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PSYCHIATRY AND PRECLINICAL PSYCHIATRIC STUDIES - REVIEW ARTICLE

Modelling the neurodevelopmental pathogenesis in neuropsychiatric disorders. Bioactive kynurenines and their analogues as neuroprotective agents—in celebration of 80th birthday of Professor Peter Riederer

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Abstract

Following introduction of the monoamine oxidase type B inhibitor selegiline for the treatment of Parkinson's disease (PD), discovery of the action mechanism of Alzheimer's disease-modifying agent memantine, the role of iron in PD, and the loss of electron transport chain complex I in PD, and development of the concept of clinical neuroprotection, Peter Riederer launched one of the most challenging research project neurodevelopmental aspects of neuropsychiatric disorders. The neurodevelopmental theory holds that a disruption of normal brain development in utero or during early life underlies the subsequent emergence of neuropsychiatric symptoms during later life. Indeed, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition and the International Classification of Diseases, 11th Revision categorize autism spectrum disorder and attention deficit hyperactivity disorder in neurodevelopmental disorders (NDDs). More and more evidence, especially from preclinical studies, is revealing that neurodevelopmental pathology is not limited to the diagnostic class above, but also contributes to the development of other psychiatric disorders such as schizophrenia, bipolar disorder, and obsessive–compulsive disorder as well as neurodegenerative diseases such as PD and Huntington's disease. Preclinical animal research is taking a lead in understanding the pathomechanisms of NDDs, searching for novel targets, and developing new neuroprotective agents against NDDs. This narrative review discusses emerging evidence of the neurodevelopmental etiology of neuropsychiatric disorders, recent advances in modelling neurodevelopmental pathogenesis, potential strategies of clinical neuroprotection using novel kynurenine metabolites and analogues, and future research direction for NDDs.

Keywords Neurodevelopmental · Neurodegenerative · Neuropsychiatric · Kynurenine · Neuroprotection · Translational

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Abbreviations

AA	Anthranilic acid
ADGL3	Adhesion G protein-coupled receptor L3
AHR	Aryl hydrocarbon receptor
ADHD	Attention deficit hyperactive disorder
ASD	Autism spectrum disorder
BBB	Blood-brain barrier
BP	Bipolar disorder
CNTNAP2	Contactin-associated protein-like 2
DISC1	Disrupted in Schizophrenia 1
DSM-5	Diagnostic and statistical manual of mental disorders, fifth edition
HD	Huntington's disease
3-HAA	3-Hydroxyanthranilic acid
3-HK	3-Hydroxy-L-kynurenine
IDO	Indoleamine 2,3-dioxygenase

ICD-11	International classification of diseases, 11th revision
KYNU	Kynureninase
KYN	Kynurenine
KAT	Kynurenine aminotransferase
KMO	Kynurenine 3-monooxygenase
KYNA	Kynurenic acid
MIA	Maternal immune activation
NMDA	N-methyl-D-aspartate
NDDs	Neurodevelopmental disorders
NAD^+	Nicotinamide adenine dinucleotide
OCD	Obsessive compulsive disorder
PD	Parkinson's disease
poly I:C	Polyinosinic polycytidylic acid
PTSD	Post-traumatic stress syndrome
PINK	Phosphatase and tensin homolog (PTEN)-induced kinase
QA	Quinolinic acid
SCZ	Schizophrenia
SHANK3	Src-homology 3 and multiple ankyrin repeat domains 3
Trp	Tryptophan
TDO	Tryptophan 2,3-dioxygenase
VPA	Valproic acid
XA	Xanthurenic acid

Introduction

Neurodevelopmental disorders (NDDs) are a group of prevalent and debilitating conditions of the central nervous system, caused by insults in brain growth and development during late first or early second trimester, or even early postnatal period, leading to the emergence of neuropsychiatric manifestations during early life, which tend to last for lifetime (Ismail and Shapiro 2019). The prevalence of NDDs is 0.76%, being that of neurological disorders are higher than that of mental conditions, with increasing tendency during last 20 years (Bitta; ACE: Health—Neurodevelopmental Disorders 2021). The signs and symptoms include intellectual disability such as memory impairment and learning difficulty, emotional disturbance such as depression and anxiety, impaired social interaction and communication, motor dysfunction such as speech problem and ataxia, impaired self-control, and attention deficit (Dubovický 2010). The underlying pathological neural development in gestational and perinatal periods affects neurulation, neuronal proliferation and migration, apoptosis, synaptogenesis, gliogenesis, and myelination (Homberg et al. 2016).

The emergence of the concept of NDDs dates back to the eighteenth century, leading to the publication of French physician Philippe Pinel who wrote that idiocy is one of psychiatric disorders including mania, melancholia, and dementia and is the most severe form of dementia, admitting the presence of acquired and innate idiocy (Pinel 1809). Étienne Jean Georget introduced the concept of psychiatric developmental disorder in On Insanity, stating that "idiocy is a lack of development of intellectual faculties", that "a developmental defect is not, strictly speaking, a disease", and that "idiots should be classified among monsters" which are nowadays understood as genetic abnormalities (Georget 1820). Later, Jean-Étienne Esquirol wrote that idiocy was not an illness, but a condition in which intellectual faculties could not achieve sufficient development (Esquirol 1838). John Langdon Down first described a unique disorder with mental deficiency, now called Down syndrome, one of the most prevalent NDDs (Langdon and Down 1862). Almost a century later Down syndrome was discovered to be caused

Fig. 1 Historical timeline of neurodevelopmental disorders

by a genetic abnormality trisomy 21 (Lejeune et al. 1959). Leo Kanner first reported childhood autism characterized by impaired social interaction, obsessiveness, stereotypy, and echolalia, concluding that autism results from abnormal development of the brain during early life, which renders innate inability of the formation of social interaction (Kanner 1943). Hans Asperger described a unique autistic condition with impaired social communication and interaction, average or superior intelligence, and no significant language delay, with high penetrance within the family of autism spectrum disorder (ASD) (Asperger 1944; MedlinePlus, Autism Spectrum Disorder). Melchior Adam Weikard first documeted adults and children who have trouble paying attention, and are distractible, lacking in persistence, overactive, and impulsive (Weikard 1799). The condition is due to differences in the development and the function of the central nervous system (Kooija 2015) (Fig. 1). Thus, the concept of NDDs has evolved over a long period of time, and now the term NDD is used as a general term referring to conditions with impaired cognitive, emotional, social, and/or motor functions resulting from disruption to brain development.

