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The Autistic Neuron: Troubled Translation?

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Autism is a complex genetic disorder, but single-gene disorders with a high prevalence of autism offer insight into its pathogenesis. Recent evidence suggests that some molecular defects in autism may interfere with the mechanisms of synaptic protein synthesis. We propose that aberrant synaptic protein synthesis may represent one possible pathway leading to autistic phenotypes, including cognitive impairment and savant abilities.

In 1943, Kanner described 11 children affected by a unique disorder that he designated "early infantile autism" (Kanner, 1943). It has since become clear that autism is comprised of a clinically heterogeneous group of disorders, collectively termed "autism spectrum disorders" (ASDs), that share common features of impaired social relationships, impaired language and communication, and limited range of interests and behavior.

Cognitive impairment is common in autism, and ~70% of autistic individuals suffer from mental retardation (Fombonne, 1999). Neuropathological studies have reported minor and inconsistent abnormalities in the autistic brain, but recent morphometric analysis has demonstrated enlargement of the hippocampus and amygdala (Schumann et al., 2004). As first noted by Kanner, a high prevalence of macrocephaly is observed among children with ASDs, possibly due to an early period of excessive brain growth (Courchesne et al., 2004). Remarkably, as many as 10% of autistic individuals paradoxically exhibit restricted domains of normal or even superior skills, termed "savant abilities," on a background of cognitive disability (Heaton and Wallace, 2004). Savant syndrome can involve excellence in a variety of cognitive or artistic domains, but declarative memory is most consistently accentuated.

Autism is among the most heritable neuropsychiatric disorders, and available evidence points to a complex genetic basis (Persico and Bourgeron, 2006). However, several disorders caused by single-gene mutations are associated with autism, often accompanied by cognitive impairment (Table 1). In these disorders, a substantial proportion of affected individuals meet diagnostic criteria for ASDs, reflecting a greatly increased risk of autism conferred by the mutation. Conversely, a small but significant percentage of children presenting with ASDs carry mutations in one of these genes. Although such monogenic disorders collectively account for a minority of cases of autism (10%–15%), the molecular alterations in these disorders may identify common pathogenic pathways shared by ASDs.

The identification of mutations in neuroligins as rare genetic causes of autism suggested that defects in synaptic function may be intimately involved in autism pathogenesis (Zoghbi, 2003; Persico and

Table 1. Single-Gene Disorders with High Rates of Autism

Gene	Disorder	Rate of Autism	Rate in Autism	MR	Gene Function
FMR1	Fragile X syndrome	15%–30%	2%–5%	+	Translational repressor
TSC1/2	Tuberous sclerosis complex	25%–60%	1%–4%	+	Inhibitor of mTOR
PTEN	PTEN hamartoma syndrome (ASD with macrocephaly)	ND	1%	+	Inhibitor of PI3K/mTOR signaling
NF1	Neurofibromatosis type I	4%	0%–4%	+	Ras GAP
MECP2	Rett's syndrome	100%	2%	+	Global transcriptional repressor
UBE3A	Angelman's syndrome	40%	1%	+	E3 ubiquitin ligase
CACNA1C	Timothy's syndrome	60%	<1%	+	L-type voltage-gated calcium channel ($Ca_v1.2$)
NLGN3/4	Familial ASD	ND	<1%	+	Synaptic adhesion
NRXN1	Familial ASD	ND	<1%	+	Synaptic adhesion
SHANK3	Familial ASD (22q13 microdeletion syndrome)	ND	<1%	+	PSD scaffolding

Several monogenic human disorders are characterized by cognitive impairment and autism. The estimated rate of autism spectrum disorders (ASDs) in each disease and the estimated rate of each disease in children with ASDs are indicated (rate of autism and rate in autism, respectively). MR refers to the association of mental retardation with each disorder. ND indicates that the prevalence of ASDs among individuals carrying mutations in the specified gene has not been determined.

