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Guest Editorial

The current issue of ***Pharmacology Biochemistry & Behavior*** addresses the roles of glutamate receptors across major neurological and psychiatric disorders. Each disorder is addressed from the preclinical and clinical perspectives, with a focus of how genetic, pharmacological and postmortem studies inform potential contributions of abnormalities in glutamate transmission towards each condition. The issue begins with an overview of glutamatergic neurotransmission in the nervous system by Sanacora and colleagues. This introductory article provides an overview of glutamate neurotransmitter system physiology and pharmacology. Authors note that the extremely high concentration of glutamate in brain tissue, paired with its excitotoxic potential, require tight physiological regulation of extracellular glutamate levels and receptor signaling in order to assure optimal excitatory neurotransmission but limit excitotoxic damage. Furthermore, the article addresses the complex physiology, with multiple regulatory processes modulating glutamate metabolism, release, receptor signaling, and uptake. Basic physiology of the various regulatory components including receptor pharmacology is briefly reviewed. Potential contributions from each of these components to the pathophysiology of neuropsychiatric illnesses are briefly discussed, as are several pharmacological targets for future therapies to treat many of the disorders noted in the specific contributing articles. The first section addresses glutamatergic dysfunction in major psychiatric conditions including schizophrenia, depression, bipolar disorder, anxiety and obsessive compulsive disorders. The second portion of the special issue then contains two contributions that address the role of glutamatergic transmission in mediating the effects of drugs of abuse, as well as potential therapies. The final section then addresses glutamatergic neurotransmission in neurological conditions across the life span, with a series of articles related to prenatal insults, autism spectrum disorders and dementia.

1. Psychiatric disorders

1.1. Schizophrenia

Section one begins with an article by Tsai and colleagues addressing glutamatergic neurotransmission, particularly through the N-methyl-D-aspartate (NMDA) receptors, in the pathophysiology of schizophrenia. Neurodevelopmental factors and genetic susceptibility for schizophrenia relevant to NMDA receptor mediated neurotransmission are discussed, with special emphasis of the relationship between NMDA receptor hypofunction and symptom. Putative treatments are addressed through description of a series of clinical trials and meta-analyses which compare currently available NMDA-enhancing agents. Authors suggest that glycine, D-serine, and sarcosine are more efficacious than D-cycloserine in improving the overall psychopathology of schizophrenia. Enhancing glutamatergic neurotransmission via activating the AMPA receptor, metabotropic glutamate receptor or inhibition of D-amino acid oxidase (DAO) are also reviewed. The need to determine long-term efficacy, functional outcome, and safety of glutamate transmission-enhancing agents in schizophrenia is also addressed.

1.2. Major depressive disorder

The next series of articles addresses both clinical and preclinical data regarding the extent to which disruptions and/or enhancements in glutamate transmission may be related to the pathophysiology, and ultimately treatment of major depressive disorder. Zarate and colleagues discuss growing evidence suggesting that the glutamatergic system is central to the neurobiology and treatment of affective disorders. To address this hypothesis, authors review data supporting the involvement of the glutamatergic system in the pathophysiology of mood disorders as well as the efficacy of glutamatergic agents such as the glutamate modulator riluzole and the NMDA receptor antagonist ketamine as novel therapeutics. This is followed by a review of the relevant preclinical data by Hashimoto and colleagues. Readers will learn about accumulating evidence suggesting that the glutamatergic system plays important roles in the pathophysiology and treatment of major depressive disorder (MDD). Specifically, preclinical animal models for depression are often characterized by changes in molecules related to glutamatergic signaling and some antidepressants exert their effects by affecting glutamatergic system in animals. Furthermore, animals with genetically modified glutamatergic function exhibit depression like behaviors or anti-depressive behavior. In addition, several types of glutamatergic agents have shown antidepressant-like effects in preclinical models for depression. This article suggests that multiple types of glutamate receptors (NMDA, AMPA, and metabotropic glutamate receptors) and/or glutamate transporters appear to be involved in the etiology of depression or in the mechanisms of action of antidepressants. As such, the potential for manipulations of functional proteins related to glutamate signal transduction are further discussed as targets for a new generation of antidepressants with faster-onset and greater efficacy than existing agents.