The term NDDs has been recognized and included for the first time as a diagnostic class in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) in 2013 and International Classification of Diseases, 11th Revision (ICD-11) which has come into effect in 2022 (American Psychiatric Association 2013; World Health Organization 2019). NDDs are applied to a group of disorders characterized by early onset, maldevelopment of both cognitive and social interaction, and multifactorial origins. Interestingly, these alterations in social cognition and social functioning, are assumed to rely on altered activity within cortical and subcortical brain structures (Battaglia et al. 2022a). Furthermore, this could be related to the interpretation of social signals: evidence from healthy individuals suggest that potentially threatening situations, such as others' proximity, can trigger different physiological responses that help regulate the distance between themselves and others during social interaction (Candini et al. 2021), showing the critical role of social signal interpretation in social interaction. Individuals with NDDs have social impairments, potentially due to the lack of social signal interpretation, and, therefore, resulting unable to interpret these signals to guide appropriate behaviors.

The disorders exhibit sex differences where males are more commonly affected than females and have a chronic course lasting into adulthood (Thapar 2015). The class includes ASD and attention deficit hyperactivity disorder (ADHD) together with other six categories but does not include more common disorders such as anxiety and depression, which are considered to have the origin in psychosocial difficulty and have an intermittent course. Asperger syndrome is not listed any more in the ICD-11 and it is grouped into a lumping category ASD. The term NDDs has gained official status in diagnostic categories; however, the class includes a wide range of neuropsychiatric disorders which have little in common. Thus, the designation may have added some value for diagnosis, but it remains of less use for the sake of prognosis and treatment (Stein et al. 2020).

Accumulating evidence suggests that neurodevelopmental pathology plays a major role in the pathogenesis of other mental illnesses and neurological diseases. Schizophrenia (SCZ) has a substantial neurodevelopmental basis in the pathogenesis; likewise, bipolar disorder (BP), anxiety disorder, obsessive compulsive disorder (OCD), and Tourette syndrome have been reported to have the neurodevelopmental backgrounds, although to a lesser extent (Keshavan et al. 2015; Hagan et al. 2015; Geschwind 2011; Georgitsi et al. 2016). Furthermore, neurodevelopmental etiology has been disclosed in the pathogenesis of neurodegenerative diseases including Parkinson's disease (PD) and Huntington's disease (HD) (Riederer 2003; van der Plas 2020). This narrative review discusses the most updated understanding of NDDs, recent advances in modelling neurodevelopmental pathogenesis, the tryptophan (Trp)-kynurenine (KYN) metabolic system as potential targets, and KYN metabolites and analogues as potential clinical neuroprotective agents for NDDs.

Table 1 Neurodevelopmental disorders in Diagnostic and statistical manual of mental disorders, fifth edition (DSM-5) and International classification of diseases, 11th revision (ICD-11)

Neurodevelopmental disorders	
DSM-5	ICD-11
Intellectual disorders	Intellectual development, developmental speech or language disorders,
Communication disorders	Autism spectrum disorder
Autism spectrum disorder	Developmental learning disorders
Attention deficit hyperactivity disorder	Developmental motor coordination disorder
Specific learning disorders	Attention deficit hyperactivity disorder
Motor disorders	Stereotyped movement disorder
Tic disorders	Other neurodevelopmental disorders
Other neurodevelopmental disorders	

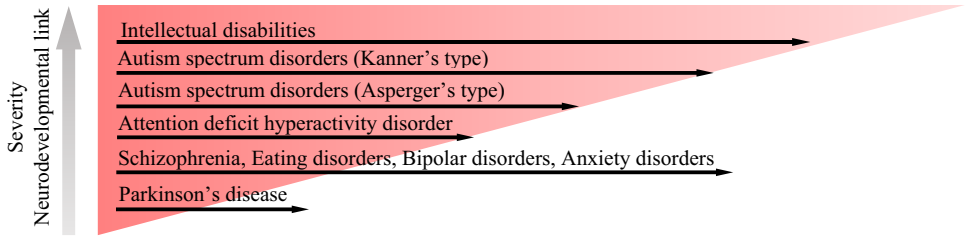

Fig. 2 The continuity and severity gradient of neurodevelopmental disorders and related disorders

Neurodevelopmental disorders: the diagnostic class

DSM-5 categorizes NDDs into intellectual disorders, communication disorders, ASD, ADHD, specific learning disorders, motor disorders, tic disorders, and other NDDs, while ICD-11 groups disorders of intellectual development, developmental speech or language disorders, ASD, developmental learning disorders, developmental motor coordination disorder, ADHD, stereotyped movement disorder, and other neurodevelopmental disorders (Table 1). A trend has been designating a more comprehensive category such as ASD, avoiding the designation of discrete entities such as Asperger syndrome and instead adding different specifiers which describe intellectual and language level, medical or genetic comorbidities, and mental health comorbidities, thus revealing the presence of the continuity of NDDs (Fig. 2) (Stein 2020). Furthermore, DSM-5 even accepts a combined diagnosis of ADHD and ASD. Accordingly, the classification of NDDs is mostly based on behavioral phenotypes which show considerable comorbidity and phenotypic overlaps between NDDs (Morris-Rosendahl 2020) (Fig. 1). However, groups of individuals with ASD, with ASD plus ADHD, and with only ADHD assessed by the Vineland Adaptive Behavior Scales, 2nd edition (VABS-II), showed significantly differently affected behavioral domains such as communication, socialization, daily living skills, motor, and adaptive behavior, suggesting the presence of considerably heterogenic phenotypes under the diagnostic classes (Scandurra 2019).

