Minireview

Rett and Rett-related disorders: Common mechanisms for shared symptoms?

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Impact Statement

The impact of this review lies in the hypothesis it tackles, which is that common molecules within neurons and astrocytes are responsible for shared behavioral and neurological abnormalities in three distinct neurodevelopmental disorders—Rett syndrome, CDKL5 deficiency disorder (CDD), and FOXG1 syndrome. Among the shared phenotypic features are epilepsy, intellectual disability, autistic features, speech deficits, and sleep and breathing abnormalities. Neurologically, patients with all three disorders display microcephaly, aberrant dendritic morphology, reduced spine density, and an imbalance of excitatory/inhibitory signaling. After reviewing the literature pertaining to the three disorders, this review identifies and describes molecules that likely play a particularly significant role in behavioral and neurobiological impairments common to all three disorders. We believe that the review furthers our understanding of the cellular and molecular underpinnings of Rett syndrome, CDD, and FOXG1 syndrome and identifies molecules that can be targeted to develop effective therapeutics for them.

Abstract

Rett syndrome is a neurodevelopmental disorder caused by loss-of-function mutations in the methyl-CpG binding protein-2 (MeCP2) gene that is characterized by epilepsy, intellectual disability, autistic features, speech deficits, and sleep and breathing abnormalities. Neurologically, patients with all three disorders display microcephaly, aberrant dendritic morphology, reduced spine density, and an imbalance of excitatory/inhibitory signaling. Loss-of-function mutations in the cyclin-dependent kinase-like 5 (CDKL5) and FOXG1 genes also cause similar behavioral and neurobiological defects and were referred to as congenital or variant Rett syndrome. The relatively recent realization that CDKL5 deficiency disorder (CDD), FOXG1 syndrome, and Rett syndrome are distinct neurodevelopmental disorders with some distinctive features have resulted in separate focus being placed on each disorder with the assumption that distinct molecular mechanisms underlie their pathogenesis. However, given that many of the core symptoms and neurological features are shared, it is likely that the disorders share some critical molecular underpinnings. This review discusses the possibility that deregulation of common molecules in neurons and astrocytes plays a central role in key behavioral and neurological abnormalities in all three disorders. These include KCC2, a chloride transporter, vGlut1, a vesicular glutamate transporter, GluD1, an orphan-glutamate receptor subunit, and PSD-95, a postsynaptic scaffolding protein. We propose that reduced expression or activity of KCC2, vGlut1, PSD-95, and AKT, along with increased expression of GluD1, is involved in the excitatory/inhibitory that represents a key aspect in all three disorders. In addition, astrocyte-derived brain-derived neurotrophic factor (BDNF), insulin-like growth factor 1 (IGF-1), and inflammatory cytokines likely affect the expression and functioning of these molecules resulting in disease-associated abnormalities.

Keywords: CDKL5 deficiency disorder, Rett syndrome, FoxG1 syndrome, neurodevelopmental disorder, seizures, autism

***Experimental Biology and Medicine* 2023; 248: 2095–2108. DOI: 10.1177/15353702231209419**

Introduction

Cyclin-dependent kinase-like 5 (CDKL5) is a ubiquitously expressed serine–threonine (Ser/Thr) kinase,[1–3] FOXG1 is a transcription factor of the forkhead family expressed selectively in the forebrain,[4,5] and methyl-CpG binding protein-2 (MeCP2) is a ubiquitously expressed protein that regulates transcription and chromatin structure by binding to methylated DNA.[6–8] MeCP2 is primarily (albeit not exclusively) a nuclear protein,[9–11] whereas FOXG1 and CDKL5 localize to both the nucleus and cytoplasm.[12–15] All three proteins are expressed most highly in the brain, with FOXG1 expression being highest in the developing forebrain. Within the mature brain, all three proteins are expressed most highly in neurons. Loss-of-function mutations of MeCP2 cause Rett syndrome, an X-linked disorder affecting girls that reveals itself by neurodevelopmental regression generally starting at about 2 years of age.[16,17] Until about a decade ago and based on striking similarities in their neurodevelopmental abnormalities and symptoms, haploinsufficiency of FOXG1 and CDKL5 was also thought to cause Rett syndrome, albeit congenital forms of the disorder, referred to as atypical or variant Rett syndrome. Among the common symptoms and brain abnormalities are intractable epilepsy, intellectual

disability, autistic features, sleep and breathing abnormalities.[18–21] However, more detailed analyses of a larger number of patients revealed that deficiency of FOXG1 and CDKL5 function causes distinct disorders that have been called FOXG1 syndrome (or FOXG1-related encephalopathy)[5,22] and CDKL5 deficiency disorder (CDD).[23,24] Interestingly, duplication of each of the three genes causes other neurological disorders revealing another similarity between them—their expression has to be maintained within a narrow range for proper brain development and function.

The realization that CDKL5, FOXG1, and MeCP2 mutations cause distinct neurodevelopmental disorders has increasingly resulted in separate focus being placed on each disorder likely under the assumption that distinct molecular mechanisms underlie their pathogenesis. However, given that many of the core phenotypic and neurobiological abnormalities are shared, it is likely that the disorders share some critical molecular underpinnings. It is possible, as discussed in this review, that CDKL5, FOXG1, and MeCP2 work **together** (as opposed to independently) to ensure proper brain development. Thus, decreased function of any one of these three proteins will affect the functioning of the other two, resulting in common neurodevelopmental abnormalities. Although efforts into the mechanisms underlying CDD, FOXG1 syndrome, and Rett Syndrome have focused largely on their roles in neurons, given the increasing appreciation of the critical role astrocytes play in brain physiology and pathophysiology. Astrocytes are crucial for both the development of neurons, synapses, and neural circuitry, and for the functioning of the nervous system during development through adulthood.[25,26] Abnormal gliogenesis or glial function at any stage of life is associated with many neurodegenerative,[27,28] neurodevelopmental,[29] neuropsychiatric disorders,[30] and in the development of gliomas. It is therefore likely that astrocyte dysfunction contributes significantly to the common symptoms in CDKL5 disorder, FOXG1 syndrome, and Rett syndrome.

