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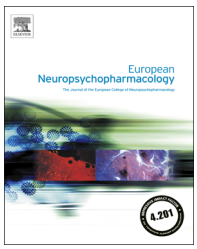

REVIEW

Autoimmune-induced glutamatergic receptor dysfunctions: Conceptual and psychiatric practice implications

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Abstract
Glutamatergic neurotransmission is mediated *via* complex receptorial systems including N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid (AMPA) and metabotropic receptor subtypes and plays a critical role in the modulation of synaptic plasticity, mood, cognitive processes and motor behavior. Glutamatergic function deficits are hypothesized to contribute to the pathogenesis of neuropsychiatric disorders, including schizophrenia, mood and movement disorders. Accumulating data are rapidly leading to the characterization of specific types of autoimmune encephalitis in which the receptors and proteins critically involved in glutamatergic neurotransmission, *e.g.*, NMDA, AMPA receptors, are antigen targets. Characteristic of these syndromes, antibodies alter the structure and/or function of the corresponding neuronal antigen resulting in clinical pictures that resemble pharmacological disease models. Presently the best characterized autoimmune glutamatergic disorder is anti-NMDA receptor encephalitis. This disorder manifests with intertwined psychiatric and neurological features, defines a new syndrome, reclassifies poorly defined clinical states and extends previous hypotheses, such as hypo-NMDA receptor function in schizophrenia. The characterization of autoimmune-induced glutamatergic receptor dysfunctions (AGRD) is likely to have a substantial conceptual impact upon our understanding of neuropsychiatric disorders including schizophrenia, affective and movement dysfunctions. Further definition of AGRD will provide additional guidelines for psychiatric diagnoses, identification of homogeneous patient subtypes within broad phenomenological classifications and will contribute to the

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development of personalized treatments. The body of knowledge already accumulated on anti-NMDA receptor encephalitis highlights the need for wide dissemination of these concepts among psychiatrists, and in suspected cases, for early recognition, prompt clinical and laboratory investigation and efficient interface between mental health and medical teams.

1. Introduction: Autoimmune encephalitis and glutamate

Limbic encephalitis (LE) refers to an inflammatory process that predominantly affects the gray matter of the medial temporal lobes, amygdala and orbito-frontal cortex and produces cognitive impairment along with emotional and behavioral disturbances, sleep disruption, seizures and sometimes dementia (Dalmau et al., 1992; Corsellis et al., 1968). Until recently, autoimmune LE was mostly viewed as a paraneoplastic disorder associated with onconeural antibodies to intracellular antigens, cytotoxic T-cell mediated pathogenesis and limited response to treatment. However, accumulating data suggest that the clinical and immunological spectra of LE are far more extensive than initially considered. During the last decade a novel category of autoimmune encephalitides is being revealed, that is characterized by antibodies against neuronal cell surface antigens, less frequent association with cancer, an antibody-mediated pathogenesis and improved treatment response following immunotherapy (rev. in Lancaster and Dalmau (2012); Vincent et al. (2011)). The main three receptor subclasses that mediate glutamatergic neurotransmission and synaptic plasticity *i.e.* N-methyl-D-aspartate, alpha-amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid, and metabotropic glutamate receptors (NMDAR, AMPAR, mGluR) are the specific, direct antibody targets in some of these disorders (Lancaster et al., 2011; Lai et al., 2009; Dalmau et al., 2007). Characteristic of these syndromes, the antibodies alter the structure and/or function of the corresponding receptor antigen resulting in clinical pictures that resemble pharmacological or genetic models in which the antigen is disrupted. Given the involvement of glutamatergic neurotransmission in a variety of psychiatric disorders, including schizophrenia and affective disorders (rev. in Heresco-Levy and Javitt (2008)), the identification of specific autoimmune-induced glutamatergic receptor dysfunctions (AGRD) is likely to have a substantial conceptual impact upon our understanding of neuropsychiatric disorders and to provide additional guidance in complex diagnostic situations.

2. Glutamate systems: Overview

Biological psychiatry research of the etiology and treatment of neuropsychiatric disorders began to focus on the role of glutamatergic neurotransmission only about two decades ago. This is surprising since the balance of CNS excitation and inhibition in mammals is determined by synaptic inputs from the major excitatory neurotransmitter glutamate (GLU) and the major inhibitory neurotransmitter γ-aminobutyric acid (GABA). This relationship between GLU and GABA controls the major inputs and outputs of brain regions involved in essentially all physiological functions (Schoepp, 2001).

Unlike dopamine, for example, which plays an important role only in isolated regions, GLU-mediated functions are critical throughout the brain. Approximately 60% of brain neurons, including all cortical pyramidal neurons and thalamic relay neurons, utilize GLU as their primary neurotransmitter. As a result, virtually all corticofugal, corticocortical and thalamocortical neurotransmission in the brain is mediated by GLU. In light of the major role of glutamatergic pathways in the modulation of mood, cognitive processes and motor behavior, their reciprocal interactions with monoaminergic networks and their intense innervation of corticolimbic structures and the basal ganglia, it is thus reasonably expected that glutamatergic neurotransmission would be highly relevant to the pathogenesis and pharmacotherapy of neuropsychotic disorders (rev. in Javitt et al. (2011); Heresco-Levy and Javitt (2008)).

GLU mediates its effects at multiple ionotropic and metabotropic receptors (Figure 1). Ionotropic receptors are characterized by sensitivity to synthetic GLU derivatives including NMDA and AMPA. Both NMDAR and AMPAR are composed of multiple subunits surrounding a central pore, with receptor properties varying depending upon exact channel composition. In addition to the GLU binding site, the NMDAR complex contains a modulatory site, at which the endogenous amino acids glycine (GLY) and D-serine (DSR) act as compulsory coagonists (Kemp and Leeson, 1993), as well as polyamine and redox-sensitive sites. The NMDAR-ion channel complex is composed of multiple subunits, including GLY/DSR-binding NR1 subunit and one of the additional polypeptides from the NR2 group (NR2A-D) or NR3 group (NR3, A, B), now termed GluN1-3 subunits (Laurie and Seeburg, 1994). NMDARs are also uniquely voltage- and ligand-dependent, permitting them to function in a Hebbian fashion to integrate information across brain pathways (Cotman et al., 1988). The majority of AMPAR are tetramers composed of GluR1, 2, 3 or 4 subunits that combine in a brain region-dependent manner (Palmer et al., 2005). The regions with highest levels of GluR1/2 and GluR2/3 receptors are the synaptic CA3–CA1 areas of the hippocampus, followed by the subiculum, cerebellum, caudate–putamen, and cerebral cortex (Sprengel, 2006).

mGluRs are divided into groups on the basis of their second messenger coupling and ligand sensitivity. Group 1 receptors (mGluR1/5) predominantly potentiate both presynaptic GLU release and postsynaptic NMDAR currents. In contrast, group II (mGluR2/3) receptors, in general, limit GLU release, particularly during conditions of GLU spillover from the synaptic cleft. Group III receptors (mGluR4/6/7/8) show more variable distribution but also generally inhibit GLU function.

In addition to controlling excitation *per se*, glutamatergic neurotransmission, through its diverse downstream signaling mechanisms, represents a major system for controlling neuronal