Anti-NMDA receptor Encephalitis

Smooth ER: Renata Daniels, Emma Worden-Sapper
Background

- Auto-immune disorder
- 81% of cases affect women
- Median age of diagnosis is 21 years
- Associated with ovarian teratomas
- 75% diagnosed recover, mortality rate is 7% (according to a 2008 study)
- Categorized and named by Joseph Dalmau, 2007
- Symptoms mimic described characteristics of demonic possession
- Commonly undiagnosed or misdiagnosed, e.g. as bipolar disorder
Symptoms

Prodromal

- Headaches
- Flu-like symptoms
- Fatigue
- Fever

Progression

- Paranoia
- Psychosis
- Seizure
- Cerebellar ataxia
- Memory deficits
- Speech problems (aphasia, perseveration, mutism)
- Motor symptoms
- Hemiparesis
- Hypoventilation
- Delusions and/or hallucination
- Catatonia

“When he suggested I try to relax, I turned to face him, staring past him like I was possessed. My arms suddenly whipped straight out in front of me, like a mummy, as my eyes rolled back and my body stiffened. I was gasping for air… Blood and foam began to spurt out of my mouth through clenched teeth… I would never regain any memories of this seizure, or the ones to come.” - Susannah Cahalan, Brain on Fire
Diagnosis

- Psychological, cognitive tests
- Anti-NMDAR antibody cerebral spinal fluid (CSF) analysis
- MRI scan for lesions (cortex, basal ganglia, thalamus)
- Brain biopsy
NMDA receptor

Specific functionality
- Glutamatergic
- Ionotropic
- Na+ and Ca++ permeable
- Excitatory response
- Magnesium plug is removed when the membrane is depolarized
- Glycine is a co-agonist
- Heterotetramer (two NR1 subunits, two NR2 subunits)

Brain functionality
- Synaptic plasticity
- Calcium can function as a second messenger after an action potential
- Memory formation, learning, synaptogenesis
NMDA receptor localization

Donor: H0351.2002, 39 yrs, M, Black or African American

Structure: parahippocampal gyrus, z-score: 1.28372, log2 level: 4.96538
Proposed Mechanisms of Action

1. BBB damage
   a. Acute inflammation
   b. CRH and mast cell interaction
   c. Autonomic dysfunction (i.e. increased blood pressure)

2. Intrathecal antibody production

3. Excessive levels of antibodies in the CSF induce degradation of NMDAR GluN1 subunit
   a. NMDAR cross-linkage
   b. Direct antagonism of NMDAR
   c. Complement cascade
NMDAR cross-linkage

A. Localization of AMPA and NMDA receptors at PSD
B. Selective binding of antibodies to NMDAR and receptor cross-linking
C. Internalization of antibody-bound NMDAR
D. Cultured rodent neurons treated with control CSF and stained for NR1, VGlut, and PSD-95
E. Patient CSF treatment
F. CSF control of mEPSC dependent on NMDAR
G. Patient CSF

Moscato et al., 2010
Genetic Factors

HLA-I-allele B*07:02

- Encodes MHC class I peptides
  - Identifies non-self peptides to antigen-presenting cells
  - Expressed in phagocytes, B cells, and others
Treatments

1. First-line immunotherapy (steroids, immunoglobulin, plasmapheresis, immunoabsorption) + removal of teratoma (if present)

2. Second-line immunotherapy: Rituximab, alemtuzumab (experimental)

3. Transcranial direct current stimulation as a treatment for associated cognitive disorders

4. Effectiveness of treatments varies from patient to patient
Clinical Trials

Immunoadsorption Therapy in Managing NMDAR Antibodies Encephalitis (IANMDAR)
Cohort: 20, Intervention: Immunoadsorption therapy in conjunction with Rituximab

Transcranial Direct Current Stimulation on Cortical Plasticity in Patients With Anti-NMDA Receptor Encephalitis
Cohort: 40, Intervention: Transcranial Direct Current Stimulation
Future Directions

Left: Potential binding pockets on the NR1 subunit of the NMDA receptor

Spreading awareness of the disease

Determine the mechanism of action, genetic factors


References