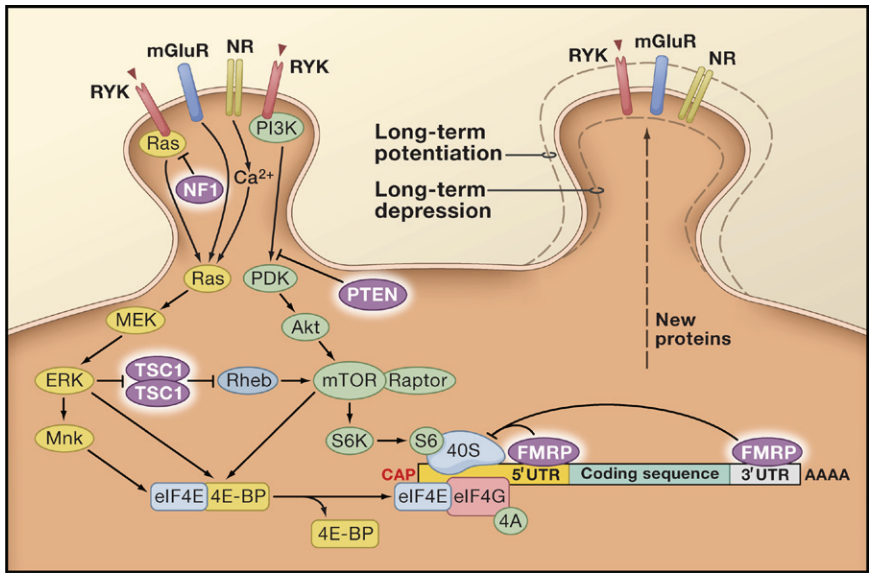

Figure 1. Neuronal Signaling Pathways in Translational Regulation

The Ras/ERK and PI3K/mTOR signaling pathways couple synaptic activity to the translational machinery and play essential roles in protein synthesis-dependent LTP and LTD. These signaling pathways are recruited downstream of the activation of NMDA receptors, group I metabotropic glutamate receptors, and neurotrophin Trk receptors. Regulation of the availability and activity of the mRNA cap-binding factor eIF4E is a primary effector mechanism through which these pathways modulate synaptic protein synthesis. Inactivating mutations in several negative regulators of the ERK and mTOR pathways, including NF1, PTEN, and TSC1/2, are responsible for genetic disorders with a high prevalence of cognitive impairment and autism. FMRP represses translation of specific target mRNAs, and loss of FMRP expression in fragile X syndrome (FXS) leads to cognitive impairment and autism. We hypothesize that loss of the normal constraints on synaptic activity-induced protein synthesis may be one of several pathogenic mechanisms leading to autism.

Bourgeron, 2006). Consistent with this view, mouse models of mutations that cause ASDs in humans consistently point to disrupted synaptic function: excessive or diminished excitatory synaptic connectivity (Chao et al., 2007; Hanson and Madison, 2007) and alterations in the balance of excitation and inhibition (Dani et al., 2005; Tabuchi et al., 2007). It appears that the "autistic neuron" has too many or too few, too strong or too weak, excitatory synapses relative to the level of inhibition. However, mutations in ASDs that directly affect synaptic structure are rare. In this Essay, we focus on recent insights into the function of gene products mutated in several other autistic disorders. We propose that dysregulation of synaptic protein synthesis in these disorders may lead to altered synaptic development and plasticity and autistic phenotypes.

Aberrant Synaptic Protein Synthesis in Autism

The gene products mutated in several single-gene disorders associated with autism act as negative regulators of protein synthesis (Figure 1). Fragile X syndrome (FXS) is an X-linked form of mental retardation caused by transcriptional silencing of the *FMR1* gene (Bagni and Greenough, 2005). The prevalence of ASDs in FXS is reportedly 15%–30%, and conversely, up to 5% of children presenting with ASDs are found to have FXS. The product of the *FMR1* gene, the fragile X mental retardation protein (FMRP), binds to specific mRNAs and represses their translation. FMRP is estimated to interact with more than 400 distinct mRNAs (Brown et al., 2001). Loss of FMRP expression in FXS would be expected to cause translational derepression of these target mRNAs. Indeed, there is a substantial (~20%) and anatomically widespread increase in the rate of cerebral protein synthesis in the *Fmr1* knockout mouse, which models the silencing of FMRP expression responsible for the human disorder (Qin et al., 2005).