Although most highly expressed in developing and postmitotic neurons, CDKL5 and MeCP2 are expressed in astrocytes,[31,32] and FOXG1 is expressed in cells of the astrocytic lineage under certain pathological conditions (e.g. in astrocyte-derived gliomas). In the case of MeCP2, mice lacking MeCP2 selectively in astrocytes display symptoms and neuropathology similar to MeCP2 knockout (KO) mice demonstrating that astrocyte dysfunction resulting from the lack of MeCP2 contributes significantly to the neurodevelopmental abnormalities in Rett syndrome.

Although there are several symptoms that are shared between CDD, FOXG1 syndrome, and Rett syndrome, this review will focus mostly on the molecular alterations underlying epilepsy and dendritic abnormalities. Intractable epilepsy is the abnormality that most significantly affects quality of life in all three disorders.[33] While seizures in CDD and FOXG1 syndrome start at around 6 months of age, in Rett syndrome, seizures start after about 2 years.[33] Interestingly, currently used antileptic medications act primarily on neurons and do not alter onset of seizures. Compelling recent evidence suggests that astrocytes play a key role in the initiation and progression of epileptic seizures via a variety of processes, including astrogliosis, abnormal uptake of neurotransmitters, abnormal release of gliotransmitters and cytokines, and metabolic alterations that can cause neuronal hyperexcitability.[34] Another abnormality in the three disorders is in the morphology of dendritic spines and the organization of postsynaptic molecules which are likely to contribute to both epilepsy and cognitive impairment in the three disorders.[22,35,36]

We propose that the deficiency of CDKL5, FOXG1, or MeCP2 results in deregulation of the proliferation and differentiation of neural stem cells, which results in microcephaly, and, subsequently in abnormal synaptic structure and function. These pathogenic alterations involve both neurons and astrocytes. Disruption of gamma-aminobutyric acid (GABA) and glutamate signaling in the developing brain resulting in an excitatory/inhibitory (E/I) imbalance is likely to underlie multiple aspects of the three disorders, including dysregulated neural progenitor cell proliferation/differentiation, epilepsy, abnormal, dendritic development and morphology, and postsynaptic organization.

Undoubtedly, a large number of molecules are involved in the promotion of the pathogenesis of any neurodevelopmental disorder. This review focuses on a small subset of them, which may play a particularly important role in CDD, FOXG1 syndrome, and Rett syndrome. These include KCC2, a chloride transporter, vGlut1, a vesicular glutamate transporter, GluD1, an orphan-glutamate receptor subunit, and PSD-95, a postsynaptic scaffolding protein. We propose that reduced expression of KCC2, vGlut1, and PSD-95, along with increased expression of GluD1, is involved in the E/I imbalance. In addition, we propose that astrocyte-derived insulin-like growth factor 1 (IGF-1) and brain-derived neurotrophic factor (BDNF) affect the expression and functioning of these molecules and also activate AKT, a protein kinase, in both neurons and astrocytes which together regulates neuronal structure and function. However, cytokines, such as interleukin-1β (IL-1β), interleukin 6 (IL-6), and tumor necrosis factor-alpha (TNF-α), impair glutamate uptake by astrocytes and impair neuronal signaling. Several studies have found that astrocyte dysfunction underlies or contributes to epilepsy.[34,37–40]

We provide below a brief description of the molecules the mutations of which cause the three disorders—CDKL5, FOXG1, and MeCP2. We then provide a description of molecules that we propose play a particularly significant role in the pathogenesis of all three disorders when their expression or functional activities are deregulated.

The principals

FOXG1 (previously called BF-1) is a transcription factor expressed selectively in the developing telencephalon during early brain development where it regulates neurogenesis by promoting proliferation of cortical stem cells while suppressing their premature differentiation into neurons.[4,41–45] Mice lacking FOXG1 have cerebral hemispheres that are severely reduced in size because of premature cell cycle exit of neural progenitor cells and differentiation.[46] Similarly, FOXG1 haplosufficiency causes microcephaly and severe intellectual impairment in humans.[47]. The proliferative action of FOXG1 occurs through stimulation of the cell cycle by FOXG1 by

inhibiting expression of CDK inhibitor 1A (Cdkn1a/p21) and cyclin B1. The inhibition of differentiation is regulated by a distinct mechanism involving the inhibition of the FOXO/SMAD complex, which normally promotes differentiation.[48,49] Subsequently, FOXG1 stimulates cortical neurogenesis while suppressing gliogenesis.[50] In addition, FOXG1 regulates patterning of the anterior brain, cell fate determination, the formation of the corpus callosum, the balance of E/I neurons, neuronal migration, axonal and dendritic organization, dendritic spine density, neuronal survival, and neural plasticity.[45,51–59] The ability of FOXG1 to influence both nuclear and cytoplasmic processes is made possible by its ability to localize to both cellular compartments.[12,13] In neural progenitor cells, FOXG1 localizes to the nucleus because of its phosphorylation by casein kinase-I (CKI). However, phosphorylation through a fibroblast growth factor (FGF)-dependent mechanism leads the export of FOXG1 from the nucleus.[12]