1.3. Bipolar disorder

Clinical evidence linking glutamatergic dysfunction to bipolar disorder is then addressed by Ginsberg and colleagues. In this article, authors discuss how functional genomic and proteomic approaches are being employed to evaluate variation for genes and protein expression in order to find novel targets for drug discovery. They describe how genome-wide association studies (GWAS) have attempted to identify valid candidate genes through single nucleotide polymorphism (SNP)

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analysis. Furthermore, they note how microarray analysis of gene expression in brain regions and discrete cell populations has enabled the simultaneous quantitative assessment of relevant genes. Subsequently, readers will learn how the ability to associate gene expression changes with a diagnosis of bipolar disorder (BP) and therapeutic response provides a novel means for interventions. This review summarizes gene and pathway targets that have been identified in GWAS studies and expression profiling of human postmortem brain in BP, with an emphasis on glutamate receptors (GluRs). Although functional genomic assessment of BP is in its infancy, results to date point towards a dysregulation of GluRs that bear some similarity to schizophrenia (SZ), although the pattern is complex, and likely to be more complementary than overlapping. The importance of single population expression profiling of specific neurons and intrinsic circuits is emphasized, as authors suggest that this approach provides informative gene expression profile data that may be underappreciated in regional studies with admixed neuronal and non-neuronal cell types. Peng and colleagues then describe complementary preclinical data relating glutamatergic function to bipolar disorder. For example, data indicate that chronic treatment with antibipolar drugs (lithium, carbamazepine, valproic acid) downregulates mRNA and protein expression of kainate receptor GluK2 in mouse brain and cultured astrocytes. Such treatments are also noted to abolish glutamate-mediated, Ca2+-dependent ERK1/2 phosphorylation in astrocytes. Further, authors note that chronic treatment with selective serotonin reuptake inhibitors enhance astrocytic GluK2 expression and increase mRNA editing, modulating glutamate-mediated ERK1/2 phosphorylation and [Ca2+]i concentrations. Authors pose that these observations suggest that the inactivation of astrocytic GluK2 activity by antidepressant/anti-bipolar therapy ameliorates depression by inhibiting astrocytic glutamate release. Additionally, they suggest that a resultant strengthening of neuronal after hyperpolarization may cause reduced NMDA-mediated activity relevant to antidepressant effects.

1.4. Obsessive compulsive disorder

The role of glutamate signaling in the pathogenesis and treatment of obsessive-compulsive disorder is discussed by Arnold and colleagues. This article discusses evidence that disrupted neurotransmission of glutamate within corticalstriatal–thalamocortical (CSTC) circuitry plays a role in OCD pathogenesis. This review summarizes the findings from neuroimaging, animal model, candidate gene and treatment studies in the context of glutamate signaling dysfunction in OCD. First, studies using magnetic resonance spectroscopy are reviewed demonstrating altered glutamate concentrations in the caudate and anterior cingulate cortex of patients with OCD. The extent to which a variety of knockout mouse models display phenotypes of compulsive grooming behavior associated with glutamate signaling dysfunction is discussed. Third, candidate gene studies noting associations between variants in glutamate system genes and OCD are described. Authors suggest that converging evidence for a role of glutamate in OCD has led to the development of novel treatment strategies involving glutamatergic compounds, particularly riluzole and memantine. The subsequent article by Rolls and colleagues provides a computational neuroscience approach to the symptoms of obsessive-compulsive disorder. Authors note that “integrate-and-fire” network simulations predict that an increase in the NMDA and/or AMPA receptor conductances, which increases the depth of the attractor basins, increases the stability of attractor networks, and makes them less easily moved on to another state by a new stimulus. Furthermore, authors suggest that increasing GABA-receptor activated currents can partly reverse this overstability. Evidence for over-activity in glutamate transmitter systems in obsessive-compulsive disorder, and the hypothesis presented are thus related to symptoms and treatment of obsessive compulsive disorder.

