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Review article

## ADHD symptoms in neurometabolic diseases: Underlying mechanisms and clinical implications

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## ABSTRACT

Neurometabolic diseases (NMDs) are typically caused by genetic abnormalities affecting enzyme functions, which in turn interfere with normal development and activity of the nervous system. Although the individual disorders are rare, NMDs are collectively relatively common and often lead to lifelong difficulties and high societal costs. Neuropsychiatric manifestations, including ADHD symptoms, are prominent in many NMDs, also when the primary biochemical defect originates in cells and tissues outside the nervous system. ADHD symptoms have been described in phenylketonuria, tyrosinemias, alkaptonuria, succinic semialdehyde dehydrogenase deficiency, X-linked ichthyosis, maple syrup urine disease, and several mitochondrial disorders, but are probably present in many other NMDs and may pose diagnostic and therapeutic challenges. Here we review current literature linking NMDs with ADHD symptoms. We cite emerging evidence that many NMDs converge on common neurochemical mechanisms that interfere with monoamine neurotransmitter synthesis, transport, metabolism, or receptor functions, mechanisms that are also considered central in ADHD pathophysiology and treatment. Finally, we discuss the therapeutic implications of these findings and propose a path forward to increase our understanding of these relationships.

## 1. Introduction

The current concept of Attention-Deficit/Hyperactivity Disorder (ADHD) has a long history. During the last century, the defining symptoms of this disorder have been attributed to various causes, ranging from a “defect of moral control” (Still, 2006) to postencephalitic brain damage, environmental agents including pre- and postnatal malnutrition, toxic agents or (mainly) a genetic predisposition (Faraone et al., 2015). According to the predominant current view, ADHD symptoms are regarded as dimensional traits due to the concerted actions of many common and rare genetic variants in interaction with multiple environmental factors. Although the majority of ADHD cases may fit into this polygenic risk model, with multiple additive genetic and environmental factors, it is also known that brain injuries, rare Mendelian diseases, and chromosomal aberrations can produce clinical symptoms that are very

similar to or even indistinguishable from “classical” ADHD; the term “attention-deficit/hyperactivity syndrome” might be appropriate for such cases. As early recognition of such secondary cases of ADHD or other ADHD-mimicking conditions may have important clinical implications, clinicians need to be aware of these conditions. Here we present an updated overview of (rare) inherited metabolic disorders that show ADHD-like symptoms. We further describe possible neurochemical mechanisms for these comorbidities and their clinical and research implications. In this context, we define neurometabolic disorders (NMDs) as inherited conditions that produce biochemical aberrations due to the complete or partial inactivation of defined enzymes or metabolite transporters. This excludes common genetic variants/polymorphisms, regulatory variants or variants in other protein targets, or variants with unknown or less established functions.

In an exploratory literature search, we identified two recent

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systematic reviews that have documented the clinical associations of ADHD and neurometabolic diseases (NMDs) (Instanes et al., 2018; Simons et al., 2017). The current review aimed to describe possible shared and unique pathophysiological mechanisms that may explain such associations. In addition to the ten distinct NMDs that were the focus in these reviews (Table 1a), we conducted an additional literature search to identify additional studies published up until August 2021. For this purpose, we searched the electronic database PubMed (March and August 2021) using a combination of the following keywords: (1) “ADHD, Attention-Deficit/Hyperactivity Disorder, hyperactive or inattention, and (2) neurometabolic disorder(s), NMDs, inborn errors of metabolism or neurometabolism”. In total, we identified 376 unique publications, 247 of which were considered relevant. We further selected articles focusing on mechanisms at the molecular genetics, neurochemical, metabolomic, proteomic, cellular, and organisms’ level. In contrast to the clinical and epidemiological literature summarized by Simons and Instanes (Instanes et al., 2018; Simons et al., 2017), our literature search revealed an extremely heterogeneous research field, with different research designs and little consensus regarding reporting practices. For this reason, it was considered unsuitable for a systematic review or meta-analysis. Instead, we present a targeted overview of what at this moment is considered the most established and promising mechanistic hypothesis explaining the associations of ADHD and some well-characterized NMDs. An overview of prevalence, pattern of inheritance, and pathophysiology of well documented NMDs is presented in Table 1a. Likewise, Table 1b provides a representative overview of reported neuropsychiatric disorders and symptoms, with an emphasis of psychiatric and neuropsychological manifestations. Both tables are based on recent reviews (when possible) or original case reports. Notably, the tables do not intend to provide an exhaustive overview of all reported disorders or ADHD-related symptoms. Supplementary Table 1 provides a more detailed summary of the literature cited in

Table 1b. Each of the NMDs is briefly introduced, with an emphasis on biochemical mechanisms. We identify common and converging evidence linking NMDs with altered central nervous system (CNS) neurotransmitter functions and cellular metabolism and the implications of these findings for brain functions and ADHD symptoms. We also summarize the clinical implications of these observations and point to several knowledge gaps that need to be addressed in future research.

## 2. Biological mechanisms for ADHD symptoms

ADHD-like symptoms have been observed in several metabolic disorders. For nearly a century, phenylketonuria (PKU) and related amino acid (AA) metabolism disorders have been considered model diseases to understand how peripheral metabolic defects may affect brain functions. Here we briefly review the neuropsychiatric manifestations of these conditions, with an emphasis on ADHD-like traits.

In PKU, an elevated risk for attentional disorders remains even after recommended dietary treatment (Ashe et al., 2019). Similar attentional difficulties (Pohorecka et al., 2012) and problems related to working memory (van Ginkel et al., 2016) are described in treated Tyrosinemia type 1 (HT1). Succinic semialdehyde dehydrogenase (SSADH) deficiency is characterized by a wide range of cognitive and somatic difficulties, including ADHD (DiBacco et al., 2019), hyperactivity, and impulsivity (Gibson et al., 2003). Maple syrup urine disease (MSUD) patients also have different comorbid neuropsychiatric conditions, including a high incidence of ADHD (Muelly et al., 2013). ADHD is probably the most common neurodevelopmental disorder in X-linked ichthyosis (XLI), with most patients having an inattentive presentation (Kent et al., 2008). Moreover, executive function and attention deficits have been found in Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome (Kraya et al., 2019). Similarly, Mucopolysaccharidosis type III (MPS III, Sanfilippo syndrome)

**Table 1a**  
Overview of prevalence, pattern of inheritance, and pathophysiology for selected NMDs.

Disease	Prevalence	Inheritance pattern	Pathophysiology	Reference(s)
Phenylketonuria (PKU)	1:8900-11226 (Caucasians) 1:13500-19000 (US)	Autosomal recessivePAH mutations	PAH deficiency causes hyperphenylalaninemia	(Ashe et al., 2019)
Tyrosinemia Type I (HT1)	1:100-120 000 (general population)1:74 800 (Norway)	Autosomal recessiveFAH mutations	FAH deficiency inhibits Tyr degradation and causes accumulation of fumarylacetoacetate and succinylacetone	(Barone et al., 2020)
Tyrosinemia Type 2 (HT2)	<1:1 000 000	Autosomal recessiveTAT mutations	TAT deficiency causes impaired breakdown and accumulation of Tyr	(Wendel, 2010)
Tyrosinemia Type 3 (HT3)	<150 cases (in literature)	Autosomal recessiveHPD mutations	4-HPPD deficiency causes impaired breakdown and accumulation of Tyr	(Heylen et al., 2012)
Alkaptonuria (AKU)	1:250 000 (general population)	Autosomal recessiveHGD mutations	HGD deficiency causes impaired Phe/Tyr breakdown and accumulation of HGA	(Davison et al., 2018)
Succinic semialdehyde dehydrogenase (SSADH) deficiency	~450 cases (in literature)	Autosomal recessiveALDH5A1 mutations	SSADH deficiency causes impaired oxidation of SSA and accumulation of GHB/GABA	(Didiasova et al., 2020)
Maple syrup urine disease (MSUD)	1:150 000 (general population)1:400 (Old Order Mennonites)	Autosomal recessiveBCKDHA, BCKDHB, DBT mutations	BCKD complex deficiency cause accumulation of BCAAs (Iso, Val, Leu) and BCKAs ( $\alpha$ -ketoisocaproic acid, $\alpha$ -keto-3-methylvaleric acid, and $\alpha$ -ketoisovaleric acid)	(Strauss et al., 2020)
X-linked ichthyosis (XLI)	1:1500-6000 (males worldwide)	X-linked recessiveSTS mutations	STS deficiency causes impaired cleavage of sulfate groups from steroid hormones and sulfatases, and accumulation of CSO <sub>4</sub> /DHEAS	(Hernandez-Martin et al., 1999; Diociaiuti et al., 2019)
Mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes (MELAS) syndrome	16-18:100 000 (Finland)0.2:100 000 (Japan)	MitochondrialMT-TL1 mutations (~90 % of cases)	Decreased synthesis of ETC complex subunits; impaired mitochondrial energy production	(El-Hattab et al., 2015)
Mucopolysaccharidosis III (MPS III, Sanfilippo syndrome)	0.3-4.1:100 000 (depending on subtype)	Autosomal recessiveSGSH, NAGLU, chromosome 8p11.21 (pericentromeric region), GNS mutations	Deficiency of one of four enzymes causes impaired degradation of the glycosaminoglycan HS	(Andrade et al., 2015)

**PAH** (phenylalanine hydroxylase); **FAH** (fumarylacetoacetate hydrolase); **TAT** (tyrosine aminotransferase); **4-HPPD** (4-hydroxyphenylpyruvate dioxygenase); **HGD** (homogentisate 1,2-dioxygenase); **HGA** (homogentisic acid); **SSA** (succinic acid, succinate); **BCKD** (branched-chain  $\alpha$ -keto acid dehydrogenase); **BCAA** (branched chain amino acids); **BCKAs** (branched chain keto-acids); **STS** (steroid sulfatase); **CSO<sub>4</sub>** (cholesterol sulfate); **DHEAS** (dehydroepiandrosterone sulfate); **ETC** (electron transport chain); **MT-TL1** (mitochondrially encoded tRNA leucine 1 (UUA/G)); **SGSH** (N-sulfoglucosamine); **NAGLU** (N-Acetyl-Alpha-Glucosaminidase); **GNS** (glucosamine (N-acetyl)-6-sulfatase); **HS** (heparan sulfate).

Table 1b

Reported neuropsychiatric symptoms and disorders in selected NMDs. Dark green: high prevalence, reported across studies, and/or found in large cohorts (relative to reported cases of the NMD). Light green: low prevalence, documented but few case reports. White: not reported (in selected references). The findings are based on recent representative reviews (when possible) or original case reports. Supplementary Table 1 provides a more detailed summary of the literature cited in this table.

	PKU	Tyrosinemias	AKU	SSADH deficiency	MSUD	XLI	MELAS	MPS III
<b>ADHD/ADD</b>	4-6	7, 8, 12		19, 20	28	29 - 32		
<i>ADHD-related symptoms</i>								
<b>Inattention/attention-deficit</b>	2, 4, 6	7, 8, 11, 13		21, 23, 24	28	31	33, 34, 36	42
<b>Impulsivity</b>	4, 6	12		22	28	31	37	41
<b>Hyperactivity</b>	1, 4	12, 16		21 - 24		31		38-44
<b>Aggression</b>	4, 6			21 - 23				40, 43
<i>Other relevant symptoms and disorders</i>								
<b>Developmental delay</b>		9, 14-16		22, 24	25	31	33	38, 40, 41
<b>Intellectual impairment/disability</b>	1, 3-5	10, 12, 14, 16		19, 20, 23, 24	25, 26, 27	29	33, 36, 37	39, 42
<b>Depression</b>	1, 4, 5	8	17, 18		26 - 28	31	35, 36	
<b>Anxiety</b>	1, 4, 5	8		19, 22	26 - 28		35, 36	41, 44
<b>Speech impairment/delay</b>	1, 2	13, 16		19 - 24	27		37	39-41, 43
<b>ASD/ASD-related symptoms</b>	1, 4, 5			21, 22		29, 31, 32		41, 43
<b>Sleep problems</b>	4, 5	12		19 - 24			36	38, 40, 41, 44
<b>Learning difficulties</b>	2, 4	12, 16		24			33, 35	
<b>Psychotic symptoms/related disorders*</b>	4, 5			23			35, 36	
<b>Self-injury</b>	1	16		19, 20, 23, 24			36	
<b>Obsessive-compulsive behavior or OCD</b>	1, 5							
<b>Impaired executive functioning</b>	2, 4	10					34, 37	
<b>Impaired social skills</b>	4	8						
<b>Bipolar disorder</b>	4, 5							
<b>Tourette's syndrome or tics</b>	1, 5					30		
<b>Hallucinations</b>				22, 23			36	

\*Psychosis, Schizophrenia.

