Received: 4 August 2020 | Accepted: 24 October 2020

DOI: 10.1002/alz.12244

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

REVIEW ARTICLE

Endogenous antagonists of *N*-methyl-D-aspartate receptor in schizophrenia

Pascal Jorratt[1,2] | **Cyril Hoschl**[1,2] | **Saak V. Ovsepian**[1,2]

[1] Department of Experimental Neurobiology, National Institute of Mental Health, Klecany, Czech Republic

[2] Department of Psychiatry and Medical Psychology, Third Faculty of Medicine, Charles University, Prague 10, Czech Republic

Correspondence
Saak V. Ovsepian, Department of Experimental Neurobiology, National Institute of Mental Health, Topolová 748, 250 67, Klecany, Czech Republic.
Email: saak.ovsepian@nudz.cz

Abstract

Schizophrenia is a chronic neuropsychiatric brain disorder that has devastating personal impact and rising healthcare costs. Dysregulation of glutamatergic neurotransmission has been implicated in the pathobiology of the disease, attributed largely to the hypofunction of the *N*-methyl-D-aspartate (NMDA) receptor. Currently, there is a major gap in mechanistic analysis as to how endogenous modulators of the NMDA receptors contribute to the onset and progression of the disease. We present a systematic review of the neurobiology and the role of endogenous NMDA receptor antagonists in animal models of schizophrenia, and in patients. We discuss their neurochemical origin, release from neurons and glia with action mechanisms, and functional effects, which might contribute toward the impairment of neuronal processes underlying this complex pathological state. We consider clinical evidence suggesting dysregulations of endogenous NMDA receptor in schizophrenia, and highlight the pressing need in future studies and emerging directions, to restore the NMDA receptor functions for therapeutic benefits.

KEYWORDS
autoimmune response, endocannabinoids, endogenous polyamines, GluN1 subunit, kynurenic acid, neurosteroids, zinc

1 | INTRODUCTION

The term schizophrenia originates from the Greek roots schizein (σχίζειν, "to split") and phrēn, phren- (φρήν, φρεν-, "mind"). It has been coined by Swiss psychiatrist Eugen Bleuler, to unify the heterogeneity of symptoms characteristic of an array of psychotic conditions of one of the most devastating diseases affecting the human mental health.[1] Unlike his German predecessor Emil Kraepelin, who combined several subtypes of psychosis with the early onset cognitive decline into a single concept of *dementia praecox* (premature dementia),[2] Bleuler recognized profound dissociation between affective and cognitive sides as the most fundamental feature of the pathology. Bleuler also viewed the emotional and cognitive ambivalence as the principal sign of the disease, allocating the hallucinations and delusions an ancillary role, and stressing their differential amenability to medication available at his time.

To date, schizophrenia is used as an umbrella term for a multifactorial and complex brain disease spanning several disorders,[3,4] which are generally classified in three sets of symptoms: (1) positive symptoms, which encompass disorganized thinking, delusions and hallucinations, and motor hyperactivity; (2) negative symptoms, comprising diminished emotional expression, loss of pleasure and drive, and antisocial stance; and (3) cognitive symptoms, which include a deficit in executive functions and planning, loss of attention and working memory, and other impairments of neurocognitive functions.[5] It is notable that the third group of symptoms, which emerge the earliest in the course of the disease is most resistant to therapeutic interventions. The third group of symptoms also plays a decisive role in deciding the clinical outcome and prognosis, and affects most of the occupational and social abilities, presenting the principal cause for institutionalization and chronic disability.[6–8] The affective and neurocognitive impairements, but not psychotic symptoms, emerge also to correlate

better with neuropathological changes in the brain of patients, which include dysplasia of dendritic spines and glutamatergic synapses, as well as macro-pathologies such as cortical atrophy and ventricular enlargement.[9–11]

As shown subsequently, the symptomatic division of schizophrenia envisioned by E. Bleuler has fundamental neurobiological implications, signifying the involvement of different neurochemical pathways and mechanisms. Over 60 years, the dopamine hypothesis dominated the thinking about the pathophysiology and treatment of schizophrenia, with however limited success in offering a cure, and especially in the management of negative and cognitive symptoms of the disease.[12,13] Since the discovery of the antipsychotic effects of chlorpromazine with follow-up rapid development of several potent antipsychotics attenuating the dopaminergic hyperactivity, the main course of the research of anti-schizophrenic drugs has been directed to the modulation of the dopaminergic drive. This conceptual framework has received support from reports with psychostimulants such as amphetamines, cocaine, and apomorphine, capable of inducing psychotic symptoms by inhibiting the transport of monoamines or reducing the concentration of dopamine and other monoamines in the synaptic cleft.[14] Although drugs and compounds enhancing the dopaminergic drive can explain positive signs of schizophrenia, the ultimate causes of disabilities, that is, the negative and cognitive symptoms, remain largely non-responsive to antipsychotic therapies targeting dopaminergic activity.

In pursuit of elucidating the neurobiological mechanisms underlying symptoms of schizophrenia that are resistant to typical antipsychotics, glutamatergic signaling and glutamate activity in specific brain regions have shown a potential role. Induction of a schizophrenia-like state by dissociative anesthetics such as ketamine and phencyclidine (PCP) in healthy humans, with the ability to cause functional impairments mimicking negative and cognitive symptoms, and demonstration of these effects being mediated via noncompetitive antagonism of the *N*-methyl-D-aspartate (NMDA) receptor subtype of glutamatergic receptors suggest NMDA receptor (NMDAR) dysfunctions as a potential causative. Results of in-depth studies led to the hypothesis that the hypofunction of NMDAR in selected brain regions might play a key role in clinical manifestation of schizophrenia.[15–17] Although many excellent reviews have focused on the analysis of the effects of exogenous modulators of NMDAR, mimicking schizophrenia-like symptoms in humans and animal studies, the role of endogenous modulators of this important glutamatergic receptor has been overlooked and warrants critical appraisal.

In this article, we present a systematic review with an analysis of the role of endogenous NMDAR inhibitors in the pathobiology of schizophrenia. We discuss major facets of the molecular biology of the NMDAR with key characteristics relevant to the pathobiology of schizophrenia. We consider the best characterized endogenous modulators implicated in this mental disorder, and overview emerging data from animal models and from clinical studies in humans. Finally, we outline key areas of future research in basic neurobiology and highlight knowledge gaps and emerging directions for future advancements.

RESEARCH IN CONTEXT

1. **Systematic review**: Although a great number of reports show induction of an acute schizophrenia-like state in humans and animal models by *N*-methyl-D-aspartate (NMDA) receptor (NMDAR) blockers, there is a major gap in elucidating the role of endogenous antagonists of NMDARs in schizophrenia.
2. **Interpretation**: We present a comprehensive overview of the neurobiology and translational aspects of endogenous NMDAR antagonists in animal models and in patients. We discuss their neurochemical origin, release and action mechanisms, and effects, which might contribute toward impairment of neuronal processes underlying the pathological state of the brain. We revisit the NMDAR hypofunction hypothesis of schizophrenia and highlight the need for future studies.
3. **Future directions**: Two principal models, that is, NMDAR deficit at fast-firing γ-aminobutyric acid (GABA)ergic interneurons, and general attenuation of NMDAR-dependent neuroplasticity at glutamatergic synapses are discussed as major research directions. Hypofunction of NMDARs in schizophrenia, thus, presents one of the most viable working hypothesis for future fundamental and translational studies.

2 | BIOLOGY AND FUNCTION OF NMDA RECEPTORS

Glutamate, the main mediator of the excitatory neurotransmission in the central nervous system (CNS), is released primarily from neurons and activates two different types of receptors—fast-acting ionotropic and slow-acting metabotropic glutamatergic receptors (iGluRs and mGluRs, respectively).[18] iGluRs are organized as receptor-channel complexes, which upon binding to glutamate turn selectively permeable to cations, and facilitate their influx into neurons, causing membrane depolarization, which after reaching the threshold level leads to the generation of action potentials. Based on activation by specific ligands, iGluR are divided into three groups: (1) α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), or AMPA-activated receptors (AMPARs), (2) kainic acid, or kainite-activated receptors (KARs), and (3) receptors that can be activated by NMDA, known also as NMDAR.[19] In neurons, functional NMDAR are formed through tetramerization of two mandatory GluN1 subunits and two GluN2 and/or GluN3 subunits,[20] which come in various molecular combinations. Figure 1 schematizes the structure and regulation of NMDAR by endogenous antagonists.

In the course of development, the expression of NMDAR subunits shows the differential spatial distribution and temporal profiles. In the mammal nervous system, during embryogenesis, the GluN2

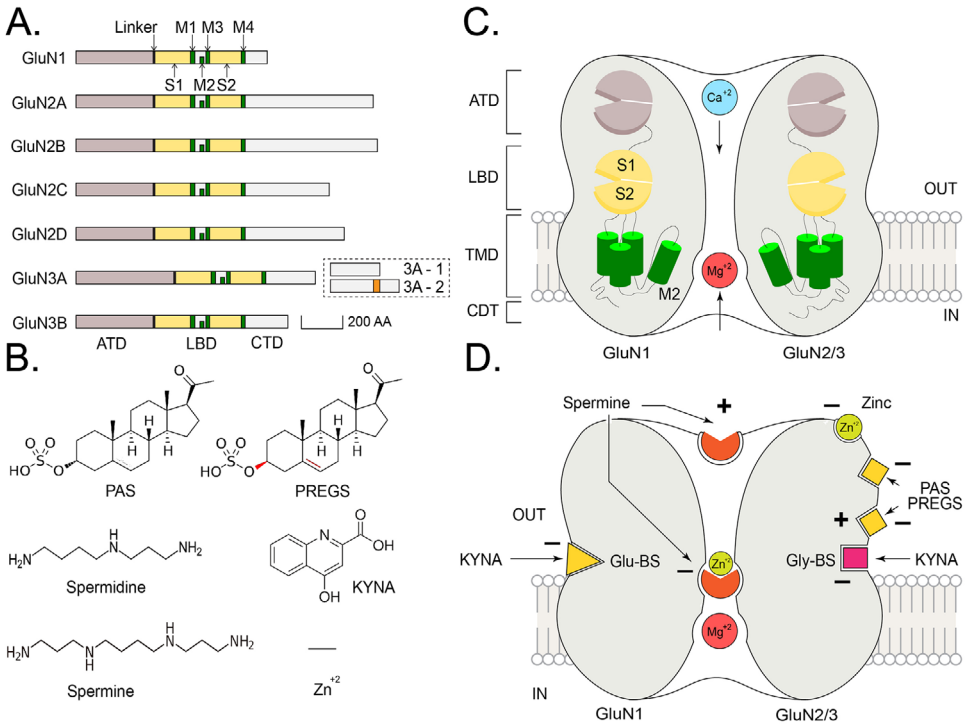

FIGURE 1 Schematized molecular structure of NMDAR sub-units with the key endogenous antagonists and their binding sites on the NMDA receptor channel complex. (A) GluN1 subunit encoded by a *GRIN1* gene (has eight splice variants, not shown). Four GluN2 (A-D) encoded by *GRIN2 (A-D)* genes, respectively. Two GluN3 (A, B) encoded by *GRIN3 (A,B)*, respectively. (B) Chemical structure of the main endogenous antagonists: PAS (pregnanolone sulfate), PREGS (pregnenolone sulfate), spermidine, spermine, and KYNA (kynurenic acid). (C) Schematic structure of NMDAR and its subdomains (side view) showing four domains of the GluN sub-units: (i) amino-terminal domain (ATD), (ii) ligand-binding domain (LBD) formed by S1 and S2 segments, (iii) transmembrane domain (TMD) containing the conducting pore (Ca^{2+} permeable channel blocked under the hyperpolarized state by Mg^{2+}), and (iv) intracellular carboxyl (C)-terminal domain (CTD). (D) NMDAR schematized showing the binding sites of endogenous antagonists. Symbols (−) and (+) denote inhibitory and facilitatory effects, respectively. Glu-BS: glutamate binding site, Gly-BS: glycine binding site. Panels a, c, and d are modified with permission from[22]

subunit comprises only GluN2B and GluN2D subunits, with GluN2A enrichment starting after birth and increasing steadily to become the most abundantly expressed NMDAR subunit in the adult brain.[21] Because non-GluN1 subunits define the major physiological and biophysical properties to NMDARs, it was proposed that the role of NMDAR expressed during embryogenesis is limited to developmental and homeostatic processes, governing the synaptogenesis and synaptic maturation, whereas subunits expressing in the post-embryonic stage mediate synaptic transmission and plasticity mechanisms.[22] In addition to the different spatiotemporal expression profiles throughout the brain, different neuronal types express distinct NMDAR subunits. In the adult hippocampus, for instance, GluN2A and GluN2B mRNAs are prominent in CA1/CA3 pyramidal cells, whereas GluN2C and GluN2D mRNAs are enriched in interneurons.[23] Although the subunit composition could play a major role in mediating the synaptic and extrasynaptic NMDAR signaling, given that peri- and extrasynaptic sites are enriched with GluN2B subunit, the idea that GluN2B only segregates outside synapses, whereas GluN2A subunits are confined to synaptic sites is an over-simplification.[22]

Figure 1C,D schematizes the structure and subdomains of NMDAR, with the location of putative binding sites of endogenous inhibitors. As shown, each NMDAR subunit contributes an extracellular amino-terminal domain (ATD) guiding the tetramerization of various subunits into a functional receptor-channel complex with allosteric regulation; the ligand-binding domain (LBD) formed by the two discontinuous S1 and S2 segments known to form glycine interaction sites in GluN1 and GluN3 subunits, and glutamate binding site in GluN2 subunits; the transmembrane domain (TMD) made of three helices, plus a pore-forming loop (M2), and the intracellular carboxyl (C)-terminal domain (CTD), a region that is involved in sorting and trafficking of the receptor to the neuronal surface with coupling to downstream signaling cascades.[24,25] Unlike the majority of ionotropic receptors that are activating as a result of ligand-induced conformational changes of the receptor, activation of the NMDAR is a cooperative process, which depends on (1) the relief of Mg^{2+} block of the ion channel pore, (2) depolarization of the postsynaptic membrane, and (3) two molecules of the agonist glutamate, and two molecules of co-agonist glycine for GluN1/GluN2 NMDAR[26] and one glycine molecule for GluN1/GluN3 NMDAR.[27] Several other co-agonists, including D-serine, L-serine, D-alanine, L-alanine,[28] and agonists such as L-glutamate, D-glutamate, NMDA, *N*-methyl-L-aspartate, D-aspartate[29] can also induce the activation of the NMDAR.