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder caused by mutations in hamartin (TSC1) or tuberin (TSC2) (Kwiatkowski and Manning, 2005). Central nervous system involvement in TSC is characterized clinically by a high prevalence of ASDs (25%–60%), cognitive impairment, and epilepsy (Wiznitzer, 2004). TSC1 and TSC2 form a heterodimeric complex with GAP activity against the small GTP-binding protein Rheb, resulting in inhibition of the mammalian target of rapamycin (mTOR) kinase (Figure 1). More specifically, TSC1/2 inhibit the activity of the rapamycin-sensitive mTOR-raptor complex (mTORC1). mTORC1, which is activated by a sequential kinase cascade downstream of phosphoinositide-3 (PI3) kinase, is a major regulator of cellular growth in mitotic cells (Wullschleger et al., 2006). One of the principal effector mechanisms of mTORC1 is activation of cap-dependent translation. Recognition of the 5′ mRNA cap by eIF4E, which leads to recruitment of eIF4G and the small ribosomal subunit, is the key regulatory step in translation initiation (Richter and Sonenberg, 2005). A family of eIF4E-binding proteins, 4E-BPs, impedes this process by sequestering eIF4E and blocking its association with eIF4G. Phosphorylation of 4E-BPs by mTORC1 relieves this inhibition, promoting eIF4E release and activation of cap-dependent initiation. Phosphorylation of another mTORC1 substrate, p70 ribosomal protein S6 kinase (S6K), also facilitates translation. Inactivation of TSC1/2 in hippocampal neurons upregulates mTORC1 activity (Tavazoie et al., 2005; Meikle et al., 2007; Ehninger et al., 2008), suggesting that loss of TSC1/2 function elicits enhanced translation in neurons.

Loss-of-function mutations in another negative regulator of PI3K-mTOR signaling, the PTEN phosphatase, have also been linked to ASD pathogenesis. PTEN antagonizes PI3K-dependent signaling by converting the second messenger PIP_3 to PIP_2, and loss of PTEN function in neurons leads to heightened mTORC1 activity (Kwon et al., 2006). Inactivating mutations in PTEN are responsible for several related familial hamartoma-tumor syndromes, the clinical spectrum of which includes macrocephaly associated with ASDs. Macrocephaly occurs in up to 20% of ASD cases, and PTEN mutations have been identified in ~5% of ASD patients with macrocephaly (e.g., Butler et al., 2005). The connection between macrocephaly and PTEN mutations is interesting in view of the role of the PI3K-mTOR pathway in regulation of

cell size, an effect thought to be mediated through translational control (Backman et al., 2002; Fingar et al., 2002). In mitotic cells, activation of this pathway increases cell size, whereas inhibition decreases cell size. It is not clear to what extent macrocephaly in ASD patients may be due to increased neuronal size; however, inactivation of either TSC1/2 or PTEN in mice causes neuronal hypertrophy and macrocephaly (Backman et al., 2002; Meikle et al., 2007).

Taken together, the association of mutations in FMRP, TSC1/2, and PTEN with autism suggests that defects in translational repression may represent one possible mechanism leading to autistic phenotypes. It will therefore be of interest to determine whether defects in additional components of such pathways might contribute to autism susceptibility.

Translational Control in Synaptic Plasticity and Cognition

As in all cells, elaborate mechanisms regulate protein synthesis in neurons to ensure adaptive responses to a changing environment (Kelleher et al., 2004b; Klann and Dever, 2004; Sutton and Schuman, 2006). There is abundant evidence for transcriptional regulation by neuronal activity and by downstream intracellular signals that are integrated in the neuronal cell body. However, patterns of activity at the thousands of synapses on each neuron dictate where and how this mRNA is used to synthesize proteins to fine-tune neuronal function. Markers of mRNA translation suggest that synaptic activity-induced protein synthesis occurs locally at or near dendritic spines in response to the synaptic release of glutamate. Two types of postsynaptic glutamate receptor have been implicated in translational regulation: the G_q-coupled metabotropic glutamate receptors 1 and 5 (mGluR1 and 5) and the calcium-permeable NMDA receptors (NMDARs). In addition to activating intracellular signaling pathways, there is evidence that NMDAR activation stimulates release of brain-derived neurotrophic factor (BDNF), which can induce neuronal protein synthesis through activation of synaptic TrkB receptors. Excitatory synaptic activity drives translation by activating these receptors, and this process is normally held in check by negative regulators such as FMRP, PTEN, and TSC1/2. Mutations that cause either overactivation of these receptors or decreased negative regulation of protein synthesis knock the system out of balance. We propose that a functional consequence is synaptic dysfunction that may manifest in humans as autism.