References for Table 1b.

1 (Mainka et al., 2021), 2 (Aitkenhead et al., 2021), 3 (Yamada et al., 2021), 4 (Ashe et al., 2019), 5 (Bilder et al., 2017), 6 (Antshel, 2010), 7 (Barone et al., 2020), 8 (van Vliet et al., 2019b), 9 (Garcia et al., 2017), 10 (van Ginkel et al., 2016), 11 (Pohorecka et al., 2012), 12 (Barroso et al., 2020), 13 (Blundell et al., 2018), 14 (Gokay et al., 2016), 15 (Scott, 2006), 16 (Ellaway et al., 2001), 17 (Kisa et al., 2021), 18 (Davison et al., 2018), 19 (Pearl et al., 2021), 20 (DiBacco et al., 2019), 21 (Knerl et al., 2008), 22 (Gibson et al., 2003), 23 (Pearl et al., 2003b), 24 (Gibson et al., 1997), 25 (Medina et al., 2021), 26 (Strauss et al., 2020), 27 (Abi-Warde et al., 2017), 28 (Muely et al., 2013), 29 (Diociaiuti et al., 2019), 30 (Rodrigo-Nicolas et al., 2018), 31 (Chatterjee et al., 2016), 32 (Kent et al., 2008), 33 (Moore et al., 2020), 34 (Kraya et al., 2019), 35 (El-Hattab et al., 2015), 36 (Anglin et al., 2012), 37 (Neargarder et al., 2007), 38 (Hoffmann et al., 2020), 39 (Kong et al., 2020), 40 (Andrade et al., 2015), 41 (Wijburg et al., 2013), 42 (Valstar et al., 2011), 43 (Heron et al., 2011), 44 (Bax and Colville, 1995).

may be mistaken for ADHD or autism spectrum disorder (ASD) since hyperactivity, impulsivity, and extreme restlessness are common (Wijburg et al., 2013).

Most of the disorders are characterized by a range of other difficulties in addition to symptoms of ADHD. However, a high level of somatic and neuropsychiatric comorbidity is also in common ADHD without diagnosed metabolic diseases. Therefore, a broad characterization of clinical phenotypes in metabolic disorders and possible biochemical mechanisms behind these may provide more insight into the heterogeneous comorbidity profiles in ADHD. A more detailed description of the biological and clinical characteristics of the disorders mentioned above is presented in the following sections of this review. As far as we know, there are no reports of ADHD-like symptoms in alkaptonuria (AKU) and only occasionally in a range of other metabolic disorders. Still, some of these disorders are briefly described as they could be interesting targets for future research.

There is still limited knowledge about the precise molecular and cellular mechanisms underlying ADHD symptoms. Although recent genetic studies (Demontis et al., 2019) in children and adults with ADHD have revealed strong associations with several genetic loci, genes, and pathways, a unifying model for the development of these symptoms is still lacking (Demontis et al., 2019; Rovira et al., 2020). Despite these limitations, several theories have gained experimental support during the past decades from different disciplines, including brain imaging, pharmacological, genetic, biochemical, and neuropsychological investigations. Briefly, such theories include altered neurotransmission and synaptic functions, disturbed brain energy homeostasis, or developmental delays of the nervous system. The latter hypothesis is

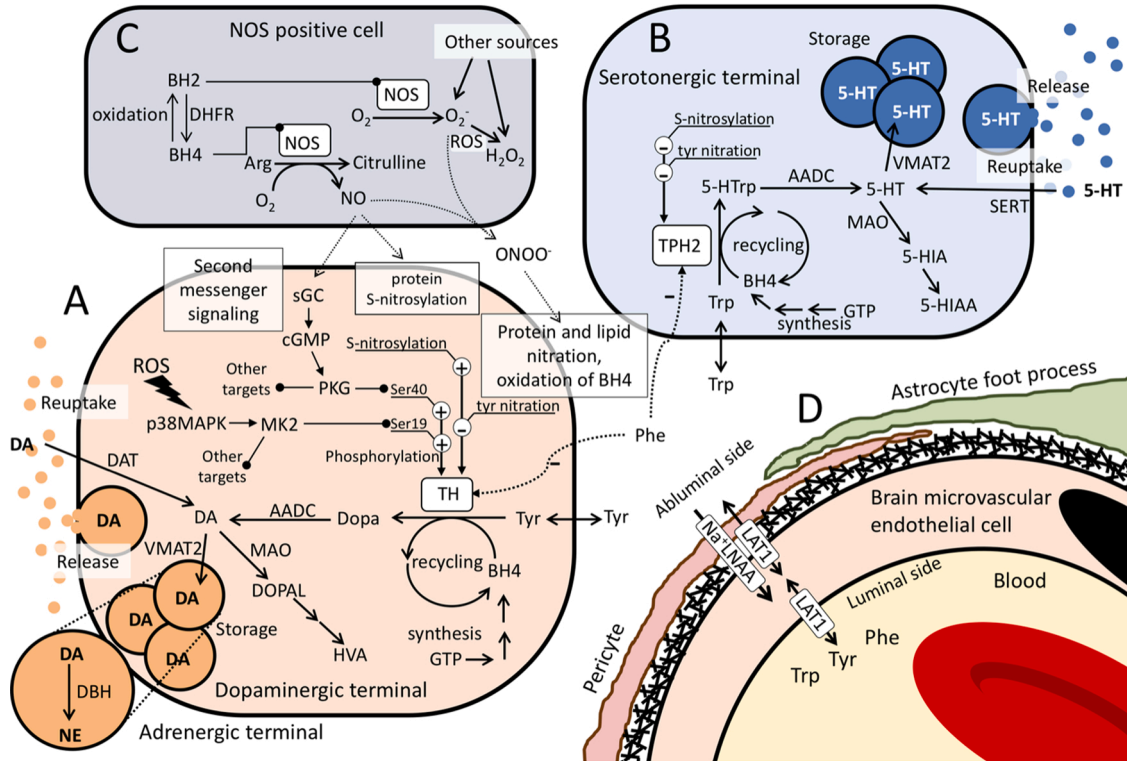
supported by the identification of risk variants involved in neurotrophin release, neuronal migration, brain differentiation, and myelination (Demontis et al., 2019; Rovira et al., 2020). Importantly, these theories neither pretend to be universal nor mutually exclusive (Killeen, 2019; Tripp and Wickens, 2009).

As the most effective pharmacological treatments used for ADHD all target catecholamine (dopamine and noradrenaline) neurotransmission, it has long been speculated that aberrations of these neurotransmitter pathways may be involved in the pathophysiology of ADHD. Thus, neurochemical alterations that affect monoamine neuromodulator functions are of particular relevance. As monoamine transmitters/neuromodulators are derived from aromatic AAs, it is not surprising that aromatic AA metabolism perturbations have been linked to brain dysfunction. Likewise, altered transport, metabolism, and functions of the amino acids glutamate, glycine, and gamma-aminobutyrate, the major excitatory and inhibitory transmitters in the CNS have received much attention. Alternatively, it has been suggested that ADHD symptoms derive from altered neuroenergetics (Reviewed by Killeen et al. (Killeen et al., 2013)). One such postulated energy deficiency may occur secondary to a catecholaminergic hypofunctionality that affects astrocyte metabolism; thus, linking the impaired energy metabolism hypothesis with altered monoaminergic neurotransmission (Russell et al., 2006). Furthermore, it is conceivable that other conditions involving altered astrocyte-neuronal metabolic coupling may influence energy homeostasis, cerebrovascular flow and neuronal activity at the neurovascular unit. Thus, *Locus coeruleus* derived noradrenergic terminals innervate the microvascular compartment of the brain to modulate oxygen and nutrient delivery in response to local neuronal activity (Bekar

et al., 2012). Notably, catecholamine synthesis is expected to be sub-saturated with oxygen under normoxic conditions (Rostrup et al., 2008), implicating that even mild hypoxia or ischemia might compromise neurotransmitter synthesis. However, although hemodynamic differences and alterations in cerebrovascular flow are noted in ADHD patients and with ADHD medication in many studies, it is still unclear if this is associated with dysregulation of the neurovascular unit.

Early candidate gene studies with small sample sizes and targeted genotyping provided some support for the involvement of monoamine transporters, receptors, and enzymes as risk factors for ADHD and other neuropsychiatric disorders. However, few of these early association and linkage findings have been confirmed with improved technology and increased sample sizes. In the largest ADHD genome-wide genetic

association study (GWAS) published to date, only one of the previously proposed ADHD candidate genes showed some association with ADHD (SLC9A9,  $P = 3.4 \times 10^{-4}$ )<sup>3</sup> and also with body mass index ( $P = 1.63 \times 10^{-5}$ ). The authors suggested that dopaminergic neurotransmission, partially through DARPP-32-dependent signaling and involving the putamen, is involved in the genetic overlap between ADHD and obesity measures (Mota et al., 2020). Overall, the analysis of common genetic variants indicates that ADHD is very polygenic, possibly involving many different biological mechanisms, where genes involved in monoamine signaling only account for a small fraction. Although analyses of common variants do not support a primary role of the “usual suspects” in disease etiology for most patients, many ADHD cases with coding variants affecting monoamine functions have been reported (Hansen et al.,



**Fig. 1. Relationship between CNS monoamine synthesis, NO signaling, and aromatic amino acid transport.** Aromatic amino acids are precursors of monoamines. The first and rate-limiting step in their synthesis is catalyzed by aromatic amino acid hydroxylases (AAAHs) (A, B), tyrosine hydroxylase (TH, EC 1.14.16.2; tyrosine 3-monoxygenase), and tryptophan hydroxylase 1 and 2 (TPH1, TPH2, EC 1.14.16.4). Therefore, the brain synthesis of these neurotransmitters relies on the circulatory supply of precursory amino acids (D) within levels that do not compromise the enzymatic output of biosynthesis and metabolism. (A) shows dopamine (DA) and norepinephrine (NE) synthesis, vesicular storage, release, reuptake and metabolism. TH is the first and rate-limiting enzyme in the biosynthesis of catecholamines and is regulated through many mechanisms including reactive oxygen species (ROS) and nitric oxide (NO) mediated signaling. ROS may stimulate p38 Mitogen Activated Protein Kinase (p38MAPK) activation, which through activation of MAPK activated protein kinase 2 (MK2) can stimulate TH through Ser19 phosphorylation. NO can activate cGMP synthesis through activation of soluble guanylate cyclase (sGC), which leads to activation of protein kinase G (PKG) and activation of TH through Ser40 phosphorylation. NO may also lead to S-nitrosylation of cysteines in TH or nitration via formation of peroxynitrate in reaction with superoxide. (B) shows serotonin (5-HT) synthesis, vesicular storage, release, reuptake, and metabolism. TPH2 catalyzes the first and rate-limiting step in the biosynthesis of 5-HT and is regulated through many mechanisms, including ROS or NO. TH and TPHs also rely on the cofactor tetrahydrobiopterin (BH4, see also Fig. 2) for their catalysis, which must be synthesized and regenerated locally in the monoamine producing cells by specific enzymes. In the synthesis pathways tyrosine (Tyr) or tryptophan (Trp) are hydroxylated by TH or TPH2 to Dopa or 5-HT, respectively. Dopa and 5-HT are subsequently decarboxylated by aromatic amino acid decarboxylase (AADC), yielding DA or 5-HT, respectively. The monoamines are transported into storage vesicles by the vesicular monoamine transporter 2 (VMAT2) for release. In the case of NE, vesicular DA is hydroxylated by dopamine β-hydroxylase (DBH) within the vesicles in a reaction relying on ascorbate and molecular oxygen. In the brain, catecholamines and serotonin are synthesized and released from neurons originating in the midbrain and extending to specific brain areas where they exert their neuromodulator effects through multiple receptor types. Much of monoamine transmission is of the so-called volume transmission type, where their diffusion-mediated spread is controlled by reuptake transporters like serotonin (SERT), norepinephrine (NET), and dopamine (DAT) transporters. The DAT and NET are major targets for the most common ADHD medication. The monoamines are metabolized by monoamine oxidases (MAOs, EC 1.4.3.4), catecholamine O-methyltransferase (COMT, EC 2.1.1.6), and aldehyde dehydrogenase. The main metabolites measured in plasma and the cerebrospinal fluid (CSF) are homovanillic acid (HVA) for DA, 3-methoxy-4-hydroxyphenyl-glycol for CNS NE, vanilmandelic acid for peripheral NE, and 5-hydroxy indole acetic acid (5-HIAA) for 5-HT. (C) shows nitric oxide (NO) synthesis and its downstream effector mechanisms through second messenger cGMP signaling, protein S-nitrosylation, and via the reaction between NO and superoxide (O<sub>2</sub><sup>-</sup>) to form the reactive peroxynitrite, which may react with proteins and lipids and oxidize BH4. (D) shows transport of aromatic amino acids (Phe, Tyr, and Trp) across the blood brain barrier of a microvascular capillary. The transporters involved at the luminal (blood) and abluminal (brain) side are shown.



