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Chapter 2

SHOULD WE BE EXCITED ABOUT GLUTAMATE DYSREGULATION IN THE ETIOLOGY OF ADHD? A REVIEW OF THE DATA

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ABSTRACT

In this chapter we review current data assessing the role of glutamate in the etiology of ADHD. A general introduction of ADHD as well as common comorbidities are briefly discussed. The glutamate system in general as well as its potential role in ADHD is thoroughly reviewed evaluating both preclinical and clinical data. The current ADHD treatments that act on the glutamate system, memantine and atomoxetine, are discussed. The chapter concludes with a discussion on the future of glutamatergic drugs in the treatment of ADHD.

Keywords: ADHD, brain energetics, glutamate, glutamatergic pharmacotherapies

INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is a disorder commonly diagnosed in children and adolescents that begins in childhood and often continue into adulthood [1, 2]. ADHD is considered a neurodevelopmental disorder that is characterized by deficits in attention and impulse control, often accompanied by hyperactivity [1, 3]. Currently, the etiological processes of ADHD are not well understood despite the fact that it affects 5% of children and 2.5% of adults worldwide [4].

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Historically speaking, the earliest reference of ADHD or a ‘disease of attention’ is rumored to be by Shakespeare in his play *King Henry VII* [1]. However, a better-documented report was in 1902 by the English physician, George Still, who focused on clinical aspects of those with ADHD-like symptoms and argued that there were certain traits similar in all those who seemed to have this ‘disorder’ [5]. Through the years ADHD has had several different nomenclatures and diagnostic criteria [1]. Currently, the DSM-V denotes three presentations of ADHD including inattentive (ADHD-PI), hyper-active/impulsive (ADHD-HI), and combined (ADHD-C) [4]. The DSM-V also established more ‘adult relevant’ symptoms as well as the classification system for severity as mild, moderate, and severe [4].

Regardless of the nomenclature used throughout the years, it has been hypothesized for decades that ADHD is a heterogeneous disorder involving interactions between genetics and the environment [6, 7]. Environmentally speaking, positive correlations are observed between ADHD and lower socioeconomic status, parent criminality, parental mental health, fetal exposure to alcohol, and maternal smoking as well as many other factors [1, 8, 9]. From a genetic standpoint most genes associated with ADHD seem to be related to malfunctions in several neurotransmitter systems with the most studied being those associated with the dopaminergic, noradrenergic, and serotonergic systems [9, 10, 11, 12].

More recently, evidence suggests that genetic and neurobiological issues related to the glutamate system may be a contributing factor in the etiology of ADHD [13, 14, 15, 16]. Here we will outline comorbidities associated with ADHD as well as discuss the glutamate system in general, review data supporting the role of glutamate in ADHD, discuss current glutamatergic pharmacotherapies, and discuss future perspectives on glutamatergic drugs in meliorating the symptoms of ADHD.

ADHD COMORBIDITIES

In a study assessing children and adolescents referred for ADHD, comorbidity ranged from ten to fifty percent for other common psychiatric disorders of youth [17]. Another study found roughly 62% of ADHD patients are likely to have one or more comorbidities and 35% of patients are likely to have two or more psychiatric comorbidities [18]. However, no differences in comorbidities seem to exist between males and females diagnosed with ADHD [18].

The main psychiatric conditions that accompany ADHD include disruptive behavior disorders (30-50%), depression (15-20%), anxiety disorders (25%), learning disabilities (10-15%), and substance abuse disorders (9-40%) [19]. Of the disruptive disorders, a strong association is seen with ODD/CD [18]. Also, those with comorbid ADHD and major depression are more likely to develop bipolar disorder later in life [20].

There is no difference in comorbidity rate between males and females with ADHD however there are differences in the type of diseases comorbid with ADHD between the sexes [18]. Specifically, males are more likely to have externalizing-only disorders (i.e., ODD/CD) and females internalizing-only disorders (i.e., anxiety) [18]. Thus, ADHD is a disorder that is likely to be accompanied by a myriad of other disorders. These comorbid data should be considered when thinking of the glutamatergic system’s role in ADHD and how the glutamate system may promote other psychiatric disorders.

ADHD AND THE GLUTATMATE SYSTEM

Several studies have shown issues with the prefrontal cortex (PFC) as well as other 'higher level' circuits in the brain in those with ADHD [21-23]. Considering the many glutamatergic projections to the PFC, as well as to other cortical regions, it is no surprise that researchers have begun exploring the glutamate system in those with ADHD [23]. Glutamatergic changes in human ADHD have also stimulated preclinical work on glutamate and ADHD [14, 24]. Thus, it is becoming apparent that dysregulations in the glutamate system may be one key etiologic factor in ADHD. In this section we will examine general aspects of the glutamate system as well as potential glutamatergic dysfunctions seen in ADHD.

