CHAPTER

59

The Neurochemistry of Autism

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OUTLINE

CLINICAL ASPECTS OF AUTISM SPECTRUM DISORDERS (ASDs)

ASDs are defined by three independent symptom clusters

In the *Diagnostic and Statistical Manual of Mental Disorders* (DSM IV, American Psychiatric Association, 1994), autism is grouped with the pervasive developmental disorders (PDDs). These include autistic disorder, Asperger's disorder, childhood pervasive developmental disorder not otherwise specified (PDD-NOS)/atypical autism, childhood disintegrative disorder (CDD) and Rett's disorder. The first three disorders are commonly referred to as the autism spectrum disorders (ASDs) and these will be discussed in detail below.

Autistic disorder or *autism* is defined by persistent and severe problems in social relatedness and early communication failure, as well as idiosyncratic preoccupations and restricted interests, repetitive behaviors and motor stereotypies, unusual sensory sensitivities and resistance to change. Once thought to be a rare disorder, newer studies place the prevalence rate of autism at about 2.0 per 1,000. Prevalence of the more broadly defined ASDs may be as high as 1–3% (Fombonne, 2009; Lord, 2011). Autism affects approximately four times as many males as females.

The term "autism" was first applied to children with problems in social relating in 1943 by Leo Kanner (Kanner, 1943). He described 11 males with what he termed "early infantile autism." Although they suffered from cognitive and language deficits, Kanner emphasized the social and emotional impairments. Present conceptualizations continue to highlight the social-emotional impairments in autism as the core deficit. The International (ICD 10) and American (DSM IV) diagnostic criteria for autism both require a triad of deficits that include (a) developmental problems with communication, (b) severe and sustained impairments in social interaction and (c) the presence of repetitive, rigid and stereotypic behaviors. However, the social impairments are given the most weight, with at least two symptom criteria from the social impairment cluster, but only one each from the communication and odd behavior clusters, required to obtain a diagnosis of AD.

More than half of persons with autism have intellectual disability, and a significant minority has a profound

disturbance of language. Most persons with autism insist on "sameness," and react negatively to changes in routine. Motor behavior is often characterized by stereotypies and a substantial proportion of individuals with autism engage in aggressive and self-injurious acts. Unusual responses to the environment, special interests and preoccupations are often present. Failure to respond to one's name, gaze aversion and failure to look at the parent's face are early and predictive developmental signs of autism (Osterling & Dawson, 1994).

About 25% of individuals with autism develop a comorbid seizure disorder, and many more show EEG abnormalities, including both diffuse and focal spike activity, as well as paroxysmal wave patterns (Rapin, 2002; Volkmar & Nelson, 1990). Persistent primitive reflexes and other neurological soft signs are also frequently present (Minshew et al., 1997).

Asperger's disorder was first described in 1944 by an Austrian pediatrician, Hans Asperger. He described four boys who were socially isolated and had trouble joining peer groups. The boys in Asperger's report were all bright and had no history of developmental language or communication difficulties. Asperger described them as "little professors," who often learned to talk before they learned to walk. They were often verbose, with extensive knowledge about narrow topics, yet they had poor motor skills. In the early 1990s Asperger's disorder was recognized as a discrete diagnostic category and incorporated into both the American (DSM IV, 1994) and the ICD-10 international psychiatric nomenclature (World Health Organization, 1992). Asperger's disorder is often viewed as a milder form of autism, and is very rarely diagnosed in association with intellectual disability (Volkmar et al., 2000). Motor mannerisms are less frequently observed, while intense special interests and preoccupations are more frequent in Asperger's disorder than in autism. Individuals meeting criteria for Asperger's disorder often have a great deal of factual knowledge about narrow topics, but typically there is not a commensurate underlying conceptual understanding. Social attempts are often verbose, one-sided and pedantic. This, along with a lack of understanding the feelings and desires of others, makes social interaction difficult (Volkmar et al., 2000).