2014; McKinney et al., 2008). Due to their low population frequencies, it is difficult to determine the role of such rare coding variants in ADHD etiology. However, as their effect sizes may be much larger than for common variants studied in GWAS, genetic alterations in monoamine-related genes can directly or indirectly contribute to this disorder. Thus, monoamines are still considered central in the conceptualization of ADHD pathophysiology and intervention strategies. The following section provides a brief review of current knowledge on monoamine synthesis and regulation and how this may be linked to ADHD pathophysiology.

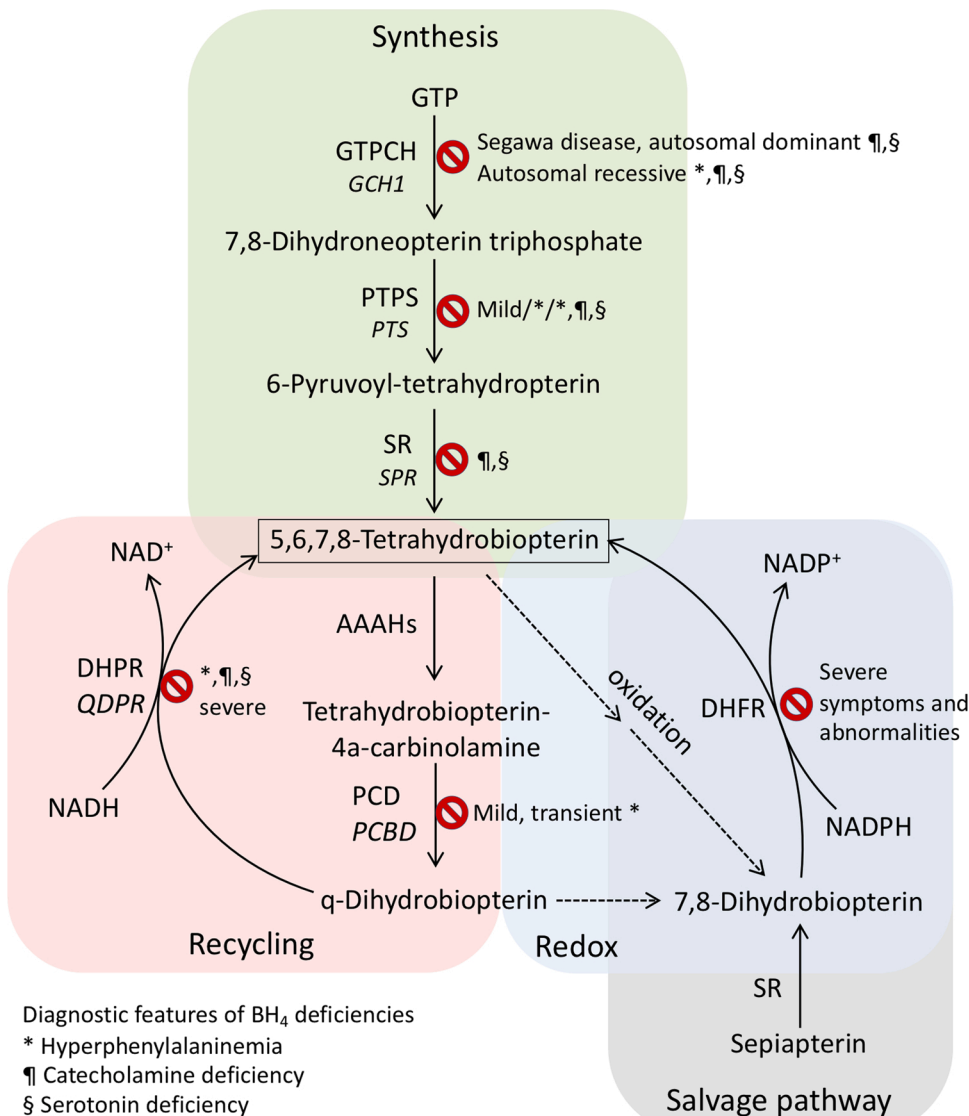
### 3. Monoamines in ADHD and mechanisms for disturbed synthesis in NMDs

#### 3.1. Monoamine synthesis and regulation

The brain synthesis of the monoamine neurotransmitters dopamine, norepinephrine, and serotonin relies on the circulatory supply of precursory AAs (Fig. 1). Below we describe several NMDs where the balance of aromatic AAs is disturbed, leading to dysregulation in monoamine homeostasis. We also describe disorders in the metabolism of the enzyme cofactor tetrahydrobiopterin (BH4), which are also associated with disturbances in monoamine homeostasis (Figs. 1 and 2). Duration

of monoamine neurotransmission is largely controlled by reuptake transporters (Fig. 1) and as briefly introduced in Section 2, the dopamine- and norepinephrine transporters are major targets for the most common ADHD medication. Thus, transporter activity, and the presynaptic quantal release, are ways to control monoamine signaling spread and duration. However, monoamines first need to be synthesized, and it is becoming clear that their synthesis rate is closely co-regulated with neurotransmission (Lindgren et al., 2001; Salvatore et al., 2016). Downstream effects of the released monoamines are mediated through a range of receptors that, except for 5-hydroxytryptamine (5-HT) type 3, are G-protein coupled receptors (GPCRs) that act through stimulation or inhibition of second messenger systems. These effector systems are outside the scope of this review and will not be discussed in further detail.

Inhibitors of monoamine metabolism, particularly the monoamine oxidases (MAO-A and -B), are used to increase the levels of these transmitters. Inhibitors of MAO-A increase 5-HT levels more than MAO-B, whereas MAO-B inhibitors have larger effects on DA metabolism (Edmondson and Binda, 2018). Increased expression of MAO-A may contribute to the development of neuropsychiatric disorders, such as depression and anxiety (Finberg and Rabey, 2016). On the other hand, low expression of MAO-A may predispose to increased aggression (McDermott et al., 2009). Notably, MAO deficiency is more often



**Fig. 2. Tetrahydrobiopterin synthesis and regeneration.** (6R)-5,6,7,8-Tetrahydrobiopterin (BH4) is synthesized from GTP by the enzymes GTP cyclohydrolase I (GTPCH), 6-Pyruvoyltetrahydropterin synthase (PTPS), and Sepiapterin reductase (SR). BH4 is a cofactor of the nitric oxide synthase and is used by the aromatic amino acid hydroxylases (AAHs), forming tetrahydrobiopterin 4a-carbinolamine, which will spontaneously dehydrate to quinonoid-dihydrobiopterin (q-BH2) or catalyzed by pterin carbinolamine dehydratase (PCD). BH4 can be regenerated from q-BH2 by the NADH-dependent dihydrobiopterin reductase (DHPR). Alternatively, q-BH2 (or BH4) may oxidize into 7,8-Dihydrobiopterin, which can be regenerated to BH4 by the NADPH-dependent Dihydrofolate reductase (DHFR). BH4 can also be synthesized from sepiapterin via 7,8-Dihydrobiopterin by SR (referred to as the salvage pathway). Different enzyme deficiencies leading to BH4-deficiency and their association with hyperphenylalaninemia (\*), catecholamine deficiency (¶), or serotonin deficiency (§) are also shown. The corresponding gene names of the enzymes are shown in italics.

observed in men since both MAO genes are located on the X-chromosome. For instance, the extremely rare Brunner syndrome is characterized by a selective deficiency of enzymatic MAO-A activity and impulsive aggression in males, not unlike symptoms that may also be observed in ADHD patients (Brunner et al., 1993).

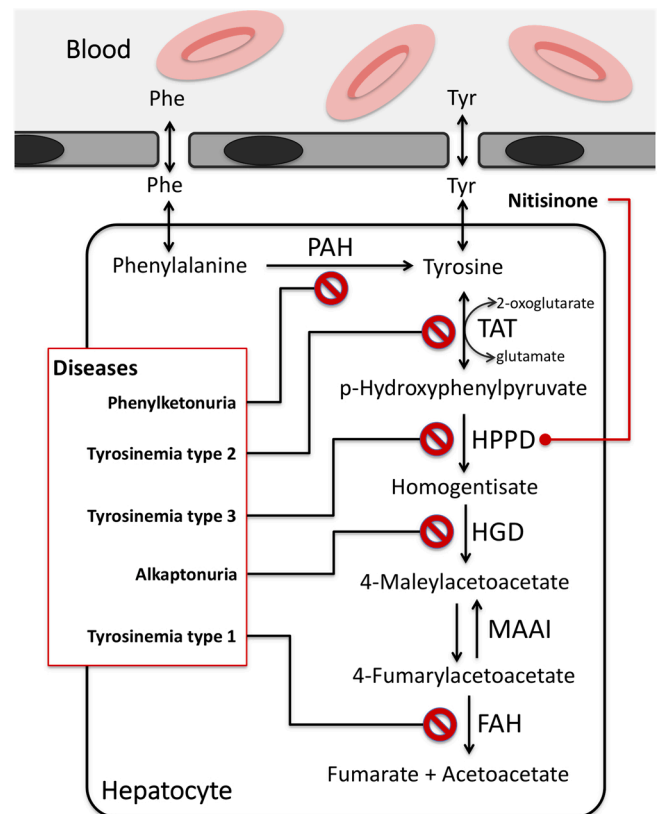
### 3.1.1. Regulation of catecholamine synthesis

Regulation of tyrosine hydroxylase (TH) abundance and activity are major mechanisms to control catecholamine synthesis, and many different regulatory mechanisms have been reported (Dunkley and Dickson, 2019; Tekin et al., 2014). In addition to feedback inhibitory coordination of catecholamines to the active site iron of TH (Andersson et al., 1988), protein phosphorylation of N-terminal Ser/Thr residues (notably Ser19, Ser31, and Ser40) are well described regulatory targeting of TH to modulate its activity, protein-protein interactions, localization, and stability. The regulation of TH by signaling pathways may open up new therapeutic options to modulate catecholamine homeostasis. Thus, Ser40 phosphorylation is a major regulatory site to modulate TH activity as it releases bound inhibitory catecholamines (Almas et al., 1992; Andersson et al., 1992). Cyclic nucleotide signaling pathways (e.g., protein kinase A (PKA) and nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) signaling 4.1, Fig. 1) are major signaling pathways that target this site as well as multiple stress and mitogen signaling regulated kinases (Almas et al., 1992; Rodriguez-Pascual et al., 1999; Thomas et al., 1997; Toska et al., 2002). Although cyclic adenosine monophosphate (cAMP) signaling is a key pathway both pre- and post-synaptic for catecholamine neurotransmission, different expression profiles of phosphodiesterases could provide opportunities for selective pharmacological targeting (Nishi et al., 2008; Sharma et al., 2021).