1.5. Anxiety and related disorders

Baca-Garcia and colleagues review data and theories suggesting that glutamate neurotransmission and the polyaminergic system play a fundamental role in the onset of anxiety-related disorders as well as the extent to which this data may open the way for new drugs to treat these conditions. Authors note that the glutamatergic system mediates the acquisition and extinction of fear-conditioning and therefore, new drugs targeting glutamatergic neurotransmission may be promising candidates for new pharmacological treatments. In particular, N-methyl-D-aspartate receptors (NMDAR) antagonists and partial agonists as well as AMPA receptor antagonists, and several allosteric modulators targeting metabotropic glutamate receptors (mGluRs) have shown anxiolytic-like effects in several animal and human studies. Additionally, several studies which suggested that polyamines may be involved in the neurobiological mechanisms underlying stress-response and anxiety-related disorders are reviewed. Harvey and colleagues next provide an overview and discussion of complementary preclinical data related to glutamatergic function in the pathophysiology and potential new treatments for anxiety disorders. Authors discuss the biological response to adversity, particularly neurobiological molecules and processes that may influence vulnerability or resilience, and those that may act to switch off or "unlearn" a response to an aversive event. The glutamate system is thus proposed as an interesting target in this respect, especially given the impact these illnesses have on neuroplasticity, cognition and affective function. The current review then discusses how these pathways are involved in fear circuitry, the therapeutic rationale as well as progress towards pharmacological validation of the glutamate pathway towards the treatment of anxiety disorders. Specific reference to their anxiolytic actions and efficacy in translational disease models of posttraumatic stress disorder, obsessive compulsive disorder, panic disorder and phobia are noted in relation to the availability of ligands necessary to assist clinical proof of concept studies.

2. Drug abuse and addictive behaviors

2.1. Drugs of abuse

The second subset of articles addresses the role of glutamatergic dysfunction in various forms of drug abuse and dependence. Clinical observation s and data are first presented by Olive and colleagues, followed by a review of preclinical models and theories by Duncan and Lawrence. This section begins with a review of evidence that has accumulated indicating that ligands acting on glutamatergic transmission are of potential utility in the treatment of drug addiction, as well as various behavioral addictions such as pathological gambling. The purpose of this review is to summarize the pharmacological mechanisms of action and general clinical efficacy of glutamatergic medications that are currently approved or are being investigated for approval for the treatment of addictive disorders. Medications with effects on glutamatergic transmission that will be discussed include acamprosate, N-acetylcysteine, D-cycloserine, gabapentin, lamotrigine, memantine, modafinil, and topiramate. Authors propose that manipulation of glutamatergic neurotransmission is relatively young but promising avenue for the development of improved therapeutic agents for the treatment of drug and behavioral addictions. Duncan and Lawrence next pose that the addicted state may be in part due to drug-induced neuroadaptations in the mesocorticolimbic and corticostriatal pathways. This review thus focuses on the role of aberrant glutamate transmission and its contribution to the hierarchical control over these systems based on preclinical animal models. Such data are noted to provide evidence that implicate metabotropic glutamate receptors (mGluRs) in contributing to the neuroadaptations pertinent to addiction, as well as the role of Homer proteins in regulating these responses. The recent discovery of receptor mosaics is further discussed to address the additional dimension

of complexity required to understand the mechanism of glutamate mediated behaviors. This review then introduces a new area related to glutamatergic responses, namely microRNAs, that may become pivotal in directing our future understanding of how to best target intervention strategies to prevent addictive behaviors.

3. Neurological conditions across the lifespan

The third and final subset of reviews addresses neurological conditions across the developmental lifecycle.

3.1. Prenatal insults

To begin this section, Holopainen and colleagues discuss how birth asphyxia and hypoxia-ischemia (HI) may affect the normal development and maturation of the central nervous system (CNS). Specifically, authors discuss how HI-induced damage at different ages is region selective depending on the maturity of the brain, with white matter (WM) peripheral to the lateral ventricles being selectively vulnerable to damage in premature infants. Squeal of primary or secondary HI in the preterm infant are described, including how brain injury leads to periventricular leukomalasia (PVL) accompanied by neuronal and axonal damage which may lead to cerebral palsy (CP), cognitive, behavioral, attentional or socialization deficits. In this review, authors discuss developmental changes in the expression of excitatory glutamate receptors (GluRs), and then in more detail elucidate the contribution of GluRs to oligodendrocyte (OL) damage both in experimental models and in preterm human infants. Finally, therapeutic interventions targeted at GluRs at a young age are discussed in the light of results obtained from recent experimental HI animal models and from humans. The following review by Keller and colleagues further discusses how glutamate receptors play an important role in brain development. Specifically, authors suggest that factors interfering with normal glutamate receptor activity might have potential harmful effects by modulation and impacting on functional brain development. Data suggesting that increased glutamate levels, and subsequent activation of glutamate receptors, can cause excitotoxic cell death is described in relation to the role of glutamate receptors in brain development. Furthermore authors discuss environmental factors that potentially modify glutamate receptors in the fetal brain and highlight the importance of glutamate receptors in the pathophysiology of brain injury in preterm born infants. The article closes with a discussion of potential anti-excitotoxic treatments currently being investigated in preclinical animal models of developmental brain injury.