Despite the well-defined structure and molecular characteristics of the NMDAR and its role in synaptic transmission, the all-inclusive

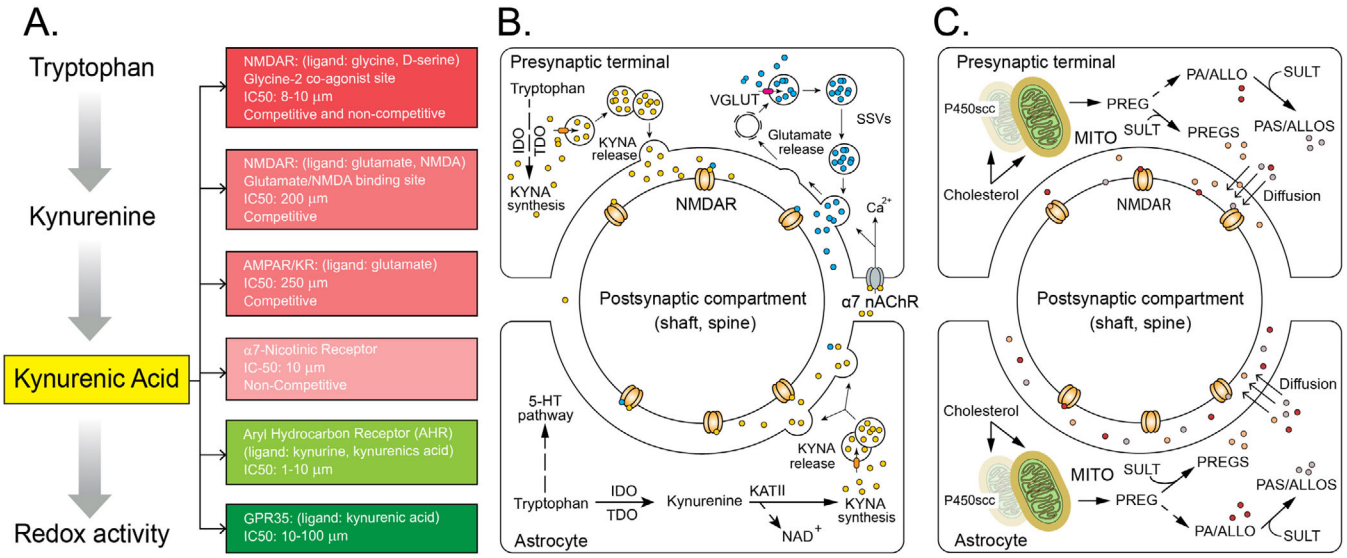

FIGURE 2 Schematic representation of the neurochemical origin and release of kynurenic acid (KYNA) and neurosteroids at glutamatergic synapses. (A, B) KYNA is a product of L-tryptophan metabolism, synthesized from its precursor kynurenine. Both kynurenine and L-tryptophan are transported into the brain across BBB. At glutamatergic synapses, KYNA is released mainly from astrocytes, but also from neurons. Depending on the concentration, it can have excitatory and inhibitory effects on several receptors (A). Released from glia or synaptic terminal, KYNA inhibits postsynaptic NMDARs. KYNA also binds and blocks presynaptic α7 nAChRs, causing inhibition of glutamate release. Although the mechanism of KYNA release remains unclear, it has been proposed to be mediated via exocytosis.[192] (C) Schematic of neurosteroid synthesis via cholesterol translocation into the mitochondria and production of pregnenolone (PREG), which is converted into PREG sulfate (PREGS), pregnanolone (PA) sulfate (PAS), and allopregnanolone (ALLO) sulfate (ALLOS), with all released from neurons and astrocytes via the diffusion process (crossing the membrane) with modulator effects on postsynaptic NMDARs

analysis and correlation of specific functional changes in this receptor with symptoms of schizophrenia remain a daunting task. In this context, elucidating the role of constitutive and context-dependent regulation of NMDAR functions by endogenous modulators is of major importance, especially in light of the rising evidence for schizophrenia-related NMDAR hypofunctions in a specific subset of neurons. In the following, we consider the principal neurobiological characteristics of major endogenous antagonists of the NMDAR and their alleged contribution to the pathobiology and manifestation of schizophrenia-like symptoms in animal models and in schizophrenia patients. As it emerges from the presented analysis, impairment of the fine regulation of NMDAR functions by endogenous antagonists might contribute to different aspects of the disease and warrant further research, to restore the exquisite functional balance for therapeutic benefits.

3 | THE ENDOGENOUS ANTAGONISTS OF THE NMDAR IN SCHIZOPHRENIA

3.1 | Kynurenic acid

Kynurenic acid (KYNA) is arguably the best-characterized endogenous antagonist of iGluR receptors implicated in the pathobiology of schizophrenia, acting as a noncompetitive blocker of the NMDAR. Figure 2A,B presents a schematic of the biosynthetic pathway with neuropharmacological profile and release of this potent endogenous antagonist of NMDARs from neurons and astrocytes. Biochemically, KYNA is derived from L-tryptophan, which is an essential amino acid involved in (1) protein biosynthesis, (2) serotonin and melatonin production, (2) as well as in the kynurenine pathway. The latter mediates over 90% of the tryptophan catabolism, of which nicotinamide adenine dinucleotide (NAD^+) is one of the final products.[30–32] The synthesis of kynurenine from L-tryptophan is catalyzed by indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO), followed by conversion into KYNA through irreversible transamination of kynurenine by four types of kynurenine aminotransferases (KAT I-IV).[33] KAT II, the major biosynthetic enzyme of KYNA in the murine and human brain, is expressed in astrocytes as well as neurons, which are mostly GABAergic interneurons.[34] Of interest, in the brain, both IDO and TDO are expressed at much lower levels, compared to other organs such as kidney and liver.[35] Unlike kynurenine that efficiently crosses the blood-brain barrier (BBB) through amino acid transporters, KYNA crossing of the BBB is very ineffective.[36] Therefore, the CNS KYNA is mainly synthesized locally from its precursors.

The inhibition of NMDAR by endogenous KYNA can be via a noncompetitive mechanism, through binding at the glycine co-agonist site ($IC_{50} \approx 15$ μM)[37] and via a competitive mechanism, acting at glutamate recognition site, but at higher concentrations (200 to 500 μM). At higher concentrations, KYNA can act also as a blocker of AMPAR and KAR[38] (Figure 2A). Of interest, although at millimolar concentrations KYNA antagonizes AMPAR, at nanomolar to micromolar concentrations, it can act as a partial agonist, enhancing AMPAR-mediated membrane currents via positive allosteric modulation, thus showing bilateral dose-dependent effects.[39] KYNA is also a potent

noncompetitive antagonist of α7 nicotinic acetylcholine receptor (nAChR) (IC_{50} $\approx$7 μM), acting with higher efficiency than that of NMDAR inhibition.[40,41] It is notable that an increase in the concentration of KYNA in the CNS can mimic the neurobehavioral signs of methyl-lycaconitine, a selective α7 nAChR antagonist, suggesting that the psychoactive effects of endogenous KYNA in vivo could be mediated partly through inhibition of this cholinergic receptor.[42]

Several recent meta-analyses showed that KYNA levels in cerebrospinal fluid (CSF) and brain tissue are significantly increased in patients with schizophrenia, as compared to healthy controls.[31,43,44] Earlier reports also showed higher levels of TDO in the postmortem frontal cortex and anterior cingulate cortex of schizophrenic patients.[45,46] Of note, KYNA dysregulation is a common response to a range of environmental and endogenous factors such as stress and inflammation, which are of major relevance to schizophrenia, since both corticosteroids and pro-inflammatory cytokines induce high levels of TDO and IDO, respectively.[44,47] The mechanisms underlying the high sensitivity of kynurenine metabolism to glucocorticoids currently remain unclear. It was proposed that, from an evolutionary standpoint, the upregulation of the kynurenine pathway under stress should push the equilibrium of tryptophan metabolism away from the serotonin synthesis pathway, favoring depressive-like behaviors with reduced exploratory activity and conservation of resources, when these are in limited supply.[48] In addition, inhibition of cognitive abilities by KYNA under stressors could mean that the "time for deep thinking has passed and the time for immediate action has arrived." Of interest, estrogen and its derivative exert an inhibitory effect on KAT I-II[49] and KYNA production, possibly contributing toward higher occurrence of schizophrenia in men, as well as toward increased incidents of psychosis during menstruation, as well as after the onset of menopause in women.[50]

The results of preclinical studies in animal models are in general agreement with the clinical data, with an intraperitoneal injection of KYNA in rats causing a reduction in pre-pulse inhibition (PPI),[51] a deficit of spatial working memory[52] and contextual fear memory and learning,[53] as well as impairments in auditory sensory gating.[54] Remarkably, when pregnant dams were fed with kynurenine from embryonic days 15 to 22, their pups also showed altered memory and learning in Morris water maze and passive avoidance tests[55] with increased levels of KYNA and reduction in the number of dendritic spines in the prefrontal cortex, evaluated at postnatal days 56 to 80.[56] These effects have been shown to be associated with reduced mRNA of GluN1 and GluN2A subunits in cortical tissue.[57] Of note, the mentioned functional and behavioral readouts are generally used as substantiation of schizophrenia-like symptoms in murine experimental models. With application of genetic knock-out (KO) in mice to lower endogenous KYNA levels, due to deletion of KAT II, significant improvements in object exploration and recognition have been demonstrated, with better spatial discrimination.[58] The increase of the activity of endogenous KYNA in animal models, on the other hand, was shown to promote the burst-firing of dopaminergic neurons in the ventral tegmental area, which was mediated by glutamatergic mechanisms rather than cholinergic effects mediated via nAChR.[59]

Overall, described preclinical and clinical data present converging evidence supporting the KYNA-induced NMDAR hypofunction as a potential contributor to the pathobiology of schizophrenia in humans as well as schizophrenia-like symptoms in animal models. Although there is a growing consensus that disruption of the activity of fast-firing GABAergic interneurons in the prefrontal cortex with disinhibition of local and extending circuits plays a key role in psychoactive effects of KYNA, this model as well as other putative mechanisms need rigorous validation and further research.[60] There is also pressing need in carefully designed preclinical and clinical studies with meta-analysis, to define molecular, neurochemical, and genetic aspects of the KYNA model of schizophrenia with identification of functional and molecular biomarkers for diagnostics and personalized treatment.

3.2 | Neurosteroids

Neurosteroids are a group of potent endogenous steroids that can rapidly modulate neuronal excitability through direct interaction with several ligand-gated ion channels and receptors, affecting a wide range of mechanisms and functions. Growing evidence suggests a potential contribution of neurosteroids in the pathobiology and symptomatology of schizophrenia and other psychiatric disorders, with molecular mechanisms remaining to be elucidated.[61,62] Figure 2C presents a schematized illustration of the major steps in the synthesis and release of neurosteroids from neurons and astrocytes. Neurosteroids of the brain are derived from cholesterol and are independent of steroids originating from peripheral endocrine glands, and their functions.[63] The first step of the biosynthetic pathway of neurosteroids involves translocation of cholesterol across the inner mitochondrial membrane of cells, which is converted by the enzyme cytochrome P450 (CYP)11A1 into pregnenolone (PREG). From PREG, subsequently, two isoforms, that is, pregnanolone (PA) and allopregnanolone (ALLO), are synthesized by the sequential catalytic actions by 3β-hydroxysteroid dehydrogenase, 5α/β reductase, and 3α/β-hydroxysteroid dehydrogenase, with release into the extracellular space governed by Ca^{2+}-dependent mechanisms.[64] Both PREG and its derivatives are potent neuromodulators affecting primarily the ionotropic channels and receptors, including TRPM1, TRPM3, $GABA_A$, glycine, glutamate, and nAChRs.[65,66] Their effects on NMDAR are considered to be of potential relevance to the pathobiology of schizophrenia.