NDDs have been better considered to be lying not solely on the continuity of behavioral phenotypes, but also on etiological continuum (Owen 2017). NDDs are highly heritable with genetic variants, but non-heritable spontaneous genetic changes may lead to NDDs. Down's syndrome is the most frequent genetic disorder phenotypically characterized by intellectual disability and psychobehavioral pathology, caused by the presence of a third copy of chromosome 21 (Vicari 2013). Many individuals with developmental delay or autism carry de novo mutation such as missense and/or gene-disruptive mutation in neurodevelopmental gene candidates (Coe 2019). Rare pleiotropic manifestations of genes such as rare copy number variants at specific loci or collectively, have been shown to be associated with intellectual disability, ASD, ADHD, and substantially higher risk of SCZ (Owen 2017). Altered epigenetic modifications have been shown to be responsible for monogenic causes of NDDs including Rett syndrome, Fragile X syndrome, Angelman syndrome, and Prader–Willi syndrome (Egger 2004). Those findings have shown genetic and epigenetic evidence in the disturbance of early brain development and thus evidence in risk factors and pathomechanism of NDDs.

Genetic factors account for only 30–40% of NDDs. Accordingly, the etiological continuum of NDDs is not limited to genetic factors, but non-genetic factors are considered to play an important role in the pathogenesis. Environmental factors directly contribute to the pathogenesis of NDDs. The systematic review of twin and sibling studies showed that advanced paternal age, low birth weight, birth defects, perinatal hypoxia, and respiratory stress are associated with ASD and that low birth weight, gestational age, and low family income or transient income decline during childhood are associated with ADHD (Carlsson 2021). Other environmental factors considered to play a certain role in NDD pathogenesis are food, pollutants, parasites, temperature, probably light and sound, and even population density or other stressors (Neurodevelopmental Disorders 2021). Furthermore, environmental factors can interact with heritable or spontaneously occurred genetic vulnerabilities to trigger harmful effects on neurodevelopmental process during the antenatal and perinatal windows of critical period in neural development (Rice and Barone 2000). Thus, hereditary or spontaneously occurred genetic vulnerabilities, various direct environmental offense, and environment-induced genetic susceptibility align together in the etiological continuum, leading to the development of NDDs in later life. The degree of underlying genetic vulnerability, the timing and the dose of environmental insults, and the predominant pattern and the sequence of abnormal neural development determine the onsets and entities of NDDs and thus disclosing the severity gradient of NDDs (Dell'Osso 2019). Generally, the earlier the age of onset and the higher the severity and persistence of the genetic, cognitive, sensorimotor, and psychopathological dysfunction, the greater the overall neurodevelopmental impairment (Morris-Rosendahl 2020). The continuum of NDDs with a gradient of decreasing neurodevelopmental impairment includes intellectual disorders, low-functioning level 3 ASD such as Kanner's syndrome,

high-functioning level 1 ASD such as Asperger's syndrome, and ADHD (Dell'Osso 2019).

Disorders with neurodevelopmental pathogenesis

The continuum of NDDs is not considered to be limited to the diagnostic classes of DSM-5 and ICD-11. The continuum can be extended to other psychiatric disorders and neurological diseases in which the initial neurodevelopmental insults take place in prenatal and/or perinatal period in the presence of genetic vulnerability and the onset of a disease emerges later in life. The continuum is less dramatic and less prominent compared to DSM-5 and ICD-11-designated NDDs due to vague genetic evidence and complex genetic pleiotropy, less severe manifestation and episodic emergence of symptoms, and significantly later onset of diseases during adolescence or adulthood. The extended continuum of other psychiatric disorders with a gradient of decreasing neurodevelopmental impairment are schizophrenia, eating disorders, BP, anxiety disorders, and posttraumatic stress disorder (PTSD) (Dell'Osso 2019).

SCZ is considered to have its origin in the neurodevelopmental insults during as early as the first and second trimesters. The aberrations in the structure, wiring, and chemistry of neural system cause functional disconnections (disconnection syndrome) and thus a failure of the functional integration of the brain, leading to the generation of psychotic symptoms during adolescence or young adulthood (Keshavan 2015). A young girl with high-functioning autistic disorder who developed Tourette syndrome and OCD later experienced partial anorexia nervosa. The case presents the longitudinal commonalities and symptomatic overlap of multiple comorbidities from ASD to eating disorder (Kerbeshian and Burd 2009). The neurodevelopmental aberration of BD is less consistently implicated in than those of SCZ, but a part of individuals with BD, particularly with the early onset and psychotic symptoms is associated with the dysfunction of neurodevelopmental pathways (Kloiber 2020). Anxiety disorders are the most prevalent mental condition in young generation with the onset prior to or during adolescent. Individuals with NDDs have a higher risk of developing anxiety disorder and the symptoms of anxiety are the same as those in the general population. The structural and functional maldevelopment of the frontolimbic circuitry during childhood and adolescence is gaining evidence in the pathogenesis of anxiety disorder (Zacharek 2021).

