



A ticking time bomb: Circulating anti-NMDA receptor autoantibodies

Scientists of the CNMPB and of the Max Planck Institute of Experimental Medicine find NMDAR autoantibodies in 10% of all tested individuals, which can cause neuropsychiatric dysfunctions in case of blood brain barrier disturbance.

(cnmpb/mpiem) “Anti-NMDA receptor encephalitis” was the name given to an acute brain disease, whose potential cause and treatment has been described in a number of recent publications. On the molecular level, this acute form of encephalitis is attended by a reduced function of glutamate receptors (NMDAR), which is caused by autoantibodies against these receptors in the brain. Symptoms of the disease can be psychosis, movement disorders, epileptic seizures or reduction of cognitive performance in various shapes. However, as most studies are based on a generally fairly small number of patients, they neither cast a light on the relevance of NMDAR autoantibodies in the blood for the pathogenesis of the disease, nor do they yield data about their prevalence in healthy individuals.

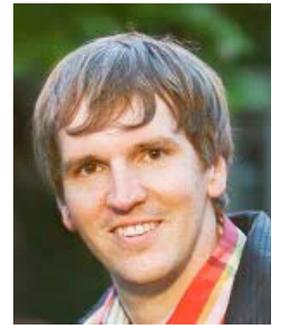
Notable new findings are now provided by a new study conducted by Prof. Hannelore Ehrenreich and her team in cooperation with the Göttingen DFG Research Center and Cluster of Excellence Nanoscale Microscopy and Molecular Physiology of the Brain (CNMPB). The study demonstrates for the first time that NMDAR autoantibodies can be found in the serum of more than 10% of a total of nearly 3000 tested individuals, irrespective of

whether they are patients or healthy individuals. Surprisingly, comparable autoantibody titers, antibody classes and functionalities were detected in healthy subjects and patients with a neuropsychiatric disease. This insight led the authors of the study to the following central question: If, in fact, these autoantibodies play some pathological role, why do healthy individuals bearing them stay healthy?

In a series of animal experiments the scientists could demonstrate that the prerequisite for a triggering of symptoms by these autoantibodies, and thus for the pathogenesis of a disease process, is a dysfunction of the blood-brain barrier. This physiological barrier in a healthy organism delimits the central nervous system like a filter from the general blood stream and thus protects it from circulating pathogenic agents and toxins. A disruption of its natural barrier function enables the NMDAR autoantibodies circulating in the blood to enter the brain. This way, they reach the NMDA receptors located in the brain and can cause an impairment of function resulting in psychosis-similar symptoms, epileptic seizures or cognitive dysfunctions.



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Source: mpiem



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"In other words, more than 10% of all individuals carry a 'ticking time bomb', the disease relevance of which is only suppressed by an intact blood-brain barrier", remarks Prof. Ehrenreich. An impaired blood brain barrier can be caused by a stroke, a brain trauma or by a viral infection, amongst others. In this context, the scientists performed an additional retrospective evaluation based on a large cohort of patients. They demonstrate an increase in the severity of neurological symptoms in subjects with a temporary or persisting blood-brain barrier dysfunction who carry NMDAR autoantibodies in their serum.

The authors of the study for the first time examined the question which factors are, in the end, responsible for triggering the generation of these NMDA autoantibodies. They found, on the one hand, an association of past influenza A or B infections with the appearance of these autoantibodies; on the other hand they identified by means of a genome-wide association study a genetic risk factor related to NMDAR biology.

The study published by first author Christian Hammer and coworkers is not only conceptually novel, it also yields considerable insight into a pathophysiological mechanism that is of crucial importance for neuropsychiatry and also for other clinical disciplines. The scientists commend that "patients with acute or chronic impairment of the blood-brain-barrier, e.g. after a brain injury, a stroke, any kind of encephalitis, epilepsy and also multiple sclerosis should be screened for the presence of NMDAR autoantibodies". This might contribute to improve the course of disease by appropriate therapeutic methods and prevent long-term complications.

Original Publication:

Christian Hammer, Beata Stepniak, Anja Schneider, Sergi Papiol, Martesa Tantra, Martin Begemann, Anna-Leena Sirén, Luis A. Pardo, Swetlana Sperling, Suhaidah Mohd Jofrry, Artem Gurvich, Niels Jensen, Katrin Ostmeier, Fred Lühder, Christian Probst, Henrik Martens, Meyke Gillis, Gesine Saher, Francesca Assogna, Gianfranco Spalletta, Winfried Stöcker, Thomas F. Schulz, Klaus-Armin Nave, Hannelore Ehrenreich (2013) Neuropsychiatric disease relevance of circulating anti-NMDA receptor autoantibodies depends on blood brain barrier integrity. *Molecular Psychiatry* (2013), Sep 3. doi: 10.1038/mp.2013.110. [Epub ahead of print]. Link: <http://www.ncbi.nlm.nih.gov/pubmed/23999527>

Additional Information:

Max Planck Institute of Experimental Medicine: <http://www.em.mpg.de/index.php>
CNMPB – Cluster of Excellence and DFG-Research Center: <http://www.cnmpb.de>
Prof. Dr. Ehrenreich: [http://www.em.mpg.de/index.php?id=36&tx_jppageteaser_pi1\[backId\]=16](http://www.em.mpg.de/index.php?id=36&tx_jppageteaser_pi1[backId]=16)

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