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Editorial

N-Methyl-D-aspartate receptors and glutamate neurotransmission: an overview in pathological conditions and treatment

Glutamate is the principal excitatory neurotransmitter in the brain. Knowledge of the glutamatergic synapse has advanced enormously in the last 10 years, primarily through application of molecular biological techniques to the study of glutamate receptors and transporters. There are three families of ionotropic receptors with intrinsic cation-permeable channels [*N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate]. There are groups of metabotropic, G protein-coupled glutamate receptors (mGluR) that modify neuronal and glial excitability through G protein subunits acting on membrane ion channels and second messengers such as diacylglycerol and cAMP (1).

NMDA receptors (NMDARs) are key glutamatergic receptors in the central nervous system. Their permeability to calcium and their voltage-dependent magnesium block make them essential for synaptic transmission, synaptic plasticity, rhythmogenesis, gene expression and excitotoxicity. An intriguing property is that their activation requires the binding of both glutamate and a co-agonist like glycine or D-serine (2).

Glutamate receptors are essential to the normal function of the central nervous system. However, their (i.e., NMDARs) excessive activation by excitatory amino acids, such as glutamate itself, is thought to contribute to neuronal damage in many neurological disorders ranging from acute hypoxic-ischaemic brain injury to chronic neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis (ALS) (3).

Alternatively, it has long been recognised that phencyclidine (PCP) produces phenomenology in normal individuals that closely resembles schizophrenia (i.e., positive, negative and cognitive symptoms) and exacerbates symptoms in patients with chronic schizophrenia. At subanaesthetic doses, PCP binds to a site within the ion channel of the NMDA receptor that blocks the influx of cations, thereby acting as a non-competitive antagonist. In short, dysfunction of glutamatergic neurotransmission, i.e., hypofunctioning at the NMDA receptor, seems to play an important role in the pathophysiology of schizophrenia (4). Interestingly, the neurodevelopmental disorder autism has been associated with both glutamate excitotoxicity (5) and, more recently, with NMDAR hypofunctioning (6). The latter is posited in the pathogenesis of core symptoms of social impairment in autism (7).

Somewhat less studied is the regulation of movement in schizophrenia, especially in regard to the role that NMDA receptors play in gross motor function and variability. Motor symptoms are frequent in schizophrenia. In fact, about 50% of psychotic patients display at least one motor symptom (8). Motor activity in schizophrenia can be agitated and restless, manifest stereotypies or repetitive behaviour, or sit inactively or even in a stupor (9).

Berle et al. demonstrated that motor activity was significantly reduced in both schizophrenic and depressed patients. However, schizophrenic patients differed from both depressed patients and controls, demonstrating motor activity patterns marked by less complexity and more structured behaviour (10). Earlier, Homayoun et al. demonstrated that when the use-dependent NMDA antagonist MK-801 was administered to male Sprague–Dawley rats, it increased horizontal locomotion and stereotypies in the latter, i.e., demonstration of motoric effects of an NMDA receptor antagonist (11).

In this issue of *Acta Neuropsychiatrica*, Johnsen et al. further the link between a role for the NMDA receptor in the regulation of motor activity by first reporting that the glutamate antagonist memantine induced distinct changes in motor activity patterns in healthy subjects and that these changes are similar to those found in patients with schizophrenia.

In closing, within the medication development framework, the modulation of glutamatergic neurotransmission has become the focus of intense research. Glutamatergic neurotransmission may be modulated at multiple levels, with glutamate receptor families and their subtypes representing a modulatory site-rich environment for drug research. Numerous types of neurotransmission modulators, acting at the NMDA, AMPA and metabotropic glutamate receptors, and/or affecting glutamate synaptic release, are hypothesised or have been demonstrated to be beneficial for various neurological and psychiatric disorders (12). For instance, there are already Federal Drug Administration-approved medications modulating glutamatergic transmission for epilepsy (i.e., topiramate, levetiracetam) (13), Alzheimer's disease (memantine) (14), ALS (riluzole) (15) and alcohol relapse prevention (acamprosate) (16). Ongoing and planned research is expected to provide, in the near future, critical information regarding the practical utility and tolerability of glutamatergic approaches to both neurological and psychiatric disorders (for instance, D-cycloserine in autism (17) and *N*-acetylcysteine in schizophrenia) (18).

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References

1. Meldrum BS. Glutamate as a neurotransmitter in the brain: review of physiology and pathology. J Nutr 2000; **130**(4S Suppl):1007S–1015S.
2. Oliet SH, Mothet JP. Regulation of *N*-methyl-D-aspartate receptors by astrocytic D-serine. Neuroscience 2009;**158**: 275–283.
3. Chen HS, Lipton SA. The chemical biology of clinically tolerated NMDA receptor antagonists. J Neurochem 2006; **97**:1611–1626.
4. Goff DC, Coyle JT. The emerging role of glutamate in the pathophysiology and treatment of schizophrenia. Am J Psychiatry 2001;**158**:1367–1377.
5. Essa MM, Braidy N, Vijayan KR et al. Excitotoxicity in the pathogenesis of autism. Neurotox Res 2013;**23**: 393–400.
6. Gandal MJ, Anderson RL, Billingslea EN et al. Mice with reduced NMDA receptor expression: more consistent with autism than schizophrenia? Genes Brain Behav 2012;**11**: 740–750.
7. Kalia LV, Kalia SK, Salter MW. NMDA receptors in clinical neurology: excitatory times ahead. Lancet Neurol 2008;**7**:742–755.
8. Walther S, Koschorke P, Horn H et al. Objectively measured motor activity in schizophrenia challenges the validity of expert ratings. Psychiatry Res 2009;**169**: 187–190.
9. Andreasen NC. The evolving concept of schizophrenia: from Kraepelin to the present and future. Schizophr Res 1997;**28**:105–109.
10. Berle JO, Hauge ER, Oedegaard KJ et al. Actigraphic registration of motor activity reveals a more structured behavioural pattern in schizophrenia than in major depression. BMC Res Notes 2010;**3**:149.
11. Homayoun H, Stefani MR, Adams BW et al. Functional interaction between NMDA and mGlu5 receptors: effects on working memory, instrumental learning, motor behaviors, and dopamine release. Neuropsychopharmacology 2004;**29**: 1259–1269.
12. Heresco-Levy U. Glutamatergic neurotransmission modulators as emerging new drugs for schizophrenia. Expert Opin Emerg Drugs 2005;**10**:827–844.
13. Surges R, Volynski KE, Walker MC. Is levetiracetam different from other antiepileptic drugs? Levetiracetam and its cellular mechanism of action in epilepsy revisited. Ther Adv Neurol Disord 2008;**1**:13–24.
14. Tariot PN, Farlow MR, Grossberg GT et al. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. JAMA 2004;**291**:371–324.
15. Zoccolella S, Santamato A, Lamberti P. Current and emerging treatments for amyotrophic lateral sclerosis. Neuropsychiatr Dis Treat 2009;**5**:577–595.
16. Yahn SL, Watterson LR, Olive MF. Safety and efficacy of acamprosate for the treatment of alcohol dependence. Subst Abuse 2013;**6**:1–12.
17. Deutsch SI, Pepe GJ, Burket JA et al. D-cycloserine improves sociability and spontaneous stereotypic behaviors in 4-week old mice. Brain Res 2012;**1439**:96–107.
18. Dean O, Giorlando F, Berk M. *N*-acetylcysteine in psychiatry: current therapeutic evidence and potential mechanisms of action. J Psychiatry Neurosci 2011; **36**:78–86.

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