Glutamate System Basics

Glutamate is the major excitatory neurotransmitter in the CNS [25]. Glutamate is synthesized in the nerve terminals of glutamatergic neurons from two major sources: α-ketoglutarate produced from the TCA cycle or from glutamine shuttled to neurons from glial cells [26-28]. In neuron terminals α-ketoglutarate and glutamine are enzymatically synthesized into glutamate and packaged into synaptic vesicles in an energy dependent fashion via vesicular glutamate transporters (VGLUT) [29].

Once packaged, glutamate can then be released into the synaptic cleft, in a Ca^{2+} dependent manner, upon the firing of an action potential [30, 31]. Once glutamate is released it is free to: (1) bind to pre and post-synaptic receptors, (2) be taken up by glial cells in a Na^{+} dependent fashion, (3) be actively transported into presynaptic neurons and repackaged, (4) diffuse away from the synapse [27, 28, 32].

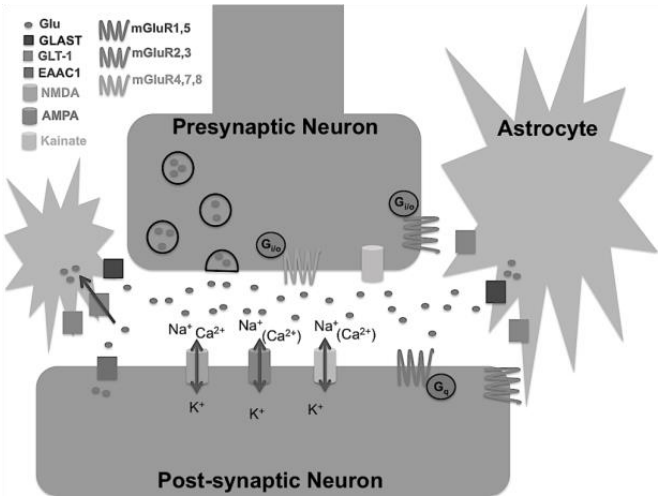

Figure 1. Glutamatergic synapse simplified. Once glutamate is released from the presynaptic neuron it is free to bind pre and post ionotropic and metabotropic receptors or be taken up by high affinity EAATs on glia cells in a Na^{+} dependent fashion. Binding to AMPA, NMDA, Kainate, or mGluR1, 5 receptors will cause excitation. Binding to mGluR2, 3, 4, 7, 8 receptors causes cellular inhibition.

In the synaptic cleft glutamate may bind to ionotropic receptors (NMDA, AMPA, Kainate), presynaptic inhibitory metabotropic receptors (mGluR2, 3, 4, 7, 8), and/or post-synaptic excitatory metabotropic receptors (mGluR1, 5) [30, 33, 34]. Approximately 90% of glutamate is taken up by astrocytes either by excitatory amino acid transporter 1 or 2 (EAAT 1 and EAAT2 respectively) [33-35]. Glutamate can also be taken up by neurons via EAAT3-5 although this seems to be a secondary process for this neurotransmitter system [33-35]. See Figure 1 for a simplified diagram of the glutamate synapse.

Bridging Old and New Thoughts about Neural Signaling in ADHD

Researchers became further interested in glutamate dynamics in the PFC in those with ADHD after realizing the reciprocal modulatory nature between these glutamatergic circuits and the dopamine system (the system historically most widely studied in ADHD) [14]. Specifically, glutamate projections from the PFC project to dopamine rich areas such as the striatum, nucleus accumbens, ventral tegmental area (VTA), and substantia nigra [33, 37]. Dopamine projections from the VTA and nucleus accumbens also project to the PFC [33, 37]. Thus, malfunctions in either of these systems could cause dysregulations in in the other [14].

Studies have shown that the NMDA receptor is crucial in stimulating dopamine neurons in the VTA and substantia nigra [38, 39]. Also, there is evidence that D2 receptor activation may inhibit the excitatory effects of NMDA receptors [40]. Similarly, D4 receptor activation may decrease the excitatory response of AMPA receptors in PFC pyramidal neurons [41]. Thus, glutamatergic dysregulations in ADHD may be as detrimental as those seen in the dopamine system and therefore normalization of this system may help alleviate symptoms seen in ADHD.

ADHD and Glutamate: Evidence from Human Studies

Decreased functioning of the PFC and subsequent deficits in cognitive functioning including working memory has been observed in those with ADHD [42, 43]. An MRI study has shown that there is an increase marker for glutamate in the anterior cingulate cortex of those with ADHD compared to controls [23]. There is also evidence that treating children with medications know to meliorate the symptoms of ADHD decreases glutamate levels in the striatum and PFC [44]. While this research is promising, there is not robust clinical data on the role of glutamate in ADHD. However, more data from preclinical models are suggestive of glutamate dysfunctions in this disorder.