Unlike KYNA, which acts invariably as an inhibitor of NMDAR, the effects and potency of PREG, PA, and ALLO on NMDAR depend on sulphation at the C3 carbon group site by cytoplasmic sulfotransferases (SULTs),[67] with the ratio of sulfated versus nonsulfated neurosteroids playing a pivotal role in defining the directionality of the effects. Although PREG sulfate (PREGS) enhances and PA sulfate (PAS) inhibits the NMDAR-mediated membrane currents, PREG and PA have no effects.[68] It has been suggested that the sulfate group attached to the carbon C3 and the double bond between C5 and C6 play a pivotal role in determining the positive or negative modulation of NMDAR by these neurosteroids. Of interest the directionality of the modulation of the NMDAR-mediated current by sulfated neurosteroids depends

also on the subunit composition of NMDAR.[69,70] Indeed, PREGS is known to potentiate GluN1/GluN2A and GluN1/GluN2B subunit-containing NMDAR and inhibit NMDAR containing GluN1/GluN2C and GluN1/GluN2D. PAS, on the other hand, inhibits NMDAR, acting on all four subunits, although these effects are more potent at GluN1/GluN2C and GluN1/GluN2D subunits.[71] The potentiation effect of PREGS on the NMDAR is higher if it is applied before application of glutamate, with analysis of the rate constant of NMDAR single-channel opening and closing attributing the PREGS effects on NMDAR to the enhancement of the channel open probability.[72] In contrast, PAS caused a significant reduction of both the frequency of NMDAR channel opening and the opening meantime.[73]

In mouse models of schizophrenia lacking the dopamine transporter (ie, DAT KO), single-time systemic administration of PREGS ameliorates the schizophrenia-like symptoms, causing normalization of the hyper-locomotion, attenuating stereotypic bouts and rescuing the pre-pulse inhibition deficit, whereas the long-term treatment of mice with PREGS normalized novel object recognition and social transmission of food preference tests.[74] PREGS also improved the acquisition of spatial information and consolidation of memory traces, as well as of object discrimination in a spatial and visual task called "Can test," with single-unit neuronal activity recordings in vivo demonstrating significant rise in the firing rate of neurons in the hippocampus and perirhinal cortex.[75] It is notable that in aged rats, the level of endogenous PREGS in the hippocampus correlates negatively with the distance passed to reach the hidden platform in a Morris water maze task.[76] Because PREGS is also a potent and selective agonist of $\sigma 1$ receptor, which can potentiate NMDAR currents,[77] described effects could be contributed by its indirect $\sigma 1$ receptor-mediated modulation on NMDAR activity and neuronal functions. Accordingly, neurophysiological experiments in hippocampal slices of rats showed that PREGS enhances LTP in the CA1 area by potentiating the activity of NMDAR, which leads to improvements in memory and hippocampus-dependent functions, and attenuates the negative schizophrenia-like symptoms.[78] Unlike potentiating effects of PREGS, ALLO can act as an effective negative modulator of NMDAR,[79] with its intraperitoneal administration causing impairment of both encoding and consolidation of object recognition and fear memory in experimental mice.[80] Correspondingly, the electrophysiological recording of the spontaneous activity of hippocampal pyramidal neurons in anesthetized rats showed strong inhibition of the action potential firing by ALLO.[81] Of note, analysis of the effects of ALLO on the structural plasticity of dendritic spines and density of synaptic connections showed an increase in the number of both dendritic spines and the excitatory synaptic contacts.[82]

Clinical studies have demonstrated that PREG concentration in the serum of patients diagnosed with schizophrenia is significantly reduced as compared to the age-matched healthy controls,[83] with postmortem analysis of brains affected by schizophrenia showing that its level and activity are selectively enhanced in the posterior cingulate and parietal cortices.[84] Encouraged by the result of behavioral studies in animal models, the effects of PREGS have been tested in humans affected with schizophrenia. It is noteworthy that unlike non-sulfated neurosteroids that can cross the BBB by passive diffusion, the crossing of the BBB by sulfated neurosteroid depends on its selective uptake and efflux.[85] Addition of PREGS to antipsychotic medications in schizophrenic patients reduced the severity of negative symptoms as compared to placebo in patients in first-episode cases,[86] whereas in patients with advanced schizophrenia (> 1-year duration of the illness), no improvements in cognitive symptom scores were observed.[87] The levels of ALLO, on the other hand, have been shown to be significantly lower in the parietal cortex in schizophrenia patients, as compared to healthy controls. Cross comparison of PREG and ALLO in the plasma in first-episode antipsychotic-naive patients with schizophrenia showed that PREG level was significantly higher, while the level of ALLO was somewhat reduced.[88] Taken as a whole, described herein findings from animal models and human clinical studies present converging evidence supporting the role of NMDAR modulation by endogenous neurosteroids in the pathobiology of schizophrenia, with their translational relevance.

3.3 | Polyamines

Among endogenous modulators of NMDAR, polyamines such as spermidine and spermine stand out by their variable and complex effects on NMDAR, suggesting multiple polyamine-binding sites, contributing to a range of functional and behavioral outcomes.[89,90] Polyamines are low-molecular-weight aliphatic poly-cations with two or more amino groups readily interacting with negatively charged molecules. Spermidine and spermine, the principal endogenous polyamines, contain three and four amino groups, respectively, and are widely distributed in the human organism. Figure 3A,B presents the atomic resolution structure of NMDA receptors with polyamine binding sites (a) with a schematic of biosynthesis and secretion of polyamines from the presynaptic terminal of neurons and astrocytes (b). As shown, ornithine, which is a non-proteinogenic amino acid formed via hydrolytic cleavage of arginine by arginase in the cytoplasm, is the main precursor of polyamines. After synthesis, ornithine undergoes decarboxylation to produce putrescine by ornithine decarboxylase (ODC).[91] An aminopropyl group is subsequently transferred to produce spermidine, whereas the transfer of a second aminopropyl group converts spermidine to spermine by spermidine synthase (SRM) and spermine synthase (SMS), respectively.[92] This pathway is reversible, as spermine can be readily converted back into spermidine and putrescine. Within the rat brain, the levels of polyamines vary depending on the area and age.[93] Although polyamines are present in both glia cells and neurons, spermine - spermidine-like immunoreactivity is most prominent in astrocytes,[94] with very low expression of ODC and SRM enzymes.[95] The latter suggests that in the brain, the polyamines are synthesized predominantly in neurons, with their release and uptake by both neuronal and glial cells, with astrocytes possessing more efficient uptake machinery.[90,96] It is in agreement with the notion that polyamines are mainly produced in neurons but are stored in glial cells.

Biochemically, polyamines are multifunctional molecules involved in a variety of cellular functions, including proliferation, antioxidant effects via scavenging reactive oxygen species (ROS) warranting

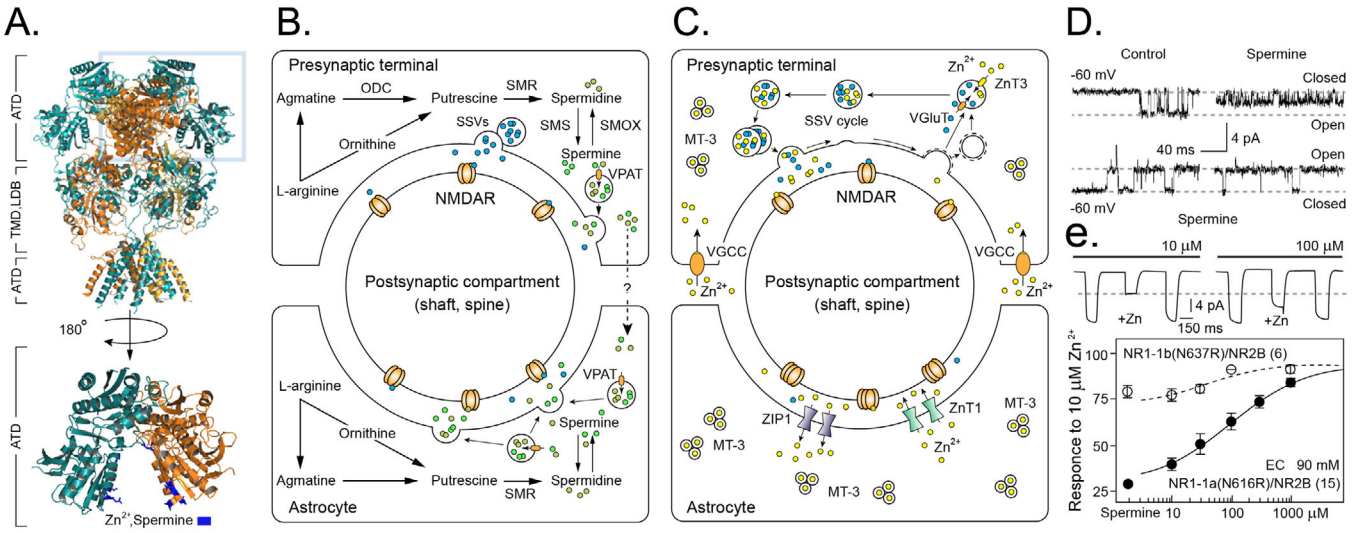

FIGURE 3 Endogenous NMDAR antagonists targeting the R-domain of NMDAR: polyamines and zinc. (A) Atomic resolution crystal structure of NMDAR showing various sub-domains (top) with an enlarged view of the ATD and putative spermine and Zn^{2+} binding sites of the GluN1-GluN2B dimer: the residues of Zn^{2+} and spermine binding are in colored blue. Amino-terminal domain (ATD), ligand-binding domain (LBD) formed by S1 and S2 segments, transmembrane domain (TMD) containing the conducting pore (Ca^{2+} permeable channel). Adapted from.[193] (B) Schematic representation of the pathways of the production and release of polyamines at glutamatergic synapses. Derived from L-arginine, polyamines are loaded and stored in secretory vesicles in neurons and astrocytes. VPAT = vesicular polyamine transporter.[194] Of note, polyamines are produced mainly in neurons but are stored in glial cells. (C) Zinc^{2+} enters the neuron mainly through activated voltage-gated calcium channels (VGCCs) and Ca^{2+} and Zn^{2+} permeable GluR2-lacking AMPA receptors.[195] Zn^{2+} is loaded in small synaptic vesicles by a specific ZnT3 transporter. The release of Zn^{2+} into the synaptic cleft produces an inhibition of the postsynaptic NMDARs. In addition, astrocytes can uptake the zinc by ZIP1 and export it to the extracellular space by ZnT1 transporting mechanisms. In both neurons and astrocytes, zinc can be transported by and stored in zinc-binding proteins (metallothioneins, MTs).[196] IDO, indoleamine 2,3-dioxygenase; TDO, tryptophan 2,3-dioxygenase; NAD^+, nicotinamide adenine dinucleotide; KATII, kynurenine aminotransferase II. SULT, sulfotransferase; ODC, ornithine decarboxylase; SRM, spermidine synthase; SMS, spermine synthase; SMOX, spermine oxidase. (D) Direct inhibitory effects of extracellular spermine on NMDAR single-channel conductance. Representative recordings at −60 mV and +60 mV from outside-out patches from hippocampal neurons. Note the increased frequency of open channels at both experimental conditions. Adapted with permission from.[102] (E) Top panel, Zn^{2+} inhibition of glutamate-evoked NMDAR current in either 10 or 100 μM spermine at 30 mV. Calibration: 150 sec, 50 nA. Bottom panel, spermine decreases the inhibition of NMDAR (NR1-1a(N616R)/NR2B) responses observed in 10 μM Zn^{2+} in a dose-dependent manner, with an IC_{50} value of 90 μM; spermine can similarly relieve the small amount of inhibition of exon 5–containing NR1-b(N637R)/NR2B receptors as well (open circles). Adapted with permission from[135]

protein and nucleic acid stability and adequate structural arrangements, as well as modulation of the activity of ion channels.[97,98] As NMDAR ligands, polyamines have dual, activator and inhibitor effects, which depend on several factors, and most importantly on binding sites with the receptor.[99] Electrophysiological studies have shown that polyamines can enhance NMDAR currents by increasing the probability of channel opening, an effect that is partly attributed to the enhancement of the affinity of the NMDAR for glycine [100,101](Figure 3D). The most studied polyamine spermine, on the other hand, can also block the NMDAR currents by producing a voltage-dependent reduction of single-channel conductance by blocking the NMDAR channel in its open state.[102] Both effects involve direct molecular interactions of polyamines with the NMDAR channel complex, with the involvement of multiple receptor subunits and cooperation with other NMDAR ligands. Spermine, for instance, potentiates NMDAR-mediated currents via the so-called glycine-independent stimulation, in the presence of saturating concentration of glycine and glutamate, by increasing the open channel probability[100] and decreasing desensitization of NMDAR to glutamate.[103] Spermine also increases the affinity of the GluN1/GluN2B and GluN1/GluN2B NMDAR for glycine via the so-called glycine-dependent stimulation, which may involve a second binding site for spermine.[104] On the other hand, spermine reduces the NMDAR sensitivity to glutamate at the GluN1/GluN2B receptor, which can mask its potentiation effects at low concentrations of glutamate.[101,105] Finally, spermine can act as a voltage-dependent blocker of NMDAR from the extracellular and intracellular sides of the channel pore, at a site related to the extracellular binding for Mg^{2+} and Zn^{2+}, although the physiological relevance of these mechanisms remains to be demonstrated.[102]

Because several neuroleptics and hallucinogens contain spermidine moiety, it was proposed that the endogenous polyamines might be related to the psychotic manifestation of schizophrenia.[106,107] Several genes involved in polyamine metabolism have been shown to be altered in patients with schizophrenia.[107,108] Assessment and comparison of polyamine levels in psychiatric patients with schizophrenia and healthy controls have shown a significant increase in the concentration of polyamine oxidative enzymes in the blood of schizophrenic patients,[107,109–111] whereas results from skin fibroblast studies

showed that polyamines were increased in antipsychotic-treated patients, as compared to drug-free patients.[112] In the human frontal cortex and hippocampus, no alteration was found in polyamines and ODC activity between patients with schizophrenia and healthy controls.[113] In preclinical studies, the administration of polyamines in animal models has been used to evaluate schizophrenia-related behavioral and cognitive effects such as social recognition, learning, and memory. Although the direct intracerebroventricular infusion of moderate to high doses of spermine before training did not alter the ability of rats to learn the position of the hidden platform in the Morris water maze, it abolished the retention of the learned platform position in experiments with infusion during the interval between training and retention tests.[114] The authors suggested that these effects might be due to inhibition of NMDAR by spermine during the critical window of memory formation. More recent studies, however, have shown that spermine improves memory functions in a novel object recognition task, and protects lipopolysaccharide (LPS)–induced memory deficits in mice by a mechanism that involves GluN2B.[115] Although these effects have been attributed to positive modulation of the NMDAR by spermine, their relevance to the pathobiology of schizophrenia remains to be defined. In this context, it is important to note that the administration of high doses of agmatine, another precursor of spermidine, that has an inhibitory effect on NMDAR, disrupted the PPI in rats.[116] Social recognition has also been tested in polyamine-treated rats, with repeated injections of spermidine decreasing the time animals spent in exporting familiar environment, without affecting the time spent exploring the novel environment.[117] In line with this finding, human cluster analysis has shown that the levels of L-arginine and its metabolites are altered in schizophrenia patients, with concentrations of agmatine significantly enhanced in the frontal cortex autopsies.[118] Overall, both clinical data from humans and preclinical evidence from studies in animal models demonstrate that dysregulation of polyamines functions might contribute to the pathobiology of schizophrenia, via disruption of NMDAR activity, although the precise pharmacological mechanisms, neurophysiological correlates, and target neural circuits remain to be determined. Although some of the effects related to polyamine dysfunctions seem to be associated with abnormal activation of neurons and might contribute toward positive symptoms of schizophrenia, their main functional and behavioral effects arise from disruption of synaptic plasticity mechanisms, contributing to the negative symptoms.