Protein synthesis in the neuron has been extensively studied in the context of memory formation in adults and, more recently, experience-dependent cortical development. In both contexts, the immediate encoding and storage of information do not require protein synthesis. However, new gene expression is required for these changes to endure for longer than a few hours. Experimental forms of synaptic plasticity display similar temporal and molecular distinctions. Hippocampal long-term potentiation (LTP) and long-term depression (LTD) exhibit persistent late phases (L-LTP and L-LTD, respectively) that require new gene expression and transient early phases (E-LTP and E-LTD, respectively) that are insensitive to inhibitors of transcription and translation.

Investigation of the molecular mechanisms mediating this process has highlighted the central importance of translational regulation. The presence of mRNAs and polyribosomes in proximity to synaptic sites suggested that local protein synthesis in dendrites could rapidly supply new gene products to activated synapses. The discoveries that BDNF-induced LTP and mGluR-dependent LTD, both of which require protein synthesis, can be supported by isolated dendrites further suggested a crucial role for translational upregulation in response to synaptic activity (Kang and Schuman, 1996; Huber et al., 2000). Comparison of the effects of transcriptional and translational inhibitors, combined with metabolic labeling, has shown that establishment of L-LTP is mediated by rapid upregulation of the translation of pre-existing mRNAs (Kelleher et al., 2004a).

Recent work from several groups has established that the ERK, MAPK, and mTOR signaling pathways couple synaptic activity to the translational machinery during both protein synthesis-dependent LTP and LTD (Figure 1). The ERK pathway, which is activated downstream of NMDAR, mGluR, and TrkB receptors, plays important roles in synaptic plasticity and memory (Sweatt, 2004). ERK activation is required for stimulation of cap-dependent translation and phosphorylation of eIF4E, 4E-BPs, and S6 in hippocampal neurons in response to L-LTP induction, NMDAR activation, and BDNF (Kelleher et al., 2004a). Targeted disruption of ERK signaling in the hippocampus prevents these translational responses and causes selective deficits in L-LTP and long-term memory. Inhibition of mTORC1 activity in hippocampal neurons attenuates synaptic activity-induced translation, 4E-BP phosphorylation, L-LTP, and BDNF-induced LTP (Tang et al., 2002; Kelleher et al., 2004a). Similarly, activation of mGluR1/5 leads to ERK- and mTOR-dependent increases in eIF4E, 4E-BP, and S6 phosphorylation, and inhibition of the ERK or mTOR pathways blocks mGluR-dependent LTD (Gallagher et al., 2004; Hou and Klann, 2004; Banko et al., 2006). Collectively, these findings support a requirement for ERK- and mTOR-regulated translation in protein synthesis-dependent synaptic plasticity and memory.

Analysis of synaptic plasticity in a mouse model of FXS illustrates how loss of the normal constraints on neuronal translation may give rise to synaptic and cognitive impairment. *Fmr1* knockout mice display a range of phenotypes reminiscent of the human disorder. Interestingly, mGluR-dependent LTD, which requires translation but not transcription for its expression, is significantly enhanced in the hippocampus of *Fmr1* knockout mice (Huber et al., 2002). Further supporting the view that increased translation of FMRP target mRNAs underlies this LTD phenotype, hippocampal mGluR-dependent LTD is rendered insensitive to translational inhibitors in *Fmr1* knockout mice (Hou et al., 2006; Nosyreva and Huber, 2006). Presumably, essential LTD proteins are constitutively overexpressed in the absence of FMRP.

What might be the consequence of this manifestation of "hyperplasticity" in the hippocampus? Recently it was shown that inhibitory avoidance learning in rats induces LTP in the CA1 region of the hippocampus (Whitlock et al., 2006). In addition to its role in LTD, mGluR-dependent protein synthesis has also been implicated in the reversal of LTP (Zho et al., 2002). Thus, one might anticipate that a manifestation of exaggerated LTD would be impaired retention or increased extinction of inhibitory avoidance memory. This

phenotype has been observed in *Fmr1* knockout mice (Dolen et al., 2007). Thus, exaggerated mGluR-dependent protein synthesis in the absence of FMRP may yield specific patterns of cognitive impairment in adults with FXS.

