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Regulation of Extrasynaptic Glutamate Levels as a Pathophysiological Mechanism in Disorders of Motivation and Addiction

A growing body of evidence suggests that changes in glutamate transporter expression may be a factor that is common to many neuropsychiatric disorders. As an example, reduced glutamate reuptake capacity has been linked to a wide variety of conditions such as depression, schizophrenia, and addiction. Mathematical models suggest that under physiological conditions glutamate may diffuse and activate NMDA receptors within a radius of 0.5 μm from the release point (Tzingounis and Wadiche, 2007). Excitatory amino-acid transporters (EAATs) bind and transport glutamate, limiting spillover from synapses due to their dense perisynaptic expression primarily on astroglia. Thus, the spatial arrangement of glutamate synapses, their glutamate transporter buffering zones, and extrasynaptic glutamate receptors will determine the extent and effects of glutamate spillover (Tzingounis and Wadiche, 2007). Increased glutamate spillover may lead to a loss of input specificity, degrading the spatial precision of synaptic transmission. Decreased glutamate spillover, particularly in regions with high levels of physiologic spillover such as the hippocampus, could also disrupt plasticity by limiting spillover transmission. Disruption of glutamate reuptake with genetic models or pharmacological agents yields region- and mechanism-specific phenotypes. For example, the homozygous GLAST (called EAAT1 in the human) KO exhibits locomotor hyperactivity, social withdrawal, and abnormal acoustic startle—deficits analogous to the positive, negative, and cognitive symptoms observed in schizophrenia (Karlsson *et al*, 2009).

Several postmortem studies found changes in EAAT expression in schizophrenia consistent with diminished regional expression of astroglial (but not neuronal) glutamate transporter expression and activity (Shan *et al*, 2012). Expression of functional EAAT isoforms appears to be increased in neurons in schizophrenia; we have also found a change in the ultrastructural localization of EAAT2 protein, with an increase in the distance between asymmetric synapses and EAAT2 protein in the frontal cortex in schizophrenia (unpublished observations).

Recent work in a rodent model of heroin relapse provides strong evidence for glutamate spillover as a mechanism of disease. The surface expression and activity of GLT1 (rodent EAAT2) were decreased in the nucleus accumbens core in heroin-dependent rats (Shen *et al*, 2014). Reinstatement of heroin seeking was inhibited by ceftriaxone, a drug that increases GLT1 protein expression and activity. The authors used a change in the NMDA receptor excitatory postsynaptic current decay time as an index of synaptic glutamate spillover, to demonstrate increased decay in heroin- *vs* saline-yoked rats (Shen *et al*, 2014). The increase in decay mimicked the effects of glutamate transport inhibitors in the model, supporting the hypothesis that synaptic glutamate spillover has a central role in relapse and addiction.

The data in schizophrenia and heroin relapse are consistent with findings in depression, where decreased levels of glial transporter expression are reported in brain samples from mood disorder subjects and rodents exposed to chronic stress (Sanacora and Banasr, 2013). Treatment with drugs that increase GLT1 expression and function, including ceftriaxone and riluzole, has antidepressant-like effects in rodent models (Sanacora and Banasr, 2013).

We postulate that diminished perisynaptic glutamate buffering and reuptake may be a common pathophysiological mechanism in psychiatric illness, associated with a number of intermediate phenotypes, including positive (reward learning, reward valuation) and negative (fear, anxiety, loss) valence systems, cognition, arousal and socialization. The diverse biology of the glutamate transporter system, with cell- and splice-variant specific expression regulated by myriad paracrine factors, canonical signaling pathways, exosomal microRNAs, as well as pharmaceuticals such as ceftriaxone, makes it a high yield target that should be exploited for the development of new treatments for a wide array of psychiatric disorders (Lee and Pow, 2010).

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Robert E McCullumsmith[1] and Gerard Sanacora[2]
[1]Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine, Cincinnati, OH, USA; [2]Clinical Neuroscience Research Unit, Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA
E-mail: robert.mccullumsmith@uc.edu

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Gene Therapy for Parkinson's Disease: Still a Hot Topic?