Stress kinase signaling downstream of the p38 mitogen activated protein kinase (MAPK) can increase TH Ser19 phosphorylation (Fig. 1B), the main target for calcium/calmodulin-dependent protein kinase II (CaMKII). TH phosphorylation of Ser19 makes the enzyme available for binding and activation by the 14-3-3 proteins (Ghorbani et al., 2016; Itagaki et al., 1999), a conserved family of multi-functional Ser/Thr phospho-targeting proteins (Cornell and Toyo-Oka, 2017). Phosphorylation of TH, in particular on Ser40, increases the affinity for the BH4 cofactor (Almas et al., 1992), whereas it has minor effects on its other substrates, oxygen and Tyr (Rostrup et al., 2008). In addition to its importance for catalysis, BH4 is essential in maintaining the active site iron in the catalytically competent Fe(II) state (Frantom et al., 2006). BH4 therapy has been suggested as an option to improve brain monoamine homeostasis in conditions where their synthesis is compromised and may even work synergistically with brain NO signaling and oxidative stress (Evers et al., 2020). TH shows pronounced substrate inhibition for tyrosine (Tyr), particularly the human recombinant enzyme (Fossbakk et al., 2014). It is still unclear if this type of kinetics plays a role under normal conditions, although its importance for monoamine homeostasis has been postulated based on mathematical modeling (Best et al., 2009). However, at hypertyrosinemic conditions, as found in the tyrosinemias (Table 1a, Fig. 3), significantly impaired TH activity can be expected, and it could be speculated if this would perturb brain dopamine or norepinephrine synthesis through substrate inhibition (Barone et al., 2020).

### 3.1.2. Synthesis and regulation of serotonin

In 2003, Walther et al. discovered that tryptophan hydroxylase (TPH) is encoded by two distinct genes, giving rise to two enzyme isoforms; TPH1 and TPH2 (Walther and Bader, 2003; Walther et al., 2003), which have different patterns of expression as well as kinetic and regulatory properties (McKinney et al., 2005). TPH1 is mainly expressed in peripheral tissues and in the pineal gland, where it contributes to the biosynthesis of melatonin (Amireault et al., 2013; Cote et al., 2003), while TPH2 is exclusively expressed in the rest of the central nervous system (Malek et al., 2005) and essential for 5-HT biosynthesis in the



**Fig. 3. Liver metabolism of phenylalanine and tyrosine.** The figure shows the enzymes involved in the catabolism of phenylalanine (Phe) and tyrosine (Tyr) to fumarate and acetoacetate and the diseases associated with deficiencies in the enzymes. Phe and Tyr from the circulation are in exchange with Phe and Tyr of hepatocytes in the liver. Phenylalanine hydroxylase (PAH) catalyzes the tetrahydrobiopterin-dependent conversion of Phe to Tyr. PAH deficiency is associated with phenylketonuria (PKU). Tyrosine aminotransferase (TAT) converts Tyr to p-hydroxyphenylpyruvate through a reversible transfer of the amino group to 2-oxoglutarate. TAT deficiency is associated with Tyrosinemia type 2. The p-Hydroxyphenylpyruvate dioxygenase (HPPD) catalyzes oxidative decarboxylation to form homogentisate. HPPD is also inhibited by nitisinone, and HPPD deficiency is associated with Tyrosinemia type 3. The next step involves oxygenation by Homogentisate 1,2-dioxygenase (HGD) to form 4-maleylacetoacetate, and HGD deficiency is associated with Alkaptonuria. 4-maleylacetoacetate spontaneously rearranges into 4-fumarylacetoacetate, but the reaction is accelerated by Maleylacetoacetate isomerase (MAAI). The final reaction converting 4-fumarylacetoacetate to fumarate and acetoacetate is catalyzed by Fumarylacetoacetate hydrolase (FAH), which is deficient in Tyrosinemia type 1.

brain. Both TPH1 and 2 can bind and hydroxylate phenylalanine (Phe) and Tyr with different catalytic efficiencies than tryptophan (Trp) (McKinney et al., 2005). Thus, under pathological conditions where Phe and Tyr are elevated, both peripheral and brain serotonin synthesis can be affected. TPH1 is more strongly inhibited by Phe than TPH2 (McKinney et al., 2005), whereas TPH2 is shown to be significantly inhibited by Tyr at levels mimicking that found in tyrosinemia patients (below) (Barone et al., 2020). Dysregulation of serotonin levels in different tissues is believed to have an essential role in the development of several disorders, including osteoporosis (Inose et al., 2011), carcinoma syndrome (Crane et al., 2015; Hallen, 1964; Macdonald et al., 1958), pulmonary arterial hypertension (Morecroft et al., 2007), and neuropsychiatric disorders, such as ADHD, autism, schizophrenia (Jacobsen et al., 2015; Watanabe et al., 2007), anxiety, and depression (Matthes et al., 2010; Zhang et al., 2005).

The mechanism behind the putative contribution of TPH to the pathogenesis of neuropsychiatric disorders such as ADHD (Halmoy

et al., 2010; Porter et al., 2008) and its comorbidities, e.g., obesity and depression (Cortese and Tessari, 2017; Crane et al., 2015) is not fully understood. Several studies have indicated that the expression of TPH1 might have a crucial role in brain development (Cote et al., 2007); a study on mice showed the involvement of TPH1 in regulating 5-HT levels in the brain during late developmental stages, but not in the adult animal (Nakamura et al., 2006). Altered fetal 5-HT levels may result in delayed brain development, which has been linked to ADHD in brain imaging studies (Faraone et al., 2015; Klein et al., 2017).

Another study, on human subjects, found that TPH1 mutations that reduce maternal 5-HT production may cause impairment in brain development and increase the risk of having ADHD in offspring (Halmoy et al., 2010). In addition, coding variants in TPH2 have been associated with a deficiency of brain serotonin (McKinney et al., 2008). Studies using knockout mice *lacking Tph2* found, as expected, low levels of central serotonin and an increase of symptoms of anxiety and depression (Sachs et al., 2015; Waider et al., 2017). As serotonin and other monoamines also are modulators of synaptic plasticity and brain development (Kandel et al., 2014), alterations of these monoamines may affect brain functions at multiple levels.

### 3.1.3. Synthesis and recycling of tetrahydrobiopterin

Several NMDs are caused by cofactor deficiencies, rather than lack of enzyme protein. All the aromatic AA hydroxylases (AAAHs) rely on the fully reduced cofactor BH4 ((6R)-5,6,7,8-tetrahydrobiopterin) and molecular oxygen for hydroxylation of the respective AA substrate. Synthesis and regeneration of BH4 are therefore crucial for the synthesis of related monoamines. BH4 is synthesized from guanosine triphosphate (GTP) in a three-step pathway via the enzymes GTP cyclohydrolase I (GTPCH), 6-pyruvoyltetrahydropterin synthase (PTPS), and sepiapterin reductase (SR). The hydroxylation reaction of the AAAHs generates the 4a-carbinolamine form of BH4, which spontaneously or by pterin-4a-carbinolaminodehydratase (PCD) can be dehydrated to the quinoid form of dihydrobiopterin (q-BH2) that can be regenerated to BH4 by the NADH-dependent dihydropteridine reductase (DHPR). BH4 and q-BH2 can be converted to 7,8-dihydrobiopterin (BH2) by different oxidation steps but may be regenerated to BH4 by NADPH-dependent dihydrofolate reductase (DHFR) (Thony et al., 2000) (Fig. 2).

Several studies have described mutations in the enzymes that play a role in the biosynthesis and regeneration of BH4, which cause a shortage of this cofactor, and as a consequence, can contribute to the development of hyperphenylalaninemia (PKU) (Scriver et al., 1987, 1994), characterized by a deficiency of phenylalanine hydroxylase (PAH, EC 1.14.16.1) activity and a depletion of the neurotransmitters dopamine and serotonin, brain degeneration, and progressive neuropsychiatric impairment (Pascucci et al., 2002; Pilotto et al., 2019; Porta et al., 2015). Other findings suggest that reduced levels of BH4 in the cerebrospinal fluid are linked to the development of several neuropsychiatric disorders, e.g., Parkinson's disease, depression, Alzheimer's disease (Thony et al., 2000), ADHD (Antshel, 2010; Antshel and Waisbren, 2003), and autistic disorders (Steiner et al., 2007).

BH4 is also a cofactor for NO synthases 1-3 (NOS 1-3), of which NOS1 is referred to as the neuronal isoform and the primary NOS expressed in the brain. Decreased NO metabolites have been found in CSF of patients with deficiencies in BH4 synthesis and regeneration (Zorzi et al., 2002), and oxidation of the cellular BH4 pool to BH2 is associated with increased uncoupling of NOS and formation of superoxide (O<sub>2</sub><sup>-</sup>) (Crabtree et al., 2009). NO has pleiotropic effects (Fig. 1A); its main effector mechanism is thought to be the stimulation of soluble guanylate cyclases, leading to increased cGMP and thus downstream targeting of several protein kinases, phosphodiesterases, and ion channels (Hofmann, 2020). However, NO can also lead to post-translational modification of amino acid residues in target proteins, i.e., nitrosylation of cysteine moieties or, via formation of peroxyxynitrite, nitration of tyrosine, tryptophan, and cysteine. These modifications may positively or negatively regulate the target proteins. Finally, NO may inhibit

heme-containing proteins by binding to heme molecules (sGC being a notable exception).

Altered NOS signaling has been linked to several neuropsychiatric disorders, including ADHD. Interestingly, NOS1 is upregulated by methylphenidate treatment (Cavaliere et al., 2012) and it was recently reported that ADHD is accompanied with peripheral changes in the NO pathway (Jansen et al., 2020; Kittel-Schneider et al., 2015), suggesting that compromised NOS signaling may be involved in ADHD pathogenesis (Freundenberg et al., 2015). Alterations of NO signaling in the *locus coeruleus* are also postulated to underly attention deficits observed in patients with argininosuccinate lyase (ASL, EC 4.3.2.1) deficiency (Lerner et al., 2019). Thus, it was found that TH and catecholamine levels were decreased by argininosuccinate lyase (ASL) knock-out through decreased cAMP-response-element-binding protein (CREB) mediated transcriptional control and TH nitrosylation. ASL is involved in the urea cycle, as well as in the regeneration of arginine from citrulline, which is important for NO synthesis as L-arginine is the primary substrate of all NOS.

### 3.2. Neurometabolic diseases affecting aromatic amino acid metabolism and transport

The essential aromatic AAs Phe and Trp must be provided through food in sufficient amounts to support development, growth, and tissue homeostasis. It has recently become clear that the microbiome can also provide the host with essential AAs through *in situ* synthesis (Heinken et al., 2013). Still, a complete overview of the involved homeostatic mechanisms for AA tissue supply and in humans at different nutrient states is lacking. In typical Western protein-rich diets, tissue uptake and liver metabolism are the major drivers to maintaining plasma levels of aromatic AAs. Phe and Tyr are of particular relevance for catecholamine-related disorders, as they are precursors for the synthesis of dopamine, noradrenaline, and adrenaline. They are degraded to fumarate and acetoacetate through a common pathway. Deficiencies in enzymes of this pathway lead to pathological accumulation of Phe, Tyr, or metabolite intermediates, which influence brain monoamine synthesis and can give rise to several neurocognitive deviations and ADHD symptoms (below).

#### 3.2.1. Liver metabolism of phenylalanine and tyrosine

PAH catalyzes the first step converting Phe to Tyr and its activity is regulated through allosteric kinetics as well as through cell signaling (Flydal and Martinez, 2013). PAH is a member of the BH<sub>4</sub>-dependent AAAHs and the synthesis and regeneration of BH4 are necessary for PAH activity. Deficient PAH activity leads to severe hyperphenylalaninemia, referred to as PKU (OMIM 261600 and 261630), which if left untreated can lead to highly elevated serum Phe levels (several mM), compared to normal fasting levels around 60 μM. PKU is an autosomal recessive disorder with a prevalence of about 1:10 000 in Caucasians and therefore one of the most frequent inherited metabolic diseases (Ashe et al., 2019). If left untreated, the high Phe levels can lead to severe cognitive dysfunctions, mainly through disturbed monoamine synthesis. However, as it is difficult to maintain low circulating Phe levels. Treated PKU patients also commonly experience neuropsychiatric symptoms. High Phe-levels may compromise catecholamine and serotonin synthesis in the brain through interfering with AA transport across the blood-brain barrier (BBB) or by their effects on enzymes involved in their biosynthetic pathways (Fig. 1 and see below) (Ashe et al., 2019).

