5. SUMMARY

In the selected strain of GAERS Wistar rats (Genetic Absence Epilepsy Rats from Strasbourg), all animals present spontaneously recurrent absence seizures characterized by bilateral and synchronous generalized spike-and-wave discharges (SWD) accompanied by behavioural arrest. SWD depend on a thalamo-cortical network connecting the reticular and relay nuclei of the thalamus and their cortical projection areas. This loop involves both GABAergic and glutamatergic synapses. In the first part of this study, we investigated the implication of glutamatergic transmission in the genesis of absence seizures in GAERS.

Intra-peritoneal or intra-cerebroventricular injections of NMDA, the competitive NMDA antagonist CGP 40116, the non-competitive NMDA antagonist (+)-MK 801 and the antagonist of the glycine modulatory site 5,7-dichlorokynurenic acid dose-dependently suppressed SWD. Bilateral infusions of the same drugs in the lateral relay nuclei of the thalamus had similar suppressive effects. Intra-cerebroventricular or intrathalamic administration of D-serine, an agonist of the glycine modulatory site, had no effect on SWD. Intrathalamic injection of the non-NMDA agonists AMPA and kainate, the selective AMPA receptor antagonist NBQX, and trans-ACPD, an agonist of the metabotropic glutamate receptor, also produced a reduction of SWD.

These data show that glutamatergic neurotransmission, especially within the thalamus, plays a major role in the control of absence seizures in GAERS. Disregulation of NMDA-mediated transmission by agonists or antagonists, interacting with various sites of the receptor complex, but also of non-NMDA and metabotropic glutamatergic transmission, suppresses the thalamo-cortical oscillatory activity which underlies SWD.

Several studies support the hypothesis that cortical hyperexcitability may, via exaggerated cortical responses to thalamic excitatory inputs, contribute to the generation of SWD in GAERS. Pharmacological properties of NMDA receptors depend on their subunit composition. In order to elucidate possible molecular mechanisms underlying cortical hyperexcitability in GAERS, we investigated the
expression of mRNA for the NMDA receptor subunits NR1 and NR2A-D in the cortex and thalamus of GAERS and controls by in situ hybridization.

We found a marked diminution of mRNA expression to about 50% for the NR2A subunit in the cortex and lateral thalamus of GAERS. NMDA receptors containing a NR2A subunit display a higher antagonist affinity and slightly lower agonist affinity than NMDA receptors with other heteromeric composition. Thus, due to such differences in receptor ligand affinity, a reduced expression of NR2A may underlie cortical hyperexcitability. Enhanced cortical responses to excitatory thalamocortical inputs may promote the development of SWD. However, whether the generation of SWD is the result of an enhanced cortical excitability or excessive thalamic oscillations or a combination of both, is as yet controversial. Further, it cannot be excluded that our finding of an altered NMDA receptor subunit expression in adult GAERS may be secondary to the repeated occurrence of absence seizures, as a manifestation of neuronal plasticity. For further elucidation, NMDA receptor subunit expression will have to be investigated in young animals before the age of seizure onset.