3.4 | Zinc

In addition to endogenous metabolites and amino acids, NMDAR activity and function are regulated by several cations, and most notably, by H^+, Na^+, Mg^{2+}, and Zn^{2+}.[119] Among these, alterations of NMDAR regulation by Zn^{2+} have emerged as of the highest significance to neurodegenerative disease such as Alzheimer's disease, Parkinson disease, Huntington disease, as well as psychiatric disorders, including depression and schizophrenia.[120] Zinc is an essential trace element, the second most abundant metal in eukaryotic organisms, and one of the most potent regulators of a wide range of neurobiological processes, ranging from control of the expression of ion channels to modulation of their activity and functions. As a major cation and cofactor, zinc is also a key constituent of many proteins, playing a pivotal role in a wide range of cellular processes relevant to mental health, including DNA replication and transcription, protein synthesis, maintenance of neuronal integrity and transport, oxidative stress, apoptosis, and aging, among others.[121,122] Zinc is found in all tissue types, including in the nervous system, with 5% to 15% in the form of free or loosely bound ions, enriched primarily in synaptic compartments of neurons.[123] Figure 3C summarizes the key processes and regulatory mechanisms of Zn^{2+} in neurons and glial cells at glutamatergic synapses. The neuronal-specific zinc transporter ZnT3 expressed in zinc-enriched neurons (ZENs)[124] is widely distributed throughout the brain, with the highest expression reported in the cortex, amygdala, and hippocampus. ZnT3-expressing neurons are likely to represent a subgroup of glutamatergic neurons, since zinc-positive boutons also show immunoreactivity for markers specific to glutamatergic cells.[125] ZnT3 and vesicular glutamate transporter 1 (VGLUT1) have been also found co-localizing in the same population of small synaptic vesicles[126] (Figure 3C), with occasional ZnT3 expression in GABAergic and glycinergic neurons also documented.[127]

In neurophysiological tests, although zinc modulates fast-excitatory neurotransmission and facilitates the release of GABA, and potentiates nAChR activity,[128,129] its role in the neurobiology of schizophrenia and depression seems to be linked primarily with modulation of the glutamatergic neurotransmission.[122,130] Currently, the mechanistic link between impairments of Zn^{2+} homeostasis with its reduced levels in the serum and psychotic symptoms of schizophrenia remains unclear, with the functional deficit of its transporters and neuroinflammation due to Zn^{2+} deficiency discussed among the principal causatives .[131] At central synapses, zinc can regulate synaptic transmission at the presynaptic level by altering the transmitter release, whereas its co-release with glutamate from axon terminals is known to modulate functions of glutamatergic receptors at the postsynaptic membrane. Indeed, after discharge in the synaptic cleft, Zn^{2+} exerts strong and direct effects on several ion channels and receptors, depending on its concentration and the sub-unit composition of target receptors.[132] In the context of regulation of NMDAR, the inhibitory effect of Zn^{2+} is voltage independent and is mediated primarily via GluN1/GluN2B subunits, with $IC_{50} \approx 9.5\ \mu M$. GluN1/GluN2A NMDARs also are subject to inhibition by Zn^{2+}, but their effects are biphasic, and depend on the concentration, with $IC_{50} \approx 5$ nM and $\approx 79\ \mu M$.[133] The inhibitory effects at higher concentrations are largely due to blockade of the channel pore. Finally, Zn^{2+} can also inhibit NMDARs containing GluN1/GluN2C and GluN1/GluN2D, but only at very high concentrations.[134] Figure 3E illustrates a typical example of inhibition of NMDAR-mediated currents by Zn^{2+}, followed by antagonizing effects caused by polyamine spermine.[135]

As already noted, changes in Zn^{2+} homeostasis and functions have been reported in several neurodegenerative conditions as well as in a variety of psychiatric disorders.[120] In schizophrenia, Zn^{2+} dysregulations have been viewed largely in association with the

abnormal functioning of its transporters.[136] Increased expression of Zn^{2+} transporter SLC39A12 in the dorsolateral prefrontal cortex in subjects with schizophrenia has been implicated in the impairment of Zn^{2+} activity and increased uptake, contributing to NMDAR hypofunctions.[136] A recent meta-analysis that evaluated 658 schizophrenia patients and 1008 controls showed that Zn^{2+} concentration in the serum of schizophrenia patients is considerably lower, with the reduction being more pronounced in drug-naive subjects.[130] This result is in agreement with the notion that excessive Zn^{2+} sequestration due to enhanced cellular uptake can lead to a deficiency of this cation, which in turn could lead to NMDAR hypofunction. In agreement with this notion, earlier reports have shown that zinc sulfate can be effective as adjuvant therapy for schizophrenia, since it decreased the score of the positive and negative syndrome scale in patients, as compared to the placebo group.[137] The moderate rise in the extracellular concentration of Zn^{2+} also could decrease the glutamate-mediated excitotoxicity, via inhibition of NMDAR activity and normalizing of glutamatergic neurotransmission in the prefrontal cortex.[122]

The results of studies of another Zn^{2+} transporter KO (ZnT3 KO) mouse model have been also consistent with the potential role of this divalent cation in regulating the synaptic vesicle cycle and excitatory transmission, with implications for schizophrenia. Although young ZnT3 KO mice showed normal learning and memory features, with their auditory pre-pulse inhibition comparable to that in WT mice,[138] in adult KO, the initial learning in hidden platform tests required longer latency.[139] The age-dependent deficit in learning and memory in ZnT3 KO mice was suggested to be associated with decreased presynaptic and postsynaptic markers such as SNAP25 and PSD95, as well as AMPAR, GluN2A, and GluN2B sub-units of NMDAR.[140] Neurophysiologic studies with measurements of synaptic plasticity have shown that in the hippocampus, at low μM dose, Zn^{2+} inhibits LTD, whereas at high μM it blocks LTP, with NMDARs playing a critical role in these effects.[141] In behavioral tests, ZnT3 KO mice spent a significantly longer time with unfamiliar mice and displayed increased social interaction, whereas the time spent in exploring familiar objects remained unchanged. These observations suggest that both social interactions and object recognition memory can be impaired under altered Zn^{2+} concentrations and activity.[139] It is important to note that in experimental rats, systemic administration of Zn^{2+} was shown to prevent the cataleptic state induced by the typical antipsychotic drug haloperidol, as well as amphetamine-induced motor hyperactivity.[142]

The available functional and behavioral evidence thus suggests that the reduction in Zn^{2+} level in the interstitial space, due to defects in homeostatic regulatory mechanisms, could lead to impairments of NMDAR activity and hypofunctions, potentially contributing toward the positive symptoms of schizophrenia. Cautious adjustments of the Zn^{2+} activity with the reinstatement of NMDAR functions, therefore, can be viewed as a potential avenue for developing antipsychotic therapeutic leads with restorative functional effects.

3.5 | Endocannabinoids

The recreational use of cannabis has been long recognized as potentially causative for psychosis and as a risk factor for schizophrenia, with the mechanistic link between cannabis intake and diseased states of mind remaining poorly defined. Heavy abuse of cannabis can trigger both the onset of psychotic episodes in predisposed individuals, and relapse in patients with schizophrenia.[143,144] It should be stressed, however, that most healthy cannabis users do not develop psychosis or schizophrenia,[145] suggesting rather a complex relationship between the use of cannabis and psychosis, with the involvement of predisposing factors, including differential genetic and epigenetic susceptibility of individuals.[146] It remains also unclear whether the differences in the activity of endogenous cannabinoids contribute toward variations in the vulnerability of cannabis users to psychosis. The results of earlier clinical and biomarker studies in humans are consistent with higher levels of endocannabinoids in the serum and CSF of patients with acute schizophrenia, as compared to healthy controls.[147,148] Among so far identified endogenous cannabinoids, anandamide and 2-arachidonoylglycerol are the two most prevalent and best characterized (Figure 4A). These are hydrophobic arachidonic acid–containing lipids produced on demand from glycerophospholipids, which are released from cells via diffusion and exert their action via autocrine and paracrine mechanisms through binding and activation of cannabinoid receptor type 1 (CB_1) and cannabinoid receptor type 2 (CB_2).[149] Both receptors are members of the G-protein–coupled receptor (GPCR) family, associated with $G_{i/o}$, with CB_1 receptor also capable of stimulating of G_s proteins.[150] Although both CB receptors are expressed throughout the body, CB_1 receptors show the highest expression in the CNS, whereas CB_2 receptors are mostly present in peripheral tissue and immune cells.[151–153] Figure 4B schematizes the major steps of synthesis and secretion of endocannabinoids from the dendritic spine of a neuron, with autocrine postsynaptic and retrograde trans-synaptic effects on the glutamate release machinery at presynaptic terminals shown.

As potent modulators of neuronal activity, the endocannabinoids have highly complex effects on neural dynamics and brain functions, involving different neurotransmitter systems.[154] According to the most prevalent functional model, endocannabinoids are released from postsynaptic neurons and via paracrine and autocrine effects act on presynaptic and postsynaptic CB_1 receptors, respectively. At presynaptic terminals, CB_1 receptor activation stimulates adenylyl cyclase and cAMP/PKA signaling, which attenuates the action potential–dependent influx of Ca^{+2} through inhibition of voltage-gated Ca^{+2} channels (VGCCs). This mechanism has been implicated in neuroprotective effects of CB_1 receptors, countering the cytotoxicity induced by excessive release of glutamate.[155] Inhibition of NMDAR-mediated synaptic currents by endocannabinoids via activation of postsynaptic CB_1 receptors, with resulting NMDAR hypofunction, on the other hand, is viewed as the main mechanism relating cellular effects of cannabis to the induction of psychosis.[156,157] Accordingly, Δ^9-tetrahydrocannabinol (THC) injection to mice over seven

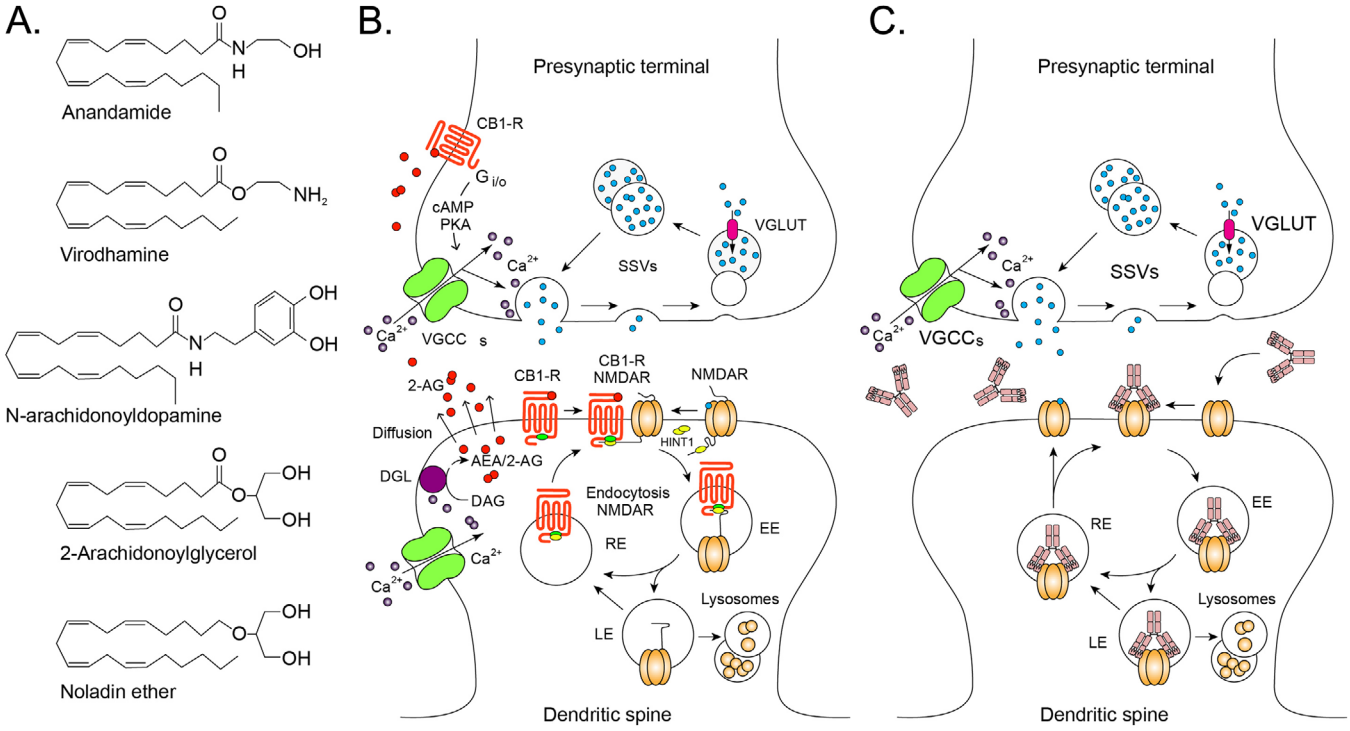

FIGURE 4 Endocannabinoids and NMDAR auto-antibodies as endogenous modulators of glutamatergic neurotransmission. (A) Chemical structure of the major endocannabinoids anandamide (AEA), virodhamine, *N*-arachidonoyldopamine, 2-arachidonoylglycerol (2-AG), and noladin ether. (B) The endocannabinoids AEA and 2-AG are synthesized from glycerophospholipids and released from the postsynaptic compartment to activate endocannabinoid signaling at the post- and pre-synaptic compartments. In pre-synaptic neurons, CB_1 receptor (CB_1-R) activation produces a reduction in the release of glutamate through the inhibition of the cAMP pathway and downstream voltage-gated calcium channels (VGCCs). In post-synaptic neurons, endocannabinoids trigger the internalization of NMDAR via the formation of NMDAR-CB_1 complex, mediated by homodimeric HINT1 protein (green). After endocytosis, the NMDAR is sorted for degradation, whereas CB_1 with HINT1 complex returns to the surface membrane. (C) NMDAR auto-antibodies bind the N368/G369 region of the amino-terminal domain (ATD) of the GluN1 subunit, causing increased clustering of receptors and their internalization and transport to the early endosome, and down to acidifying late endosome, and to degradation in lysosome or re-exported via endosomal membrane recycling system. cAMP, cyclic adenosine monophosphate; DAG, diacylglycerol; DGL, diacylglycerol lipase; PKA, protein kinase A; SSV, small synaptic vesicles; VGCC, voltage-gated calcium channels; VGLUT1, vesicular glutamate transporter 1

consecutive days impaired the hippocampal NMDAR-dependent LTP and decreased the expression of GluN2A and GluN2B sub-units.[158] Of interest, attenuation of NMDAR-mediated synaptic currents by CB_1 receptor activation, in addition to acting at postsynaptic elements, could also result from presynaptic inhibition of the glutamate release.[159] Prenatal exposure of rats to endogenous cannabinoid analog WIN 55,212-2, which is a potent and selective CB_1 receptor agonist, caused significant inhibition of cortical glutamatergic transmission manifested in the reduction of basal and depolarization-induced glutamate release at excitatory synapses, consistent with presynaptic action mechanism.[160] This effect is associated with the downregulation of the NMDAR-dependent mobilization of intracellular Ca^{2+} at presynaptic terminals.[161] Attenuation of NMDAR-mediated glutamatergic drive-by endocannabinoids is thought to result largely from direct interaction of CB_1 receptor with the GluN1 sub-unit of NMDAR on the surface membrane, which triggers rapid internalization of the NMDAR-CB_1 receptor complex. Such composite cross-regulation of NMDAR functions by CB_1 receptor, which prevents the glutamatergic hyperactivity and overstimulation of NMDARs, involves the HINT1 adaptor protein,[156] which cooperates with CB1 receptor in down-regulating the NMDAR expression and glutamatergic activity in neurons.[162] It is worth noting that the CB_1 receptor can also regulate neural and synaptic activity through effects on astrocytes, thereby mobilizing intracellular Ca^{2+}, which in turn stimulates glutamate release with excitatory effects on pyramidal cells.[163]