Cognitive impairment and autism may also reflect, at least in part, defects in synaptic development and/or developmental plasticity. Ocular dominance plasticity in the developing visual cortex, a commonly studied model for experience-dependent rearrangement and refinement of synaptic connectivity, requires both ERK activation and new protein synthesis, suggesting that similar translational mechanisms contribute to synaptic plasticity in the developing and adult brain (Maffei and Berardi, 2002; Taha and Stryker, 2002). Studies of ocular dominance plasticity in the fragile X mouse model again revealed hyperplasticity—an exaggerated response to visual deprivation (Dolen et al., 2007).

Neuronal activity-induced protein synthesis is crucial for long-lasting modifications of neural circuits. However, these findings in the mouse model of FXS suggest that impairments in synaptic and cognitive function can result from too much of what is normally a good thing. Further evidence that excessive translation can compromise cognitive function comes from mouse models deficient in PTEN and TSC1/2 function, in which elevated mTORC1 activity is associated with impaired hippocampal memory (Kwon et al., 2006; Goorden et al., 2007; Ehninger et al., 2008).

Aberrant Synaptic Tagging and Capture

To facilitate consolidation of synaptic modifications, newly synthesized proteins must be targeted specifically to active synapses. The phenomenon of synaptic tagging and capture suggests that synaptic stimulation creates an immobile "tag" at active synapses that "captures" essential protein products (Frey and Morris, 1997). Induction of L-LTP in one synaptic pathway can effectively convert E-LTP to L-LTP in a second independent synaptic pathway, suggesting that proteins synthesized in response to stimulation of one group of synapses are available to other stimulated synapses within the same neuron. Synaptic tagging and capture are also observed with LTD, and in fact, cross-capture has been reported between LTP and LTD: induction of L-LTP in one synaptic pathway can convert E-LTD to L-LTD in another pathway, and vice versa (Sajikumar and Frey, 2004). Crosscapture suggests that induction of L-LTP and L-LTD may stimulate the synthesis of overlapping sets of proteins capable of enabling either process, consistent with evidence for the use of similar ERK- and mTOR-dependent translational mechanisms outlined above. In essence, synaptic capture implies that the local availability of essential proteins is sufficient to promote the consolidation of LTP and LTD. If the supply of essential proteins is limiting, competition can also be observed among groups of tagged synapses for consolidation of the accompanying synaptic changes (Fonseca et al., 2004).

From a behavioral standpoint, new proteins synthesized during a learning episode enable associative and competitive interactions among neighboring synapses experiencing LTP and LTD, and the resulting pattern of persistent synaptic weight changes is likely to be crucial for proper long-term memory representation (Govindarajan et al., 2006). By altering the levels and/or identities of available proteins, dysregulation of neuronal protein synthesis would interfere with the establishment of appropriate patterns of synaptic modification. In particular, increased availability of plasticity-related proteins would promote consolidation of synaptic changes that would otherwise be lost. Such inappropriate synaptic consolidation would generally be expected to compromise the cognitive performance of neural circuits, reducing the specificity and signal-to-noise ratio of synaptic changes that underlie normal learning.

It is interesting to consider the possibility that excessive synaptic capture and consolidation may in certain situations allow for enhanced long-term memory formation. Superior declarative memory, which depends on the hippocampus, is a common feature of savant abilities in autistic individuals (Heaton and Wallace, 2004). Whereas effective memory consolidation and retention typically benefit incrementally from repeated exposure to new information, individuals with savant abilities are remarkable in their capacity for rapid or "single trial" learning. Thus, in the case of mnemonic savant abilities, excessive protein synthesis could promote rapid and efficient synaptic capture and consolidation of hippocampal memory traces, regardless of their salience, while at the same time causing a more generalized impairment of cognitive function. In this way, cognitive impairment and savant abilities could be two sides of the same coin. It will be of interest to determine whether mutations causing elevated synthesis or abundance of neuronal proteins are associated with savant abilities in autism.