PDD-NOS is a catchall category in the DSM IV, and the ICD–10 contains a similar category entitled Atypical Autism. The category is for those individuals with fewer than the required number of symptoms, or symptoms of lesser severity, than are needed for a diagnosis of autism or Asperger's disorder, but who still have ". . . a severe and pervasive impairment in the development of reciprocal social interaction associated with impairment in either verbal or nonverbal communication skills or with the presence of stereotyped behavior, interests, and activities" (DSM IV, 1994). Finally, the term "broader autism phenotype . . ." (BAP) is often used to refer to the isolated traits or milder social disability sometimes found among relatives of individuals diagnosed with ASD and among the general population.

Autism is heterogeneous from a behavioral, neurobiological and genetic standpoint

Approximately 5–10% of individuals diagnosed with autism have some genetic, medical or neurological problem that contributes entirely or substantially to the observed autistic behavior (Dykens et al., 1997; Rutter et al., 1994). These conditions include deafness, cerebral palsy, multiple congenital abnormalities, chromosomal abnormalities, inborn errors of metabolism, Fragile X syndrome (FraX) and tuberous sclerosis (TS). This heterogeneity has long been recognized; however there is an increasing appreciation of heterogeneity within the idiopathic autism and ASD category.

The autism field is moving towards a more dimensional and less categorical perspective

Most research on autistic behavior has considered autism categorically, but the increasingly apparent genetic and phenotypic complexities are prompting a more dimensional approach. There is accumulating empirical support for viewing autism-related behaviors as separable and fractionable, and often occurring in isolation in family members and the general population. Dissection of components in autism, as in other areas of neuropsychiatry, appears to offer a fruitful simplifying approach. A number of researchers have suggested that autism might be best understood by examining the component behavioral and cognitive abnormalities of autism (for review see Anderson, 2008). As early as 1971, Wing & Wing (1971) stated that the "multiple impairments (of autism) can vary in severity and . . . can occur independently in various childhood conditions. " In 1996, McBride and colleagues (McBride et al., 1996) also argued for a more dimensional approach, saying, ". . . the components can be considered individually," and adding that "(p)rogress will come from careful description and metrification, and from thorough consideration of the interactions between domains." More recently, Gupta & State (2007) stated that "If autism is not a single entity but a collection of overlapping phenotypes resulting from the combined action of multiple risk alleles, it appears logical that an approach that parses the clinical presentation into biologically relevant components might be more powerful than one that relies on categorical diagnoses." The quotes reflect a growing dissatisfaction with the rate of progress in explicating underlying biology and causative factors.

In their 2006 review, Happé et al. (2006) presented a thorough and compelling case that the behaviors that define the autism spectrum disorders should be considered from a component perspective, and used the term "fractionable" to emphasize this point. They pointed to accumulating evidence, much from their own research, supporting the idea that alterations in the separate defining domains of social relatedness, language/communication and restricted interest/repetitive behavior are separable and suggested that genetic and behavioral approaches that consider autism as an entity or unitary phenomenon may be inefficient and counterproductive. Evidence marshaled in support of the separable or fractionable approach include the smooth continua of severity seen for domain traits, the occurrence of autism-related traits in isolation in family members and the general population, the modest within-individual correlations seen for the different domains, the different developmental trajectories seen across domains, and the apparent independent heritability of relevant traits.

In general, support for a more dimensional and "phenomic" component trait or endophenotype approach to mental disorders appears to offer advantages in terms of metrification and from an individualistic, descriptive and idiographic standpoint (IGDA

Workgroup, 2003; Meehl, 1979). It remains to be seen how this will play out in psychiatry and in the upcoming revision of the *Diagnostic and Statistic Manual-IV* (DSM-5, due May, 2013).

Current pharmacological treatment of autism is usually effective for only certain aspects of the symptom constellation

A wide range of agents have been employed to treat the symptoms associated with ASDs, including antidepressants, anxiolytics, neuroleptics, anticonvulsants, and stimulants, with selective serotonin reuptake inhibitors and atypical neuroleptics the most commonly prescribed medications (Esbensen et al., 2009; Martin et al., 1999). In general, response rates are poorer than for treatment of the same symptoms in non-ASD individuals (Brkanac et al., 2008; Erickson et al., 2007; Nazeer, 2011). The importance of patient selection and proper choice of outcome measures have been stressed (Scahill & Lord, 2004). Although there are concerted efforts to find agents useful for treating the "core" ASD symptoms in the social relatedness domain (Posey et al., 2008), for the time being an approach separately targeting the often associated problems of irritability, rigidity, impulsiveness, hyperactivity, anxiety, aggression and sleep problems appears most fruitful.