The tissue level of Tyr is maintained by protein recycling and by a balance between Phe hydroxylation and further degradation by the reversible, pyridoxal phosphate-dependent activity of Tyrosine Aminotransferase (TAT; EC 2.6.1.5) (Fig. 3). TAT activity is deficient in Tyrosinemia Type 2 (HT2, OMIM 276600), giving rise to very high plasma levels of Tyr. The subsequent two steps, conversion of p-hydroxyphenylpyruvate to homogentisate and further to 4-maleylacetoacetate are catalyzed by dioxygenase enzymes (HPPD and HGD),



whose activities are compromised in Tyrosinemia Type 3 (HT3, OMIM 276710) and AKU (AKU, OMIM 203500), respectively (Fig. 3). The p-hydroxyphenylpyruvate dioxygenase (HPPD, EC 1.13.11.27) is also targeted by nitisinone (2-[2-nitro-4-(trifluoromethyl) benzoyl] cyclohexane-1,3-dione), which is used to treat HT1 (OMIM 276700) and is tested for AKU (Ranganath et al., 2018).

HT1 is caused by 4-fumarylacetoacetate hydrolase (FAH, EC 3.7.1.2) deficiency, which is the last enzyme of the Phe-/Tyr-degradation pathway. Prior to this step is the cis-trans isomerization of 4-maleylacetoacetate (MAAI, EC 5.2.1.2), which also occurs spontaneously or by alternative routes as MAAI deficiency gives no apparent symptoms other than the accumulation of fumarylacetoacetate and succinylacetone in the urine (Fernandez-Canon et al., 2002). The severity of HT1 results from the accumulation of toxic metabolites generated by the decomposition of 4-fumarylacetoacetate; thus, inhibiting pathway upstream of HGD with nitisinone could relieve much of the extreme symptoms. However, this leads to a large increase in plasma Tyr levels as the reaction catalyzed by TAT is reversible. The properties of TAT are not well studied, but it appears that the mammalian enzyme has a restricted substrate specificity, meaning that many AAs cannot replace glutamate or tyrosine. Thus, the relative abundance of the substrates and the enzyme kinetic constants will be important in determining the Tyr levels. There is reason to believe that species differences exist for TAT specificity and kinetics, which may influence the tolerance for aromatic AA disturbances in different animal models (Meher et al., 2010; Sivaraman and Kirsch, 2006).

### 3.2.2. Amino acid transport over the blood brain barrier

Neurons and glial cells of the brain are surrounded by extracellular matrix and brain interstitial fluid (bISF), which has a different composition than plasma. The exchange of compounds between bISF and the brain microvasculature occurs over the BBB, which is maintained by tight junctions between the endothelial cells of the brain microvasculature (Hawkins et al., 2006). In addition, there is an exchange occurring between the bISF and the cerebrospinal fluid (CSF), mainly over the ependymocytes of the ventricles and through the subarachnoid spaces (Tumani et al., 2017). The blood CSF barrier is maintained by epithelial cells of the choroid plexuses, where most of the CSF is generated. It is generally considered that the composition of the CSF and bISF is similar, although different barriers control much of the transport from plasma (Tumani et al., 2017).

The BBB is of major importance for the transport of AAs into the bISF that must pass through both the luminal (towards the blood) and the abluminal (towards the brain) plasma membranes of the endothelium before reaching the basal membrane or matrix of the vasculature (Hawkins et al., 2006) (Fig. 1). In addition, extending processes from surrounding astrocytes and pericytes cover the basal membrane on the abluminal side, thereby further controlling transport. The barrier function is essential for several reasons, one being the differences in extracellular AA levels in the brain relative to plasma (in CSF about 10 % for most AAs, 5 % for acidic AA, and about 80 % for glutamine) as many amino acids and their derivatives are vital neurotransmitters in the CNS. Similarly, monoamines are not transported across the BBB and must be synthesized from Tyr and Trp in the CNS.

AAs are transported over the endothelial layer by specific transporters located on both luminal and abluminal sides by facilitated passive transport, whereas Na<sup>+</sup> dependent transporters located on the abluminal side only, pump AAs out of the brain (O'Kane and Hawkins, 2003) (Fig. 1). Most essential AAs are transported into the brain by the same transporter system, i.e., the Large Neutral Amino Acid (LNAA) of the L1 type (LAT1, SLC7A5), and they are therefore mutually competing for transport into the brain. The LAT2 (SLC7A8) is prominent at the blood CSF barrier (Dolgodilina et al., 2020). The cationic amino acid transporter, referred to as the  $\gamma$  + system, transports arginine, lysine, and ornithine with high affinity. However, in the presence of Na<sup>+</sup>, low-affinity transport of several non-basic amino acids, including Phe,

also takes place by this transporter.

The abluminal Na<sup>+</sup> dependent transporters are key to maintaining the low AA levels in the brain. These transporters have somewhat overlapping substrate specificities, e.g., the Na + LNAA system, which transports all essential AAs except cysteine, has overlapping substrate specificity with the Alanine, Serine, Cysteine (ASC) preferring transporter. However, only Na<sup>+</sup> LNAA seems to transport aromatic AAs out of the brain (O'Kane and Hawkins, 2003). The endothelial cells of the BBB also have high  $\gamma$ -glutamyl transpeptidase activity and an active  $\gamma$ -glutamyl cycle (Ogawa et al., 1998). This has been postulated to activate the Na + dependent abluminal AA transporters via its pyroglutamate intermediate.

Since many AAs compete for the same transporter systems, disturbances in the balance of circulating AAs can affect their transport into the brain. Deficiencies of LAT1/SLC7A5 have been linked to ASDs (Tarlungeanu et al., 2016). In PKU, high serum Phe levels give rise to severe intellectual disabilities, growth retardation, and seizures if left untreated (see below). The highly elevated Phe can be expected to lower CSF Tyr and Trp levels. However, since they compete for both in- and out transport, their ratios may not be significantly shifted or even opposite (Antoshechkin et al., 1991; Lykkelund et al., 1988; Tanaka et al., 2006), depending on the kinetics of the transporter systems involved and the AA levels on either side of the barrier. Still, inhibited transport into the brain in addition to inhibition of AAAs has been linked to lowered monoamine synthesis in the brain (Pilotto et al., 2019), and supplementation with tyrosine has been shown to increase homovanillic acid (HVA), although individual responses are quite different (Lykkelund et al., 1988; Scala et al., 2020; van Vliet et al., 2019a). Still, even under a strict dietary regime, cognitive and neuropsychiatric symptoms are commonly observed. Today, a life-long low-Phe diet is recommended to keep the blood Phe levels between 2-6-fold (US) or <10 fold (Europe) that of normal levels (about 60  $\mu$ M). Disorders of tyrosine metabolism can lead to highly elevated plasma levels of Tyr, such as in tyrosinemias (above), with elevated CSF Tyr levels (Thimm et al., 2011).

Alterations of AA transport have also been described in other neuropsychiatric disorders, particularly ASDs where altered peripheral levels of the tryptophan-derived monoamine serotonin are among the best-documented biomarkers. As many ASD patients have ADHD symptoms or a diagnosis of ADHD, this connection is particularly relevant. Missense mutations in subunits of the SLC3A2, SLC7A5, and SLC7A8 subunits of the LAT1 and LAT2 protein complexes have been observed in ASD patients (Cascio et al., 2020; Tarlungeanu et al., 2016). The effect of some of these mutations has been modeled in knockout mice, providing insights into their mechanisms (Tarlungeanu et al., 2016).

## 4. Clinical phenotypes in PKU, Tyrosinemias, and AKU

As presented in Table 1b, reported cognitive symptoms are quite diverse, both between and within different NMDs. Likewise, in classical Mendelian diseases, the phenotypes are not only dictated by the primary metabolic defect but also by a wide range of modifying environmental and inherited factors, as well as their interactions. As such, discovering diffuse cognitive problems and recognizing them as part of the metabolic disorder (or its treatment), can be challenging. Still, awareness about the possible significant impact of such problems on, e.g., treatment adherence (and thereby the prognosis for the metabolic condition itself) is important, especially since studies indicate that underdiagnosis of comorbid psychiatric conditions ("diagnostic overshadowing") in somatic diseases are common (e.g., in neurological diseases) (Hendriksen et al., 2015).

### 4.1. PKU

Irreversible neurological impairment, severe intellectual disability, stereotypy, and hyperactivity are reported in untreated PKU. Although



dietary treatment has improved outcomes, it is difficult to maintain full lifelong dietary control, and the risk of different psychiatric disorders is high, even with optimal maintenance. Attentional, mood and anxiety disorders are common, and a range of cognitive and neuropsychiatric changes at varying levels of hyperphenylalaninemia have been described (Ashe et al., 2019). In contrast to earlier beliefs, it is now increasingly recognized that maintenance of treatment (recommended Phe-values are between 120–360  $\mu\text{mol/L}$  in the US and up to 600  $\mu\text{mol/L}$  in Europe) also in adult age are associated with better psychosocial and cognitive outcomes. Nonetheless, these levels are still significantly higher than in individuals without PKU (Ashe et al., 2019).

Neurodevelopmental problems described in diet-treated PKU are very similar to those described in ADHD, and in a study by Arnold, 26 % of children with PKU used stimulant medication for attentional dysfunction (Arnold et al., 2004). As in tyrosinemia, reduced motor function, attention, and working memory are reported (this is summarized in a meta-analysis by (Stevenson and McNaughton, 2013)) in addition to lower executive functioning (Huijbregts et al., 2013) and lower social skills (Jahja et al., 2016). Normal IQ levels are reported in early-treated patients (infants); however, compared to siblings without PKU, these levels may be lower ((Berry et al., 1979; Diamond et al., 1997; Dobson et al., 1976; Koch et al., 1984; O'Flynn and Hsia, 1968) in Diamond et al., 1997 (Diamond et al., 1997)). Diamond et al. found worse performance on executive functions (working memory and inhibitory control) in children with PKU whose Phe levels in plasma were three to five times higher than PKU children with lower levels, their siblings, matched controls, and children from the general population (Diamond et al., 1997). This deficit seemed to influence the dorsolateral prefrontal cortex selectively, as performance on control tasks affecting other parts of the brain was similar to the control groups (Diamond et al., 1997). Berguig et al. found that lowering Phe in plasma to  $<360 \mu\text{M}$  increases neurotransmitters and neurotransmitter-metabolites to an almost normal range in PKU, in addition to reducing inattention symptoms (Berguig et al., 2019). This is in accordance with a study by Burton et al. where 20 % or more reduction in blood Phe levels were found in 57 % of subjects on sapropterin, and both inattentive symptoms and executive function improved with this therapy (Burton et al., 2015).

#### 4.2. Tyrosinemias

Several neurocognitive difficulties, as inattentiveness (Pohorecka et al., 2012), problems related to working memory and social cognition (van Ginkel et al., 2016), learning difficulties (Masurel-Paulet et al., 2008), and lower IQ (Thimm et al., 2012), have been described in treated HT1. Such problems also occur in patients diagnosed with HT2 or HT3. While tyrosine concentrations in HT3 patients are comparable to treated HT1 patients, HT2 patients display higher tyrosine levels and more prominent neurocognitive difficulties (Mitchell et al., 2001). Different mechanisms have been suggested to explain these problems, from sequelae from liver disease to toxic levels of Tyr. Van Vliet et al. found that high Tyr levels over the lifespan, especially the last year before testing, were related to internalizing behavior and health-related quality of life (van Vliet et al., 2019b). This is in line with a study showing correlations between inattentiveness and plasma levels of Tyr in treated patients with HT1 (Barone et al., 2020), with a stronger correlation ( $r = .780$ ) between recent levels of Tyr and inattention than long time levels ( $r = .707$ ). However, separate pathways for different cognitive outcomes may be present within the same disorder. For instance, diagnosis of HT1 before eight months of age was related to a decline in IQ over time (Garcia et al., 2017), while this was not found in children diagnosed later. It has therefore been speculated (Barone et al., 2020) if low IQ and symptoms of inattention in HT1 are affected by different pathways; one by the disorder itself (by affecting the vulnerable infant brain), the other by its treatment (Barone et al., 2020). Van Ginkel et al. highlight that close monitoring of patients is important

because of uncertain long-term effectiveness and new potential toxicities of the treatment, (van Ginkel et al., 2019).