Possible Mechanistic Connections with Other Autistic Disorders

The functions of gene products mutated in other monogenic disorders that overlap with autism lead us to speculate that overexpression of plasticity-related proteins may be one possible molecular mechanism underlying autism (Table 1). Neurofibromatosis type I is caused by inactivating mutations in neurofibromin (NF1), a Ras GAP, resulting in upregulation of Ras-dependent ERK and mTOR activation (Dasgupta and Gutmann, 2003). Mutations in the E3 ubiquitin ligase UBE3A have been identified in Angelman's syndrome, suggesting that ubiquitin-dependent protein turnover may be impaired in this disorder, possibly leading to elevated synaptic protein levels (Jiang and Beaudet, 2004). Timothy's syndrome is caused by mutations in the L-type voltage-gated calcium channel (VGCC) $Ca_v1.2$, which impair channel inactivation and prolong inward calcium ion currents (Splawski et al., 2004). Although the resulting enhancement of calcium ion influx may have pleiotropic effects, activation of the ERK pathway and CREB-dependent transcription are major effector mechanisms regulated by L-type VGCCs (Dolmetsch et al., 2001). The molecular defects in these disorders suggest that a common consequence may be an overabundance of plasticity-related proteins.

Rett's syndrome is caused by loss-of-function mutations in the methyl-CpG binding protein 2 (MeCP2), which can function as both a transcriptional activator and repressor (Chahrour et al., 2008). In rare cases, a Rett-like syndrome can also be caused by duplication of the *MECP2* locus, indicating that decreased and increased MeCP2 dosage produce similar phenotypes. Analysis of mouse models

either lacking or overexpressing MeCP2 revealed that neuronal transcription of a large number of target genes is decreased by loss of MeCP2 function, whereas transcription of the same group of target genes is increased by gain of MeCP2 function. Interestingly, the number of excitatory hippocampal synapses is decreased in mice lacking MeCP2 and increased in mice overexpressing MeCP2 (Chao et al., 2007), indicating that altered transcription of MeCP2 target genes, which presumably results in altered synthesis of the encoded proteins, produces corresponding changes in synaptic connectivity.

As emphasized above for other autistic disorders, these findings suggest that cognitive deficits and autistic features arise in the MeCP2 duplication syndrome as a result of exaggerated protein expression. Conversely, findings from the mouse model of Rett's syndrome suggest that inadequate protein expression can also produce cognitive impairment and autism. Supporting this notion, multidisciplinary studies in mice have demonstrated that defects in synaptic protein synthesis impair hippocampal learning and memory (Kelleher et al., 2004a; Costa-Mattioli et al., 2007). In a recent human genetic study, ASD-linked deletion mutations affected several genes whose expression is stimulated by neuronal activity, further arguing that defects in synaptic activity-induced gene expression contribute to ASD pathogenesis (Morrow et al., 2008). Based on these observations, we suggest that the performance of neuronal networks mediating cognition depends on the level of synaptic protein synthesis (Figure 2). Deviations in either direction from the optimal level of synaptic protein synthesis can adversely affect synaptic capture and consolidation, and the resulting perturbations in synaptic connectivity may underlie the development of cognitive impairment and autistic traits. The manner in which synaptic properties are affected by aberrant protein synthesis is likely to depend on the identities of the individual proteins whose expression is altered.

A parsimonious view of autism pathogenesis would envision the convergence of diverse molecular triggers on a final common disease-causing pathway. The identification of ASD-linked mutations in the synaptic adhesion molecules neuroligins 3 and 4 has suggested that synaptic abnormalities play a central role in autism (Zoghbi, 2003; Persico and Bourgeron, 2006). Our proposed model provides an additional molecular mechanism leading to synaptic dysfunction in autism. How might defective synaptic adhesion and aberrant synaptic protein synthesis produce a common synaptic phenotype? Recent evidence indicates that neuroligins stabilize new synapses and specify their functional properties, thereby regulating the balance of excitatory and inhibitory transmission (Chubykin et al., 2007) (see Essay by Walsh et al., page 396 of this issue). Interestingly, an ASD-linked missense mutation in neuroligin 3 shifts this balance of excitation and inhibition in favor of increased inhibitory drive (Tabuchi et al., 2007). Dysregulated protein synthesis could similarly alter the balance of excitation and inhibition by promoting the net strengthening or weakening of excitatory relative to inhibitory synapses. For example, excessive protein synthesis-dependent LTD, as observed in the hippocampus of *Fmr1* knockout mice, could promote a net weakening of excitatory relative to inhibitory synapses. Reduced excitatory and/or increased inhibitory synaptic activity has been observed in the hippocampus and neocortex of several other mouse models of ASDs, suggesting that an imbalance of excitation and inhibition may be a common synaptic phenotype underlying autism (Cline, 2005; Dani et al., 2005; Chao et al., 2007; Hanson and Madison, 2007). It remains to be seen whether altered protein synthesis-dependent plasticity at excitatory and/or inhibitory synapses contributes to imbalances of excitation and inhibition in mouse models of autism.