Loss-of-function mutations in FOXG1 cause FOXG1 syndrome, a neurodevelopmental disorder characterized by microcephaly, seizures, autistic symptoms, disrupted sleep patterns, and severe speech deficits.[4,5] Although believed to be a variant form of Rett syndrome until about a decade ago, distinctive features of the disorder were identified, including much more pronounced motor and speech impairments along with marked microcephaly and corpus callosum agenesis, leading to its recognition in 2016 as a separate and distinct disorder.[60] Among the effects that FOXG1 deficiency has on brain development and function, is an imbalance in E/I circuitry, which likely contributes to some of the defining problems of the disorder, including seizures and autistic-like behavior.[61]

Individuals with FOXG1 gene duplications also display seizures, autistic symptoms, and cognitive impairments, although these are milder than displayed by patients with FOXG1 syndrome.[5,22,62] Interestingly, autistic features in FOXG1 duplication syndrome mice are also associated with an imbalance of E/I signals.[61] In iPSC-derived neural organoids from autism spectrum disorder (ASD) patients, elevated FOXG1 expression has been proposed to cause dysregulated proliferation/differentiation and an overproduction of GABAergic neurons.[51]

CDKL5 is a Ser/Thr protein kinase encoded by the X-chromosome-linked CDKL5 gene (previously the STK9 gene). CDKL5 is expressed ubiquitously, but highest in the brain where it is expressed in neurons and at lower levels in glial cells.[2,23,63] The highly conserved catalytic domain is in the N-terminus region of the protein, whereas the C-terminus regulates its intracellular localization. Autophosphorylation of CDKL5 activates its catalytic function.[63] At early stages of brain development, most CDKL5 is cytoplasmic but its presence increases in the nucleus as the brain matures.[15,64] Consequently, potential substrates of CDKL5 include both nuclear and cytoplasmic proteins although few bonafide substrates have been experimentally identified so far. Among the cytoplasmic functions of CDKL5 are the regulation of synaptic vesicle recycling, excitatory synapse stability (through actions on PSD-95), dendritic and dendritic spine morphology, and neuronal cell death.[1,23] In neuroblastoma cells, CDKL5 inhibits proliferation while also promoting differentiation.[65] Deregulated proliferation and differentiation, along with increased cell death is observed in the hippocampus of CDKL5 KO mice.[66]

As a result of alterative splicing and alternative promoter usage, five CDKL5 transcripts are expressed, which are designated at CDKL5-1 to CDKL5-5. The CDKL5-1 transcript is the most highly expressed isoform in the embryonic and adult rodent and human brain.[67,68] There is evidence that the isoforms have different functions within neurons.[69]

Deficiency of CDKL5 deficiency causes CDD, a highly rare disorder that was referred to as atypical Rett syndrome or early seizure variant of Rett until 2013 when it was suggested to be, and subsequently recognized, as a distinct disorder.[3,70–72] Most CDD-causing mutations are *de novo* mutations that result in a failure to produce the protein or mutations that lie in the catalytic domain / ATP-binding region of the CDKL5 protein indicating that loss of kinase activity underlies the abnormalities associated with the disorder. A hallmark of CDD is the early onset of epileptic seizures which typically begin between six weeks and three months of age and which are not responsive to antileptic medications.[73] Other symptoms include sleep disturbances, gastrointestinal issues, musculoskeletal problems, visual impairment, autistic symptoms, and severe intellectual disability.[3,70,71] Neuropathological abnormalities include microcephaly, reduced dendritic arborization, and spine density. CDKL5 gene duplications cause autistic symptoms, language impairment, hyperactivity, and macrocephaly.[23,74]

Interestingly, CDD-related symptoms can be reversed in mice when CDKL5 protein is restored through adeno-associated virus-mediated expression.[75] Although clearly a promising finding in terms of treatment of patients, the study was conducted using male mice only, while CDD affects females almost exclusively. Moreover, while exhibiting many of the symptoms observed in patients, CDKL5-deficient mice do not display spontaneous early-onset seizures, the cardinal feature of CDD.[76–79]

MeCP2: Methyl-CpG binding protein-2 is a methylated DNA-binding protein encoded by a gene on the X-chromosome that is expressed widely in the body, but with highest levels in the brain.[7,8] Although expressed in all cells of the brain, MeCp2 expression is highest in maturing and postmitotic neurons. MeCP2 plays a key role in the brain development acting at different phases, including early neurogenesis, migration, dendritic arborization, synapse and circuit formation, and synaptic plasticity.[7,8,80,81] In humans, loss-of-function mutations in MeCP2 cause Rett syndrome, a neurodevelopmental disorder suffered almost exclusively by females who display microcephaly, seizures, gastrointestinal issues, and sleep disturbances.[17,82] However, a modest increase in the level of MeCP2, resulting from gene duplication, causes MeCP2 duplication syndrome, characterized by severe cognitive and motor deficits, seizures, and premature death.[83,84] It is now known that both neuronal and glial dysfunction contribute to the pathogenesis of Rett syndrome and MeCP2 duplication disorder.[85–88]