GENETIC STUDIES

The genetics of autism are complex, heterogenetic and, in most cases, polygenetic

Twin and family studies have provided convincing evidence that autism is largely genetically determined (Bailey et al., 1995; Folstein & Rutter, 1977; Steffenburg et al., 1989). The family genetic data and genome-wide screening studies indicate that the genetics are complex. In most cases, it appears that multiple genetic factors are involved, with each likely contributing only a small amount of risk. There is also good evidence that autism is genetically heterogeneous, with differing sets of risk alleles combining in different groups of affected individuals (Cook, 2001; Folstein & Rosen-Sheidley, 2001; Launay et al., 2001; Lauritsen et al., 2001; Risch et al., 2000; Rutter, 2000; Santangelo & Tsatsanis, 2005; The Autism Genome Project Consortium, 2007). Reports of increased rates of de novo copy number variants (CNVs) in groups of individuals with autism have further increased the genetic complexity. This apparent polygenetic and heterogenetic nature of autism, the unclear role of epigenetic factors and de novo mutations (Gottesman & Hanson, 2005; Sebat et al. 2007), as well as the possible role of environmental influences on expression (Herbert et al., 2006), makes an elucidation of the genetic basis of autism extremely challenging. The simpler genetics of Fragile X syndrome may offer a particularly useful parallel approach to relevant neurobiological mechanisms (see box).

Roles of epistasis and emergenesis are unclear

Epistasis (gene–gene interaction) and *emergenesis* (synergistic interaction between components) appear to play important roles that will be difficult to elucidate. Some of the more common and characteristic phenomena observed in individuals diagnosed with autism do not run in their families. These novel, "emergent" or "emergenic" (Lykken, 2006) phenomena may arise in the individual from interacting co-occurring traits or from the interaction of underlying genetic and biological factors (Anderson, 2008).

The emergence of new and novel phenomena in the autistic individual is probably best represented by intellectual disability (ID). A number of other autism-associated phenomena can be suggested as being possibly emergenic, based on their apparent rarity in relatives. These phenomena include seizures, stereotypies, persistence of primitive reflexes, self-injurious behavior, sleep problems, special skills, minor physical anomalies and abnormal brain size/growth. Other possible emergent phenomena include gait disturbances, postural control, clumsiness and brain alaterality. Although these various phenomena can be nominated as potentially emergent, further careful family studies are needed in most cases to determine the extent to which particular phenomena can be considered emergent. It is remarkable that most of the phenomena that satisfy these criteria do not appear to belong to any of the three major domains of behavior that are taken to define autism (Anderson, 2009).

NEUROCHEMICAL STUDIES

A range of neurochemical abnormalities has been reported for autism, including alterations in serotonergic, glutamatergic, GABAergic, cholinergic and stress response systems (Anderson et al., 1990; Cook, 1990; Deutsch et al., 2010; Lam et al., 2006; McDougle et al., 2005; Pickett & London, 2005; Polleux & Lauder, 2004; Waterhouse et al., 1996). However, many of the observations are not fully replicated. The main areas of research have examined dopamine; stress response systems, including the noradrenergic-sympathetic/adrenomedullary system and the hypothalamic-pituitary-adrenal (HPA) axis; and the serotonergic system. The postmortem brain studies are limited but deserve special mention, as do the studies of melatonin.

Limited postmortem brain data are available and are not definitive

The recent increased availability of postmortem brain specimens from individuals with autism provides a tremendous opportunity to study the neurobiology of autism. Among initial neurochemical studies were reports of altered $GABA_A$ receptor binding in cortical regions (Blatt et al. 2001; Oblak et al., 2011), glutamate-related abnormalities (Purcell et al., 2001), reduced reelin protein in the cerebellum (Fatemi et al., 2001), reduced nicotinic receptors in cortical regions (Perry et al., 2001), and decreased 5-HT2A binding in cortical regions (Antzoulatos et al., 2005). These studies all require confirmation, but give an indication that postmortem brain research in autism is beginning to contribute to the field, thanks largely to the efforts of Margaret Bauman and colleagues and the Autism Tissue Project.