In HT2 patients, intellectual deficit and neurological findings are identified in up to 60 % of cases. The intellectual deficit ranges from mild to severe and is the most common feature. Behavioral problems, nystagmus, tremor, ataxia, and convulsions have also been reported (Wendel, 2010). The full clinical spectrum of HT3, the rarest form of tyrosinemia, is unknown. Neurodevelopmental problems reported in these patients are summarized in a recent review by Barroso et al. and include ADHD, intellectual impairment, learning difficulties, dyslexia, behavioral disturbance, ataxia, microcephaly, and seizures (Barroso et al., 2020), but the classical phenotype is not yet established (Cerone et al., 1997; Ellaway et al., 2001; Russo et al., 2001).

#### 4.3. AKU

This rare inherited metabolic disease affects the tyrosine metabolic pathway leading to the accumulation of homogentisic acid. Nitisinone reduces the accumulation of this metabolite, but the clinical implications are uncertain. Khedr et al. (2020) found that nitisinone increases Tyr not only in serum but also in tissues (Khedr et al., 2020), and it has been speculated if hypertyrosinemia could alter mood (Davison et al., 2018). However, Davison et al. found no changes in monoamine neurotransmitters in brain tissues when using a murine model of AKU where mice were treated with nitisinone (Davison et al., 2019). The authors suggested that hypertyrosinemia during nitisinone treatment does not affect the metabolism of monoamine transmission and, therefore, is unlikely to result in deficits in cognition and altered mood (Davison et al., 2019). In contrast, Harding et al. found an increase in dopamine by 36 % following nitisinone treatment in brain tissue, using a mouse model of PKU. This may be because Phe decreased by 44 %, possibly mediating inhibition of TH, thereby enabling dopamine biosynthesis (Harding et al., 2014).

### 5. Clinical phenotype and biochemical mechanisms of other ADHD-related NMDs

As briefly introduced in Section 2, several other NMDs (in addition to PKU, tyrosinemias, and AKU) present with ADHD and related behavioral phenotypes, such as SSADH deficiency, MSUD, XLI, MELAS syndrome, and MPS III syndrome. The known biochemical alterations of these disorders could shed light on ADHD pathophysiology; however, the details of these mechanisms and their effects on neurocognition are still unknown. This section provides an overview of the clinical phenotypes and biochemistry of the mentioned NMDs, and potential explanations for the many neuropsychiatric comorbidities observed.

#### 5.1. SSADH deficiency

SSADH deficiency (OMIM 271980) is a disorder of  $\gamma$ -aminobutyric acid (GABA) metabolism caused by *ALDH5A1* mutations (Jakobs et al., 1981; Wang et al., 2019). A wide range of cognitive and related somatic features are present in SSADH patients, including ADHD (DiBacco et al., 2019), mood and anxiety disorders (Gibson et al., 2003), and autistic behavior/ASD (Pearl et al., 2021, 2003a). Moreover, patients commonly present with additional symptoms, i.e., intellectual impairment (DiBacco et al., 2019; Pearl et al., 2021), obsessive-compulsion, irritability or aggression, hallucinations (Gibson et al., 2003; Pearl et al., 2003a), hyperactivity, impulsivity (Gibson et al., 2003; Knerr et al., 2008), language difficulties, and sleep disturbances (DiBacco et al., 2019; Gibson et al., 2003). SSADH may be underdiagnosed because of the variable phenotype (Knerr et al., 2008). Research indicates worsening of epilepsy, sleep, and behavioral disturbances (e.g., obsessive-compulsive behavior) with age (DiBacco et al., 2019), and Knerr et al. suggest that families of patients with SSADH deficiency need counseling and support about the anticipated persistence of

neuropsychiatric symptoms into adulthood (Knerr et al., 2008).

As illustrated in Fig. 4, SSADH deficiency impairs the final step of GABA degradation where SSA is, under normal conditions, oxidized to succinate and enters the tricarboxylic acid (TCA) cycle for energy utilization. Instead, the accumulated SSA is reduced to  $\gamma$ -hydroxybutyric acid (GHB) (Pearl et al., 1993). As a result, patients can have elevated levels of GHB (65-230-fold increase) and GABA (up to 3-fold increase) (Gibson et al., 2003; Jakobs et al., 1981). SSADH activity regulation coupled with increased levels of GHB and GABA can influence multiple CNS mechanisms through receptor dysfunction and possible neurotoxicity. With increased GHB, primary receptor activity shifts from presynaptic G-protein coupled GHB-receptors to GABA<sub>B</sub> receptors, consequently altering the presynaptic release of several important neurotransmitters (Kolker, 2018; Snead and Gibson, 2005). In addition, GHB elevation influences neurotransmitter release by depression of N-methyl-D-aspartate (NMDA) and  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor-mediated function (Berton et al., 1999). GHB and GABA elevations also change MAP kinase activity through a GABA(B)R-mediated mechanism or by effects on myelination (Knerr et al., 2007; Kolker, 2018). Murphy et al. found that 4-hydroxy-*trans*-2-nonenal (HNE), a major oxidative stress marker in neurodegenerative diseases, is mainly oxidized by SSADH in CNS mitochondria (Murphy et al., 2003).

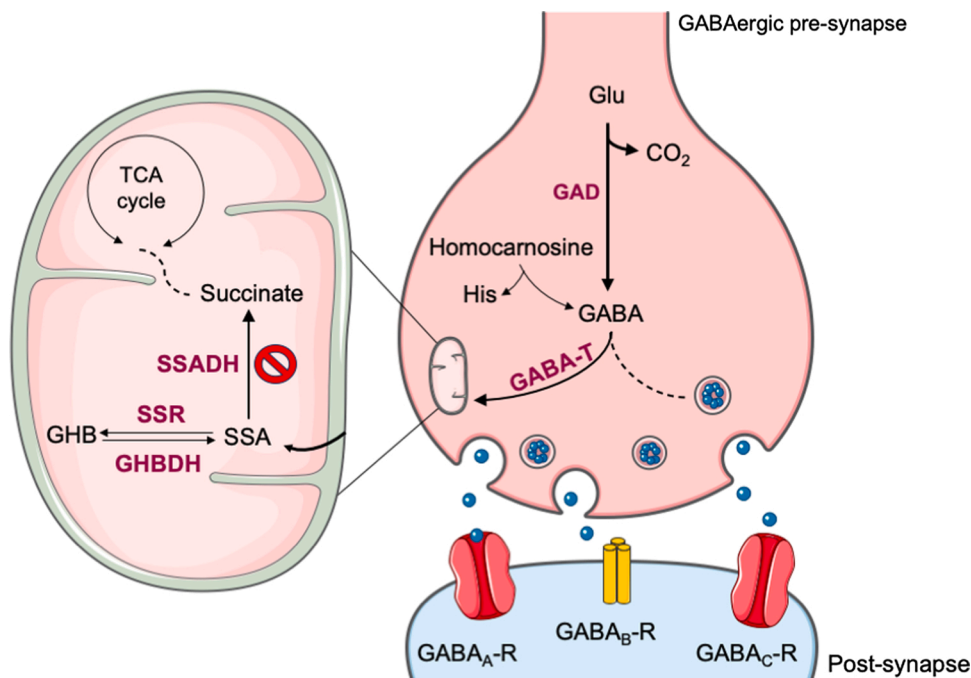
The behavioral problems observed in SSADH patients may result from altered dopamine and serotonin metabolism, as suggested by Gibson et al. and Pearl et al. (Gibson et al., 2003; Pearl et al., 2003b). The authors reported correlations between elevated GHB levels and the end-products of dopamine and serotonin metabolism: HVA and 5-hydroxyindoleacetic acid (5-HIAA), respectively (Gibson et al., 2003; Pearl et al., 2003b). Likewise, increased levels of homocarnosine might influence the observed neurocognitive phenotype since other homocarnosine disorders (i.e., homocarnosinosis and GABA-transaminase) primarily present with neurological impairment ((Gibson and Jakobs, 2001) in (Gibson et al., 2003)). The anticonvulsant Vigabatrin, an irreversible inhibitor of GABA transaminase (GABA-T), is (currently) the most common therapeutic intervention for SSADH patients. However, the clinical outcomes diverge, and, in some cases, patients show a neurological decline as it may aggravate the hyper-GABAergic status. Moreover, *in vitro* studies show that it could down-regulate SSADH

activity. Hence, Vigabatrin should be used with caution (Knerr et al., 2007).

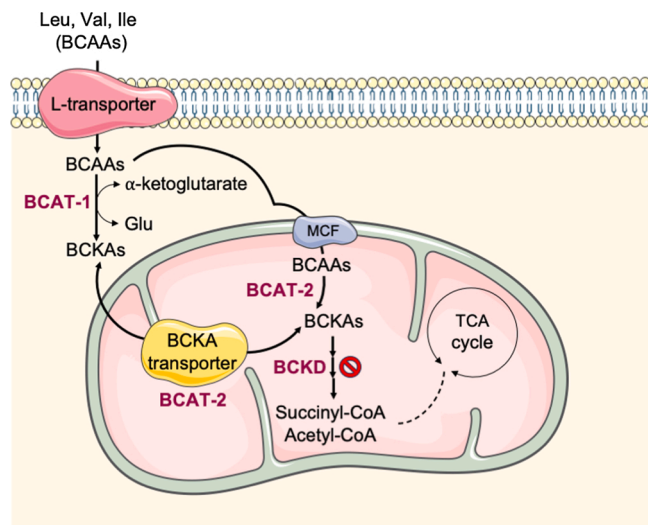
## 5.2. MSUD

MSUD (OMIM 248600) is caused by mutations in one of three genes (*BCKDHA*, *BCKDHB*, *DBT*, resulting in mitochondrial branched-chain  $\alpha$ -ketoacid dehydrogenase (BCKD) deficiency (Strauss et al., 1993). As shown in Fig. 5, the BCKD complex is responsible for the irreversible oxidative decarboxylation in the catabolism of branched-chain amino acids (BCAAs). Consequently, leucine (Leu), valine (Val), isoleucine (Ile), and their responding  $\alpha$ -ketoacids (BCKAs;  $\alpha$ -ketoisocaproic acid,  $\alpha$ -keto-3-methylvaleric acid, and  $\alpha$ -ketoisovaleric acid) accumulate rapidly (Strauss et al., 1993). MSUD patients are categorized into three subtypes based on enzyme activity levels: classic (most fatal), intermediate, and intermittent. A lifelong, protein-restricted diet is necessary to keep the plasma BCAA levels within the recommended ranges (Leu; 75–200  $\mu\text{mol/L}$   $\leq$  five years of age, 75–300  $\mu\text{mol/L}$   $>$  five years of age, Ile, Val; 200–400  $\mu\text{mol/L}$ ) (Frazier et al., 2014).

MSUD-patients have increased prevalence of anxiety, depression, inattention, and impulsivity compared to controls, with a lifetime cumulative incidence by age 36 years of 83 % for these conditions (Muelly et al., 2013). Patients remaining clinically asymptomatic during the newborn period were also compared with neonates that were encephalopathic at diagnosis. The latter were five times more likely to suffer from anxiety and ten times more likely to suffer from depression, but not significantly more likely to suffer from ADHD. However, ADHD had a cumulative lifetime incidence of 54 % in MSUD patients on dietary therapy and 82 % on transplant treatment (Muelly et al., 2013). Results from this study are in line with a study by Strauss et al., showing that cognitive and psychiatric disabilities are not entirely prevented by dietary therapy or liver transplantation (Strauss et al., 2020). In a study by Abi-Wardé et al., negative psychiatric outcomes tended to be associated with higher Leu levels, highlighting the importance of compliance to dietary treatment (Abi-Wardé et al., 2017). Strauss et al. also describe how constant BCAA fluctuations affect mechanisms related to several important neurophysiological processes. These processes include cerebral uptake of neurotransmitters, unbalanced amino acid transport across the BBB, continued neonatal encephalopathy, and disturbed



**Fig. 4. Overview of SSADH deficiency in the GABAergic synapse.** GABA synthesis occurs when glutamate (Glu) is decarboxylated by glutamic acid decarboxylase (GAD) in the pre-synapse. In the synaptic cleft, GABA binds either the ionotropic receptors GABA<sub>A</sub> and GABA<sub>C</sub>, or the G-protein coupled receptor GABA<sub>B</sub>. After neurotransmission stops, GABA transaminase (GABA-T) converts GABA to succinic semialdehyde (SSA). SSADH deficiency impairs the oxidation of SSA to succinate, which then enters the tricarboxylic acid (TCA) cycle; therefore, SSA is reduced to  $\gamma$ -hydroxybutyric acid (GHB), resulting in the accumulation of both GABA and GHB. The figure was made with Smart Servier Medical Art templates, licensed under a Creative Commons Attribution 3.0 License (<https://smart.servier.com/>).