Best known for its role as a transcriptional regulator (both activator and repressor), MeCP2 also regulates chromatin structure, splicing, and miRNA processing.[7,8,80] The MeCP2 gene encodes two proteins, MeCP2-E1 and MeCP2-E2,

as a result of alternative splicing, which differ only at the N-terminals.[8,89,90] Although often assumed to be functionally interchangeable, E1 and E2 isoforms of MeCP2 differ in their temporal and spatial pattern of expression and in their relative abundance during brain development and have important non-overlapping functions.[90–92]

Experiments in mice suggest that the neurological defects of Rett syndrome are reversible both in adolescent and adult mice by restoring MeCP2 expression.[93] A recent study described that reactivating the MeCP2 gene locus in the silenced but normal X-chromosome by demethylation rescues abnormalities in Rett neurons.[94] Separate studies have described that suppressing MeCP2 expression using antisense oligonucleotides and other genetic methods can reduce behavioral defects in a transgenic mouse model of MeCP2 duplication syndrome.[95,96] However, in these studies, the line of MeCP2 used exhibits very mild symptoms relative to patients with MeCP2 duplication syndrome.[95,96] Mice expressing MeCP2 at about three times the normal level and that better recapitulate the human disorder exhibit neurodegeneration in the cortex and hippocampus that is associated with highly elevated release of glutamate from astrocytes.[87,88] Whether these serious neurological deficits associated with neuronal loss can be reversed remains to be experimentally tested.

The close relationship between CDKL5, FOXG1, and MeCP2 at the molecular level

CDKL5 and MeCP2 interact directly both *in vivo* and *in vitro*.[97] Moreover, autophosphorylated CDKL5 can phosphorylate MeCP2 *in vitro*.[97,98] In comparison to normal CDKL5, disease-causing mutations of CDKL5 are impaired in their ability to phosphorylate MeCP2.[98] MeCP2 can be phosphorylated at several sites and these can affect MeCP2 activity in different ways.[99] For example, neuronal activity increases phosphorylation at Ser41 of MeCP2 but leads to dephosphorylation at Ser80. Which residue(s) in MeCP2 is phosphorylated by CDKL5 and how this modification affects its function remains to be resolved.

Neuronal activity has effects on survival and dendritic morphology, synaptic development, and plasticity. The activity and functions of CDKL5, FOXG1, and MeCP2 are all regulated by neuronal activity. Through calcium influx, membrane depolarization stimulates the phosphorylation of MeCP2 at Ser421 while reducing phosphorylation of Ser80.[100] It has also been reported that depolarization reduces the level of MeCP2 in the nucleus of cultured neurons, whereas treatment with IGF-1 increases it.[101] Whether this increase affects both MeCP2 isoforms equally, or whether it is selective for one of the isoforms is unclear. As described above, FOXG1 interacts with the E2 isoform of MeCP2 thereby suppressing the apoptotic activity of this isoform and promoting neuronal survival.[91] However, phosphorylation of MeCP2 at Ser80 reduces interaction with FOXG1 and promotes apoptosis.[102] Unlike the E2 isoform, MeCP2-E1 is not bound by FOXG1 and does not promote apoptosis when overexpressed. In contrast to the regulation of MeCP2 phosphorylation, both depolarization and IGF-1 increase phosphorylation of FOXG1.[54] Furthermore, depolarization maintains elevated level of FOXG1 in cultured neurons.[54] In cultured neurons, depolarizing stimuli induce a rapid increase in synthesis in CDKL5 levels.[103] While this induction is prolonged in immature neurons, it is more short-lived in mature neurons. Whether the depolarization-induced increase in CDKL5 expression is necessary for the survival-promoting activity, possibly via BDNF or IGF-1 stimulation, remains to be examined. It is known that CDKL5 also has anti-apoptotic effects.[66,104]

Cocaine or serotonin treatment stimulates MeCP2 expression in the brain while repressing the expression of CDKL5.[105] This repression is transcriptionally mediated by MeCP2 through binding to methylated regions in the upstream region of the CDKL5 gene.[105] Although suggesting to be an inverse relationship between MeCP2 levels and CDKL5 transcription, a comparison of MeCP2 and CDKL5 mRNA levels indicated that a loss-of-function of one of these genes does not influence the mRNA expression of the other.[97] However, this latter study was conducted using lymphoblastoid cells and it is possible that transcriptional regulation of these genes in neurons or the brain might differ from that in lymphoid cells.

Another commonality in the three disorders is the abnormal activation of glia leading to inflammation. Abnormal systemic inflammation and brain neuroinflammation have been described in Rett syndrome and CDD in all three disorders.[106–113] In fact, Rett syndrome has been suggested to be an autoimmune disease.[114] Reduced FOXG1 expression in experimental models increases sensitivity of neurons to inflammatory stimuli.[115]

Potential common effectors

A common causative feature of all three disorders is likely to be a disruption of the transition of GABA-modulated neurons from providing excitatory signals to providing inhibitory signals in the developing brain, impacting the proliferation/differentiation balance and the E/I balance, which starts a cascade of pathogenic events resulting in the abnormal dendritic development and dysfunction of neurons. We propose that the inability of astrocytes to maintain glutamate homeostasis along with deregulation in the release of neurotrophic factors and inflammatory cytokines plays a key role in neuronal dysfunction and the proper working of neural networks. Several studies have found that astrocyte dysfunction underlies or contributes to epilepsy.[34,37,38,39] A number of studies have described dysfunction of astrocytes or disruption of astrocyte-neuron signaling as being a major contributor to ASD pathology.[29,116–118]