ADHD and Glutamate: Evidence from Animal Research

The spontaneously hypertensive rat (SHR) is the most widely used model of ADHD specifically for studying ADHD combined type [45, 46]. The SHR shows attention deficits, hyperactivity, and impulsivity in motor movements [47-49]. While this model has been widely used in studying ADHD pathology there are recent arguments about how well this animal model translates to the human disease, what animal models may represent other

subtypes, and what the appropriate control should be in experiments [50]. That being said, most agree that the SHR from Charles River (SHR/NCrl) is the most appropriate animals model for ADHD-C, the Winstar-Kyoto from Charles River (WKY/NCrl) is best suited as a model for ADHD-PI (predominately inattentive type), and that the WKY from Harlan (WKY/NHsd) is the most appropriate control with the outbred Sprague-Dawley (SD) being another potential control [46, 51-53]. Several different studies have shown glutamate dysregulation in these animals.

Studying glutamate dynamics, specifically in the PFC, seems to be particularly important in understanding the etiology of ADHD [21-23]. Evidence from our lab has shown a significant increase in KCl-evoked glutamate release in regions of the PFC, the cingulate and infralimbic cortices, in the SHR compared to the WKY [24]. It is worth noting that evidence suggests that the cingulate cortex may regulate emotions in humans as well as be a primary center for motivation [54, 55]. On the other hand the infralimbic region seems to be related to attentional focus as well as attentional set-shifting [56]. Note that the defecits with tasks related to the aforementioned brain areas are often seen in ADHD [57-59].

Data collected also suggest that glutamate release may be increased in the striatum of the SHR compared to the WKY [24]. This finding may relate to ADHD in that the striatum is related to movement and reward circuitry both of which seem to be disrupted in ADHD [60, 61]. It also takes a significantly higher volume of ejected glutamate to achieve similar peak amplitudes in SHR rats compared to WKY control suggesting uptake may be faster in the PFC of SHRs; this may be a potential compensatory response to increased vesicular glutamate release in this area [24]. Considering the differences seen above in anesthetized rats our lab has also attempted to assess glutamate dynamics in freely-moving animals.

Evidence suggests that tonic glutamate concentrations are higher in SHR animals compared to WKY rats regardless of treatment with methylphenidate [24]. Specifically, higher tonic levels were seen in the cingulate, prelimbic, and infralimbic cortices compared to WKY [24]. Similarly, tonic glutamate levels are increased in the PFC of both intermediate and chronically treated methylphenidate animals compared to SHR saline controls [24]. Further, phasic glutamate was decreased in SHR rats treated chronically with methylphenidate compared to SHR rats treated with saline [24].

It is worth noting that the type of phasic signal seen in the animals in this experiment differed between strain and treatment [24]. Specifically, SHR's treated intermediately with methylphenidate had more rapid, multi-peaks compared with WKY's treated with methylphenidate [24]. However, when treated chronically with methylphenidate, the SHR rats had more slow phasic events compared to SHR saline controls [24]. Overall, these freely-moving data suggest that there are dynamic changes in PFC tonic and phasic glutamate levels in the SHR treated with a well know dopamine acting drug often prescribed to those with ADHD.

More 'indirect measures' have also shown differences in glutamate signaling in the SHR. For example, there is evidence that NMDA receptor activation resulted in less calcium influx in SHR PFC slices compared to those obtained from WKY [62]. Glutamate applied to SHR PFC slices also showed an increase in norepinephrine release by activation of NMDA receptors compared to WKY controls [63].

Increased glutamate levels have also been shown to stimulate release of dopamine in the substantia nigra of SHR rats compared to WKY controls suggesting that there may be altered regulation of dopamine by glutamate in the SHR [39]. Further, mice with inactivation of the

dopamine transporter showed increased hyperactivity when administered NMDA antagonists and the hyperactivity decreased when given drugs that increased glutamate signaling [64, 65]. Neonatal 6-hydroxydopamine lesions in rats caused dose dependent decreases in D4 receptors and increases in glutamate transporters in the striatum [66]. All of this data further suggests tightly coupled interactions between the glutamate and dopamine systems in ADHD [66]

Inactivation of mGluR5 increases hyperactivity in mice [67]. Further, impairment of presynaptic mGLuR7 receptors using MMPIP in the prelimbic cortex decreased visuospatial attention [68]. However, in this same study no other NMDA antagonists used or mGluR2/3 inhibitors caused any changes in impulse control when infused into the prelimbic or infralimbic areas [68]. Nevertheless, considering the above, mGluR drugs may work to normalize glutamatergic signaling. Namely, agonist of mGluR receptors may normalize the glutamatergic system and behavior in these animals [69]. Along with this, downstream effectors of mGluRs may be dysregulated in ADHD as well.

Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) and protein kinase C (PKC) signaling in the PFC in glutamatergic neurons may contribute to ADHD symptomology. CaMKII and PKC are essential for long-term potentiation (LTP); a process highly associated with glutamatergic signaling. In fact it was found that increase in CaMKII auto-phosphorylation and GluR1 phosphorylation was found in the mPFC of stroke prone spontaneous hypertensive rats (SHRSP) compared to WKY controls suggesting mPFC pathology. This mPFC pathology was realated to impaired performance on both the Y maze task and a novel discrimination task [70]. Furthermore, methylphenidate treatment not only increased SHRSP performance on behavioral tasks but also decreased CaMKII autophosphorylation and GluR1 phosphorylation in the mPFC compared to WKY controls [70].