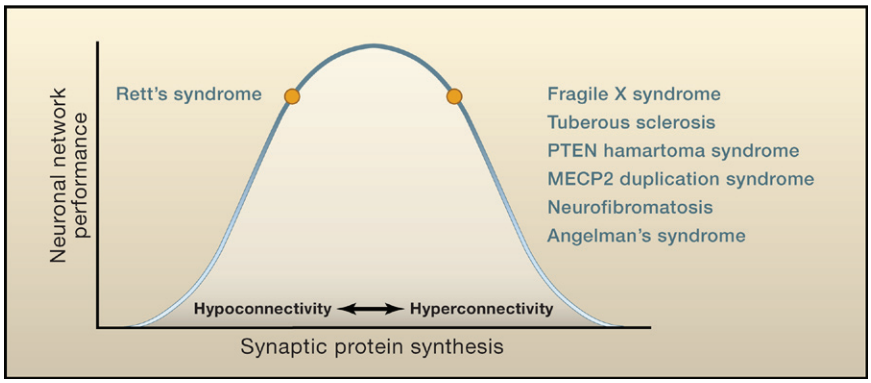

Figure 2. Bidirectional Alterations in Synaptic Protein Synthesis in Monogenic Disorders
We propose that the performance of neuronal networks mediating cognition is a function of the level of synaptic protein synthesis. Increases or decreases in the levels of plasticity-related proteins available to active synapses in autistic neurons may cause corresponding changes in synaptic connectivity, compromising network performance and producing cognitive impairment. In several single-gene disorders associated with autism, such as Fragile X syndrome, levels of synaptic protein availability and connectivity are increased, but in Rett's syndrome these levels are decreased.

Future Directions

Single-gene disorders that increase autism risk in humans offer an exciting window into autism because they can be modeled in mice. Mouse models for several of these disorders display behavioral phenotypes resembling human autism, including impairments in cognition and social interaction (Moy et al., 2006). However, it should be emphasized that the synaptic pathology that yields autistic behavior in humans might have distinct effects in other species due to differences in brain circuitry. Thus, the failure of a single-gene mutation in mice to phenocopy the full spectrum of clinical features does not diminish the importance of the mouse models to reveal pathophysiology and, potentially, new treatments. Based on the findings in mice discussed above, we hypothesize that mutations that lead to excessive or dysregulated synaptic protein synthesis could be one mechanism contributing to autism in humans. One prediction of our hypothesis that can be tested in mice is that there should be some observable commonalities in the synaptic dysfunction wrought by the loss of FMRP, TSC1/2, and PTEN. If our hypothesis proves to be correct, approaches to restoring normal

levels of protein expression may provide a therapeutic strategy for treating these disorders, and perhaps mental retardation and autism. In the case of FXS, the discovery of enhanced mGluR-dependent LTD suggests that inhibition of mGluR activity may be one way to limit the excessive translational response to mGluR activation (Bear et al., 2004). Indeed, a range of phenotypes displayed by mice lacking *Fmr1* can be rescued by genetic reduction of mGluR5 activity (Dolen et al., 2007). Similarly, the mTOR inhibitor rapamycin rescues abnormal hippocampal LTP and memory in a mouse model of TSC (Ehninger et al., 2008). Other approaches that restrain the activity of the molecular machinery regulating synaptic protein synthesis may have therapeutic potential in autism.

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