Undoubtedly, the mechanisms responsible for the neurodevelopmental impairments associated with CDD, FOXG1 syndrome, and Rett syndrome involve many molecules and molecular interactions. However, we propose, based on published research, that some of these molecules play a more central role. These include KCC2, a chloride transporter, vGlut1, a vesicular glutamate transporter, GluD1, an orphan-glutamate receptor subunit-1, and PSD-95, a postsynaptic scaffolding protein. We propose that reduced expression of KCC2, vGlut1, and PSD-95, along with increased expression

of GluD1, is involved in the E/I imbalance. In addition, we propose that astrocyte-derived IGF-1 and BDNF affect the expression and functioning of these molecules and also activate AKT, a Ser/Thr protein kinase in both neurons and astrocytes which together regulates neuronal structure and function. However, cytokines, such as IL-1β, IL-6, and TNF-α, impair glutamate uptake by astrocytes and proper neuronal signaling. Several studies have found that astrocyte dysfunction underlies or contributes to epilepsy.[34,37–40]

KCC2: KCC2, encoded by the Slc12a5 gene, is potassium-chloride transported that is in the plasma membrane of cells and dendrites of neurons. KCC2 plays a critical role in establishing the Cl^- gradient in cells, which in the brain, regulates the actions of GABA. Although the primary inhibitory neurotransmitter in the adult brain, during embryonic development, GABA acts as an excitatory neurotransmitter playing a key role in the proliferation of neural progenitor cells.[119–121] This is because in the embryonic brain, the intracellular Cl^- concentration is high. Consequently, the binding of GABA to its ionotropic receptor, GABA-A receptor, causes depolarization because of an outflow of Cl^-. However, in maturing neurons, there is a massive upregulation of KCC2 expression, which extrudes Cl^- thereby lowering intracellular Cl^- concentration.[122] Binding of GABA to its receptor now results in Cl^- influx and therefore a hyperpolarizing signal. Therefore, by causing the hyperpolarizing influx of Cl^-, KCC2 shifts the GABA signal from excitatory to inhibitory. Expression of KCC2 expression in immature cortical neurons before the endogenous upregulation is sufficient to switch of GABAergic response from inhibitory to excitatory.[123,124] The E/I functional shift of GABA is a highly significant event contributing to a variety of neurodevelopmental processes, including proliferation, differentiation, cell survival, neuronal maturation, and early network wiring.[122] Reduced expression of KCC2 disrupts the E/I balance causing brain dysfunction, including intractable epilepsy.[125–129] Indeed, KCC2 mutations that impair extrusion of Cl^- humans result in severe seizures in mice and in humans[130–132] and are associated with schizophrenia and ASD.[130] Similarly, psychological stress and neuroinflammation during early prenatal development reduce KCC2 expression delaying the E/I GABA shift, which has been implicated in neurodevelopmental and psychiatric disorders.[133–136] Reduced KCC2 function also contributes to circadian rhythm disruption[137] and age-associated neurodegenerative diseases, such as Alzheimer's and Huntington's disease, through impairment of GABAergic inhibition.[136,138,139]

As a result of alternative promoter usage, the Scl12a5 gene produces two proteins, KCC2a and KCC2b which differ in their N-termini.[140] Although both isoforms are widely expressed in the brain, KCC2a expression is low in cortical regions, whereas KCC2b is expressed more highly and more widely.[141–143] The absence of both isoforms leads to death at birth because of motor deficits and failure to breathe.[122] At the cellular level, KCC2a is expressed in many cell types while KCC2b is expressed highly in neurons and is likely to be the isoform that is responsible for the developmental shift in GABAergic responses, KCC2a is expressed in other cell types as well. KCC2b-specific KO mice have seizures and die within two weeks.[144] The roles of KCC2a are less clear although it is known to be critical for respiration soon after birth.[145] Besides its function as a channel protein that regulates hyperpolarizing inhibitory responses, KCC2 acts as a structural protein to regulate dendritic spine development through interaction with synaptic proteins[146–149] and in a BDNF-dependent manner.[149] While the Cl^- extrusion function is managed by the N-terminus region of KCC2, the C-terminus domain (CTD) regulates the structure, motility, and function of dendritic spines likely through interaction with cytoskeleton-associated proteins and a variety of membrane proteins, including neurotransmitter receptor subunits, suggesting transporter-independent ways by which KCC2 can affect synaptic function and neurotransmission.[148] Finally, the CTD of KCC2 mediates anti-apoptotic effects in the developing cortex.[148]

Astrocytes regulate KCC2 expression in neurons through the release of neurotrophic factors, such as BDNF and IGF-1, and inflammatory cytokines, such as TNF-α, IL-6, and IL-1β.[150–153] Astrocyte-released BDNF stimulates KCC2 expression in neurons by the activation of PI3K–AKT and Ras-MAPK pathways.[150,154,155] Astrocytes also maintain physiological levels of extracellular K+ and glutamate.[156] As a K+-dependent Cl^- exporter, the functioning of KCC2 depends on low extracellular K+ concentrations, which depends on proper functioning of astrocytes. Elevated levels of glutamate also impact KCC2 function by downregulating its expression via the NMDA receptor resulting in depolarizing GABA signals.[157] Interestingly, treatment with chemical activators of KCC2 has therapeutic effects in neurons derived from human Rett iPSCs and in MeCP2-deficient mice. In sum, astrocyte dysfunction impairs KCC function, and consequently its ability to balance E/I signals and to regulate proper dendritic structure and function.