Studies in murine models have demonstrated that schizophrenia-like behavior can be induced by a single systemic administration of selective CB_1 receptor agonists, in agreement with the potential contribution of endocannabinoid-induced hypofunction of NMDAR on the onset of psychosis.[164,165] Indeed, WIN 55,212-2 administration in rats has been reported to lead to transient suppression of both pre-pulse inhibition and social recognition.[166] Injection of the endocannabinoid transport inhibitor AM404 in rats, on the other hand, did not cause a difference in the acoustic startle reflex or PPI, but exerted a dose-dependent anxiolytic-like effect.[167] It is interesting to note that similar to in humans, schizophrenia-like effects induced in murine models by exogenous cannabinoids vary not only depending on the administration dose and baseline endocannabinoid drive but also on the animal strain.

In male Swiss mice, for instance, single cannabidiol does did not alter the PPI or the amplitude of startle response,[168] whereas a single-time treatment of C57BL/6JArc mice with the same dose of cannabidiol showed increased startle response without changes in PPI.[169] Although the data for differential sensitivity of rats to endocannabinoids remain inconclusive,[170,171] they are in general agreement with the notion that the risk of developing schizophrenia-like symptoms in animal models, similar to that in humans, depend on complex interactions between the effects of exogenous cannabis and endocannabinoid drive. The true cause and mechanisms underlying the differential sensitivity remain unknown and require rigorous studies.[145]

Taken as a whole, while it emerges that acute and chronic hypofunctions of NMDAR induced by endogenous cannabinoids seem to contribute to the pathobiology of schizophrenia, partly via activation of CB_1-GPCR mechanisms, and partly through inhibition of glutamate release at presynaptic terminals, the emerging conflicting data with lack of mechanistic details warrant further in-depth preclinical and clinical research. Elucidating the role of the constitutive activity of endogenous cannabinoids in setting the threshold for psychosis induced by the intake of cannabis will not only shed a light on the neurobiology of schizophrenia but also provide clues toward its prevention, with potential therapeutic intervention.

3.6 | NMDAR auto-antibodies

Perhaps the most compelling evidence for the potential role of NMDAR in the neurobiology of schizophrenia has emerged from clinical reports on the brain inflammatory disease caused by the autoimmune response to the GluN1 subunit of NMDAR. Identified for the first time by Dalmau et al., this condition leads to major disruption of normal glutamatergic signaling and brain functions, manifested also in acute swelling of the neural tissue with histopathological aberrations, known as anti-NMDAR encephalitis.[172] Both men and women are susceptible to the pathology, which can strike from a relatively young age, although the share of women with this condition is somewhat higher.[173] Molecular studies have demonstrated that the immune response in anti-NMDAR encephalitis is directed against ATD of the GluN1, which contains the epitope for recognition by auto-antibodies.[174,175] Clinical assessment of subjects with autoimmune anti-NMDAR encephalitis revealed an array of symptoms varying in their severity, with neuropsychiatric symptoms being among the most prominent. Although the estimated incidence of this disease is 1.5 cases per million people each year, its impact on brain mechanisms and higher functions have been remarkable,[176] owing to a range of severe mental disorders with early onset in the course of the disease. Of note, approximately 5% of the patients with anti-NMDAR encephalitis showed only neuropsychiatric signs, such as delusional thinking, mood disturbances, or aggression, without any neurologic symptoms during the first strike of the disease or in the first relapse episode.[177]

The molecular and cellular effects of anti-NMDAR encephalitis, which could contribute toward the clinical manifestation of the disease, have been analyzed in primary neuronal cultures and in animal models *in vivo*, using NMDAR auto-antibodies obtained from patients. Figure 4C schematizes putative mechanisms underlying the development of NMDAR hypofunction caused by this autoimmune encephalitis. In rat hippocampal neuronal cultures, for instance, NMDAR auto-antibodies from humans caused a reversible decrease in the surface density of this receptor and synaptic currents it mediates, without changing AMPAR-mediated currents or expression of AMPAR.[178] Noteworthy, the number of synaptic contacts, dendritic spines, and neuronal survival have also remained unchanged. Of note, rapid-onset endocytosis of NMDAR induced in primary neuronal cultures by auto-antibodies extracted from patients occurs in both excitatory and inhibitory hippocampal neurons and involves internalization and transport through recycling endosomes to acidifying late endosomes, and lysosomes to degradation.[179] Of note, these alterations caused by anti-GluN1 antibodies are not associated with compensatory molecular adjustments of the expression of glutamate receptor transcripts but are related to a notable decrease in density of inhibitory synapses onto excitatory neurons.[179] In addition, NMDAR auto-antibodies from patients caused alterations in the horizontal trafficking and distribution of NMDAR on the surface membrane with a different effect, which depends on the sub-unit composition of NMDAR and partners of GluN1 sub-unit, as well as interactions between the NMDAR and its synaptic anchoring protein Ephrin-B2 receptor.[180] Of note, before inducing endocytosis, auto-antibodies produced an increased clustering of both synaptic and extra-synaptic NMDARs, preferentially those that contain GluN2B sub-units.[181] In addition to changes in NMDAR expression, the application of GluR1 auto-antibodies alters the NMDAR channel functions, by stabilizing it at the open conformation state, increasing the duration of open and decay time of the channel.[182] Alterations in NMDAR characteristics and glutamatergic signaling induced by auto-antibodies were also confirmed *in vivo* in rats by injection of human CSF and purified immunoglobulins type G in the CA1 area of the hippocampus and premotor cortex, which caused a rise in glutamine concentration in the extracellular space.[183]

NMDAR auto-antibodies from patients have been also tested in behavioral experiments of murine models. The 14 day exposure of mice to the anti-NMDAR encephalitis patient's CSF through ventricular catheters connected to osmotic pumps caused a severe memory deficit in novel object recognition in the open field and V-maze tests.[184] Likewise, these mice displayed anhedonia-like behavior in the sucrose preference test, as well as depressive-like behavior in tail suspension and forced swimming tests, without alterations in anxiety, aggression, and general locomotor activity.[184] Another study showed that mice with continued intracerebroventricular pump infusion of CSF of autoimmune patients exhibited impaired spatial memory in Morris water maze tests with a significantly decreased content of NMDAR protein in the hippocampal region.[185] Finally, the injection of CSF from NMDAR-autoimmune patients into both hippocampi produced a suppression of NMDAR-dependent LTP in slices of hippocampal CA1 area, with altered novel object exploration, without affecting the spontaneous locomotor activity or change in anxiety-related behavior.[186]

TABLE 1 A summary of the endogenous antagonists of NMDA receptors with their action mechanisms

Antagonists	Effect on NMDAR	Binding site	NMDA sub-unit	Behavioral effect
Kynurenic acid	Inhibition	Non-competitive at the glycine site	GluN1	Alteration in pre-pulse inhibition, spatial working memory, contextual fear memory and learning, auditory sensory gating by intraperitoneal injection of kynurenic acid in rats.
	Inhibition	Competitive at glutamate site	GluN2	
Neurosteroids				
PAS	Inhibition	ATD in GluN2D, S1S2 in GluN2B	All GluN2, more potent in GluN2C and GluN2D	–
PREGS	Inhibition	ATD in GluN2D	GluN2C and GluN2D	PREGS administration ameliorates schizophrenic-like symptoms, such as deficit in pre-pulse inhibition and novel object recognition in DAT KO mice. It also suppressed the acquisition of spatial information and spatial/visual object discrimination in rats.
	Potentiation	S1S2 in GluN2B	GluN2A and GluN2B	
Polyamines				
Spermidine	-	-	-	-
Spermine	Inhibition	Voltage-dependent pore blocker from extracellular and intracellular sides	All GluN2, more potent in GluN2A and GluN2B	Abolished the retention of the learned platform position in Morris water maze, but improve memory in a novel object recognition task
	Potentiation	Glycine-dependent potentiation: Increase affinity for glycine	GluN2A and GluN2B	
	Potentiation	Glycine-independent potentiation: reduction of tonic proton inhibition	ATD at the lower lobe of GluN1/GluN2B subunit interface	
Zinc	Inhibition	Voltage-dependent pore blocker (low affinity)	NR1/NR2A	The age-dependent deficit in learning and memory in ZnT3-KO mice. Impairment in learning, memory, and social behavior in the zinc-deficient rodent.
	Inhibition	High affinity, voltage-independent	ATD domains of GluN2A (low sensitivity to GluN2B)	
NMDAR auto-antibodies	Endocytosis	ATD	GluN1	Alteration in novel object recognition, spatial learning, depression-like, and anhedonia-like behaviors in rodents using NMDAR auto-antibodies obtained from human patients.
Endo-cannabinoids	Endocytosis	CB1 with CTD	GluN1	Alteration in pre-pulse inhibition and social recognition using an intraperitoneal injection of cannabinoid analog in rats.

Abbreviations: DAT, Dopamine transporter; Inh, inhibition; Int, internalization; PAS, pregnanolone sulfate; Pot, potentiation; PREGS, pregnenolone sulfate.

It is important to note that the presence of NMDAR auto-antibodies has also been investigated in patients with psychosis and schizophrenia, without autoimmune condition. Although some studies failed to detect the presence of serum immunoglobulin G (IgG) GluN1 antibodies in patients with first-episode psychosis[187] and schizophrenia,[188] other groups have reported high titers of those antibodies in both first-episode psychosis[189] and schizophrenia [190] patients. The relevance of changes in NMDAR auto-antibodies in serum to the expression of the neuropsychiatric symptoms depends on their accessibility to the brain and the integrity of the BBB, and can differ between different brain regions, potentially explaining the case-by-case variability of symptoms and severity of the disease.[191]

4 | CONCLUDING REMARKS

Although impairments of glutamatergic signaling have long been considered among the key causative factors of schizophrenia, it was the discovery of the induction of schizophrenia-like symptoms in healthy subjects and animal models by NMDAR antagonizing dissociative anesthetics that placed glutamatergic hypothesis of schizophrenia on a firm footing. The subsequent demonstration of NMDAR inhibition by endogenous antagonists with changes in their concentrations in the serum and in CSF of patients has consolidated further the glutamatergic hypothesis, offering a new framework for basic and translational studies, with the potential use of pharmacological means to alleviate the negative and cognitive symptoms, which are largely resistant to

antipsychotic drugs targeting the monoaminergic mechanisms of the brain. Notwithstanding the considerable progress and rapidly advancing research of the role of endogenous NMDAR blockers in schizophrenia, the major gap remained in the systematic analysis and review of their effects with action mechanisms from the molecular neurobiology and behavioral neuroscience point of view, with a range of key questions open for debate and experimental verification.

Throughout this review, we presented an in-depth analysis of advances in the neurobiology of endogenous NMDAR inhibitors, which are of key relevance to schizophrenia research and therapy (Table 1). We discussed molecular and cellular data, as well as clinical and behavioral evidence supporting the contribution of NMDAR hypofunction to the initiation and progression of the disease, as well as clinical manifestation. Due to the highly complex nature of glutamatergic neurotransmission and NMDAR receptors, the seamless integration of molecular and cellular data with results of functional tests and behavioral symptoms remain problematic and open for future debate and in-depth studies. Nonetheless, two mechanistic models have emerged, explaining how the NMDAR deficiency might contribute to specific clinical facets of schizophrenia. The first is related to impairment of short working memory, attributed to the deficit of NMDAR function in selected brain circuits, which causes disruption of coordinated neuronal activity and signal processing. As a major mediator of synaptic transmission, NMDAR plays a key role in temporal precision of neuronal firing with discriminatory activation of specific neural networks, warranting the stability of memory traces and neural representations. Disruption of these mechanisms, due to changes in the NMDAR activity, could, therefore, lead to impairments of encoding of new information, which in turn might contribute to neurocognitive symptoms of schizophrenia. The second, related to synaptic neurotransmission mechanisms, which also involves NMDAR hypofunction, entails a reduction of excitatory glutamatergic drive, preferentially at fast-firing GABA interneurons, leading to disinhibition and hyperactivity of cortical pyramidal cells. In addition to downgrading temporally coordinated activity and synchrony of neural ensembles, the latter can elevate the noise level in neuronal networks, with disruptive effects on intracortical associative, as well as long-range cortico-subcortical integrative processes.