3.2. Autism spectrum disorders

Rajamma and colleagues describe and discuss how glutamate actively participates in complex regulatory events during neurodevelopmental. Authors note that excitatory neurotransmitter signaling via glutamate receptors modulates cognitive functions such as memory and learning, which are usually impaired in ASD. Therefore, they suggest that glutamate and its regulatory molecules are considered as potential targets for these disorders. The pharmacological, biochemical and behavioral studies related to possible involvement of the glutamatergic system in ASD pathology is discussed in detail, especially as an increase in electrical activity resulting from excessive glutamate signaling causes prolonged alterations in behaviors commonly seen in ASDs. On the contrary authors note that reports using animal models of hypoglutamatergia demonstrate phenotypes that overlap with features seen in autism. Thus, this review addresses apparent discrepancies as to whether autism is a hyper- or hypoglutamatergic disorder. This paper further reviews the role of glutamate and its regulatory proteins such as different receptors, transporters and metabolizing enzymes in the pathophysiology of ASD based on evidences gathered through multidisciplinary approaches. Next, Greg Carlson discusses evidence that metabotropic and ionotropic glutamate receptors are affected in ASD, but notes that there are few candidate genes indicating involvement of these receptors. Thus, this review argues that glutamate receptor dysregulation may primarily be involved in the expression of ASD, but alterations in specific receptors are an uncommon etiology. Alternatively the author suggests that, metabotropic glutamate receptor type 5 (mGluR5), which has been implicated in models of fragile-X with ASD phenotypes, appears to be an effective pharmacologic target in a number of models of ASD. Review and discussion of a number of other ASD models also provide evidence of a role for kainate, NMDA, and AMPA receptors in the neurophysiology of ASD, though the relationship between dysfunction in those receptors and ASD-associated phenotypes is not well understood. Development of preclinical models focusing on glutamate receptors are then described and discussed as a means to target a clinically important subset of ASD symptoms.

3.3. Dementia

The last article aptly focuses on the potential involvement of glutamate receptors in diseases of senescence. Rowan and colleagues note that the cognitive and related symptoms of Alzheimer's disease (AD) are mainly attributable to synaptic failure. They review recent research on how the Alzheimer's disease amyloid ß-protein (Aß) affects glutamate receptors and fast excitatory synaptic transmission and plasticity of that transmission. This review begins by describing how L-glutamate has long been implicated in causing NMDA receptor-mediated excitotoxicity leading to neurodegeneration in the late stages of the disease. This is followed by leading the reader through extensive evidence that soluble Aß oligomers disrupt synaptic transmission and especially synaptic plasticity via non-excitotoxic glutamatergic mechanisms. These new data highlight the relatively selective involvement of certain glutamate receptor subtypes including GluN2B (NR2B) subunit-containing NMDA receptors and mGlu5 receptors. Further, data suggesting that Aß exerts direct and indirect effects on synaptic plasticity-related glutamate receptor signaling and trafficking between different neuronal compartments is described. Given the role of glutamatergic transmission in regulating Aß production and release, authors end by proposing that future therapies targeting glutamate offer an opportunity to remedy both misprocessing of Aß and cellular mechanisms of synaptic failure in early AD.

4. Summary

Taken together, these 17 articles provide a framework in which glutamate receptors may impact the pathophysiology for a wide variety of neurological and psychiatric disorders across the life span. As such, glutamatergic receptors and glutamate signaling pathways provide a wealth of therapeutic targets in the future.

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