Using the 5-choice serial reaction time task (5CSRTT) it has been reported that NMDA antagonism by MK-801 in the infralimbic cortex increased impulsive responding [68]. In another study assessing the role of the glutamate system in impulsive choice (delay and probability discounting) it was found that systemic injections of MK-801 decreased discounting rate for the larger reinforcer (less impulsive) [71]. These discrepancies may be due to the different underlying processes thought to contribute to impulsive action compared to impulsive choice [72]. Regardless, these data do suggest that some kind of interaction is occurring with the glutamate system in models of impulsivity although from these studies the directionality is not clear.

Glutamate, ADHD, and Genetic Correlates

Latrophilin-3 (LRHN3), an adhesion G-protein coupled-receptor indicated in synaptogenesis and synaptic plasticity, has been shown to promote ADHD like behaviors in experimental models with loss-of-function mutation in the *LRHN3* gene [73]. Specifically, LRHN3 knockdown causes increased locomotor activity and dopamine signaling and can be rescued by drugs used to treat ADHD [74].

Fibronectin (FLRT3) is a transmembrane protein and a natural ligand of LRHN3; this binding is essential to glutamatergic signaling [75]. When FLRT3 and LRHN3 bind this action seems to regulate excitatory synapses and plasticity both pre and post-synaptically

[76]. Some with ADHD have been shown to contain mutations in FLRT3 further suggesting links between glutamate signaling and ADHD [77].

Mutations resulting in malfunctioned SHANK proteins may also cause ADHD symptoms [78]. SHANK proteins are synaptic multi-domain scaffold proteins of the post-synaptic density that connect receptors, ion channels, and other types of membrane proteins to actin cytoskeleton G protein-coupled pathways involved in dendrite maturation and synapse formation [79]. Gene mutations in nitric oxide synthase-1 (NOS-1), a protein closely associated with the NMDA receptor and responsible for nitric oxide generation, have been linked to ADHD behaviors and impulsivity as well [16, 80].

Mutations in several other genes including those that code for NMDA receptor subunit-2A and 2B as well as genes encoding for glial glutamate transporter EAAT1 and mGluRs have all been shown to be associated with ADHD [79, 81-83].

Brain Energetics and Glutamate: A New Way to View ADHD?

The brain is an interesting organ in the fact that it is about 2% of a human's mass but utilizes approximately 20% of its oxygen and glucose [84]. Further, unlike other organs in the body the brain can only use sugars for energy due to the blood-brain barrier [85]. Neurons are also interesting in the fact that they are mercurial in nature; they can go from quiescence to rapid firing in seconds [86]. Even more interesting is that neurons cannot store their own energy; this is a task left to glia that store energy in the form of glycogen [87]. While these aforementioned facts are generally accepted the molecule used as the primary energy source in the brain is still debated [88].

It is a well-accepted scientific fact that most of the body uses glucose as its primary energy source. While the brain does seem to use glucose to some degree evidence suggest that lactate may be used more frequently as an energy source by the brain [88]. The balance and shuttling of glucose and lactate in the brain is tightly performed and regulated by neuron-glia coupling [89].

Glucose is transported into the brain through blood vessels and into astrocytes via glucose transporters (GLUT1) [89]. Glucose is then transformed into glucose-6-phosphate then either enzymatically transformed into glycogen via glycogen synthase or turned into pyruvate then lactate via pyruvate kinase and lactate dehydrogenase respectively [88, 89]. Lactate can then be shuttled out of astrocytes via monocarboxylate transporter 4 (MCT4) and shuttled into neurons via MCT2 [88, 89]. Once lactate is in neurons it is then transformed back into pyruvate and taken up by mitochondria for use in the TCA cycle (Figure 2) [88, 89].

It has been shown that there is tight coupling between glutamate signaling and lactate shuttling [89]. Evidence suggests that when glutamate is release from neurons and taken up by glia via EAATs that this Na^+ dependent process causes lactate to be released to neurons to further support their firing [89]. Also, memory formation, a process highly associated with glutamate, also seems to be associated with lactate [90, 91]. Research shows that blocking lactate transport in the brain may inhibit memory formation [90, 91]. Also, lactate but not glucose could 'rescue' this loss of memory [91]. Further, evidence suggest that beyond lactate's inherent energy properties is may also serve as a second messenger for potentiating LTP likely by regulating the redox state of neurons [92]. Considering this research, there is ample evidence to suggest that the dysregulations in brain energy can directly affect

glutamate signaling. Thus, insufficiencies in how the brain acquires energy could directly affect neurotransmitter systems and cause disease.