The extent and precise mechanisms of how these processes are controlled by endogenous NMDAR modulators under physiological conditions and how they are altered in schizophrenia-affected brain remain a matter of debate and ongoing research. Demonstration of psychotic and schizoaffective symptoms in humans associated with the hypofunction of NMDARs, and the possibility of accurate modeling specific schizophrenia-like symptoms in experimental animals with NMDAR antagonists, or immunogenic challenge, represent a major advance and provide a highly instructive framework for future mechanistic and translational studies. Given the limited success in the management or treatment of negative and cognitive symptoms of schizophrenia with present-day antipsychotic drugs, and the growing recognition of the role played by endogenous NMDAR modulators in higher brain mechanisms, the stakes are growing high for their future therapeutic use, to improve the management and treatment of schizophrenia. It should be stressed, however, that a highly complex and polygenic disease such as schizophrenia is unlikely to succumb to a single medication, irrespective of its action mechanism, but warrants a complex approach. With more than one-third of schizophrenia cases not showing any response to first-line antipsychotics, any advancement in this direction would be welcome news for patients, health care providers, and the public.

ACKNOWLEDGMENTS

This study was supported by the project Sustainability for the National Institute of Mental Health, under grant number LO1611, with financial support from the Ministry of Education, Youth and Sports of the Czech Republic under the NPU I program.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

AUTHOR CONTRIBUTIONS

Pascal Jorratt, Cyril Hoschl, and Saak V. Ovsepian conceived the study; Pascal Jorratt and Saak V. Ovsepian prepared the manuscript; Pascal Jorratt, Cyril Hoschl, and Saak V. Ovsepian reviewed, commented, and approved the final submission version.

ORCID

Saak V. Ovsepian https://orcid.org/0000-0002-9522-4159

REFERENCES

1. Bleuler E, Jung C. Komplexe und Krankheitsursachen bei Dementia praecox. *Zentralblatt für Nervenheilkunde und Psychiatrie*. 1908;31:220-227.
2. Kraepelin E. *Dementia Praecox and Paraphrenia*. Edinburgh: ES Livington; 1919. Translated by RM Barclay.
3. Gaebel W, Zielasek J. Schizophrenia in 2020: trends in diagnosis and therapy. *Psychiatry Clin Neurosci*. 2015;69:661-673.
4. Owen MJ, Sawa A, Mortensen PB. Schizophrenia. *Lancet*. 2016; 388:86-97.
5. Kahn RS, Sommer IE, Murray RM, et al. Schizophrenia. *Nat Rev Dis Primers*. 2015;1:15067.
6. Harvey PD, Strassnig M. Predicting the severity of everyday functional disability in people with schizophrenia: cognitive deficits, functional capacity, symptoms, and health status. *World Psychiatry*. 2012;11:73-79.
7. Bowie CR, Harvey PD. Cognitive deficits and functional outcome in schizophrenia. *Neuropsychiatr Dis Treat*. 2006;2:531-536.
8. Correll CU, Schooler NR. Negative symptoms in schizophrenia: a review and clinical guide for recognition, assessment, and treatment. *Neuropsychiatr Dis Treat*. 2020;16:519-534.
9. Tripathi A, Kar SK, Shukla R. Cognitive Deficits in schizophrenia: understanding the biological correlates and remediation strategies. *Clin Psychopharm Neu*. 2018;16:7-17.
10. Lesh TA, Niendam TA, Minzenberg MJ, Carter CS. Cognitive control deficits in schizophrenia: mechanisms and meaning. *Neuropsychopharmacology*. 2011;36:316-338.
11. Glausier JR, Lewis DA. Dendritic spine pathology in schizophrenia. *Neuroscience*. 2013;251:90-107.
12. Uno Y, Coyle JT. Glutamate hypothesis in schizophrenia. *Psychiat Clin Neuros*. 2019;73:204-215.

13. McCutcheon RA, Krystal JH, Howes OD. Dopamine and glutamate in schizophrenia: biology, symptoms and treatment. *World Psychiatry*. 2020;19:15-33.
14. Howes O, McCutcheon R, Stone J. Glutamate and dopamine in schizophrenia: an update for the 21st century. *J Psychopharmacol*. 2015;29:97-115.
15. Snyder MA, Gao WJ. NMDA hypofunction as a convergence point for progression and symptoms of schizophrenia. *Front Cell Neurosci*. 2013;7.
16. Nakazawa K, Jeevakumar V, Nakao K. Spatial and temporal boundaries of NMDA receptor hypofunction leading to schizophrenia. *NPJ Schizophr*. 2017;3:7.
17. Javitt DC. Glutamatergic theories of schizophrenia. *Isr J Psychiatry Relat Sci*. 2010;47:4-16.
18. Kew JN, Kemp JA. Ionotropic and metabotropic glutamate receptor structure and pharmacology. *Psychopharmacology (Berl)*. 2005;179:4-29.
19. Madden DR. The structure and function of glutamate receptor ion channels. *Nat Rev Neurosci*. 2002;3:91-101.
20. Ulbrich MH, Isacoff EY. Rules of engagement for NMDA receptor subunits. *P Natl Acad Sci USA*. 2008;105:14163-14168.
21. Paoletti P. Molecular basis of NMDA receptor functional diversity. *Eur J Neurosci*. 2011;33:1351-1365.
22. Paoletti P, Bellone C, Zhou Q. NMDA receptor subunit diversity: impact on receptor properties, synaptic plasticity and disease. *Nat Rev Neurosci*. 2013;14:383-400.
23. Monyer H, Burnashev N, Laurie DJ, Sakmann B, Seeburg PH. Developmental and regional expression in the rat brain and functional properties of four NMDA receptors. *Neuron*. 1994;12:529-540.
24. Vyklicky V, Korinek M, Smejkalova T, et al. Structure, function, and pharmacology of NMDA receptor channels. *Physiol Res*. 2014;63:S191-S203.
25. McBain CJ, Mayer ML. N-methyl-D-aspartic acid receptor structure and function. *Physiol Rev*. 1994;74:723-760.
26. Clements JD, Westbrook GL. Activation kinetics reveal the number of glutamate and glycine binding sites on the N-methyl-D-aspartate receptor. *Neuron*. 1991;7:605-613.
27. Pachernegg S, Strutz-Seebohm N, Hollmann M. GluN3 subunit-containing NMDA receptors: not just one-trick ponies. *Trends Neurosci*. 2012;35:240-249.
28. Chen PE, Geballe MT, Katz E, et al. Modulation of glycine potency in rat recombinant NMDA receptors containing chimeric NR2A/2D subunits expressed in Xenopus laevis oocytes. *J Physiol*. 2008;586:227-245.
29. Erreger K, Geballe MT, Kristensen A, et al. Subunit-specific agonist activity at NR2A-, NR2B-, NR2C-, and NR2D-containing N-methyl-D-aspartate glutamate receptors. *Mol Pharmacol*. 2007;72:907-920.
30. Sainio EL, Pulkki K, Young SN. L-Tryptophan: biochemical, nutritional and pharmacological aspects. *Amino Acids*. 1996;10:21-47.
31. Plitman E, Iwata Y, Caravaggio F, et al. Kynurenic acid in schizophrenia: a systematic review and meta-analysis. *Schizophr Bull*. 2017;43:764-777.
32. Hoglund E, Overli O, Winberg S. Tryptophan metabolic pathways and brain serotonergic activity: a comparative review. *Front Endocrinol (Lausanne)*. 2019;10:158.
33. Han Q, Cai T, Tagle DA, Li J. Structure, expression, and function of kynurenine aminotransferases in human and rodent brains. *Cell Mol Life Sci*. 2010;67:353-368.
34. Heredi J, Berko AM, Jankovics F, et al. Astrocytic and neuronal localization of kynurenine aminotransferase-2 in the adult mouse brain. *Brain Struct Funct*. 2017;222:1663-1672.
35. Dang Y, Dale WE, Brown OR. Comparative effects of oxygen on indoleamine 2,3-dioxygenase and tryptophan 2,3-dioxygenase of the kynurenine pathway. *Free Radic Biol Med*. 2000;28:615-624.
36. Fukui S, Schwarcz R, Rapoport SI, Takada Y, Smith QR. Blood-brain barrier transport of kynurenines: implications for brain synthesis and metabolism. *J Neurochem*. 1991;56:2007-2017.
37. Kessler M, Terramani T, Lynch G, Baudry M. A glycine site associated with N-methyl-D-aspartic acid receptors: characterization and identification of a new class of antagonists. *J Neurochem*. 1989;52:1319-1328.
38. Birch PJ, Grossman CJ, Hayes AG. Kynurenic acid antagonises responses to NMDA via an action at the strychnine-insensitive glycine receptor. *Eur J Pharmacol*. 1988;154:85-87.
39. Prescott C, Weeks AM, Staley KJ, Partin KM. Kynurenic acid has a dual action on AMPA receptor responses. *Neurosci Lett*. 2006;402:108-112.
40. Stone TW. Does kynurenic acid act on nicotinic receptors? An assessment of the evidence. *J Neurochem*. 2020;152:627-649.
41. Hilmas C, Pereira EF, Alkondon M, Rassoulpour A, Schwarcz R, Albuquerque EX. The brain metabolite kynurenic acid inhibits alpha7 nicotinic receptor activity and increases non-alpha7 nicotinic receptor expression: physiopathological implications. *J Neurosci*. 2001;21:7463-7473.
42. Carpenedo R, Pittaluga A, Cozzi A, et al. Presynaptic kynurenate-sensitive receptors inhibit glutamate release. *Eur J Neurosci*. 2001;13:2141-2147.
43. Wang AK, Miller BJ. Meta-analysis of cerebrospinal fluid cytokine and tryptophan catabolite alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder, and depression. *Schizophrenia Bull*. 2018;44:75-83.
44. Kindler J, Lim CK, Weickert CS, et al. Dysregulation of kynurenine metabolism is related to proinflammatory cytokines, attention, and prefrontal cortex volume in schizophrenia. *Mol Psychiatry*. 2020;25(11):2860-2872.
45. Miller CL, Llenos IC, Dulay JR, Weis S. Upregulation of the initiating step of the kynurenine pathway in postmortem anterior cingulate cortex from individuals with schizophrenia and bipolar disorder. *Brain Res*. 2006;1073-1074:25-37.
46. Miller CL, Llenos IC, Dulay JR, Barillo MM, Yolken RH, Weis S. Expression of the kynurenine pathway enzyme tryptophan 2,3-dioxygenase is increased in the frontal cortex of individuals with schizophrenia. *Neurobiol Dis*. 2004;15:618-629.
47. Lestage J, Verrier D, Palin K, Dantzer R. The enzyme indoleamine 2,3-dioxygenase is induced in the mouse brain in response to peripheral administration of lipopolysaccharide and superantigen. *Brain Behav Immun*. 2002;16:596-601.
48. Javitt DC. Distress intolerance, kynurenic acid, and schizophrenia. *JAMA Psychiatry*. 2014;71:749-750.
49. Jayawickrama GS, Nematollahi A, Sun G, Gorrell MD, Church WB. Inhibition of human kynurenine aminotransferase isozymes by estrogen and its derivatives. *Sci Rep*. 2017;7:17559.
50. Meltzer-Brody S, Howard LM, Bergink V, et al. Postpartum psychiatric disorders. *Nat Rev Dis Primers*. 2018;4:18022.
51. Erhardt S, Schwieler L, Emanuelsson C, Geyer M. Endogenous kynurenic acid disrupts prepulse inhibition. *Biol Psychiatry*. 2004;56:255-260.
52. Chess AC, Simoni MK, Alling TE, Bucci DJ. Elevations of endogenous kynurenic acid produce spatial working memory deficits. *Schizophr Bull*. 2007;33:797-804.
53. Chess AC, Landers AM, Bucci DJ. L-kynurenine treatment alters contextual fear conditioning and context discrimination but not cue-specific fear conditioning. *Behav Brain Res*. 2009;201:325-331.
54. Shepard PD, Joy B, Clerkin L, Schwarcz R. Micromolar brain levels of kynurenic acid are associated with a disruption of auditory sensory gating in the rat. *Neuropsychopharmacology*. 2003;28:1454-1462.
55. Pocivavsek A, Thomas MA, Elmer GI, Bruno JP, Schwarcz R. Continuous kynurenine administration during the prenatal period, but

