful tool for genes mediating neuronal functions. Phenotyping of neurological, cognitive and behavioral dysfunctions in rat and mouse mutants requires a rigorous experimental design that considers breeding and background gene issues, genotype control groups, and a sufficient sample size for meaningful statistical analysis. For phenotyping of interesting mutants, we use a strategy of an initial neurological test battery, followed by specific, hypothesis-driven choices of a constellation of neurological and behavioral tasks. Our main interest in rat and mouse mutants is to characterize new genetic animal models of epilepsy which may contribute significantly to our understanding of epilepsy mechanisms. Based on the frequency at which epileptic mouse mutants appear and the diversity of the proteins involved, it has been suggested that about 1000 genes could influence seizure susceptibility when appropriately mutated. As in humans with epilepsy, epilepsy in mouse and rat mutants is often associated with cognitive and behavioral disturbances. Thus, using such genetic animal models for drug development may help to identify new drugs which do not only effectively block seizures but also the comorbidities of epilepsy.

Fig. 2: Assessment of the epileptic phenotype in mutant mice deficient for the presynaptic active zone protein Bassoon (from Altrock et al., *Neuron* 36, 787–800, 2003).



EEG recordings from cortex (A) and hippocampus (B, C) of *-/-* mice. Regular EEG pattern interrupted by interictal spikes in the absence of seizures in cortex (Aa) and hippocampus (Ba). (Ab, Bb) Early phase of an electrographic seizure pattern, characterized by high frequency spiking with increasing amplitude and synchronicity. This pattern is associated with behavioral seizures. (Ac, Bc) Late phase and end of an electrographic seizure pattern characterized by high amplitude spiking at a reduced frequency and abrupt termination of paroxysmal activity, followed by low-amplitude EEG (postictal depression). (C) Hippocampal EEG of a mutant mouse before (a) and after (b) administration of the glutamate receptor antagonist MK-801. MK-801 markedly

increased the frequency of spikes in the hippocampal EEG (Cb). (D) Response of fEPSPs (measured in the presence of 100 mM picrotoxin) to trains of 200 stimuli applied at frequencies 5, 20, 50 and 100 Hz. The gaps in 20 and 50 Hz plots are due to technical constraints. Note that *-/-* mutants displayed a stronger augmentation at 5 Hz and a smaller depression at higher frequencies (* $p < 0.05$; ** $p < 0.01$; Mann-Whitney U-test).

Future Projects and Goals

One major goal is the characterization of the mechanisms underlying the progression of epilepsy into a difficult-to-treat chronic disease. Studies of several groups, including our own, indicate that both disease-induced alterations in drug uptake into the brain (by overexpression of multi-drug transporters) and alterations in drug targets are involved. Thus, pharmacological strategies to prevent or reverse these alterations would be a major breakthrough in the therapy of epilepsy.

Selected Publications

- [1] Gernert, M., M. Hamann, M. Bennay, W. Löscher, and A. Richter (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] Löscher, W. (2002) Current status and future directions in the pharmacotherapy of epilepsy. *Trends Pharmacol. Sci.* 23:113–8.
- [3] Potschka, H., E. Krupp, U. Ebert, C. Gumbel, C. Leichtlein, B. Lorch, A. Pickert, S. Kramps, K. Young, U. Grune, A. Keller, M. Weischöf, G. Vogt, B. Xiao, P.F. Worley, W. Löscher, and H. Hiemisch (2002) Kindling-induced overexpression of Homer 1A and its functional implications for epileptogenesis. *Eur. J. Neurosci.* 16:2157–65.
- [4] Altrock, W.D., S. tom Dieck, M. Sokolov, A.C. Meyer, A. Sigler, C. Brakebusch, R. Fassler, K. Richter, T.M. Boeckers, H. Potschka, C. Brandt, W. Löscher, D. Grimberg, T. Dresbach, A. Hempelmann, H. Hassan, D. Balschun, J.U. Frey, J.H. Brandstatter, C.C. Garner, C. Rosenmund, and E.D. Gundelfinger (2003) Functional inactivation of a fraction of excitatory synapses in mice deficient for the active zone protein bassoon. *Neuron* 37:787–800.
- [5] Rogawski, M.A. and W. Löscher (2004) The neurobiology of antiepileptic drugs for the treatment of nonepileptic conditions. *Nature Medicine*, in press.

Group Structure

Group leader:	Wolfgang Löscher
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Postdoctoral fellows:	Claudia Brandt, Maren Fedowitz, Steffen Baltes, Katrin Hoffmann, Alexandra Gastens
Graduate students:	Cordula Baars, Marc Nolte, Marko Schirmer, Holger Volk, Anton Pekcec
Technicians:	Christiane Bartling, Martina Gramer, Maria Halves, Doris Pieper-Matriciani, Britta Sterzik, Michael Weissing, Nicole Ernst

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