Confirming that elevating KCC2 expression could have therapeutic effects for CDD, FOXG1 syndrome, and Rett syndrome is the finding that small-molecule compounds that stimulate KCC2 gene expression ameliorated behavioral deficits in MeCP2-mutant mice.[158] Whether KCC2 expression is restored to normal levels in mice in which MeCP2 expression has been restored remains to be seen. However, given the alleviation of major behavioral deficits in these Rett mice with restored MeCP2, this is likely.

vGluT1: Within the presynaptic terminal, glutamate is loaded into recycled synaptic vesicle by a family of three vesicular glutamate transporter, vGluT1–3 for a new round of exocytosis.[159–161] Of these, vGluT1 transports most of the glutamate. Besides glutamate, vGlut1 conducts Cl^-, and the extrusion of Cl^- from the synaptic vesicle is necessary for influx of glutamate in excitatory neurons.[162–165] Efficient extrusion of Cl^- depends on low Cl^- levels outside the vesicle, which depends on KCC2 activity. Mice hemizygous for vGluT1 deletion display anxiety, depressive-like behavior, and impairment of some types of memory.[166] Decreased vGluTt1 activity results in cognitive deficits and epilepsy,[159,167] and severe neurological and neuropsychiatric disorders.[168–170] Cortical neurons generated from FOXG1-deficient mouse pluripotent stem cells express reduced level of vGluTt1.[171] Similarly, patient-derived iPSCs and from mice hemizygous for FOXG1 deletion display reduced vGlut1.[172]

With regard to astrocytes—expressing MeCP2 in MeCP2-lacking astrocytes results in the elevation of vGlut1 in

MeCP2-deficient neurons and restoration of normal dendritic morphology.[173] Another study described that depleting microglia increased vGluT1 expression and resulted in increased density of dendritic spines.[174] Although this suggests that microglia regulate vGluT1 expression, it was observed that depletion of microglia caused astrocyte activation, raising the possibility that the effects were more directly mediated by astrocytes.[174] Loss of IGF-1 in astrocytes impairs glutamate uptake[175] which can promote excitotoxicity and seizures *in vivo*. Both BDNF and IGF-1 increase vGlut1 expression in differentiating and mature neurons and reduced availability of these factors reduces vGlut1 levels.[176–178] While astrocytic factors affect vGluT1, via is role in glutaminergic signaling, vGluT1 regulates the maturation of astrocytes during development.[179]

GluD1: GluD1 is an orphan δ-glutamate receptor subunit-1 encoded by the GRID1 gene that is widely expressed in the adult mouse brain.[180,181] Rather than functioning as a postsynaptic ion channel, however, GluD1 is part of a synaptic complex that interacts with presynaptic neurexin to induce presynaptic differentiation, synaptic connectivity, and glutamate receptor activity (Figure 1).[180–182] Mice lacking GluD1 display increased dendritic spine number, higher number of synapses, and greater excitatory neurotransmission along with stereotyped and depressive behaviors, memory impairment, anxiety, and abnormal social behavior.[183–186]

GluD1 expression is increased in iPSCs-derived neurons from FOXG1 syndrome patients and in the brains of FOXG1-deficient mice, although whether this represents a compensatory mechanism is unclear.[172] Similarly, expression of GluD1 is elevated in neurons generated from both patient-derived mutant MECP2- and CDKL5 iPSCs.[187] It is known that GluD1 plays a key role in maintaining E/I balance and in establishing synaptic architecture.[180,188,189] GluD1 has been found to preferentially stimulate the formation of inhibitory GABAergic synapses.[180] However, another study described induction of both presynaptic GABAergic and glutaminergic synapses, suggesting that developmental stage and neuron-specific effects may influence the actions of GluD1.[190,191] GluD1 mutations and mutations in proteins functionally associated with GluD1 are linked to autism, schizophrenia, and bipolar disorder.[180]

PSD-95: Postsynaptic density protein-95 (PSD-95) is a membrane-associated scaffold protein that plays a central role in the development of synapse development, number, stabilization, and function.[192–194] A well-studied action of PSD-95 is the anchoring AMPA and NMDA receptors in the postsynaptic terminal, which regulates neurotransmission by glutamate.[195] Not surprisingly, altered PSD-95 function has been implicated in epilepsy.[196–199] In addition, PSD-95 regulates dendritic morphology, stabilizes dendritic spines, and regulates their morphogenesis.[200–204] PSD-95 plays a critical role in controlling the ratio of E/I synapses with a reduction in PSD-95 levels being sufficient to reduce the E/I ratio.[205] PSD-95 expression is reduced in iPSC-derived neurons from FOXG1 syndrome patients and FOXG1-deficient mice[172] and in MeCP2-deficient mice.[206] Targeting of PSD-95 to the synapse and stabilizing it, is mediated through interaction with CDKL5.[207] Consequently, PSD-95 levels are lower