Dopaminergic functioning appears normal

Altered dopamine (DA) functioning in autism has been postulated based on DA's clear role in mediating motoric disturbances (e.g., stereotypies) and the observation that DA- blocking agents including neuroleptics are effective in treating some aspects of autism. While a lone positron emission tomographic (PET) study using fluorine-18–labeled fluorodopa (FDOPA) reported lower dopaminergic activity in the medial prefrontal cortex (Ernst et al., 1997), most studies of DA have had to rely on the examination of levels of the major DA metabolite homovanillic acid (HVA). Results have been inconsistent, with the concentration of HVA in cerebrospinal fluid (CSF) reported to be slightly decreased, apparently normal, or significantly increased in autism (Narayan et al., 1993). Measurements of HVA in urine also have been discrepant, and the only study of plasma HVA reported similar levels in autistic and control subjects (Minderaa et al., 1989). Other relevant measures include urinary DA and plasma prolactin, which have also been reported to be normal in autistic subjects (McBride et al., 1989; Minderaa et al., 1989; Anderson et al., 2008). Thus, on balance, the available evidence suggests that peripheral and global central dopaminergic functioning or metabolism is normal in autism.

Stress response systems: basal functioning is normal, but hyperreactive in autism

The noradrenergic-sympathetic/adrenomedullary system and the hypothalamic-pituitary-adrenal (HPA) axis are considered the two major components of the stress response system (Chrousos & Gold, 1992; Ch. 55). This system has been of interest in autism due to the hyperarousal and hyperactivity, and the overreactivity to novel situations, often seen in autism. The functioning of the sympathetic/adrenomedullary system has been assessed through measurements of norepinephrine (NE) and epinephrine (EPI) in plasma or urine. In addition, plasma and urine levels of the major NE metabolites, 3-methoxy-4-hydroxyphenylethylglycol (MHPG) and vanillylmandelic acid (VMA), have been determined. Serum levels of dopamine-β-hydroxylase, the synthetic enzyme secreted along with NE from sympathetic neurons, have also been studied. Indices reflecting basal functioning of the sympathetic/adrenomedullary system generally have been found to be normal in patients with autism (including plasma MHPG, serum DBH and the various urine measures). On the other hand, most of the studies measuring indices of acute stress response (including plasma NE, heart rate and blood pressure) have found elevations in patients with autism. Taken together, the data support the idea that autistic patients are not in a chronic state of hyperarousal, but that the sympathetic/adrenomedullary system is hyperresponsive when individuals with autism are stressed (Minderaa et al., 1994). Findings from studies of HPA axis function are consistent with this idea and support the same conclusions (Tordjman et al., 1997). The apparent increased response to stressors could be due to a difference in the level of perceived stress, to an overelicitation of the physiological response, or to an abnormality in the stress response systems themselves.

The serotonin system: a focus on platelet hyperserotonemia and the 5-HT2 receptor

Serotonin (5-hydroxytryptamine, 5-HT) was first identified as a serum chemical that causes vasoconstriction and an important regulator of intestinal function secreted by enterochromaffin cells (Erspamer & Asero, 1952; Rapport et al., 1948). Shortly afterward, 5-HT was discovered in mammalian brain and has since been found to be an important neurotransmitter/neuromodulator and growth factor. Cell bodies of central 5-HT neurons are found in the dorsal midbrain and brainstem and project throughout the brain. 5-HT has been shown to play a role in various behaviors and processes including sensory gating, behavioral inhibition, appetite, aggression, sleep, mood, affiliation and neuroendocrine secretion (see Ch. 15).

The rationale for studying 5-HT in autism has theoretical and empirical bases. The critical influence of 5-HT on neurogenesis and synaptogenesis and the extended ontogeny of the central serotonergic system suggest a possible role for 5-HT in the etiology and pathophysiology of autism. Identification of a role for 5-HT in embryogenesis has only increased interest in its developmental functions (Cote et al., 2007).