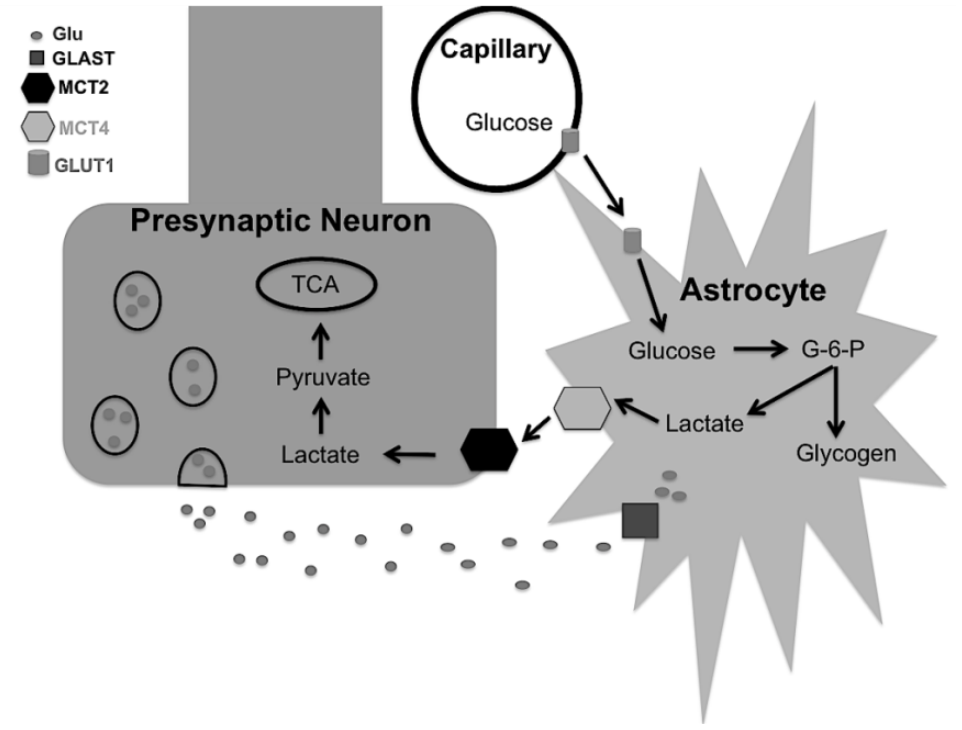

Figure 2. The Astrocyte Neuron Lactate Shuttle. Glucose is transported into the brain through blood vessels and into astrocytes via glucose transporters (GLUT1). Glucose is then transformed into glucose-6-phosphate (G-6-P) then either transformed into glycogen or into lactate. Lactate can then be shuttled out of astrocytes via monocarboxylate transporter 4 (MCT4) and shuttled into neurons via monocarboxylate transporter 2 (MCT2). Once lactate is in neurons it is then transformed into pyruvate and taken up by mitochondria for use in the TCA cycle.

Energetics and astrocytic control of glucose was proposed as a possible etiology for ADHD by a review paper in 2001 [93]. More recently some research has shown that lactate hypo-function in the brain can cause aberrant neuronal firing promoting the symptoms seen in ADHD [94]. In their elegant paper Killeen et al. (2013) proposed the behavior neuroenergetics theory of ADHD. The neuroenergetics theory assumes brain lactate hypo-function in those with ADHD and uses the lactate-neuron shuttle as a 'bottle neck' in neuronal energy acquisition. Using the neuroenergetics theory, with the help of the neuroenergetics mass-action model, these authors derived equations tying neuron physiology to behavior [94].

This model inferred that those with ADHD could only bring approximately 75-80% of their neurocognitive energy to exhibit on tasks [94]. Further, ADHD individuals could only allocate approximately 85% of their cognitive resources to behavioral tasks compared to controls [94]. Even more impressive then the aforementioned was that parameters derived from the model predicted performance on behavioral tasks suggesting that brain lactate levels

are predictive of behavioral outcomes [94]. This fact alone suggests hypo-energetics and changes in glutamate signaling may be very important in the etiology of ADHD.

Other researchers have also found a link between brain energetics, neurotransmitter dysregulations, and ADHD. For example, MRI studies suggest that the ability of those with ADHD to 'summon' glucose for oxidative metabolism is impaired in the fronto-parietal system compared to typically developing controls [95]. Further, some data support that those with ADHD may have enzyme deficiencies related to energy supply and that these deficiencies may cause developmental delays in the fronto-striatal circuitry [96]. Evidence also suggests that those with ADHD may require more brain energy than controls to function due to inefficient neural networks lacking full myelination [97].

Dysfunctional GABAergic fibers are also implicated in promoting impulsivity in those with ADHD due to lack these interneurons to inhibit upper motor neurons [98]. This GABAergic dysfunction may be caused by lack of energy supply; this is especially relevant when considering that fast-spiking GABAergic neurons may fail to completely inactivate their sodium channels upon action potential firing thus allowing two times the amount of sodium to enter the cell [99]. This larger intake of sodium then increases the ATP needed for GABA cells to adequately restore membrane potential thus this may making these cells especially vulnerable to energy insufficiencies [94].