PTSD has been considered to be a psychologic disorder triggered by a terrifying event. However, the altered brain structures and abnormal neurochemical regulation have been observed, which include the size of the right amygdala and catecholamine, serotonin, amino acids, peptides, and opioids (Bowirrat 2010). PTSD is now considered to have its etiological basis in polygenic disposition and environmental triggers (Blum 2019). Abnormal brain structure and function in the neural circuitry are characteristic findings in pediatric PTSD (Herringa 2017). As PTSD may develop from an aberrant fear learning process and from its persistence, several studies have suggested the effectiveness of non-invasive brain simulation (NIBS) to interfere and modulate the abnormal activity of neural circuits (i.e., amygdala-medial prefrontal cortex-hippocampus) involved in the acquisition and consolidation or reconsolidation of emotional–fear–memories (i.e., traumatic memories), which are altered in this fear-related disorder (Borgomaneri et al. 2020a, b, 2021a). Furthermore, individuals with autistic traits show a hyperarousal type of PTSD characterized by insomnia, anger, anxiety, and difficulty in concentration (Haruvi-Lamdan 2019). Young children who experience a terrifying event are considered to be at even higher risk of affecting normal neurodevelopmental process which may predispose to the development of PTSD (LeardMann 2010).

Other psychiatric disorders which are considered to have their etiological basis in abnormal neurodevelopmental process include OCD and ADHD. Olfactory dysfunction is a neurodevelopmental disorder which may lead to global neural dysfunction. Olfactory performance deficits are statistically relevant to individuals with ASD and OCD (Crow 2020). The imaging studies have revealed the alteration of the orbitofrontal cortex, the anterior cingulate cortex, and the head of the caudate nucleus in neuropsychological deficits in individuals with OCD (Maia 2008). Structural and functional imaging studies have revealed developmental abnormalities affecting the prefrontal parietal, temporal, and motor cortices; furthermore, longitudinal studies have showed a maturational delay (Vaidya 2012). The machine learning analysis integrating neuroanatomy and diagnostic phenotypes of ASD, OCD, and ADHD, revealed disagreement between diagnostic labels and the diagnosis-agnostic homogeneous groups, suggesting possibly no evidence of the diagnostic labels reflecting cortical morphology and thus the possible presence of complex neuroanatomical pathogenesis (Kushki 2019).

The second most common neurodegenerative disorder PD has been considered to also have its etiological basis in neurodevelopmental process. PD is a progressive neurological disorder that affects the motor system with muscle rigidity, tremors, and changes in speech and gait. Furthermore, it has been shown that there could be alterations in motor imagery or in the suppression of on-going action (Sellitto et al. 2022; Borgomaneri et al. 2020a, b) since the cortical and subcortical network in these processes are the same that are functionally altered in PD. Notwithstanding typical motor symptoms, PD patients frequently experience psychological and behavioral symptoms named non-motor symptoms (NMS), which include sensory complaints, mental disorders, sleep disturbances and autonomic dysfunction. NMS often occurs in

Parkinson's due to the loss of dopamine-producing cells and the presence of Lewy bodies in the brain, having negative impacts on the quality of life and causing major challenges for disease management. Studies in healthy individuals have revealed that modulation of autonomic nervous system responses is fundamental for behavioral regulation, indicating how this function is impaired in PD patients (Ellena et al. 2020; Borgomaneri et al. 2021c). Infantile and juvenile PD subtypes with the onset of less than 20 years old, have been linked to gestational viral and bacterial infection such as influenza and bacterial lipopolysaccharide, exposure to pesticides, complications during pregnancy, and perinatal incidents (Becker 1974; Widhalm 1985; Riederer 2003; Barlow 2007). However, a majority of PD patients does not show symptoms early in their life. The neurodevelopmental hypothesis of PD holds that predisposing developmental defects are caused by genetic and/or environmental factors and subsequent neural maldevelopment are compensated and thus stay silent during an early period of life but the susceptibility increases after the second and multiple triggers, leading to the onset of PD in later life (Schwamborn 2018). HD is a hereditary neurodegenerative disease with mutation in the huntingtin gene, but 10% of the mutation takes place spontaneously. The symptoms typically appear in the age of 30s to 40s, but a juvenile subtype of HD with the onset of 20 years old shows different symptoms and progresses faster (Huntington's Disease 2022). The huntingtin gene mutation holders have a long symptom-free period. Thus, HD is a genetic neurologic disorder with neurodevelopmental components. Epilepsy is considered to have a neurodevelopmental basis in the pathogenesis, including congenital brain maldevelopment, abnormal embryonic neural signaling, and maldevelopment of neuronal networks during postnatal period (Shankar 2020). The impaired healthy neural development during prenatal and perinatal periods leads to an hyperexcitability phenotype in adulthood, cortical maldevelopment, and excitatory/inhibitory imbalance, leading to an epileptic episode (Bozzi, 2012). Furthermore, a higher frequency of migraine symptoms is reported in individuals with ASD, suggesting a possible link between migraine and ASD in common genetic background, pathogenesis, immune response, cortical disorganization, and gut–brain axis. However, the association remains almost unknown (Vetri 2020).

Modeling neurodevelopmental pathogenesis

Developing in vitro and in vivo models of neuropsychiatric diseases has been under extensive research (Fu 2022; Thabault 2022; Swingler 2022; Jeong 2021; Quirant-Sánchez 2021; Tsay 2021; Bellon 2021; Castillo-Mariqueo 2021; Hsu 2021; Lee 2021; Garro-Martínez; Abuaish 2021). Preclinical animal research is the essential arena for medical sciences to identify risk factors, to understand pathology and disease progression, and to search for potential therapeutic agents (Tanaka 2012; Telegdy 2011; Tanaka and Vécsei 2021b). Modeling NDDs is a crucial step but remains a challenging task due to their polygenic, pleiotropic, and multifactorial etiologies. Most of animal models are genetic models carrying defective mutations or gene knockouts that can be observed in subtypes of NDDs or pharmacological models in which normal neural development is disrupted by pharmacological agents.

