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Research profile

Cooperative research with the Department of Neurology and Clinical Neurophysiology at Hannover Medical School (Director Professor Dr. Reinhard Dengler) on basic mechanisms of general and local anaesthetic and analgesic action.

- molecular mechanisms involved in the anaesthetic action of the aromatic alcohol propofol
- mechanisms of action of a novel class of sodium channel blockers
- mathematic modelling of drug action on voltage- operated sodium channels
- novel treatment strategies in pain

Molecular mechanisms involved in the general anaesthetic effect of propofol

The intravenous anaesthetic propofol modulates the activity of several ion channels and receptors potentially relevant to general anaesthesia. Important molecular targets for its anaesthetic effect are inhibitory ligand- gated receptors, especially the γ - aminobutyric acid (GABA) receptor A. Propofol has co- activating as well as directly activating effects at both GABA_A and glycine receptors. Working with structural analogues of propofol we have shown that analogues that possess anaesthetic activity in- vivo activate the GABA_A receptor in the absence of the natural agonist in- vitro, - the potency for this effect paralleled the in- vivo anaesthetic effect (Mohammadi et al.,

2001). The effects of propofol on glycine receptors and their potential contribution to the general anaesthetic effect in- vivo were further studied using a non- anaesthetic structural analogue of propofol (2,6 di-*tert*-butylphenol) on the one hand, and point mutations in the postulated anaesthetic binding site on the glycine receptor α subunit on the other. We have shown that propofol differs from its non- anaesthetic structural analogue not in its potential to enhance the effect of small glycine concentrations (receptor co-activation), but in its potential to activate the receptor in the absence of the natural agonist. A substantial contribution of glycine receptor co- activation to the general anaesthetic effect of propofol seems unlikely as the non- anaesthetic propofol analogue 2,6 di-*tert*-butylphenol has positive allosteric effects at glycine receptors in the same concentration range as propofol. These studies suggest that anaesthetics might differ from non-anaesthetics by differentially modulating the function of the same molecular target site (Ahrens et al., 2004). Furthermore, we have shown that modulatory and direct actions of phenol derivatives in general (structural analogues of propofol) at glycine receptors are structurally separable not only by increasing the size of the aliphatic side chains at either the receptor binding site (Ahrens et al., in preparation) or the phenol derivative (Ahrens et al., 2004), but also by increasing polar interactions. Insertion of a halogen in the benzene ring in para position to the phenolic hydroxyl altering its hydrogen bond donor / acceptor properties increased the potency of a phenol derivative to co- activate glycine receptors, but abolished the ability for direct receptor activation (Haeseler et al., 2005). These results are first steps in the design of drugs with a selective mode of action at glycine receptors.

Mechanisms of local anaesthetic action and novel treatment strategies in pain

We have characterized the pharmacological interaction of a new group of sodium channel blockers, phenol derivatives, with voltage- operated sodium channels which are a molecular target site for potential local anaesthetic, anti- arrhythmic or anti- epileptic actions of these compounds (Haeseler et al., 1999- 2006; Leuwer et al., 2004). As a result of these studies, a patent application for several compounds as anti-arrhythmic drugs has been submitted in November 2001 in co-operation with the pharmaceutical industry (B. Braun, Melsungen, Germany). The patent has been granted in November 2005.

Blockade of sodium channels by phenol derivatives

Applicant: B. Braun Melsungen AG

Inventors: G. Haeseler, M. Leuwer

Appl. Nr. 01996375.0-2112-EPO113082

Furthermore, we have characterized lidocaine- like actions of compounds that are not typically used as local anaesthetics in the clinical setting (i.e. ketamine, opioids; Haeseler et al., 2003, 2006). For example, our studies show that sufentanil, fentanyl and tramadol, but not morphine block voltage- operated sodium channels, preferentially in slow- inactivated conformations. Potency to block voltage- gated sodium channels did not parallel opioid potency of the compounds. These results suggest a potential for therapeutic exploitation of membrane- stabilizing effects of selected opioids in chronic pain and offer novel therapeutic opportunities (Haeseler et al., 2006).

Further projects and co- operations

- Development, in- vitro and in- vivo testing of a novel class of positive allosteric modulators of strychnine- sensitive glycine receptors (*Collaborative Research and Intellectual Property Generation with D. Belelli and J.J. Lambert, The University of Dundee and M. Leuwer, The University of Liverpool, UK*)
- Gating characteristics of voltage- operated sodium channels in the background of a sialylation deficiency (*Collaborative Research with R. Gerardy- Schahn, Department of Cellular Chemistry, MHH*)
- Direct effects of endotoxin on voltage-gated skeletal muscle sodium channels - a potential factor in the development of „intensive care myopathy“.

Selected Publications

Haeseler G, Tetzlaff D, Bufler J, Dengler R, Münte S, Hecker H, Leuwer M. Blockade of voltage-operated neuronal and skeletal muscle sodium channels by S-(+)- and R-(-)-ketamine. *Anesth. Analg.* 2003, 96 (4): 1019-1026.

Leuwer M, **Haeseler G**, Hecker H, Bufler J, Dengler R, Aronson J. An improved model for the binding of lidocaine and structurally related local anaesthetics to depolarized states of voltage-operated sodium channels. *Br. J. Pharmacol.* 2004, 141: 47-54.

Ahrens J, **Haeseler G**, Leuwer M, Mohammadi B, Krampfl K, Dengler R, Bufler J. 2,6-Di-*tert*-butylphenol, a non-anesthetic propofol analogue, modulates $\alpha 1\beta$ glycine receptor function in a manner distinct from propofol. *Anesth. Analg.* 2004, 99: 91-96.

Haeseler G, Bufler J, Ahrens J, Mohammadi B, Dengler R, Hecker H, Aronson JK, Leuwer M. Structural features of phenol derivatives determining potency for activation of chloride currents via $\alpha 1$ and $\alpha 1\beta$ glycine receptors. *Br. J. Pharmacol.* 2005, 145: 916-925.

Haeseler G, Foadi N, Ahrens J, Hecker H, Dengler R, Leuwer M. Sufentanil, fentanyl and tramadol but not morphine block voltage-operated sodium channels. *Pain* 2006, Aug 31 [e-pub ahead of print; PMID 16949748].

Group structure

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