GABA A receptor subtypes: structure, function, distribution, and pharmacology

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GABA A receptor subtypes: structure, function, distribution, and pharmacology

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Project details

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<td>Not available</td>
<td>0405 - Cell to cell communication in the nervous system</td>
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Objective

GABAA receptors, the major inhibitory neurotransmitter receptors in the brain, are ligand gated chloride ion channels that are formed from five protein subunits. The different, but overlapping regional distribution of the 15 GABAA receptor subunits so far identified in mammalian brain, indicates an enormous structural heterogeneity of these receptors.

GABAA receptors, located in distinct brain regions, can modulate anxiety, convulsions, motor function, behaviour, cognition, vigilance and memory. A multiplicity of clinically important drugs, such as benzodiazepines, barbiturates, neuroactive steroids, and anesthetics, produce their action by non-selectively modulating most of the GABAA receptor subtypes via distinct allosteric binding sites located on these receptors. Compounds selectively interacting with individual GABAA receptor subtypes in different brain regions will avoid some of the side effects of these drugs and will have important therapeutic potential for the treatment of human diseases. Such compounds, thus, are of considerable interest for European society and industry.

Development of compounds selectively interacting with specific GABAA receptor subtypes, however, is seriously hampered by the lack of knowledge on the subunit composition and regional, cellular and subcellular distribution of GABAA receptor subtypes in the central nervous system, and by the lack of information on the function of individual receptor subtypes in the brain. The present proposal aims to provide all this information by integrating the efforts of four highly recognized European laboratories with long standing interest in GABAA receptor research, that supplement each other by their different scientific background, working techniques and experimental approaches. Thus, the proposal is coordinated by W. Sieghart (Vienna, Austria), who will identify the subunit composition and stoichiometry of GABAA receptor subtypes in recombinant receptors and in the brain by quantitative Western blot analysis after purification of receptors by subunit specific antibodies. The results obtained from this approach will be supplemented by work from the laboratory of P. Somogyi (Oxford, England), who will investigate the regional, cellular and subcellular distribution of the various GABAA receptor subunits by immunocytochemical and electron microscopic techniques. E. Sigel (Bern, Switzerland), will identify the amino acids involved in the formation of the benzodiazepine binding pocket of GABAA receptors by mutagenesis and electrophysiological studies on recombinant receptors. R.H. Dodd (CNRS, France), will synthesize new ligands for the GABA-binding site of these receptors, that are urgently needed for the development of the pharmacology of this binding site. These and other compounds, obtained in the course of a collaboration with Schering AG, Germany (benzodiazepine binding site ligands, steroids) or Synthelabo Recherche, France, (benzodiazepine binding site ligands), will be investigated by binding studies (W. Sieghart) and electrophysiological experiments (E. Sigel) for their interaction with several GABAA receptor subtypes that actually do occur in the brain but so far have not been studied. Finally, P. Somogyi will combine electrophysiological and immunocytochemical techniques for an investigation of the function and pharmacology of receptor subtypes in identified synapses.

Results obtained from work performed in this project will be communicated by scientific publications and presented at European meetings organized by the members of our group. Results can be directly exploited by the pharmaceutical industry, and will lead to an accelerated development of new compounds with significant interest for the European community.
Related information

Report Summaries

- Identification of amino acid residues contributing to the formation of the benzodiazepine binding pocket
- Identification of two new classes of compounds that enhance the action of GABA on GABAA receptors
- Organization and function of the GABAergic system in the cerebral cortex and hippocampus
- Sub-unit composition and sub-cellular localization of GABAA receptor subtypes

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