The empirical evidence for 5-HT's involvement in autism includes the well-replicated platelet hyperserotonemia of autism, therapeutic benefit of serotonergic agents, abnormal expression or functioning of 5-HT2 receptors, and reported associations of autism with 5-HT genes. The finding of platelet hyperserotonemia in autism has generated the most interest and studies.

The pharmacological data are limited and not entirely consistent. Tryptophan depletion, which is presumed to cause decreased extracellular 5-HT, leads to worsened repetitive behaviors and irritability in autism (McDougle et al., 1996). Initial studies suggested that selective serotonin reuptake inhibitors (SSRIs) relieve symptoms of irritability and rigid-compulsive behavior in autism, and SSRIs have been widely prescribed to individuals meeting criteria for autism (Esbensen et al., 2009; Martin, 1999). However, recent trials of the SSRIs are less supportive of their utility (King et al., 2009). More consistent data support the use of risperidone (McCracken et al., 2002), an atypical antipsychotic with antagonism at multiple receptors, including the serotonin 5-HT2A receptor.

A number of researchers have measured cerebrospinal fluid (CSF) levels of 5-HIAA, the primary metabolite of 5-HT, in an attempt to assess central 5-HT synthesis. Most of the studies of CSF 5-HIAA levels have not observed significant differences (Narayan et al., 1993). Although altered cortical 5-HT synthesis has been reported using the PET ligand 11C-α-methyltryptophan (Chugani et al., 1999), the basic methodology has been questioned (Shoaf et al., 2000). The neuroendocrine challenge studies have used a variety of serotonergic agents to provoke prolactin release, including fenfluramine, which acutely increases extracellular 5-HT; 5-hydroxytryptophan (5-HTP), a 5-HT precursor; and sumatriptan, a mixed 5-HT1B/1D receptor agonist (McBride et al., 1989; Novotny et al., 2000). The fenfluramine and 5-HTP studies found a decreased prolactin response, but sumatriptan led to an increased prolactin response in autism.

Hyperserotonemia or elevated blood serotonin was first detected in autism by Schain & Freedman (1961). Follow-up

studies have usually reported group mean increases of 25–50% in autism compared to typical controls. Typically more than one-quarter of autistic children are reported to have elevated whole blood 5-HT levels (Cook & Leventhal, 1996). A study of a relatively homogeneous Dutch population found an apparent bimodal distribution of platelet 5-HT in autism (Mulder et al., 2004), with approximately half of the individuals in the upper mode. Because substantial overlap exists with the general population, hyperserotonemia does not have sufficient sensitivity or specificity to be useful as a marker for autism. Some attempts have been made to link hyperserotonemia with particular patterns of symptoms in autism with little consistency.

The platelet contains more than 99% of circulating 5-HT (Anderson, 1987) and accumulates 5-HT over its 10-day lifespan by uptake through the plasma membrane 5-HT transporter (SERT). The issue of platelet exposure to 5-HT has been examined by measuring urine serotonin and 5-HIAA (Mulder et al., 2009) as well as platelet-poor plasma 5-HT levels (Anderson, 2007). In summary, the results indicate that the platelet is probably not exposed to increased amounts of 5-HT, but this possibility cannot be ruled out.

Understandably, most studies attempting to identify the underlying mechanism of hyperserotonemia in autism have targeted the platelet, with much of the work focusing on the SERT. Although some studies of platelet serotonin uptake and/or SERT binding have reported alterations in autism, these findings have been inconsistent. Some studies have also reported decreases in binding of the platelet serotonin receptor 5-HT2 (Cook et al., 1993; McBride et al., 1989), an important regulator of SERT (Carneiro & Blakely, 2006). The inconsistency in functional studies may indicate that multiple different mechanisms account for elevated whole blood 5-HT in autism, including regulation of gut production, serotonin receptor function, and platelet 5-HT uptake.

