11th ESN MEETING, GRONINGEN, THE NETHERLANDS

A

ACUTE MYOCARDIAL INFARCTION AND CYTOKINE-MEDIATED SELECTIVE BLOOD BARRIER LEAKAGE IN THE RAT.


Inflammation in the coronary vessels accompanies acute myocardial infarction (AMI). This inflammatory response may reach the brain when it becomes systemic. Mediators of inflammation like the pro-inflammatory cytokines can locally affect the integrity of the vascular wall which may lead to serum protein extravasations. In the brain this may have adverse effects on neuronal functioning to trigger asthma unexplained cognitive dysfunctions in heart disease patients. The aim of this investigation is to reveal neuroanatomically the vulnerable parts of the cerebral vasculature.

Material and Methods: Male Wistar rats received a myocardial infarction through ligation of part of the left ventricular wall between 2-14 days after surgery the rats were perfused. A second group of rats was treated intravenously with 1 μg human recombinant Tumor Necrosis factor alpha (TNFα). Results: Evidence for inflammation in the brain after AMI came from immunocytochemical detection of ICAM-positive small vessels in certain areas, including the prefrontal cortex, the somatosensory cortex, and the reticular formation. Staining for albumin and IgG revealed that specifically around the ICAM-positive vessels there had been extravasation of serum proteins. This indicates leakage of the blood brain barrier (BBB), probably caused by cytokine producing leukocytes adhering to the vessel wall. In order to assess whether the inflammation rather than the surgery resulted in leakage of the BBB, we injected TNFs in the tail vein. Compared to the myocardial infarcted rats, after TNFs injections the ICAM-positive vessels and Albunin and IgG extravasation was observed in the same areas of the brain (Conclusions).

Myocardial infarction results in a systemic inflammation which possibly causes unexplained cognitive disfunctions in heart disease patients. The aim of this investigation is to reveal neuroanatomically the vulnerable parts of the cerebral vasculature.

B

BEHAVIORAL, CELLULAR AND MOLECULAR CONSEQUENCES OF DISRUPTION OF THE DOPAMINE TRANSPORTER GENE IN MICE BY HOMOLOGOUS RECOMBINATION.

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Hyperactivation of the dopamine system is suggested to play a major role in the etiology of schizophrenia. Psychostimulants, such as amphetamine and cocaine, bind preferentially to the dopamine transporter and thus increase the amount of dopamine available at the synaptic level. Disruption of the mouse dopamine transporter gene results in spontaneous hyperlocomotion despite minor adaptive changes, such as decreases in dopamine receptor levels. This phenotype is a direct consequence of the extended length of time that dopamine spends in the extracellular space following release. The dopamine transporter is an obligatory target of cocaine and amphetamine, as these psychostimulants have no effect in lcoreceptor activity or dopamine release and uptake in mice lacking the transporter. These results establish not only the central importance of the transporter as the key element controlling synaptic dopamine levels but its role as an obligatory target for the behavioral and biochemical action of amphetamine and cocaine. We have investigated the regulation of gene expression of tyrosine hydroxylase, the rate limiting enzyme of dopamine synthesis. While tyrosine hydroxylase mRNA levels were not modified, protein levels were dramatically decreased (>95%) in the ventral midbrain of homozygote mice. This decrease is correlated with a decrease in dopamine levels (>95%) in the striatum. Immunohistochimistry with a tyrosine hydroxylase polyclonal antibody shows no difference in the number of dopamine neurones of the ventral midbrain in homozygote compared to wild type mice.

Moreover, the decrease in tyrosine hydroxylase levels is less marked in the arcuate and olfactory tubercle than the striatum where dopamine transporter levels are normally higher. The dramatic extent of the down regulation documented here is only achieved in other animal models by destruction of dopamine neurones, which ultimately induce Parkinson-like syndromes. The mice lacking the dopamine transporter show a spontaneous increase in their locomotor activity despite the marked down regulation of tyrosine hydroxylase and dopamine levels strongly suggests that blockade of the dopamine transporter with highly selective antagonists could be beneficial in alleviating symptoms of Parkinson disease in humans.

C

THE HUMAN BRAIN QUISQUATE RECEPTOR AS AN ANTIGEN IN BLOOD SERUM TEST-KIT ALLOWING DIAGNOSIS OF EPILEPSY.

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The immunoreactive epitopes of human brain quisqualate receptor (QR) were used as an antigens for determination of autoantibodies (aAb) level to QR in the blood serum by ELISA technique. The blood serum analysis allowing carry out diagnostics of epilepsy by paroxysmal activity test (Pa-test) was developed.

The increased aAb level to QR (more than two-three times above the control value) was revealed in the blood samples of patients with epilepsy and paroxysmal activity. In the neurological patient's groups this effect was not seen. In majority (85 %) of patients with epilepsy, revealed by Pa-test, demonstrated positive correlation with long-time of the disease, frequencies of attack and the type of paroxysms. The level of autoantibodies to QR epitopes could be new clinical index substantially facilitating unbiased diagnosis of epilepsy, additional to clinical, neurophysiological and other method of examination. The role of quisqualate receptor in the molecular mechanism of epilepsy is discussed.

D

GABA DEPENDENT MODULATION OF [3H]TBOB BINDING

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The molecular mechanisms of compounds interacting with the GABA<sub>A</sub>-receptor complex are not yet fully unravelled. We investigated the effects of thiopental and propofol, either in the absence or in the presence of GABA, in receptor binding studies to rat brain membranes.

Both compounds displaced [3H]-t-butylbicycloorthobenzoate ([3H]TBOB) binding to the GABA<sub>A</sub>-receptor complex. The data were fitted to the Sigmoid Emax model (Eq1) and the Hill parameter were dependent on the GABA concentration: The addition of 8 μM GABA decreased the EC<sub>50</sub> of thiopental from 100 μM to 15 μM and that of propofol from 40 μM to 5 μM. The Hill parameter of thiopental decreased from 2.2 to 1.4 and of propofol from 2.4 to 0.9. The sigmoid Emax model does not correspond to a molecular model.

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