N-Acetylaspartate (NAA) levels, a neuro-specific energy storage molecule important for energy metabolism and myelin sheath formation, is altered in ADHD [100-102]. Evidence suggests that treatment with methylphenidate increased NAA levels in the anterior cingulate cortex in those with ADHD [103]. Considering that the anterior cingulate cortex is essential in error processing and learning from mistakes (a deficit seen in those with ADHD) this increase in the energy metabolite NAA may be crucial to ADHD symptoms [104]. The implication of NAA levels in ADHD etiology is even more pronounced when we again consider that neurons in the ADHD brain may be slower processing, more energy insufficient, and variable due to lack of myelination [97, 105, 106].

It is worth noting that there is evidence against lactate as an energy source for neurons, glutamate-lactate coupling, and energy deficits in those with ADHD [107, 108]. However, considering the overwhelming evidence for a relationship between energy dynamics, glutamate, and ADHD it is likely that issues with brain energy may be a primary cause of the disease and perhaps even a potential target of future medications.

TARGETING THE GLUTAMATE SYSTEM TO TREAT ADHD

Recently studies have suggested that not only may the glutamate system promote ADHD pathology but also that targeting the glutamate system with pharmacological agents may normalize the system and alleviate symptoms associated with ADHD [109-111]. It is worth noting that research has currently suggested that staple treatments in ADHD such as methylphenidate and amphetamines may also affect the glutamate system indirectly [14]. However, here we will only discuss current pharmaceuticals approved/suggested to treat ADHD that act directly on the glutamate system namely atomoxetine and memantine. For each drug a brief pharmacological profile will be discussed followed by research from animal models and human studies.

Atomoxetine: Basic Pharmacology

Atomoxetine is a non-stimulant medication associated with less abuse liability than traditional ADHD treatments [112]. Further, data suggest that it is well tolerated with minimal adverse advents in children with ADHD [113]. Initially the primary mechanism of action of atomoxetine was thought to be as a blocker of the norepinephrine transporter (NET) with minimal activity at other neurotransmitter systems [114]. However, more recent evidence suggests that atomoxetine also works as a non-competitive antagonist at NMDA receptors at relevant physiological levels [115, 116]. In children and adolescents atomoxetine was absorbed with peak plasma concentrations occurring in 1-2 hours with a half-life of approximately 3 hours [117]. Generally speaking, the recommended dose of atomoxetine for children is 80 mg/day with a maximum recommended dose of 100 mg/day [118]. Atomoxetine is primarily metabolized by in the liver by CYP2D6; those who are poor metabolizers use the CYP2C19 pathway [118]. Note that it is important to assess for poor metabolism because the drug dose will need to be adjusted accordingly [118].

Atomoxetine and ADHD: Evidence from Animals Models

Several studies have been conducted using atomoxetine in animal models of ADHD and impulsivity. A recent study showed that rats with a lesion in the dorsal noradrenergic ascending bundle given atomoxetine had increased performance on the 5-CSRTT task suggesting that not only can atomoxetine decrease impulsivity but that atomoxetine's effects on the NET are not the sole reason for the drug's pharmacological efficacy [119]. A separate study also found atomoxetine to decrease impulsivity as measured by the 5-CSRTT task [120].

Contrary to the previous studies, Dommett (2014) found that atomoxetine had no effect on SHR performance in the 5-CSRTT. The author of this study suggested that lack of statistical significance could be due to poor sensitivity of the test to adequately tap into the hypothetical construct of impulsivity or that the SHR is not a good model of ADHD [121]. While these explanations cannot be completely ruled out it is worth noting that there is ample evidence to suggest that this may not be the case; however, these topics are discussed elsewhere [47, 122, 123]. It is also worth noting that Dommett (2014) had a difficult time training the SHR on the 5-CSRTT with only ten out of eighteen completing the task. Thus, there may have been an issue in the way the task was set up in this experiment that may have confounded the results.

Another study showed that atomoxetine reversed locomotor activity, impaired novel object recognition, and prepulse inhibition in impulsive mice [124]. A study assessing probability discounting in rats showed that a low dose of atomoxetine increased choice for the larger reinforcer suggesting a decrease in impulsive choice [125]. However, rats in a adjusting delay discounting procedure showed no changes in impulsivity when atomoxetine was infused into the mPFC or OFC [126]. These data suggest that these two brain regions in isolation cannot account for atomoxetine's observed effects in other studies where impulsivity was shown to decrease upon drug administration.

Using DAT knockout mice another study found that atomoxetine decreased cognitive deficits on an H maze task while having no effect on hyperactivity [127]. This suggests that

atomoxetine may improve the cognitive symptoms seen in ADHD without having any action on the dopamine system; however, an effect on the dopamine system may be necessary to decrease symptoms of hyperactivity. Another study was also interested in assessing how atomoxetine may affect the dopamine system as well as how this drug may affect performance on an open field task [128].