The hyperserotonemia of autism has also focused research on the genetic control of platelet 5-HT levels, with the belief that common regulatory mechanisms in the platelet and the central nervous system may reveal genes important in autism susceptibility. In the Hutterites, a large founder population not ascertained for brain disorders, whole blood 5-HT levels were under nearly complete genetic control, with a broad heritability of 0.99 (Abney et al., 2001). Following the demonstration of high heritability, Cook and colleagues used linkage and association to map genetic loci contributing to this quantitative trait (Weiss et al., 2004). The first analysis found significant association with a functional polymorphism in the integrin 3 subunit gene (ITGB3) (Weiss et al., 2004). Follow-up analyses revealed that ITGB3 was primarily associated with whole blood 5-HT levels in males, where association with markers in the serotonin transporter gene (SLC6A4) was also found. A functional interaction between the corresponding proteins in controlling platelet 5-HT uptake as well as aggregation was subsequently demonstrated (Carneiro et al., 2008).

As mentioned, several studies have reported decreases in platelet serotonin receptor 5-HT2 binding in autism (Cook. et al., 1993; McBride et al., 1989). These findings are consistent with a report of lower central 5-HT2 responsivity in autism using a neuroendocrine challenge paradigm (McBride et al., 1989) and with recent neuroimaging studies. Thus, a SPECT study in adults with Asperger's syndrome (Murphy et al., 2006) and a PET study in parents of children with autism (Goldberg et al., 2009) both have reported lower 5-HT2 binding. Researchers also reported decreased 5-HT2A binding in a postmortem brain study in autism (Antzoulatos et al., 2005). The studies have provided converging evidence of lower central 5-HT2 receptor expression or function in autism and provide support for the idea that peripheral alterations in the serotonin system may be an important marker of central abnormalities in autism.

Several of the studies have reported inverse correlations for platelet 5-HT level and platelet (Cook et al., 1993; McBride et al., 1989) or central (Goldberg et al., 2009) 5-HT2 receptor density in individuals with autism. While the correlations between platelet 5-HT levels and central or platelet 5-HT2 receptor density are intriguing and suggest the possibility that some 5-HT2 receptor–related factor may play a role in the platelet hyperserotonemia of autism, the nature of this relationship has yet to be determined.

Decreased production of melatonin in autism has been reported and focuses attention on circadian processes

The hormone melatonin is of interest in autism due to theoretical considerations and reports of altered melatonin production in individuals with autism. The pineal gland is the predominant source of melatonin, with markedly greater production occurring during the night. Pineal melatonin is important for the regulation of human circadian rhythms including the sleep–wake, neuroendocrine and body temperature cycles (Ch. 57). Measurements of melatonin in plasma and saliva, and of urinary 6-sulfatoxymelatonin (6-SM, the predominant metabolite of melatonin), are considered the best indices of melatonin production. Several studies have reported sleep–wake rhythm disorders in autism, suggesting possible therapeutic uses of melatonin. There is also an increasing appreciation that melatonin is critically involved in early development through its direct effects on the placenta, developing neurons and glia, and its role in the ontogenetic establishment of diurnal rhythms (Ch. 28).

The physiological increase in melatonin secretion during the night is well established: plasma levels typically peak around 2 AM and nighttime melatonin values are usually at least three times greater than daytime values. It has been suggested that most daytime production of melatonin occurs outside the pineal gland, with a prominent source being the wall of the gut (Bubenik, 2002). The prior six studies of melatonin production in autistic disorder have all reported abnormalities in the melatonin production. Taken together, the studies indicate that nighttime melatonin production is substantially lower in autism and suggest that daytime release is also reduced (reviewed in Mulder et al., 2009; Tordjman et al., 2005).

CONCLUSION

The heterogeneity of autism has hampered neurobiological and genetic research in this realm. To date, there are only a limited number of replicated neurochemical findings. Future

efforts will be directed at understanding the mechanisms of the known neurochemical alterations and at identifying biomarkers with greater specificity and sensitivity. It can be expected that increasingly autism research will be carried out in a manner that at least considers the separate, apparently fractionable, domains of behavior. A number of recent genetic and neurobiological studies of autism have taken this approach and varied efforts are directed toward the development of measures of specific domain or component traits. Most autism-related phenomena might best be assessed and studied separately, and research on the neurobiology and genetics of autism might most fruitfully examine specific aspects/impairments.