**Fig. 5.** Overview of BCAA catabolism in MSUD patients. First, BCAAs are transported into liver cells by the L-transporter. Second, they are either (1) converted to BCKAs by branched-chain amino acid transaminase (BCAT) 1 and transported into the mitochondria by the BCKA transporter, or (2) transported into the mitochondria directly by the mitochondrial carrier family (MCF) and then converted to BCKAs by BCAT-2. Third, the branched-chain  $\alpha$ -ketoacid dehydrogenase (BCKD) complex facilitates complete BCKA degradation to succinyl-CoA and acetyl-CoA, which then enters the tricarboxylic acid (TCA) cycle. Hence, MSUD patients with deficient BCKD complex will rapidly accumulate BCAAs and BCKAs. The figure was made with Smart Servier Medical Art templates, licensed under a Creative Common Attribution 3.0 License (<https://smart.servier.com/>).

energy metabolism and tricarboxylic acid flux (Strauss et al., 2020). Even though dietary treatment enriched with SLC7A5-substrates (Tyr, Phe, Trp, Met, His, and Thr) maintained the substrates plasma concentrations, the cerebral uptake of certain AAs (Trp, Glu, Met, and His) was 25–34 % below the normal reference values (Strauss et al., 2020).

In a recent review by Xu et al., the authors discuss the impacts of BCAA dysregulations on the neuropsychiatric phenotype observed in MSUD patients (Xu et al., 2020). For instance, low BCAA levels are frequently observed in ASD patients (Arnold et al., 2003; Evans et al., 2008; Garcia-Cazorla et al., 2014; Perry et al., 1978; West et al., 2014) reviewed in (Xu et al., 2020). Moreover, several studies propose a link between alterations in glutamate metabolism, decreased levels of N-Acetylaspartate (NAA), and elevated lactate to ADHD and ADHD-related symptoms, depression, anxiety, obsessive-compulsion disorder (OCD), and psychosis in MSUD patients (reviewed in (Xu et al., 2020). Low levels of precursors for monoamine neurotransmitters could also explain the clinical similarities between untreated PKU and MSUD patients (Xu et al., 2020), particularly comorbidities such as depression (Nutt, 2008), anxiety (Zarrindast and Khakpai, 2015), and ADHD (Doummar et al., 2018).

The neurological impairment in MSUD patients could also be a result of inflammatory processes and oxidative stress. For instance, Scaini et al. reported that inflammation caused by high BCAA levels resulted in BBB breakdown (Scaini et al., 2014). Further, De Simone et al. showed that high BCAA levels modify the microglial immune properties, resulting in an intermediate M1 (pro-inflammatory)/M2 (anti-inflammatory) phenotype. A less efficient microglial response combined with increased free radicals may increase the susceptibility to neurodegeneration (De Simone et al., 2013). Likewise, clinical diagnostics show that, in some cases, patients suffer from antioxidant and L-carnitine (L-car) deficiency. However, whether this is a primary MSUD effect or secondary to insufficient nutritional intake is debated. In addition to maintaining energy balance, L-car modulates the mitochondrial transport of long-chain fatty acids and the following  $\beta$ -oxidation (Mescka et al.,

2015).

### 5.3. XLI

XLI (OMIM 308100) patients suffer from steroid sulfatase (STS) deficiency as a result of mutations in or complete deletion of (85–90%) the *STS* gene (Diociaiuti et al., 2019). In 2008 Brookes et al. reported an association between *STS* (SNP markers rs2770112 and rs12861247) and ADHD, making *STS* a candidate gene for ADHD susceptibility (Brookes et al., 2008). XLI may also be associated with ASD or related communication/language difficulties (Kent et al., 2008), in addition to epilepsy, motor disabilities, and mental retardation (Diociaiuti et al., 2019). However, ADHD seems to be the most common neurodevelopment disorder in XLI patients. In one study, 40 % fulfilled the DSM-IV criteria for ADHD, of which 80 % were categorized as the inattentive subtype (Kent et al., 2008). Other studies (Diociaiuti et al., 2019; Rodrigo-Nicolas et al., 2018) have found a prevalence of ADHD around 30 %.

In addition to elevated ADHD prevalence, patients have a distinct somatic phenotype of dark-brown scaling, dry skin, increased skin permeability, hyperkeratosis, opacification of the corneal stroma, and cryptorchidism that appear during early infancy (Rodrigo-Nicolas et al., 2018). Under normal conditions, STS cleaves sulfate groups from steroids and sulfatases, e.g., cholesterol sulfate ( $CSO_4$ ) and dehydroepiandrosterone sulfate (DHEAS).  $CSO_4$  plays a vital role in desquamation and alters the physical cell membrane properties, stabilizing cells in the stratum corneum (SC) (Elias et al., 2004). Epstein et al. (1984) introduced the epidermal  $CSO_4$  cycle, where  $CSO_4$  is sulphurated in the lower epidermis and desulphated in the outer epidermal layers regenerating cholesterol (Epstein et al., 1984). Consequently, STS may indirectly regulate steroid production in the granular layer of the epidermis (Hernandez-Martin et al., 1999). XLI patients can have up to ~50 % reduction of cholesterol content in the SC (Williams and Elias, 1981); however, several studies argue that subsequent permeability barrier abnormalities are caused by  $CSO_4$  accumulation rather than cholesterol deficiency (Zettersten et al., 1998).

In contrast, DHEAS and dehydroepiandrosterone (DHEA) accumulation are likely to influence the neuropsychiatric phenotype in XLI patients. These excitatory neurosteroids modulate GABA<sub>A</sub> and NMDA receptor activity and are known to alter biological and neurophysiological processes in the CNS (Maayan et al., 2003). For instance, Strous et al. (2001) found an inverse correlation between clinical symptoms of ADHD, particularly hyperactivity, and DHEA blood levels, suggesting a protective effect of neurosteroids on ADHD symptom expression (Strous et al., 2001). Trent et al. (2013) later confirmed this correlation in a mouse model, arguing that DHEA's influence on activity is particularly strong when encountering a novel environment (Trent et al., 2013). Further, treatment with standard medication for ADHD (methylphenidate) over three months was related to an increase in serum concentrations of DHEAS and DHEA in boys with ADHD, suggesting that the effects of methylphenidate may be partly related to these neurosteroids (Maayan et al., 2003).

### 5.4. MELAS syndrome

MELAS syndrome (OMIM 54000) is a mitochondrial, multisystem disorder most frequently caused by MT-TL1 mutations (m.3243A > G), decreasing the metabolic stability of tRNA<sup>Leu(UUR)</sup> (Chomyn et al., 2000; El-Hattab et al., 2015). This results in impaired mitochondrial translation, subsequent decrease in the electron transport chain (ETC) subunit synthesis, and, thus, lack of sufficient ATP production (El-Hattab et al., 2015). Although this mechanism is debated, MELAS patients are reported to have specific alterations of neurological functions instead of global neurological impairment (Kraya et al., 2019). Kraya et al. found particular deficits in executive functioning, attention, visuosperception, and construction (Kraya et al., 2019). These cognitive changes were significantly correlated with everyday life disturbances and high scores



on the Newcastle Mitochondrial Disease Adult Scale (NMDAS) (Schaefer et al., 2006), measuring the severity of the syndrome. Similarly, Neargarder et al. reported deterioration in executive functioning, language, attention, memory, visuospatial, and motor functioning in two MELAS cases (Neargarder et al., 2007). It has been suggested that mitochondrial disorders are underdiagnosed in psychiatric patients. Thus, Anglin et al. reported that anxiety, psychosis, cognitive deterioration, and mood disorders were the most common psychiatric presentations in 50 cases with mitochondrial disorders, of which 52% had a MELAS mutation (Anglin et al., 2012).

Kraya et al. also reported a significant correlation between clinical symptoms and higher lesion load, suggesting that the cognitive phenotype in MELAS is partially caused by degeneration and metabolic alterations (Kraya et al., 2019). A predominant feature of MELAS is the stroke-like episodes related to dysregulation of NO synthesis and mitochondrial proliferation that influence the availability of NO and its precursors (citrulline, arginine). The resulting NO deficiency can cause impaired blood perfusion in the microvasculature (Fig. 1, Section 4) (reviewed in (El-Hattab et al., 2015)). As reviewed in El-Hattab et al., the fluctuation in NO levels, and resulting in impaired NOS activity, could also be caused by reactive oxygen species (ROS) overproduction, increased oxidative stress, and subsequent increased levels of the endogenous NOS inhibitor asymmetric dimethylarginine (AMDA) ((El-Hattab et al., 2014, 2012; Teerlink et al., 2009) in (El-Hattab et al., 2015)).

The accumulation of cortical injuries obtained during stroke-like episodes could influence the neurocognitive phenotype observed in patients ((Sproule and Kaufmann, 2008) in (El-Hattab et al., 2015)). Hence, it is not clear if the neuropsychological impairment in MELAS syndrome is caused by stroke-like episodes only or also by neurodegeneration or energy production (Kraya et al., 2019). In addition, MR studies show a correlation between the degree of neurological impairment and elevated lactate levels; patients also had decreased levels of NAA (Cakmakci et al., 2010). These findings are consistent with those in MSUD (Section 4.2), connecting NAA and lactate levels to depression, anxiety, and ADHD (reviewed in (Xu et al., 2020)).

### 5.5. MPS III (Sanfilippo syndrome)

MPS III, known as Sanfilippo syndrome, is a lysosomal storage disorder. It is divided into four subcategories depending on the genetic mutation; (1) MPS IIIA (*SGSH* gene), (2) MPS IIIB (*NAGLU* gene), (3) MPS IIIC (pericentromeric region of chromosome 8p11.12), and (3) MPS IIID (*GNS* gene) (reviewed in (Andrade et al., 2015)). As a result, patients have; (1) heparan-N-sulfatase (HS), (2)  $\alpha$ -N-acetylglucosaminidase, (3)  $\alpha$ -acetylglucosaminidase transferase, or (4) N-acetylglucosamin-6-sulfatase deficiency (Zhou et al., 2020). These enzymes all participate in the degradation of heparan sulfate (HS), a proteoglycan, thus affecting cell homeostasis and signaling pathways (Andrade et al., 2015). Compared to MPS I (Hurler syndrome) and MPS II (Hunter syndrome), where somatic symptoms such as facial dysmorphism are extensive, MPS III primarily presents with neurological deficits (Wijburg et al., 2013).

MPS III patients have a distinct neuro(psychiatric) phenotype that gradually develops; most patients display symptoms between age 2 and 6. Wijburg et al. reported that patients are often initially misdiagnosed with ADHD or ASD due to symptoms of hyperactivity, impulsivity, aggression, and extreme restlessness (Wijburg et al., 2013). In addition, sleep disorders, mood and anxiety disorders, language issues, obsessive-compulsion, and mental retardation are observed in these patients (Andrade et al., 2015; Hoffmann et al., 2020; Kong et al., 2020; Montenegro et al., 2021; Wijburg et al., 2013; Zhou et al., 2020). Magnetic resonance imaging (MRI) studies show that patients have severe neurological degeneration and distinct morphological changes, such as ventriculomegaly or symptomatic hydrocephaly. Andrade et al. reported that the degree of ventricular dilation is linked to the severity

of mental retardation (Andrade et al., 2015). Further, the degree of neurocognitive impairment (and neuropathology) is dependent on the type of MPS III. For instance, the prevalence of behavior problems is higher in patients diagnosed with MPS IIIA, which is the most frequent type of MPS III (60 %) (reviewed in (Andrade et al., 2015)).