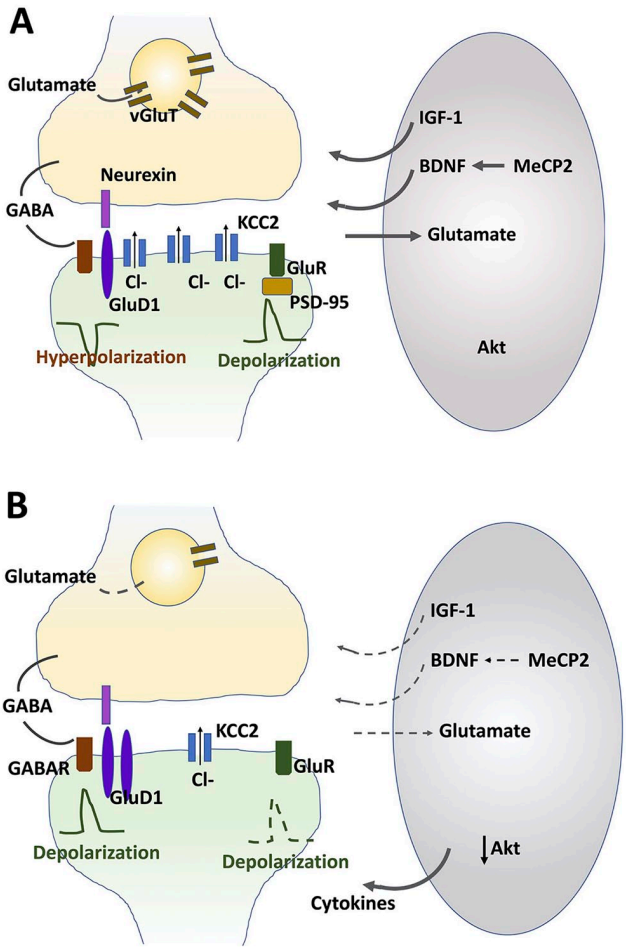

Figure 1. Predicted molecular changes in FOXG1-deficient neurons and astrocytes. (A) Under normal conditions, astrocytes release IGF-1 and BDNF, and take up glutamate from the synapse. Because KCC2 level increases in maturing neurons and remains high, Cl^- is extruded and GABA has a hyperpolarizing effect. Synaptic formation and function are normal with high PSD-95 and low GluD1. (B) With FOXG1 deficiency, IGF-1/BDNF release and glutamate uptake is low, whereas the release of inflammatory cytokine, such as IL-1, IL-6, and TNF-α, is elevated. Because KCC2 level is low, intracellular Cl^- in maturing neurons is high leading to a depolarization signal by GABA. The developmentally regulated switch of GABA-responsive neurons from excitatory to inhibitory signaling is delayed resulting in an E/I imbalance within neuronal circuitry. Glutamate loading is altered in the presynaptic neuron and organization of the postsynaptic neuron is abnormal. AKT is reduced in both astrocytes and neurons. Dotted lines denote a reduction.

in the cortex of CDKL5-deficient mice and in mutant CDKL5 iPSC-derived neurons that possess abnormal dendritic spines.[208] Reduced PSD-95 would affect E/I signaling, dendritic number and morphology, and synaptic organization, all features of CDD, FOXG1 syndrome, and CDD. Besides these disorders, PSD-95 dysfunction has been implicated in schizophrenia, depression, and autism.[209]

AKT: AKT (or PKB) is a family of three closely related Ser/Thr protein kinases—AKT1, AKT2, and AKT3—that is widely expressed and regulates several processes, including cell proliferation, growth, survival, and metabolism.[210] The three isoforms have overlapping and distinct expression patterns and functions. AKT1 and AKT3 are of particular important to brain function.[211–213] AKT3 is expressed selectively in the brain and displays the highest expression of the developing and mature brain.[214] Activation of AKT occurs

downstream of PI-3 kinase (PI3K), a lipid kinase. Once activated, AKT regulates different targets of by phosphorylating them, of which the inhibition of GSK3β and the activation of mTOR are among the best studied.[215,216] AKT is involved in a variety of functions in the developing and mature brain, including neuronal migration, dendritic structure, synaptic plasticity, memory, and neuroprotection.[79,212,217–220] In addition, deregulation of PI3K–AKT–mTOR signaling is implicated in several brain disorders, including microcephaly, macrocephaly, neurodegeneration, intellectual disability, autism, epilepsy, and schizophrenia.[214,221–224]

Although reduced AKT signaling has well documented detrimental effects on brain development and function, as in the case of CDKL5, FOXG1, and MeCP2, elevated AKT activity may also adversely affect brain health. PI3K–AKT signaling is negatively regulated by phosphatase and tensin homologue (PTEN), which dephosphorylates phosphoinositides that are phosphorylated by PI3K and that then activate Akt.[225] For example, deleting PTEN, a negative regulator of AKT, in neural stem cells or in developing neurons of mice results in an expected elevation of AKT but the mice display seizures and autistic behaviors, along with macrocephaly, increased soma size, and increased dendritic arborization and spine density.[225,226] As described above, patients and mice with Rett syndrome display E/I imbalance, reduced soma size, and reduced dendritic arborization and spine density supporting the idea that some of the neurobiological abnormalities in the disorder are due to reduced Akt function. Indeed, AKT signaling is reduced in both Rett mice and patients.[227] In contrast to early deletion of PTEN, ablation in mature excitatory neurons does not affect dendritic morphology but compromises synaptic plasticity and memory.[228]

Overactivation of AKT–mTOR signaling accompanies cortical seizures in FOXG1-haplosufficient mice, although whether this occurs in neurons or glial cells, or which isoform(s) were responsible is not clear.[229] Also, the expression of vGluT2 was increased and KCC2 expression is reduced, which likely increases the excitation/inhibition ratio.[229] Mice lacking CDKL5 display decreased AKT–mTOR and AKT–GSK3β signaling along with reduced dendritic growth and branching, abnormal neural synapses and circuit function, and behavioral deficits.[66,76,77] Levels of IGF-1, which plays critical roles in the development and functioning of the nervous system, are reduced in Rett mice and patients. IGF-1 is a potent stimulator PI3K–AKT signaling in the brain and impaired IGF-1–PI3K–AKT has been described in neurodevelopmental disorders.[223] Administration of IGF-1 or recombinant forms of it ameliorate Rett-related deficits in mice.[206,230,231] IGF-1 administration increases PSD-95 expression and dendritic spine density and stability in CDKL5 mice (both of which are reduced in mutant mice).[208]