Autism spectrum disorder

The Src-homology 3 and multiple ankyrin repeat domains 3 (*SHANK3*) gene encodes a multidomain scaffold protein of the postsynaptic density. The hemi-deletion of *SHANK3* has been observed in patients with Phelan–McDermid syndrome which exhibit ASD-like behaviors. 1–2% of ASD population carries the mutation of *SHANK3* (Phelan and McDermid 2012). The heterozygous *Shank3*$^{\Delta c/\Delta c}$ mice with C-terminal 508 deletions show impairments in social novelty preference and grooming, while the homozygous counterparts show significant impairments in social novelty preference, stereotyped behavior, and gait. The impairments are more prominent in males than in females (Thabault 2022).

The Contactin-associated protein-like 2 (*CNTNAP2*) is the longest gene in the human genome, which encodes a neurexin that regulates the interactions of neurons and glial cells during brain development. The *Cntnap2* mutant backcrossed strains and *Cntnap2* knockout mice show ASD-like behavior such as impaired social interaction and repetitive behaviors but normal growth and final weight. Interestingly, *Cntnap2*$^{-/-}$ mice exhibit hyperactive traits and develop epileptic seizures after 6 months. Adhesion G Protein-Coupled Receptor L3 (*ADGRL3*) encodes latrophilins which may function in cell adhesion, signal transduction, and synapse stability (Dalla Vecchia 2019). *ADGRL3*$^{-/-}$ mice show hyperactivity in open-field test and less depression-like behavior in forced swim test but no motor coordination in rotarod test. In addition, the null mice exhibits higher locomotor response to cocaine, which may suggest a link to substance use disorder (Dalla Vecchia 2019).

Attention deficit hyperactivity disorder

The ADHD line of mice are generated through within-family selection of over 16 generation, which exhibit motor impulsivity that is ameliorated with a low dose of amphetamine. The strain shows the hypoactivation of the prefrontal cortex and the dysregulation vermal activation (Majdak 2016). The valproic acid (VPA) model is one of the most widely used animal models of ASD. The VPA injection of 400 mg/kg, i.p. to pregnant females at embryonic day 12.5 [E12.5] yields offspring with motor incoordination and gait deficits which

are more pronounced in males than females and with severe social dysfunction only in males (Thabault 2022). An environmental model of ADHD simulating viral infections and subsequent maternal immune reaction during the gestational period has been developed. Polyinosinic:polycytidylic acid (poly I:C) is a double-stranded RNA analogue which models the actions of extracellular dsRNA and induces maternal immune activation (MIA). The poly I:C injection of 20 mg/kg, i.p. at E12.5 produces a MIA phenotype in only males with abnormal social behavior and motor coordination but with normal gait and walking skills (Thabault 2022). Thus, the poly I:C-induced model is less prominent in autism phenotype than the VPA model. Nevertheless, the model has been playing an active role in search for novel drug targets for symptomatic as well as preventive therapeutic strategies in psychiatric disorders (Reisinger 2015). Other chemically induced models of ADHD include prenatal or early postnatal exposure to ethanol, nicotine, polychlorinated biphenyls, 6-hydroxydopamine, and scopolamine.

Schizophrenia

The Disrupted in Schizophrenia 1 (*DISC1*) gene encodes a synaptic scaffold protein that regulate neural development and brain maturation and is associated with dopaminergic dysfunction. The balanced translocation t(1;11)(q42.1;q14.3) has been observed in Scottish pedigree with high prevalence of psychiatric disorders including SCZ, BP, and major depression (Bradshaw 2012). The heterozygous 129*DISC1*^{Del} transgenic mice show neuroanatomical morphology consistent with SCZ and exhibit hyperlocomotive in males, hypolocomotive in females, deficits in pre-pulse inhibition, and increased depression-like behavior, resembling pathological traits associated with psychiatric disorders (Winship 2019; Gómez-Sintes 2014). The chromosome 22q11.2 deletion causes a disorder affecting multi organ system including cardiovascular and immune systems, a cleft palate, calcium metabolism, and neurodevelopment. The most frequent psychiatric manifestations in patients with 22q11.2 deletion syndrome include SCZ, ASD, ADHD (Gambini 2016). The Df1/+ mouse model of 22q11.2 deletions shows abnormal neuroanatomical morphology in grey mater, ventricles, and neurons and aberrant behavioral traits such as deficits in motor function, pre-pulse inhibition, fear conditioning, and spatial memory (Stark 2008; Sumitomo 2018; Karayiorgou 2010). The mutations of the cell adhesion molecule neuregulin 1 (*NRG1*) and its receptor rb-B2 receptor tyrosine kinase 4 (ErbB4) which are involved in neural development, have been associated with the increased risk of SCZ (Stefansson 2002). The hypomorphic heterozygous knockout mice variably show neuroanatomical aberrations in the hippocampus, reduced N-methyl-D-aspartate (NMDA) receptors, memory impairments, and reduced pre-pulse inhibition (O'Tuathaigh 2006; Karl 2007).

The reduced expression of presynaptic homeostatic signaling dysbindin and neurodevelopmental glycoprotein reelin has been linked to the risk of developing SCZ and SCZ patients, respectively (Mohammadi 2018). The homozygous dysbindin-1 Dys1$^{-/-}$ mutant mice show behaviors consistent with SCZ and working memory deficits with the disruptions of glutamatergic and dopaminergic neurotransmission (Carlson 2011). The heterozygous mutant mice of the single allele deletion of the *reelin* gene exhibit the changes in neuroanatomical morphology associated with SCZ, but the presence of SCZ-like behaviors remained inclusive (Tsuneura 2021). In addition, the efficacy of NMDA receptor co-agonist D-serine for cognitive symptoms of SCZ is under extensive study. The genes coding the enzymes involved in D-serine metabolism such as D-amino acid oxidase activator, D-amino acid oxidase, and serine racemase and manipulations of those enzyme activity are of particular interest in developing animal models of SCZ (MacKay 2019).

