Hochschule Kaiserslautern
University of Applied Sciences

Applied Research Center
Integrated Miniaturised Systems

IMS

Functional preclinical evaluation of advanced substances for the benzodiazepine binding site of the $GABA_A$ receptors

γ-Aminobutyric acid type A receptors ($GABA_A$) are responsible for the fast synaptic inhibitory neurotransmission in the mammalian brain. Their structural diversity forms the basis for the functional and pharmacological heterogeneity of the GABAergic neurotransmission.
Most of the known pharmacological heterogeneity concerns the sensitivity of the benzodiazepine site. It depends, firstly, on the a variant, with α4 and α6 subunit-containing receptors being practically insensitive to benzodiazepine site agonists and, secondly, on the presence of a γ subunit in αXβXγX receptors for the formation and function of the binding site
The advanced compounds will be characterized for their activity at the $GABA_A$ receptor using the whole cell variation of the patch-clamp-technique. Therefore, HEK293 cells will be transiently transfected and the recombinant receptors will be tested at their individual EC_{20} of GABA together with increasing concentrations of the new compounds. By the use of the compounds alone at increasing concentration a potential intrinsic activity will be analyzed.

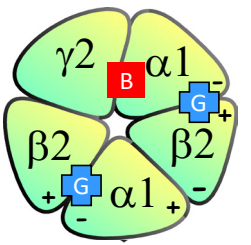

Figure 1: binding sites of agonist (G) and benzodiazepine drugs (B). Modified from Böhme, Rabe, Diazepam is an unselective BZ agonist.

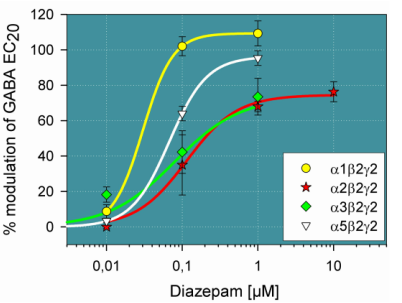

Figure 2: Whole-cell recordings of HEK 293 cells expressing recombinant rat αiβ2γ2 (i=1-3, 5) GABA receptors (Rabe et al. 2005).

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