### 5.6. Other conditions

As mentioned, ADHD-related NMDs are not limited to the disorders described above (Sections 3.2.1, 4, and 5). For instance, Fraidakis et al. reported a 12.5 % incidence of psychiatric manifestations in cerebrotendinous xanthomatosis (CTX) patients found in the literature between 1937 and 2012, where behavior problems accounted for 5.6 % (Fraidakis, 2013). This is a rare autosomal recessive disorder of the bile acid synthesis which is associated with elevated levels of cholestanol in blood and cholestanol and cholesterol in the brain, bile and tendons. Clinical manifestations include neurologic dysfunction, in addition to chronic diarrhea, bilateral cataracts and tendon xanthomas (Salen and Steiner, 2017). Attentional problems, including ADHD, could be the presenting symptoms in young children (Fraidakis, 2013). Similarly, ADHD and behavioral problems are observed in urea cycle disorders (Serrano et al., 2010). In albinism, which comprises diseases characterized by impairment of the melanin synthesis, ADHD was found in 22, 7% of children and 6,8% of adults (Kutzbach et al., 2007). Iwański et al. (Iwanski et al., 2015) showed problems in several aspects of attention in patients with Wilson's disease (rare inherited disorder where copper accumulate in the body) with neurological symptoms, and an isolated deficit in sustained attention in neurologically asymptomatic patients. Another relevant disorder is MAO deficiency, also described in Section 3.1. In their review, Bortolato and Shih (Bortolato and Shih, 2011) argued that variations in enzymatic activity of MAO may influence behavioral regulation and be involved in a spectrum of mental disorders, such as autism and ADHD. Creatine transporter deficiency is characterized by several clinical symptoms, such as epilepsy, motor dysfunction, gastrointestinal symptoms, developmental delay, intellectual disability and autism, in addition to ADHD (Farr et al., 2020). In Cystathionine  $\beta$ -synthase deficiency, psychiatric complications, including symptoms of hyperactivity, were found in 51 % of adults (Abbott et al., 1987). Hyperactivity has also been reported in  $\beta$ -mannosidosis (Bedilu et al., 2002). In addition, ADHD-like symptoms have been mentioned sporadically in several other metabolic disorders (Dinopoulos et al., 2005; Sedel et al., 2007), but this falls without the scope of the present paper.

## 6. Clinical implications

In our review, we have summarized (a) NMDs reported to be associated with an increased prevalence for ADHD and (b) which molecular mechanisms might underly such comorbidity. This knowledge is interesting from a pathophysiological perspective and should also aid in identifying novel treatments and provide personalized care. However, knowledge about the connection between NMDs and ADHD is also relevant on a very practical level for the clinician.

For clinicians involved in managing metabolic and/or neuropsychiatric disorders, knowledge of their relationships is crucial in several settings. These include the optimization of treatment plans for persons with known metabolic diseases, screening for possible underlying metabolic diseases, as described here, in persons with (atypical) neuropsychiatric symptoms, and systematically collecting genotype-phenotype data that can increase our knowledge base of these connections and pave the way for improved future diagnosis and treatment.

The complex relationship between NMDs and (neuro)psychiatric difficulties, as described above, illustrates that somatic and mental health are deeply intertwined and that there is a need for broad, interdisciplinary assessments to prevent overlooking important symptoms. For example, Hendriksen et al. have suggested that somatic features



could overshadow ADHD in neurological diseases (Hendriksen et al., 2015). This may also be the case in metabolic disorders, as fear of death and serious complications from the metabolic disorder could be part of daily life both for patients and their closest family members and move focus away from cognitive difficulties. In line with this hypothesis, it has been speculated if parents of children with Tyrosinemia type 1 systematically underreport attention problems in their children because diffuse cognitive problems may be overlooked in the presence of serious somatic concerns (Barone et al., 2020). Paradoxically, this could lead to an underdiagnosis of ADHD, thereby adding problems with managing the strict treatment regime required for the metabolic disorder. This hypothesis is supported by a study showing poor treatment adherence in adolescents with type 1 diabetes and undiagnosed ADHD (Nylander et al., 2018).

Because of the possible underreporting of symptoms, the symptom load from ADHD may need to be higher to be detected in patients with NMDs. This is very unfortunate, as unrecognized ADHD may be more harmful in this patient group, because of higher dependency on functions that are compromised by their ADHD symptoms. Thus, even symptoms below the conventional diagnostic threshold for ADHD may cause significant problems with treatment adherence. Therefore, focusing on dimensional traits, such as relevant executive functions and attention, may be a more fruitful approach than only focusing on categorical diagnoses.

Clinical phenotypes of metabolic disorders are cutting across traditional diagnostic boundaries. Overlapping symptoms of different (neuro)psychiatric conditions are common (see Table 1b). The dimensional nature and overlapping symptoms in (neuro)psychiatric disorders could lead to both over- and underdiagnosis of these conditions. As an example of possible overdiagnosis, Arvidsson et al. reported that fewer symptoms are required to get a diagnosis of autism today than previously. They suggested that the impairment in cases with less obvious symptoms of autism may stem from other "comorbid" problems, like ADHD (Arvidsson et al., 2018). They also suggested that individuals with complex constellations of psychiatric problems, but without a "correct" diagnosis (as autism), could risk being denied community support and that this may be part of the explanation for the rise in diagnoses in the autism spectrum. Such "strategic" categorical misdiagnosis of (neuro)psychiatric conditions could lead to biased conclusions about their relationships with metabolic disorders, while examining dimensional functions may increase the knowledge about metabolic and (neuro)psychiatric disorders across diagnostic boundaries. The assessment of dimensional functions across different disorders would also make it possible to include a higher number of participants, as many patients may not fulfill the criteria for a specific diagnosis but still have significant symptoms. Increased participant size could be especially important in rare metabolic diseases, where the literature is dominated by case studies that carry an inherent risk of publications bias towards positive findings.

Although it could be preferable to evaluate cross-diagnostic, dimensional cognitive deficits, like executive function (EF) problems in NMDs, such problems could also be difficult to recognize. It has been suggested that ADHD primarily is a disorder of EF (Barkley and Murphy, 2010). Still, when using standard neuropsychological tests, impairment in executive functioning is only found in a minority of the cases (Biederman et al., 2006; Nigg et al., 2005). It is uncertain if this is because EF deficits only exist in a subgroup of patients with ADHD or if it is due to the low ecological validity of the neuropsychological tests used to assess these functions. The latter hypothesis is supported by studies showing that scores on neuropsychological tests of EF only modestly predict behavioral EF performance (Krieger and Amador-Campos, 2018) and that questionnaires and tests measure different underlying constructs of EF (Chevignard et al., 2012). Some researchers, therefore, suggest that a combination of EF tests and questionnaires may be the optimal way to assess EF as they provide complementary information (Barkley and Murphy, 2010; Krieger and Amador-Campos, 2018).

Broad assessments, including questionnaires, neuropsychological tests, and clinical interviews where potential cognitive difficulties are assessed, may be necessary to recognize the full range of cognitive difficulties in this heterogeneous group of diseases. In addition to parents, teachers, employers, or other people close to the patient could also provide useful information, as they may have a different point of reference. A closer collaboration across somatic and psychiatric health care in combination with increased consciousness and knowledge about ADHD, the nature of EF, and other cognitive functions, in addition to awareness about metabolic disorders in psychiatric health care, may also facilitate a comprehensive understanding of the complex interactions between somatic, cognitive, and (neuro)psychiatric difficulties. To identify these patients and their wide range of different symptoms, clinicians must be open-minded and look for them both in somatic and psychiatric health care.

Clinicians treating NMDs need to be aware that such conditions could be accompanied with ADHD and related neuropsychiatric disorders. This calls for proactive screening of affected children, especially during the first decade of life, with a subsequent in-depth assessment if screening positive. In this respect, both clinician case ratings, parent and teacher reports should be considered. Given that some NMDs require strict, life-long, and demanding dietary interventions, ADHD treatments targeting impulsivity and inattention might also enable patients to obtain better self-control; interventions that ultimately could improve the long-term outcome of NMDs. Still, potential beneficial effects of stimulant medications should be weighed against possible interactions with the core metabolic disturbances and somatic symptoms of the NMDs.

Another clinical scenario is that unrecognized NMDs are present in children presenting primarily with ADHD symptoms. Although the risk that the classical NMDs mentioned above go undetected is rather low, milder variants with non-Mendelian genetic transmission could be overlooked. Because of the possible underreporting of symptoms and diagnostic overshadowing, it is possible that cognitive deficits in metabolic disorders are more common than previously estimated and if that the recommended levels of e.g., tyrosine and phenylalanine should be even stricter. A more conservative approach may prevent cognitive problems that are difficult to recognize using traditional neuropsychological tests and questionnaires but still lead to significant impairments in daily life. Therefore, we call for increased awareness of the NMD-ADHD comorbidity in primarily (neuro)pediatric settings. In this context, close collaboration between pediatrics, child and adolescent psychiatry, and later in life the respective adult services, is crucial. Grand case rounds, case reports, journal clubs, and related clinical education may be instrumental in fostering better education and interdisciplinarity.

To conclude, NMDs often produce behavioral symptoms or syndromes indistinguishable from (idiopathic) neuropsychiatric disorders, including ADHD. Irrespective of their etiology, such symptoms need to be adequately diagnosed and treated. Beyond these practical implications, it has been debated whether such comorbid manifestations of a metabolic disease should be termed ADHD as well, or rather ADHD-like syndrome, secondary ADHD, or similar. At the moment, this is a rather semantical question that can only be resolved when the pathophysiology of idiopathic ADHD is known, so we can evaluate whether NMD-associated ADHD has shared or distinct mechanisms of disease.

Together, NMDs constitute a large and heterogenous group of conditions with a range of severities and possibly involving many different biological mechanisms. In addition to explaining mechanisms of NMDs, the elucidation of such underlying mechanisms may help uncover ADHD pathophysiology in general and provide fundamental biological insights. Here we have mainly focused on NMDs that directly interfere with the production, transport, or metabolism of amino acid or monoamine neurotransmitters/neuromodulators. As catecholamines appear to be of primary importance in the action of stimulants and other drugs that are used to treat ADHD, it is striking that NMDs that inhibit the

synthesis of catecholamines also produce ADHD-like symptoms.

## 7. Implications for research

This review has revealed several problems that need to be addressed in future research. First, there are strong indications of publication bias in the existing literature. Although ADHD symptoms are common in the general population, particularly in clinical samples, systematic examination and reporting of such symptoms are often missing in the clinical literature. For instance, although ADHD is often comorbid with ASD, learning disorders, and intellectual disabilities, many studies fail to include and report how ADHD was assessed in these patient groups. Thus, the overview of clinical features listed in [Tables 1a and 1b](#) are by no means comprehensive or exhaustive. Skewed or missing information will inevitably lead to a systematic bias in prevalence rates, with negative implications for guidelines and clinical practice.

Historically all the rare metabolic diseases described here were discovered using various targeted laboratory tests in small clinical samples with striking clinical phenotypes and Mendelian patterns of inheritance. However, this procedure may gradually be replaced with a more systematic approach, including next-generation metabolic screening. Thus, the -omics revolution has paved the way for examining metabolic aberrations in many traits and clinical conditions, including conditions with less striking phenotypes and lower penetrance.

As the available sample sizes and significance of GWA studies examining ADHD and related traits keep growing, these data sources should be systematically examined to explore the contribution of common variants of small effects to metabolic pathways. Such studies are needed to determine the role of polygenic alterations affecting metabolic pathways in complex, multifactorial neuropsychiatric disorders, beyond the classical NMDs mentioned in this review. So far, our insights into the pathophysiology of NMDs have often been limited to the use of surrogate measurements such as blood biomarker profiles. With the introduction of more sensitive, non-invasive technologies, such as brain magnetic resonance spectroscopy (MRS), functional magnetic resonance imaging (fMRI), positron emission tomography (PET), or functional near-infrared spectroscopy (fNIRS), it is possible to measure biochemical alterations and neurotransmitter receptors and transporter levels directly in intact brain tissue of patients and to correlate such measurements with their clinical manifestations. These approaches may be combined with computational methods to handle high dimensional, heterogeneous data types and systems biology modeling, e.g., genome-scale metabolic models ([Berndt et al., 2020](#); [Brunk et al., 2018](#)). Systems medicine approaches may help uncover hidden relationships between genetic variants, metabolic deviations, and neuropsychiatric symptoms. Such studies may have important clinical implications.

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## Declaration of Competing Interest

J.H. has served as a speaker for Eli-Lilly, HB Pharma, Biocodex, Takeda and Shire. The other authors declare no competing interest. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.neubiorev.2021.11.012>.

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