Modelling a mechanism responsible for the delayed emergence of psychobehavioral symptoms is a particular challenge (Weinberger 1996). A neurodevelopmental model of SCZ has been reported to elicit delayed postpubertal manifestations of impairments in startle amplitude and pre-pulse inhibition of acoustic startle by the lesions of the ventral hippocampus induced by postnatal administration of neurotoxin ibotenic acid (Lipska 1995). However, the brain maldevelopment implicated in human SCZ is much more subtle than preclinical models designed with gene manipulation or pharmacological intervention (Weinberger 1996). Furthermore, the heritability estimates of over 80% warrants the presence of genetic components and thus, a SCZ model with gene susceptibility must be a necessary construct.

Parkinson's disease

The *PARK2* gene encodes cytosolic ubiquitin-E3-ligase, called the Parkin protein, which regulate mitophagy. The cytosolic Parkin interacts with PTEN-induced kinase 1 which accumulates in the outer membrane of mitochondria to control a wide range of mitochondrial functions. The mutation of *PINK1* is associated with hereditary early onset form of PD (Valente 2004). *Park2*$^{-/-}$ mice exhibit affected cognitive functions including cognition, working memory, habituation, exploratory activity, and locating object in Y maze. However, the strain does not show impairments of motor functions such as coordination and gait performance and depression-like behavior but the anxiety-like behavior remains inconclusive (Dalla Vecchia 2019). The BTBR T^{+}Itpr3^{tf}/J mouse (BTBR), originally bred for studies on insulin-resistance, diabetes-induced nephropathy, and

phenyloketonuria, was identified to display autism-relevant behaviors (Meyza and Blanchard 2017).

A wide range of chemicals has been applied for pharmacological models of PD in search of symptomatic relief agents for PD. They include an insecticide and an herbicide rotenone, an herbicide paraquat, and neurotoxins 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, 1-methyl-4-phenylpyridinium, and 6-hydroxydopamine (Wen 2020). As mentioned for pharmacological models of SCZ, their action is immediate and could hardly simulate animal models of neurodevelopmental pathogenesis in PD.

The tryptophan–kynurenine metabolic system and the opportunity for neuroprotection

The alteration of the Trp–KYN metabolic system has been observed in a wide range of diseases including cancers, immune diseases, neurologic diseases, and psychiatric disorders (Encyclopedia 2022; Tanaka et al. 2020c, 2021c). Clinical manifestations of altered KYN metabolism include impairments in memory and learning, poor planning, defects in set-shifting, adapt behavior to the environment, impaired working memory, emotional regulation, and altered executive function, which are common in neurological and psychiatric diseases and which correlate with a typical cognitive pattern due to frontal lobe dysfunction (Garofalo et al. 2019; Battaglia et al. 2018, 2020, 2021, 2022b; Battaglia and Thayer 2022). Furthermore, the maternal nutritional status during gestational period affects neurodevelopment and cognitive functions in infants and children, which links to activation of the Trp–KYN metabolic system (Cohen Kadosh 2021; Notarangelo 2017). Elevated prenatal and adolescent KYNA exposure changes hippocampal morphology and long-term potentiation, respectively (Wright et al. 2021; DeAngeli et al. 2015). Prenatal and neonatal inflammation has been linked to alteration of Try–KYN metabolism, resulting behavioral disturbances including cognitive and social dysfunctions (Murakami et al. 2021; Liu et al. 2014; Baratta et al. 2019). Prenatal stress disrupts microbial and host Trp metabolism, and the Trp–KYN metabolism is improved by methylphenidate in patients with ADHD (Galley et al. 2021; Molina-Carballo 2021).

Over 95% of essential amino acid Trp is metabolized into a number of various bioactive molecules, leading to the synthesis of nicotinamide adenine dinucleotide (NAD^+). The tryptophan 2,3-dioxygenase (TDO), indoleamine 2,3-dioxygenases (IDOs), kynurenine aminotransferases (KATs), kynureninase (KYNU), and kynurenine 3-monooxygenase (KMO) play a major role in the Try–KYN metabolism. TDO and IDOs convert the rate-limiting reaction of L-Trp to L-KYN. L-KYN is converted to kynurenic acid (KYNA), 3-hydroxy-L-kynurenine (3-HK), and anthranilic acid (AA) by KATs, KMO, or KYNU, respectively. In addition, the KAT isoform kynurenine–oxoglutarate transaminase 3, aka KAT III converts 3-HK to xanthurenic acid (XA). Prenatal exposure to KYN causes hippocampus-dependent memory deficit which is attenuated by KATII inhibitor BFF816 (Pocivavsek et al. 2019). The prenatal administration of KMO inhibitor Ro61-8048 leads to morphological changes in neocortex, the hippocampus, and cerebellum and alteration of protein expression and synaptic transmission in the brain of adult offspring (Pisar et al. 2014; Khalil et al. 2014; Forrest et al. 2013). Furthermore, the prenatal KYN administration and KMO gene deletion altered hippocampal plasticity (Forrest et al. 2015). KYNU further converts 3-HK to 3-hydroxyanthranilic acid (3-HAA) which is also formed from AA by spontaneous hydroxylation. 3-HAA is converted by 3-hydroxyanthranilate oxidase to 2-amino-3-carboxymuconate semialdehyde (ACMSD) which spontaneously cyclizes to quinolinic acid (QA). QA is further converted by quinolinate phosphoribosyltransferase (QPRT) to nicotinic acid mononucleotide, then by nicotinamide-mononucleotide adenylyltransferase to nicotinic acid adenine dinucleotide, and finally by nicotinamide-dinucleotide adenylyltransferase, concluding the de novo formation of NAD^+ (Fig. 3) (Tanaka et al. 2021b, c).