FRAGILE X SYNDROME AND AUTISM SPECTRUM DISORDER

Joseph T. Coyle

Autism spectrum disorder (ASD) is now known to be a common condition affecting approximately 1% of the population (Levy et al., 2009; Lord, 2011). Family and twin studies suggest high heritability (0.8) although the pattern of inheritance is not consistent with Mendelian genetics. The evidence, rather, points to complex genetics with many common alleles interacting to cause the phenotype. Recent studies suggest that *de novo* copy number variants, which are stretches of DNA several hundred to several million base pairs in size consisting of microinsertions, microdeletions and transpositions in the human genome, may also account for 10% or more of the cases. One strategy for understanding the underlying neurobiology of ASD is to characterize highly penetrant single-gene mutations that share clinical features with ASD. One such hereditary disorder is Fragile X syndrome (FraX).

FraX is the most common inherited cause of intellectual disability, affecting approximately one in 4,000 males (Lightbody & Reiss, 2009). The genetic basis of the disorder was first noted when a constriction or fragile site was observed at the end of the X chromosome in affected individuals, prompting the name of the disorder. The fragile site is caused by a mutation in the 5′ non-coding region of a gene (fragile X mental retardation; *FMR1*) that causes a CGG trinucleotide repeat to expand to more than 200 copies. In normal individuals, this site contains approximately 30 copies; and in those with the pre-mutation, the site has 50 to 200 copies. The expanded CGG repeat causes hypermethylation of the promoter region of the *FMR1* gene, thus limiting the expression of its product, FMR1 protein (FMRP).

One-half or more of the males affected with FraX satisfy the diagnostic criteria for ASD, depending upon the diagnostic instrument used (Hall et al., 2010). The shared behaviors include gaze aversion, stereotypies, communicational problems and repetitive vocalizations. Epilepsy frequently occurs in both disorders. Unlike ASD, males with FraX also have characteristic physical features including a long narrow face, prominent ears, hypotonia and enlarged testes. Whereas the IQ can range from above normal to well below in ASD, males with FraX invariably exhibit intellectual disability.

The neuropathologic feature most consistently described in FraX is abnormal dendritic spines, which are long and thin with a small synaptic contact area. A recombinant mouse was developed in which *fmr1* gene was inactivated so that as in FraX, no FMRP is expressed. These mice exhibit the dendritic pathology observed in FraX with a high density of long, immature spines.

Not surprisingly, FMRP is expressed predominantly in brain and in the testes. FMRP was found to be an mRNA binding protein that was associated with polyribosomes, thereby implicating it in the regulation of protein synthesis. Subsequent studies demonstrated that FMRP functions as a translational repressor of certain mRNAs. Furthermore, FMRP is concentrated in the dendritic spines where it regulates protein synthesis at synapses (McKinney et al., 2005). Thus, the synaptic pathology of FraX is consistent with the loss of FMRP function.

The synaptic role of FMRP became clearer when its interactions with metabotropic glutamate receptor 5 (mGluR5) in long-term depression were elucidated (Kao et al., 2010). Activation of mGluR5 drives translation of dendritic mRNAs including FMRP, which serves to inhibit subsequent translation. In the absence of FMRP, dendritic protein synthesis is poorly regulated, resulting in spine dysgenesis. A compelling demonstration of this role of FMRP came from experiments in which *fmr1* −/− mice were rendered heterozygous for the mGluR5 null mutation (*Grm5* +/−). The reduced mGluR5 activity reversed seven out of eight phenotypic characteristics of FraX observed in the *fmr1* −/− mice. MPEP [2-methyl-6-(phenylethynyl)-pyridine] is a potent allosteric negative modulator for mGluR5 that crosses the blood–brain barrier. MPEP has been shown to reverse many of the behavioral, electrophysiologic and morphologic phenotypes associated with FraX in the *fmr1* −/− mice (Krueger & Bear, 2011).

This translational research on the most common heritable cause of intellectual disability, FraX, has led to the identification of a potential therapeutic intervention. It remains to be seen whether the treatment simply ameliorates symptoms such as anxiety or whether continuous treatment reverses the underlying synaptic deficits. Furthermore, a major unanswered question is whether the potential therapeutic effects of activating mGluR5 observed in *fmr1* −/− mice extend to some or most individuals with ASD.

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