not during adolescence, causes learning and memory deficits in adult rats. *Psychopharmacology (Berl)*. 2014;231:2799-2809.
56. Pershing ML, Bortz DM, Pocivavsek A, et al. Elevated levels of kynurenic acid during gestation produce neurochemical, morphological, and cognitive deficits in adulthood: implications for schizophrenia. *Neuropharmacology*. 2015;90:33-41.
57. Pershing ML, Phenis D, Valentini V, et al. Prenatal kynurenine exposure in rats: age-dependent changes in NMDA receptor expression and conditioned fear responding. *Psychopharmacology (Berl)*. 2016;233:3725-3735.
58. Potter MC, Elmer GI, Bergeron R, et al. Reduction of endogenous kynurenic acid formation enhances extracellular glutamate, hippocampal plasticity, and cognitive behavior. *Neuropsychopharmacology*. 2010;35:1734-1742.
59. Linderholm KR, Andersson A, Olsson S, et al. Activation of rat ventral tegmental area dopamine neurons by endogenous kynurenic acid: a pharmacological analysis. *Neuropharmacology*. 2007;53:918-924.
60. Savitz J. The kynurenine pathway: a finger in every pie. *Mol Psychiatry*. 2020;25:131-147.
61. Cai H, Cao T, Zhou X, Yao JK. Neurosteroids in schizophrenia: pathogenic and therapeutic implications. *Front Psychiatry*. 2018;9:73.
62. Ratner MH, Kumaresan V, Farb DH. Neurosteroid actions in memory and neurologic/neuropsychiatric disorders. *Front Endocrinol (Lausanne)*. 2019;10:169.
63. Baulieu EE, Robel P. Neurosteroids: a new brain function?. *J Steroid Biochem Mol Biol*. 1990;37:395-403.
64. Baulieu EE, Robel P, Schumacher M. Neurosteroids: beginning of the story. *Int Rev Neurobiol*. 2001;46:1-32.
65. Rupprecht R, Holsboer F. Neuroactive steroids: mechanisms of action and neuropsychopharmacological perspectives. *Trends Neurosci*. 1999;22:410-416.
66. Harteneck C. Pregnenolone sulfate: from steroid metabolite to TRP channel ligand. *Molecules*. 2013;18:12012-12028.
67. Schumacher M, Liere P, Akwa Y, et al. Pregnenolone sulfate in the brain: a controversial neurosteroid. *Neurochem Int*. 2008;52:522-540.
68. Weaver CE, Land MB, Purdy RH, Richards KG, Gibbs TT, Farb DH. Geometry and charge determine pharmacological effects of steroids on N-methyl-D-aspartate receptor-induced Ca2+ accumulation and cell death. *J Pharmacol Exp Ther*. 2000;293:747-754.
69. Vyklicky V, Krausova B, Cerny J, et al. Block of NMDA receptor channels by endogenous neurosteroids: implications for the agonist induced conformational states of the channel vestibule. *Sci Rep-Uk*. 2015;5:10935.
70. Tuem KB, Atey TM. Neuroactive steroids: receptor interactions and responses. *Front Neurol*. 2017;8:442.
71. Malayev A, Gibbs TT, Farb DH. Inhibition of the NMDA response by pregnenolone sulphate reveals subtype selective modulation of NMDA receptors by sulphated steroids. *Br J Pharmacol*. 2002;135:901-909.
72. Horak M, Vlcek K, Petrovic M, Chodounska H. Molecular mechanism of pregnenolone sulfate action at NR1/NR2B receptors. *J Neurosci*. 2004;24:10318-10325.
73. Petrovic M, Sedlacek M, Horak M, Chodounska H. 20-oxo-5beta-pregnan-3alpha-yl sulfate is a use-dependent NMDA receptor inhibitor. *J Neurosci*. 2005;25:8439-8450.
74. Wong P, Sze Y, Chang CCR, Lee J, Zhang X. Pregnenolone sulfate normalizes schizophrenia-like behaviors in dopamine transporter knockout mice through the AKT/GSK3 beta pathway. *Transl Psychiat*. 2015;5:e528..
75. Plescia F, Sardo P, Rizzo V, et al. Pregnenolone sulphate enhances spatial orientation and object discrimination in adult male rats: evidence from a behavioural and electrophysiological study. *Behav Brain Res*. 2014;258:193-201.
76. Vallee M, Mayo W, Darnaudery M, et al. Neurosteroids: deficient cognitive performance in aged rats depends on low pregnenolone sulfate levels in the hippocampus. *Proc Natl Acad Sci U S A*. 1997;94:14865-14870.
77. Monnet FP, Maurice T. The sigma1 protein as a target for the non-genomic effects of neuro(active)steroids: molecular, physiological, and behavioral aspects. *J Pharmacol Sci*. 2006;100:93-118.
78. Sliwinski A, Monnet FP, Schumacher M, Morin-Surun MP. Pregnenolone sulfate enhances long-term potentiation in CA1 in rat hippocampus slices through the modulation of N-methyl-D-aspartate receptors. *J Neurosci Res*. 2004;78:691-701.
79. Wang CS, Marx CE, Morrow AL, Wilson WA, Moore SD. Neurosteroid modulation of GABAergic neurotransmission in the central amygdala: a role for NMDA receptors. *Neurosci Lett*. 2007;415:118-123.
80. Rabinowitz A, Cohen SJ, Finn DA. The neurosteroid allopregnanolone impairs object memory and contextual fear memory in male C57BL/6J mice. *Horm Behav*. 2014;66:238-246.
81. Tokunaga S, McDaniel JR, Morrow AL, Matthews DB. Effect of acute ethanol administration and acute allopregnanolone administration on spontaneous hippocampal pyramidal cell neural activity. *Brain Res*. 2003;967:273-280.
82. Shimizu H, Ishizuka Y, Yamazaki H, Shirao T. Allopregnanolone increases mature excitatory synapses along dendrites via protein kinase A signaling. *Neuroscience*. 2015;305:139-145.
83. Ritsner M, Maayan R, Gibel A, Weizman A. Differences in blood pregnenolone and dehydroepiandrosterone levels between schizophrenia patients and healthy subjects. *Eur Neuropsychopharmacol*. 2007;17:358-365.
84. Marx CE, Stevens RD, Shampine LJ, et al. Neuroactive steroids are altered in schizophrenia and bipolar disorder: relevance to pathophysiology and therapeutics. *Neuropsychopharmacology*. 2006;31:1249-1263.
85. Grube M, Hagen P, Jedlitschky G. Neurosteroid transport in the brain: role of ABC and SLC transporters. *Front Pharmacol*. 2018;9:354.
86. Ritsner MS, Bawakny H, Kreinin A. Pregnenolone treatment reduces severity of negative symptoms in recent-onset schizophrenia: an 8-week, double-blind, randomized add-on two-center trial. *Psychiatry Clin Neurosci*. 2014;68:432-440.
87. Marx CE, Keefe RS, Buchanan RW, et al. Proof-of-concept trial with the neurosteroid pregnenolone targeting cognitive and negative symptoms in schizophrenia. *Neuropsychopharmacology*. 2009;34:1885-1903.
88. Cai H, Zhou X, Dougherty GG, et al. Pregnenolone-progesterone-allopregnanolone pathway as a potential therapeutic target in first-episode antipsychotic-naive patients with schizophrenia. *Psychoneuroendocrinology*. 2018;90:43-51.
89. Guerra GP, Rubin MA, Mello CF. Modulation of learning and memory by natural polyamines. *Pharmacol Res*. 2016;112:99-118.
90. Skatchkov SN, Antonov SM, Glia EatonMJ, Polyamines Glial. Role in brain function in health and disease. *Biochem Mosc Suppl S*. 2016;10:73-98.
91. Coleman CS, Hu G, Pegg AE. Putrescine biosynthesis in mammalian tissues. *Biochem J*. 2004;379:849-855.
92. Pegg AE. Mammalian polyamine metabolism and function. *IUBMB Life*. 2009;61:880-894.
93. Liu P, Gupta N, Jing Y, Zhang H. Age-related changes in polyamines in memory-associated brain structures in rats. *Neuroscience*. 2008;155:789-796.
94. Laube G, Veh RW. Astrocytes, not neurons, show most prominent staining for spermidine/spermine-like immunoreactivity in adult rat brain. *Glia*. 1997;19:171-179.

95. Bernstein HG, Muller M. The cellular localization of the L-ornithine decarboxylase/polyamine system in normal and diseased central nervous systems. *Prog Neurobiol*. 1999;57:485-505.
96. Masuko T, Kusama-Eguchi K, Sakata K, et al. Polyamine transport, accumulation, and release in brain. *J Neurochem*. 2003;84:610-617.
97. Pegg AE. Functions of polyamines in mammals. *J Biol Chem*. 2016;291:14904-14912.
98. Miller-Fleming L, Olin-Sandoval V, Campbell K, Ralser M. Remaining mysteries of molecular biology: the role of polyamines in the cell. *J Mol Biol*. 2015;427:3389-3406.
99. Williams K. Interactions of polyamines with ion channels. *Biochem J*. 1997;325:289-297.
100. Araneda RC, Zukin RS, Bennett MV. Effects of polyamines on NMDA-induced currents in rat hippocampal neurons: a whole-cell and single-channel study. *Neurosci Lett*. 1993;152:107-112.
101. Williams K. Extracellular modulation of NMDA receptors. *Biol Nmda Receptor*. 2009:235-257.
102. Araneda RC, Lan JY, Zheng X, Zukin RS, Bennett MV. Spermine and arcaine block and permeate N-methyl-D-aspartate receptor channels. *Biophys J*. 1999;76:2899-2911.
103. Lerma J. Spermine regulates N-methyl-D-aspartate receptor desensitization. *Neuron*. 1992;8:343-352.
104. McGurk JF, Bennett MV, Zukin RS. Polyamines potentiate responses of N-methyl-D-aspartate receptors expressed in xenopus oocytes. *Proc Natl Acad Sci U S A*. 1990;87:9971-9974.
105. Williams K. Mechanisms influencing stimulatory effects of spermine at recombinant N-methyl-D-aspartate receptors. *Mol Pharmacol*. 1994;46:161-168.
106. Richardson-Andrews RC. A central role for the polyamines in the aetiology of schizophrenia. *Med Hypotheses*. 1983;11:157-166.
107. Fiori LM, Turecki G. Implication of the polyamine system in mental disorders. *J Psychiatry Neurosci*. 2008;33:102-110.
108. Middleton FA, Mirnics K, Pierri JN, Lewis DA, Levitt P. Gene expression profiling reveals alterations of specific metabolic pathways in schizophrenia. *J Neurosci*. 2002;22:2718-2729.
109. Baytunca MB, Ongur D. Plasma spermine levels in patients with schizophrenia and bipolar disorder: a preliminary study. *Schizophr Res*. 2020;216:534-535.
110. Flayeh KA. Spermidine oxidase activity in serum of normal and schizophrenic subjects. *Clin Chem*. 1988;34:401-403.
111. Das I, Adams C, Essali MA, Debelleroche J, Hirsch SR. Blood polyamines in schizophrenia: a study of clozapine in drug-resistant schizophrenic-patients. *Schizophr Res*. 1992;6:175.
112. Das I, Ramchand CN, Gliddon A, Hirsch SR. Nitric oxide, free radicals and polyamines may have a role in the membrane pathology of schizophrenia. *Neuropsychobiology*. 1998;37:65-67.
113. Gilad GM, Gilad VH, Casanova MF. Polyamines and their metabolizing enzymes in human frontal cortex and hippocampus: preliminary measurements in affective disorders. *Biol Psychiatry*. 1995;38:227-234.
114. Conway EL. Brain lesions and delayed water maze learning deficits after intracerebroventricular spermine. *Brain Res*. 1998;800:10-20.
115. Fruhauf PK, Ineu RP, Tomazi L, Duarte T, Mello CF, Rubin MA. Spermine reverses lipopolysaccharide-induced memory deficit in mice. *J Neuroinflammation*. 2015;12:3.
116. Uzbay T, Kayir H, Goktalay G, Yildirim M. Agmatine disrupts prepulse inhibition of acoustic startle reflex in rats. *J Psychopharmacol*. 2010;24:923-929.
117. Mikolajczak P, Okulicz-Kozaryn I, Kaminska E, Niedopad L, Polanska A, Gebka J. Effects of acamprosate and some polyamine site ligands of NMDA receptor on short-term memory in rats. *Eur J Pharmacol*. 2002;444:83-96.
118. Liu P, Jing Y, Collie ND, Dean B, Bilkey DK, Zhang H. Altered brain arginine metabolism in schizophrenia. *Transl Psychiat*. 2016;6:e871.
119. Traynelis SF, Wollmuth LP, McBain CJ, et al. Glutamate receptor ion channels: structure, regulation, and function. *Pharmacol Rev*. 2010;62:405-496.
120. Prakash A, Bharti K, Majeed AB. Zinc: indications in brain disorders. *Fundam Clin Pharmacol*. 2015;29:131-149.
121. Plum LM, Rink L, Haase H. The essential toxin: impact of zinc on human health. *Int J Environ Res Public Health*. 2010;7:1342-1365.
122. Petrilli MA, Kranz TM, Kleinhaus K, et al. The emerging role for zinc in depression and psychosis. *Front Pharmacol*. 2017;8:414.
123. Frederickson CJ. Neurobiology of zinc and zinc-containing neurons. *Int Rev Neurobiol*. 1989;31:145-238.
124. Wenzel HJ, Cole TB, Born DE, Schwartzkroin PA, Palmiter RD. Ultrastructral localization of zinc transporter-3 (ZnT-3) to synaptic vesicle membranes within mossy fiber boutons in the hippocampus of mouse and monkey. *Proc Natl Acad Sci U S A*. 1997;94:12676-12681.
125. Martinez-Guijarro FJ, Soriano E, Del Rio JA, Lopez-Garcia C. Zinc-positive boutons in the cerebral cortex of lizards show glutamate immunoreactivity. *J Neurocytol*. 1991;20:834-843.
126. Salazar G, Craige B, Love R, Kalman D, Faundez V. Vglut1 and ZnT3 co-targeting mechanisms regulate vesicular zinc stores in PC12 cells. *J Cell Sci*. 2005;118:1911-1921.
127. Wang ZY, Li JY, Dahlstrom A, Danscher G. Zinc-enriched GABAergic terminals in mouse spinal cord. *Brain Res*. 2001;921:165-172.
128. Blakemore LJ, Trombley PQ. Zinc as a neuromodulator in the central nervous system with a focus on the olfactory bulb. *Front Cell Neurosci*. 2017;11:297.
129. Barberis A, Cherubini E, Mozrzymas JW. Zinc inhibits miniature GABAergic currents by allosteric modulation of GABA(A) receptor gating. *J Neurosci*. 2000;20:8618-8627.
130. Joe P, Petrilli M, Malaspina D, Weissman J. Zinc in schizophrenia: a meta-analysis. *Gen Hosp Psychiatry*. 2018;53:19-24.
131. Doboszewska U, Wlaz P, Nowak G, Radziwon-Zaleska M, Cui RJ, Mlyniec K. Zinc in the monoaminergic theory of depression: its relationship to neural plasticity. *Neural Plast*. 2017;2017:3682752.
132. Marger L, Schubert CR, Bertrand D. Zinc: an underappreciated modulatory factor of brain function. *Biochem Pharmacol*. 2014;91:426-435.
133. Chen N, Moshaver A, Raymond LA. Differential sensitivity of recombinant N-methyl-D-aspartate receptor subtypes to zinc inhibition. *Mol Pharmacol*. 1997;51:1015-1023.
134. Rachline J, Perin-Dureau F, Le Goff A, Neyton J, Paoletti P. The micromolar zinc-binding domain on the NMDA receptor subunit NR2B. *J Neurosci*. 2005;25:308-317.
135. Traynelis SF, Burgess MF, Zheng F, Lyuboslavsky P, Powers JL. Control of voltage-independent zinc inhibition of NMDA receptors by the NR1 subunit. *J Neurosci*. 1998;18:6163-6175.
136. Scarr E, Udawela M, Greenough MA, et al. Increased cortical expression of the zinc transporter SLC39A12 suggests a breakdown in zinc cellular homeostasis as part of the pathophysiology of schizophrenia. *NPJ Schizophr*. 2016;2:16002.
137. Mortazavi M, Farzin D, Zarhghami M, Hosseini SH, Mansoori P, Nateghi G. Efficacy of zinc sulfate as an add-on therapy to risperidone versus risperidone alone in patients with schizophrenia: a double-blind randomized placebo-controlled trial. *Iran J Psychiatry Behav Sci*. 2015;9:e853.
138. Cole TB, Martyanova A, Palmiter RD. Removing zinc from synaptic vesicles does not impair spatial learning, memory, or sensorimotor functions in the mouse. *Brain Res*. 2001;891:253-265.
139. Martel G, Hevi C, Kane-Goldsmith N, Shumyatsky GP. Zinc transporter ZnT3 is involved in memory dependent on the hippocampus and perirhinal cortex. *Behav Brain Res*. 2011;223:233-238.
140. Adlard PA, Parncutt JM, Finkelstein DI, Bush AI. Cognitive loss in zinc transporter-3 knock-out mice: a phenocopy for the synaptic and memory deficits of Alzheimer's disease?. *J Neurosci*. 2010;30:1631-1636.