In the Moon study SHR were divided in to four atomoxetine treatment groups: control, 1, 5, 0.25 mg/kg/day doses (oral administration). The animals were then assessed in the open field at one, two, and three-week intervals and after the experiment their D2 receptor concentration from the PFC, striatum, and hypothalamus were analyzed using immunohistochemistry. It was found that the 1 mg/kg/day dose significantly decreased open field hyperactivity in the SHR and that D2 receptor concentration decreased in all brain regions in a dose dependent manner. These data suggest that atomoxetine may decrease hyperactivity by normalizing the dopamine system [128]. It is worth noting again that evidence suggests that normalizing the dopamine system may also normalize the glutamate system and vise versa thus glutamate function may play a crucial role here as well [14].

SHR treated with atomoxetine in adolescence self-administer cocaine to a lesser degree compared to those treated with methylphenidate suggesting a decrease in potential drug abuse later in life for those taking this medication [129, 130]. Thus, all things considered, atomoxetine may not only be superior in treating ADHD symptoms compared to traditional treatments but may also be less likely to promote abuse behaviors in the future.

Atomoxetine and ADHD: Evidence from Clinical Trials

Although effect sizes are usually not as large as with stimulants, several clinical trials have been conducted on atomoxetine in the ADHD population with the vast majority showing positive results [131]. For example, a six-month, placebo controlled, double-blind trial showed an improvement in attention scores in adults with ADHD compared to placebo controls [132]. In another double-blind, placebo-controlled study it was found that once-daily atomoxetine improved ADHD symptoms in adolescents according to investigator, parent, and teacher ratings [133]. A meta-analysis conducted on 25 double-blind, placebo controlled studies also showed that atomoxetine decreased several symptoms associated with ADHD such as hyperactivity, impulsivity, and inattention compared to placebo in children and adolescents [134].

An integrated analysis of three Eli Lilly clinical studies showed that that atomoxetine increased emotional control in those with ADHD and that emotional control was also found to correlate to improvements in core ADHD symptoms [135]. Note that it has also been suggested that atomoxetine is equally efficacious regardless of prior stimulant medication treatment although crossover studies are currently occurring to address this question [136].

In a 3-year open label study atomoxetine was found to be more effective in adult, female ADHD patients that also had other emotional dysregulations [137]. Further, an 8-week open-label study in Japanese adults with ADHD showed a significant improvement in ADHD symptoms and a low medication discontinuation rate [138]. In a longer open-label study (12-weeks) atomoxetine was found to be an effective treatment in adults with ADHD that also had comorbid responsive generalized anxiety disorder [139]. A meta-analysis conducted on data from 13 atomoxetine studies (placebo controlled and open-label) further concluded that

this drug decreases ADHD symptoms in adolescents with little to no drug tolerance or adverse events after two years of use [140]. Overall there seems to be ample evidence that atomoxetine is safe and effective in children, adolescence, and adults with ADHD.

Memantine: Basic Pharmacology

Memantine is an uncompetitive NMDA antagonist with low to moderate affinity for the NMDA receptor; initially this drug was developed for the treatment of Alzheimer's disease [141]. Pharmacokinetically, memantine is absorbed readily from the gut reaching maximum plasma concentration in 3-8 hours with a half-life of approximately 60-80 hours [110]. Most of the drug is metabolized by the kidneys with very little of the drug being metabolized in the liver by cytochrome p450 enzymes [142]. Memantine appears to have little side effects with the most commonly reported being dizziness, constipation, headache, hypertension, and somnolence [143]. Considering increased glutamate levels are suggested in those with ADHD, it is theorized that memantine's ability to decrease glutamate signaling is a possible reason for its therapeutic value in ADHD [14].

Memantine and ADHD: Evidence from Animal Models

There seems to be a paucity of data assessing memantine's effects on impulsivity in animal models; however, the studies found present mixed results. For example, one study showed that the time spent in the central area on a locomotor task increased in both SHR and WKY controls after a high dose of memantine (32 mg/kg) suggesting an increase in impulsivity [144]. However, at low memantine doses (5.6 mg/kg) the SHR group spent a smaller amount of time in the central area suggesting a decrease in impulsivity [144]. In this same study memantine seemed to have little to no effect on SHR and WKY rats in delay discounting suggesting that this drug did little to impulsivity [144].

In another study memantine seem to increase impulsive choice in low impulsive rats [145]. However, the fact that these authors used a median split in order to divide their rats into low and high impulsive groups may confounded their results; thus, this should be considered when interpreting their data. All things considered, animal models assessing the effects of memantine on impulsivity are mixed; however, clinical trials seem to present more consistent results.

Memantine and ADHD: Evidence from Clinical Trials

Clinical trials have assessed the efficacy of memantine for the treatment of ADHD in children, adolescence, and adults [111, 146]. An eight-week, open-label trial found that a dose of 10 mg/day and 20 mg/day showed dose dependent benefits in both inattention and hyperactivity/impulsivity in adolescents with ADHD-C [111]. Another open-label study showed that memantine titrated to a dose of 10 mg twice a day meliorated ADHD symptoms in adults [146].