The Try–KYN metabolic enzymes are under the constant control of inflammatory responses, oxidative stress, the antioxidant system, and the hypothalamic–pituitary–adrenal axis. The stress hormone cortisol stimulates TDO. The lipopolysaccharide and pro-inflammatory cytokines upregulate and the antioxidant enzyme superoxide dismutase and anti-inflammatory cytokines down regulate IDOs (Tanaka & Vécsei 2021b). Oxygen molecules and pro-inflammatory cytokines stimulate and the superoxide dismutase and anti-inflammatory cytokines inhibit KMO activity. KYN metabolites exhibits a wide range of biological activities. L-KYN has antioxidant activities in vitro and in vivo (Ramírez Ortega et al. 2021). 3-HK, 3-HAA, and QA are generally reported as oxidants; however, 3-HK and 3-HAA may become antioxidants in a certain condition (Tanaka & Vécsei, 2021b). QA is a glutamate receptor agonist and KYNA act as agonist and antagonist for the subgroups of the glutamate receptors in a concentration-dependent manner (Tanaka and Vécsei 2021b). AA is close to nonsteroidal anti-inflammatory drugs diclofenac and mefenamic acid, possibly serving as a neuroprotectant (Badawy 2018). L-KYN, KYNA, XA, and cinnabarinic acid are the aryl hydrocarbon receptor (AHR) agonists which relays signals to induce immune tolerance. 3-HK stimulates TDO in vivo and NADH stimulates KMO, forming positive feedback loops, while NADH inhibits TDO, forming a negative feedback loop (Tanaka et al. 2021c). Thus, Trp–KYN metabolic system relays various biological signals to the oxidative stress complex, the antioxidant system, the serotonin and glutamate neurotransmission, the tetrahydrobiopterin pathway, the

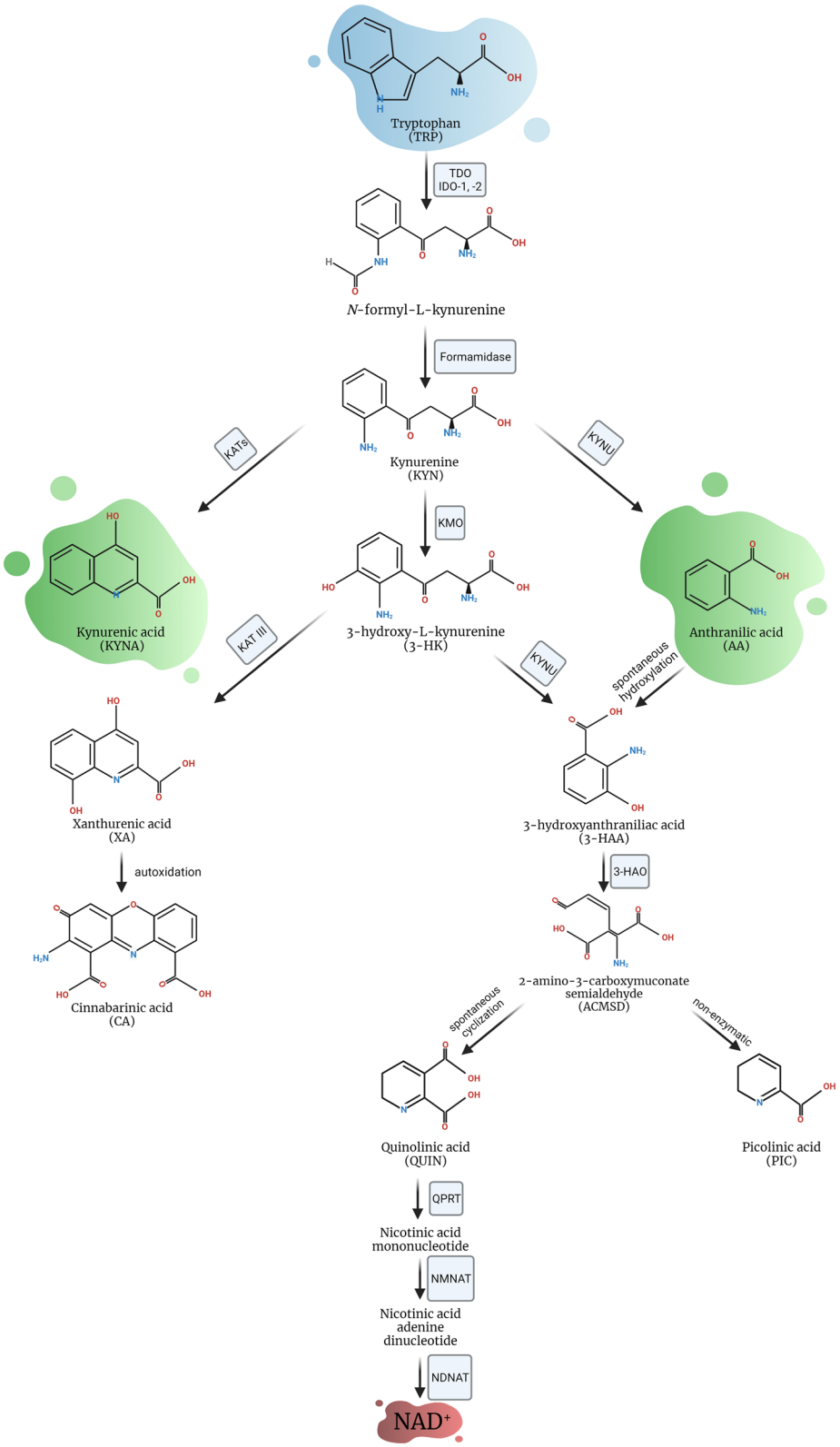

Fig. 3 The tryptophan–kynurenine metabolic system. Tryptophan (blue) is the initial amino acid of which 90–95% is catabolized through this metabolic pathway. Kynurenic acid (KYNA, green) and anthranilic acid (AA, green) are main metabolites which may play a crucial role in neuroprotection. The end-product is nicotinamide adenine dinucleotide (NAD^+, red). TDO: tryptophan 2,3-dioxygenase; IDO-1: indoleamine 2,3-dioxygenase 1; IDO-2: indoleamine 2,3-dioxygenase 2; KATs: kynurenic acid; KMO: kynurenine 3-monooxygenase; KYNU: kynureninase; 3-HAO: 3-hydroxyanthranilate dioxygenase; QPRT: quinolinate phosphoribosyltransferase

cannabinoid system, the NAD^+/NADH redox system, and the AHR system (Tanaka and Vécsei 2021b).