Parkinson's disease is a synucleinopathy with widespread degeneration within the peripheral nervous system and across a variety of brains regions. The best studied and understood region of neural degeneration is the dopaminergic nigrostriatal system. Striatal dopamine insufficiency and nigral neuronal loss underlie the cardinal motor symptoms of PD. Levodopa and deep brain stimulation (DBS) are the most potent therapies for these symptoms. However, they have side effects that warrant the investigation of new therapies.

One novel therapy is gene transfer (or therapy), in which, for the most part, viruses are used to deliver therapeutic molecules. Gene therapy methodologies can be divided into two general types: symptomatic and disease modifying (for review, see Kordower and Bjorklund, 2013). The first gene therapy clinical trial for PD was the delivery of aromatic amino decarboxylase (AADC) (Mittermeyer *et al*, 2012). This approach was aimed at symptomatic benefit. AADC is the enzyme that converts levodopa to dopamine and AADC gene delivery attempts to make the conversion of the exogenous levodopa to dopamine more efficient. In animal studies, lower doses of levodopa result in the same antiparkinsonian benefit as high doses when it is combined with gene delivery of AADC. Lower doses would also obviate or delay the emergence of dopa-induced dyskinesias. AADC gene delivery was safe and well tolerated in a Phase 1 clinical trial (Mittermeyer *et al*, 2012). An open-label assessment demonstrated some benefit in a small number of patients. Oxford Biomedica employed a equine lentivirus to deliver tyrosine hydroxylase, AADC, and GTP cyclohydrolase, the combination of which makes dopamine. Preclinical studies in rodents and monkeys delivering lenti-dopamine demonstrated significant antiparkinsonian benefit. A Phase 1/2 clinical trial has been completed again demonstrating safety and tolerability with some measure of efficacy as determined via open-label assessments (Palfi *et al*, 2014). Another series of studies models gene therapy after deep brain stimulation (DBS). In PD, the subthalamic nucleus is hyperactive and DBS blocks that hyperactivity. Glutamic acid decarboxylase (GAD) reduces cellular activity and reverses motor dysfunction in rodent and nonhuman primate models of PD. A Phase 2 randomized sham controlled trial was performed and met the primary endpoint (LeWitt *et al*, 2011). However, the magnitude of the effect was small and it is unclear whether this approach is going forward.

Disease-modifying gene therapy strategies have focused on the glial cell family of ligands (GFLs), namely, GDNF and neurturin. Gene delivery of both of these trophic factors protects nigrostriatal circuitry and motor function in numerous rodent and nonhuman primate models of PD (Kordower and Bjorklund, 2013). A new clinical trial using gene delivery of GDNF is currently underway. Unfortunately, two Phase 2 clinical trials testing neurturin failed (Marks *et al*, 2010; Olanow *et al*, manuscript in preparation). Why is this molecule so potent in preclinical models but ineffective in patients with PD? We have postulated that the failure is due to the extensive degeneration of the nigrostriatal system at the time the patients were treated (Kordower *et al*, 2013). Furthermore, the few fibers that are remaining are defective in axonal transport mechanisms and thus the trophic factor fails to be efficiently transported, either retrogradely or anterogradely, to nigral perikary.

Gene therapy for PD still has great promise. Multiple approaches are safe and well tolerated. However, at this time, no study has demonstrated *robust* clinical benefit using rigorous double-blind assessments. However, it is possible that a resolution of delivery issues, which will maximize the spread of the vector to the target area, as well as moving to a less-impaired patient population, might unlock the potential of this strategy. Additionally, as currently practiced, gene therapy for PD only addressed the cardinal motor symptoms, and other signs, including potentially disabling psychiatric symptoms, require a different gene therapy approach.

Jeffrey H Kordower[1]
[1]Department of Neurological Sciences, Rush University Medical Center, Chicago, IL, USA
E-mail: jkordowe@rush.edu

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