In a randomized, double-blind, placebo-controlled clinical trial memantine in conjunction with stimulant medications were shown to improve behavior ratings on ADHD inventories in adult ADHD [147]. To the authors' knowledge, these are the few clinical trials that have assessed memantine in the ADHD population directly. However, there have been other trials assessing memantine in impulsive-like disorders such as gambling, drug addiction, and kleptomania [147, 148].

In a study by Grant et al. (2010) 28 patients diagnosed with pathological gambling received between 10-30 mg/day of memantine for 10 weeks. After study completion participants reported a decrease in compulsive and impulsive behaviors as well as improved cognitive flexibility [149]. In other studies assessing those with substance abuse disorders it was found that memantine reduces cue-induced craving in alcoholics as well as decreases withdrawal symptoms associated with opiate abstinence [150, 151]. Another study showed that a dose of 10 mg/day titrated to 30 mg/day of memantine decreased impulsive stealing behavior in those with kleptomania [148]. Thus, memantine may disrupt impulsive like behaviors associated with ADHD, gambling, and addiction. Further, memantine's action on the glutamate system is likely responsible for this therapeutic effect.

FUTURE PERSPECIVE FOR GLUTAMATE MODULATING DRUGS FOR THE TREATEMENT OF ADHD

The data reviewed in this chapter presents ample evidence of glutamatergic dysfunction in ADHD. Further, data supports that using pharmaceuticals that target the glutamate system (i.e., memantine and atomoxetine) may stabilize glutamatergic signaling and meliorate the behavioral issues associated with ADHD in both animal models and humans. Another interesting thought presented in this chapter is the relatively new idea that the neuro-transmitter imbalances seen in ADHD could be due to issues with how the brain obtains energy. Thus, future pharmaceuticals for the treatment of ADHD targeting the glutamate system and systems that can increase energy flow to the brain could be beneficial.

As previously mentioned, when glutamate is released from synapses and taken up by astrocytes lactate is shuttled from astrocytes to fuel neuronal firing [152]. Further, stimulation of β-adrenergic receptors on astrocytes stimulates glycogenolysis causing an increase in astrocytic glucose that is transformed to lactate and shuttled to neurons [153]. Also, stimulation of α2A-aderendergic receptors on astrocytes may increase astrocytic glycolysis in the long-term thus increasing their energy storage [154]. This becomes interesting considering that a current treatment for ADHD (i.e., atomoxetine) works on both the norepinephrine, dopamine, and glutamate pathways and that a current hypothesis for ADHD is dopamine/norepinephrine hypo-function that in turn may cause glutamatergic hyper-function [14].

Considering the above, it is easy to imagine a situation where lack of brain energy eventually causes catecholamine hypo-function because not enough energy is available to sustain normal neuronal firing. This catecholamine hypo-function then promotes an increase in glutamatergic firing which then puts more energy stress on an already vulnerable system. This could create a feed-forward pathological situation that may lead to the symptoms seen in ADHD as well as other psychiatric illnesses. Thus, the development of drugs which act

similar to atomoxetine both to decrease glutamate signaling (i.e., glutamate antagonists) and increase catecholamine signaling (i.e., agonists or uptake inhibitors) may help to increase the energy supply to the brain and directly act on the neurotransmitter systems dysregulated; both effects should normalize brain physiology and meliorate the symptoms of ADHD.

As proposed by Todd and Botteron in 2001, if we consider ADHD to be primarily an issue with how the brain gets energy and that this energy problem causes neurotransmitter dysregulations then a simplistic possibility is that diet and exercise may also help to alleviate symptoms seen in ADHD. The current research from animal models suggests that the data on modulating diet to improve ADHD symptoms is mixed [155, 156]. However, the evidence from human studies seems promising [157]. Although clinical anecdotes from patients with ADHD attest to the importance of exercise in reducing symptoms, evidence from animal models and human studies on exercise and ADHD are mixed but seem promising [158-161]. Thus, perhaps in the future a standard of care for ADHD will not only be using pharmaceuticals that work to increase brain energy but also by prescribing a certain diet and exercise regimen in order to normalize glutamate and catecholamine neurotransmission in the brain.

CONCLUSION

In this chapter we have reviewed current, relevant data from animal models and humans on the glutamate system and how this system may be dysregulated in ADHD. We have also alluded to how other neurotransmitter systems such as the dopamine and norepinephrine systems may interact with the glutamate system to produce ADHD symptoms. Along with these ideas, the thought that an overarching cause of all of the neurotransmitter dysregulations seen in ADHD may be issues with brain energetics. Current pharmacotherapies that work on the glutamate system were discussed, as were thoughts for future treatments in ADHD that work on the glutamate system either directly or indirectly. It is the hope of the authors that the data reviewed in this book chapter as well as the novel ideas discussed will be helpful to researchers currently working on treatments for ADHD and will encourage further research in this field.

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