141. Izumi Y, Auberson YP, Zorumski CF. Zinc modulates bidirectional hippocampal plasticity by effects on NMDA receptors. *J Neurosci*. 2006;26:7181-7188.
142. Joshi M, Akhtar M, Najmi AK, Khuroo AH, Goswami D. Effect of zinc in animal models of anxiety, depression and psychosis. *Hum Exp Toxicol*. 2012;31:1237-1243.
143. Schoeler T, Petros N, Di Forti M, et al. Association between continued cannabis use and risk of relapse in first-episode psychosis: a quasi-experimental investigation within an observational study. *Jama Psychiatry*. 2016;73:1173-1179.
144. Foti DJ, Kotov R, Guey LT, Bromet EJ. Cannabis use and the course of schizophrenia: 10-Year follow-up after first hospitalization. *Am J Psychiat*. 2010;167:987-993.
145. Sanchez-Blazquez P, Rodriguez-Munoz M, Garzon J. The cannabinoid receptor 1 associates with NMDA receptors to produce glutamatergic hypofunction: implications in psychosis and schizophrenia. *Front Pharmacol*. 2014;4:169.
146. Szutorisz H, Hurd YL. Epigenetic Effects of Cannabis Exposure. *Biol Psychiat*. 2016;79:586-594.
147. Leweke FM, Giuffrida A, Wurster U, Emrich HM, Piomelli D. Elevated endogenous cannabinoids in schizophrenia. *Neuroreport*. 1999;10:1665-1669.
148. De Marchi N, De Petrocellis L, Orlando P, Daniele F, Fezza F, Di Marzo V. Endocannabinoid signalling in the blood of patients with schizophrenia. *Lipids Health Dis*. 2003;2:5.
149. Wang J, Ueda N. Biology of endocannabinoid synthesis system. *Prostag Oth Lipid M*. 2009;89:112-119.
150. Pertwee RG. The pharmacology of cannabinoid receptors and their ligands: an overview. *Int J Obes (Lond)*. 2006;30 Suppl 1:S13-8.
151. Mackie K. Distribution of cannabinoid receptors in the central and peripheral nervous system. *Handb Exp Pharmacol*. 2005:299-325.
152. Gong JP, Onaivi ES, Ishiguro H, et al. Cannabinoid CB2 receptors: immunohistochemical localization in rat brain. *Brain Res*. 2006;1071:10-23.
153. Zou SL, Kumar U. Cannabinoid Receptors and the Endocannabinoid System: signaling and Function in the Central Nervous System. *Int J Mol Sci*. 2018;19:833.
154. Kruk-Slomka M, Dzik A, Budzynska B, Biala G. Endocannabinoid System: the Direct and Indirect Involvement in the Memory and Learning Processes-a Short Review. *Mol Neurobiol*. 2017;54:8332-8347.
155. Castillo PE, Younts TJ, Chavez AE, Hashimotodani Y. Endocannabinoid signaling and synaptic function. *Neuron*. 2012;76:70-81.
156. Sanchez-Blazquez P, Rodriguez-Munoz M, Vicente-Sanchez A, Garzon J. Cannabinoid receptors couple to NMDA receptors to reduce the production of NO and the mobilization of zinc induced by glutamate. *Antioxid Redox Signal*. 2013;19:1766-1782.
157. Colizzi M, Weltens N, McGuire P, et al. Delta-9-tetrahydrocannabinol increases striatal glutamate levels in healthy individuals: implications for psychosis. *Mol Psychiatry*. 2019. https://doi.org/10.1038/s41380-019-0374-8.
158. Fan N, Yang H, Zhang J, Chen C. Reduced expression of glutamate receptors and phosphorylation of CREB are responsible for in vivo Delta9-THC exposure-impaired hippocampal synaptic plasticity. *J Neurochem*. 2010;112:691-702.
159. Brown TM, Brotchie JM, Fitzjohn SM. Cannabinoids decrease corticostriatal synaptic transmission via an effect on glutamate uptake. *J Neurosci*. 2003;23:11073-11077.
160. Antonelli T, Tomasini MC, Tattoli M, et al. Prenatal exposure to the CB1 receptor agonist WIN 55,212-2 causes learning disruption associated with impaired cortical NMDA receptor function and emotional reactivity changes in rat offspring. *Cereb Cortex*. 2005;15:2013-2020.
161. Hampson RE, Miller F, Palchik G, Deadwyler SA. Cannabinoid receptor activation modifies NMDA receptor mediated release of intracellular calcium: implications for endocannabinoid control of hippocampal neural plasticity. *Neuropharmacology*. 2011;60:944-952.
162. Vicente-Sanchez A, Sanchez-Blazquez P, Rodriguez-Munoz M, Garzon J. HINT1 protein cooperates with cannabinoid 1 receptor to negatively regulate glutamate NMDA receptor activity. *Mol Brain*. 2013;6:42.
163. Navarrete M, Araque A. Endocannabinoids mediate neuron-astrocyte communication. *Neuron*. 2008;57:883-893.
164. Ruggiero RN, Rossignoli MT, De Ross JB, Hallak JEC, Leite JP, Bueno-Junior LS. Cannabinoids and Vanilloids in Schizophrenia: neurophysiological Evidence and Directions for Basic Research. *Front Pharmacol*. 2017;8:399.
165. Rodriguez-Munoz M, Sanchez-Blazquez P, Callado LF, Meana JJ, Garzon-Nino J. Schizophrenia and depression, two poles of endocannabinoid system deregulation. *Transl Psychiatry*. 2017;7:1291.
166. Schneider M, Koch M. The cannabinoid agonist WIN 55,212-2 reduces sensorimotor gating and recognition memory in rats. *Behav Pharmacol*. 2002;13:29-37.
167. Bortolato M, Campolongo P, Mangieri RA, et al. Anxiolytic-like properties of the anandamide transport inhibitor AM404. *Neuropsychopharmacology*. 2006;31:2652-2659.
168. Pedrazzi JFC, Issy AC, Gomes FV, Guimaraes FS, EA Del-Bel. Cannabidiol effects in the prepulse inhibition disruption induced by amphetamine. *Psychopharmacology*. 2015;232:3057-3065.
169. Long LE, Malone DT, Taylor DA. Cannabidiol reverses MK-801-induced disruption of prepulse inhibition in mice. *Neuropsychopharmacology*. 2006;31:795-803.
170. Levin R, Peres FF, Almeida V, Calzavara MB, Zuardi AW, Hallak JEC, et al. Effects of cannabinoid drugs on the deficit of prepulse inhibition of startle in an animal model of schizophrenia: the SHR strain. *Frontiers in Pharmacology*. 2014:5.
171. Gururajan A, Taylor DA, Malone DT. Effect of cannabidiol in a MK-801-rodent model of aspects of Schizophrenia. *Behav Brain Res*. 2011;222:299-308.
172. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol*. 2011;10:63-74.
173. Venkatesan A, Adatia K. Anti-NMDA-Receptor Encephalitis: from Bench to Clinic. *ACS Chem Neurosci*. 2017;8:2586-2595.
174. Sharma R, Al-Saleem FH, Panzer J, et al. Monoclonal antibodies from a patient with anti-NMDA receptor encephalitis. *Ann Clin Transl Neurol*. 2018;5:935-951.
175. Jones BE, Tovar KR, Goehring A, et al. Autoimmune receptor encephalitis in mice induced by active immunization with conformationally stabilized holoreceptors. *Sci Transl Med*. 2019:11.
176. Dalmau J, Armangue T, Planaguma J, et al. An update on anti-NMDA receptor encephalitis for neurologists and psychiatrists: mechanisms and models. *Lancet Neurol*. 2019;18:1045-1057.
177. Kayser MS, Titulaer MJ, Gresa-Arribas N, Dalmau J. Frequency and characteristics of isolated psychiatric episodes in anti-N-methyl-d-aspartate receptor encephalitis. *JAMA Neurol*. 2013;70:1133-1139.
178. Hughes EG, Peng X, Gleichman AJ, et al. Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. *J Neurosci*. 2010;30:5866-5875.
179. Moscato EH, Peng X, Jain A, Parsons TD, Dalmau J, Balice-Gordon RJ. Acute mechanisms underlying antibody effects in anti-N-methyl-D-aspartate receptor encephalitis. *Ann Neurol*. 2014;76:108-119.
180. Mikasova L, De Rossi P, Bouchet D, et al. Disrupted surface cross-talk between NMDA and Ephrin-B2 receptors in anti-NMDA encephalitis. *Brain*. 2012;135:1606-1621.
181. Ladepeche L, Planaguma J, Thakur S, et al. NMDA Receptor Autoantibodies in Autoimmune Encephalitis Cause a Subunit-Specific

Nanoscale Redistribution of NMDA Receptors. *Cell Rep*. 2018;23: 3759-3768.
182. Gleichman AJ, Spruce LA, Dalmau J, Seeholzer SH, Lynch DR. Anti-NMDA receptor encephalitis antibody binding is dependent on amino acid identity of a small region within the GluN1 amino terminal domain. *J Neurosci*. 2012;32:11082-11094.
183. Manto M, Dalmau J, Didelot A, Rogemond V, Honnorat J. In vivo effects of antibodies from patients with anti-NMDA receptor encephalitis: further evidence of synaptic glutamatergic dysfunction. *Orphanet J Rare Dis*. 2010;5:31.
184. Planaguma J, Leypoldt F, Mannara F, et al. Human N-methyl D-aspartate receptor antibodies alter memory and behaviour in mice. *Brain*. 2015;138:94-109.
185. Li Y, Tanaka K, Wang L, Ishigaki Y, Kato N. Induction of Memory Deficit in Mice with Chronic Exposure to Cerebrospinal Fluid from Patients with Anti-N-Methyl-D-Aspartate Receptor Encephalitis. *Tohoku J Exp Med*. 2015;237:329-338.
186. Kersten M, Rabbe T, Blome R, et al. Novel Object Recognition in Rats With NMDAR Dysfunction in CA1 After Stereotactic Injection of Anti-NMDAR Encephalitis Cerebrospinal Fluid. *Front Neurol*. 2019;10:586.
187. Masopust J, Andrys C, Bazant J, Vysata O, Kuca K, Valis M. Anti-NMDA receptor antibodies in patients with a first episode of schizophrenia. *Neuropsychiatr Dis Treat*. 2015;11:619-623.
188. Rhoads J, Guirgis H, McKnight C, Duchemin AM. Lack of anti-NMDA receptor autoantibodies in the serum of subjects with schizophrenia. *Schizophr Res*. 2011;129:213-214.
189. Zandi MS, Irani SR, Lang B, et al. Disease-relevant autoantibodies in first episode schizophrenia. *J Neurol*. 2011;258:686-688.
190. Tsutsui K, Kanbayashi T, Tanaka K, et al. Anti-NMDA-receptor antibody detected in encephalitis, schizophrenia, and narcolepsy with psychotic features. *BMC Psychiatry*. 2012;12:37.
191. Castillo-Gomez E, Oliveira B, Tapken D, et al. All naturally occurring autoantibodies against the NMDA receptor subunit NR1 have pathogenic potential irrespective of epitope and immunoglobulin class. *Mol Psychiatry*. 2017;22:1776-1784.
192. Yamamura S, Hoshikawa M, Dai K, et al. ONO-2506 inhibits spike-wave discharges in a genetic animal model without affecting traditional convulsive tests via gliotransmission regulation. *Brit J Pharmacol*. 2013;168:1088-1100.
193. Mony L, Zhu S, Carvalho S, Paoletti P. Molecular basis of positive allosteric modulation of GluN2B NMDA receptors by polyamines. *EMBO J*. 2011;30:3134-3146.
194. Moriyama Y, Hatano R, Moriyama S, Uehara S. Vesicular polyamine transporter as a novel player in amine-mediated chemical transmission. *Biochim Biophys Acta, Biomembr*. 2020:183208.
195. Sensi SL, Paoletti P, Bush AI, Sekler I. Zinc in the physiology and pathology of the CNS. *Nat Rev Neurosci*. 2009;10:780-U38.
196. Xu YS, Xiao GR, Liu L, Lang ML. Zinc transporters in Alzheimer's disease. *Mol Brain*. 2019;12:106.

How to cite this article: Jorratt P, Hoschl C, Ovsepian SV. Endogenous antagonists of *N*-methyl-D-aspartate receptor in schizophrenia. *Alzheimer's Dement*. 2020;1-18.
https://doi.org/10.1002/alz.12244