BDNF, IGF-1, and inflammatory cytokines: The role of BDNF in promoting neuronal and synaptic development and function is well established.[232,233] Some of these effects are mediated through PSD-95 and AKT stimulation.[234–236] The relationship between FOXG1 and BDNF remains to be resolved, although one study described that both proteins are upregulated during adult hippocampal neurogenesis induced by antidepressant administration.[237] In that study, knockdown of FOXG1 failed to block the upregulation of BDNF raising the possibility that upregulated BDNF might increase FOXG1 expression.[237] CDKL5 is required for the stimulatory effect of BDNF on dendritic morphogenesis.[2] Taken together, these results suggest a CDKL5-BDNF-FOXG1 sequence of action.

Numerous studies have described the activation of AKT by BDNF. Phosphorylation of FOXG1 by AKT is necessary for its function in neurons. BDNF levels are reduced in patients with Rett syndrome.[82,238] Depletion of BDNF in Rett mice results in an earlier onset of disease symptoms, whereas increasing BDNF expression or administration of exogenous BDNF reduces synaptic dysfunction and disease symptoms, and extends lifespan.[151,152,239] It deserves mention that seizures increase the expression of BDNF, a finding that was first described in 1991 and subsequently confirmed in other studies.[240] Subsequent studies have described protective effects of BDNF against seizures.[241] However, some studies have described that increased activation of the high-affinity BDNF receptor, TrkB, can promote hyperexcitability and seizure activity, particularly after brain injury or insult.[242–244] Taken together, it is likely that either upregulation of reduced expression of BDNF can promote seizures depending on the context and whether it is released from neurons or glia.

Like BDNF, IGF-1 plays a key role in neuronal maturation, survival, and plasticity.[245–247] It is possible that BDNF and IGF-1 play overlapping roles in non-overlapping neuronal populations although, relative to BDNF, less attention has been placed on IGF-1. FOXG1-mediated neuronal survival requires IGF-1.[54] As described above, IGF-1 administration alleviates abnormalities in dendritic morphology and synaptic function in MeCP2-deficient mice.[206,239] Degenerative effects caused by astrocytes derived from iPSCs obtained from Rett patients are reduced by treatment with IGF-1.[248] The efficacy of a recombinant form of IGF-1, Mecasermin, has been clinically assessed in clinical studies involving girls with rett syndrome (RTT). These studies have reported good safety, tolerability, and pharmacokinetic profiles of Mecasermin in RTT patients.[249] More importantly, recombinant IGF-1 was found to improve apnea, improved anxiety and mood, and ameliorated breathing and some behavioral abnormalities.[249] Another study also described significant improvement in social and cognitive severity.[250] While both studies had a relatively small number of patients (11 in one and 12 in the other) and the outcome measures were limited, the findings suggest that IGF-1 has beneficial treatment in Rett syndrome. Other studies have described that IGF-1 stimulates AKT and PSD-95 in neurons and in the brains of CDD and Rett mice.[206,208,223] In addition, IGF-1 protects against dendritic spine instability in CDKL5 mice.[208]

However, elevated glial-released cytokines, such as IL-1, IL-6, and TNF-α, negatively impact brain function and contribute to neurological, neurodevelopmental, and psychiatric disorders.[251–254] Although their role in FOXG1 function or dysfunction is unclear, elevated levels of inflammatory cytokines are associated with CDD and Rett syndrome although the upstream and downstream signaling mechanisms are unresolved.[106,255,256]

Conclusions

The literature is consistent with the following common mechanisms for CDD, FOXG1, and Rett syndrome—the switch of GABA from excitatory to inhibitory signaling in a normal manner is likely a key, an abnormality that impacts not only the E/I balance but also developmental regulated processes, including the transition of neural stem cells from proliferation to differentiation and the formation of the dendrites and dendritic spines in proper numbers and morphology. Among the key molecular alterations are a downregulation of KCC2, vGluT1, PSD-95, and AKT function and an upregulation of GluD1 activity that occurs in presynaptic or postsynaptic neurons. Astrocytic dysfunction involving glutamate dyshomeostasis and deregulated release of BDNF, IGF-1, and inflammatory cytokines disrupts both the functioning of neurons and neuron–astrocyte interactions. Together, these abnormalities result in seizures and intellectual disability displayed in all three disorders and contribute to other disease-associated symptoms, including speech and language deficits and gastrointestinal problems. We believe that this review, along with several others, define a cellular and molecular framework that could facilitate a deeper understanding of disease mechanisms and ultimately lead to effective therapies for children with CDD, FOXG1, and Rett syndrome.

It deserves mention that while this review has provided evidence for common mechanistic underpinnings for three related neurodevelopmental disorders, it is unlikely that these are specific for CDD, FOXG1 syndrome, and Rett syndrome. Indeed, it is possible (and perhaps even likely) that some of the molecules and mechanisms described above are involved in other neurodevelopmental and neuropsychiatric disorders, such as ASD and schizophrenia.

AUTHOR'S CONTRIBUTIONS

This review was written by SRDM.

ACKNOWLEDGEMENTS

The author thanks the support from the Louisiana State University Shreveport and the Louisiana Biomedical Research Network.

DECLARATION OF CONFLICTING INTERESTS

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

FUNDING

The author disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by startup funds from the Louisiana State University Shreveport.

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