Peter Riederer maintained that there is overwhelming evidence of neuroprotective action in prodromal stage of PD, but it is not so obvious in clinical stage and

thus, neuroprotective treatment well deserves to start as soon as possible (Riederer et al. 2002). Growing attention has been paid to endogenous neuroprotective molecules AA and KYNA. Once considered to be a water-soluble vitamin, AA is a sweetish amphoteric aromatic acid which is used as a precursor of pharmaceutical production of anti-inflammatory drugs. Mefenamic acid, tolfenamic acid, flufenamic acid, and meclofenamic acid are AA derivatives (Badawy 2018). Little is known about the action of AA and endogenous AA derivatives in the cellular environment. Further research is expected to explore the beneficial role of AA and the merit of AA potentiation in health and for various diseases.

KYNA is another biomolecule considered to possess neuroprotective property. Preclinical studies have revealed that the intraventricular administration of KYNA exerts memory enhancement, antidepressant-like, and antimigraine-like effects in animal models of learning, depression, and migraine, respectively (Tanaka et al. 2020a; Spekker et al. 2021a, b; Spekker et al. 2021a, b). Furthermore, it has been reported that KYNA may serve as a potential biomarker for depression (Balogh 2021). However, the impermeability of KYNA through the blood–brain barrier (BBB) imposes a challenge to the delivery of KYNA to the central nervous system (Török et al. 2020). Several synthetic KYNA analogues SZR72, SZR81, and SZR104 have been synthesized to overcome the BBB impermeability and their biological and electrophysiological activities were studied. SZR104 is found to be the most permeable to the BBB (Nagy et al. 2011; Marosi et al. 2010; Molnár et al. 2021). KYNA analogue N-(2-N,N-dimethylaminoethyl)-4-oxo-1H-quinoline-2-carboxamide hydrochloride increased longevity, normalized hypolocomotion, reduced the weight loss, and prevented striatal atrophy in the N171-82Q transgenic mouse model of HD (Zádori 2011). The intraperitoneal administration of KYNA analogue SZR81 exhibited antidepressant-like effects in forced swim test of mice (Tanaka et al. 2021a). Furthermore, SZR72 was found to affect inflammation, behavior, thermal regulation, and mitochondrial respiration (Varga et al. 2010; Érces et al. 2012; Knyihar-Csillik et al. 2008; Kassai, et al. 2015; Balog et al. 2021). SZR104 inhibited drug-induced seizure and microglial activation (Demeter et al. 2012; Lajkó et al. 2020; Molnár et al. 2021). However, SZR104 influenced the production of inflammatory cytokines and the action is contrary to that of KYNA (Mándi et al. 2019). Thus, the BBB permeability of KYNA analogues is relatively well characterized but their biological activities especially in vivo actions remain to be explored.

Conclusion and future perspective

Nearly 250 years have passed since the concept of NDDs has vaguely loomed and later coined as idiocy. Even though magnificent figures in the field of mental illnesses suggested the presence of genetic and developmental basis in the pathogenesis of NDDs, the first evidence in the genetic basis of Down's syndrome was discovered just about 50 years ago. Accumulating evidence has been revealing that NDDs have their etiological basis in neurodevelopmental abnormality caused not only by a single genetic defect, bult also by polygenic, epigenetic, and/or environmental factors. NDDs gained their own right as a diagnostic labelling in the last decade; however, this may have been just grouping a wide range of heterogenic behavioral disorders solely based on abnormal neurodevelopment and thus, it may be misleading to understand pathogenesis, estimate disease course, and make a proper treatment plan. Furthermore, other psychiatric disorders such as SCZ, OCD, BD, and PTSD and even neurological diseases such as PD and HD have been found to have their pathogenic basis in abnormal neurodevelopmental process. The subtypes of some diseases have clear genetic defects leading to neurodevelopmental symptoms, but a majority of diseases are initiated, influenced, and subsequently caused by complex multifactorial interactions of predisposing factors. A number of preclinical animal models are generated by manipulating genes to simulate genetics, pathophysiology, and/or behavioral phenotypes, which is pathognomic to a disease. However, a definite genetic link has not been identified in a majority of diseases caused by neurodevelopmental abnormality. Pharmacological animal models well simulate the pathophysiology and abnormal behaviors, but it remains questionable if those models represent the entity of diseases. Therefore, development of multiple trigger models in which abnormal phenotypes can emerge by (a) trigger(s) after a certain period of the presentation of normal phenotypes is of particular and imminent interest. For example, age-dependent or sex-dependent models may serve as primers for multiple trigger models. Such models may be able eventually to bridge a gap between NDDs and neurodegenerative disorders, leading to redefinition of diseases which have neurodevelopmental basis and thus may open the path to therapeutic approaches. Peter Riederer observed that neuroprotection takes place in the prodromal period of PD, but not after the onset and thus proposed prophylactic use of neuroprotective agents. KYN metabolites are bioactive endogenous molecules of which AA and KYNA are attracting growing interest for their neuroprotective properties. The little is known about the role of AA in the cellular environment and the potential intervention through AA metabolites is to be explored. KYNA is a promising biomolecule for the purpose of neuroprotection;

moreover, synthetic KYNA analogues are to be thoroughly investigated to characterize their biological, immunological, and neuroprotective properties in search of novel neuroprotective agents.

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