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NMDA receptor activation regulates sociability by its effect on mTOR signaling activity

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Abstract

Tuberous Sclerosis Complex is one example of a syndromic form of autism spectrum disorder associated with disinhibited activity of mTORCl in neurons (e.g., cerebellar Purkinje cells). mTORCl is a complex protein possessing serine/threonine kinase activity and a key downstream molecule in a signaling cascade beginning at the cell surface with the transduction of neurotransmitters (e.g., glutamate and acetylcholine) and nerve growth factors (e.g., Brain-Derived Neurotrophic Factor). Interestingly, the severity of the intellectual disability in Tuberous Sclerosis Complex may relate more to this metabolic disturbance (i.e., overactivity of mTOR signaling) than the density of cortical tubers. Several recent reports showed that rapamycin, an inhibitor of mTORCl, improved sociability and other symptoms in mouse models of Tuberous Sclerosis Complex and autism spectrum disorder, consistent with mTORCl overactivity playing an important pathogenic role. NMDA receptor activation may also dampen mTORCl activity by at least two possible mechanisms: regulating intraneuronal accumulation of arginine and the phosphorylation status of a specific extracellular signal regulating kinase (i.e., ERK1/2), both of which are “drivers” of mTORCl activity. Conceivably, the prosocial effects of targeting the NMDA receptor with agonists in mouse models of autism spectrum disorders result from their ability to dampen mTORC1 activity in neurons. Strategies for dampening mTORC1 overactivity by NMDA receptor activation may be preferred to its direct inhibition in chronic neurodevelopmental disorders, such as autism spectrum disorders.

Keywords

D-Cycloserine; mTOR; NMDA receptor; Sociability; Tuberous sclerosis

1. Mouse models of Tuberous Sclerosis Complex

Tuberous Sclerosis Complex (TSC), a syndromic form of autism spectrum disorder (ASD) due to the effects of single major genes, has stimulated interest in a metabolic contribution to impaired sociability, intellectual disability and seizures seen in nonsyndromic forms of

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ASDs (Cambiaghi et al., 2013; Ehninger, 2013; Ehninger and Silva, 2011; Meikle et al., 2007, 2008; Tsai et al., 2012). TSC is an autosomal dominant disorder resulting from mutations in either the *TSC1* or *TSC2* gene, whose protein products (i.e., hamartin or tuberin, respectively) form a heterodimer. The heterodimeric TSC protein is an important negative regulator of mammalian target of rapamycin complex 1 (mTORC1), which possesses serine/threonine kinase activity and regulates mRNA translation in the periphery of neurons, among other functions (Crino, 2011; Ehninger, 2013; Talos et al., 2012). Ordinarily, the heterodimeric TSC protein inhibits the activity of Rheb (*Ras* homolog enriched in brain), whose function is to activate mTORCl. Thus, genetic mutations of hamartin or tuberin result in disinhibition of Rheb and (over)activation of mTOR. Disinhibited mTORC1 activity may contribute significantly to the social impairment, cognitive deficits and comorbid seizures of patients with TSC, an autosomal dominant disorder; comorbid presentations of ASDs are seen in about 25–60% of patients with TSC (Ehninger, 2013; Ehninger and Silva, 2011; Sahin, 2012). Thus, targeting the primary metabolic disturbance of TSC (i.e., mTORC1 overactivity) may improve core neuropsychiatric symptom domains even in the presence of cortical tubers in brain; in fact, there are data to suggest that the density of cortical tubers is not solely responsible for the shift to the left in IQ scores observed in these patients (Ehninger and Silva, 2011). Importantly, in addition to TSC, other syndromic forms of ASDs due to major effects of single genes that impact mTOR signaling have been well-described (Brodkin, 2008; Garg et al., 2014; Kim et al., 2015; Peça and Feng, 2012; Sharma et al., 2010; Won et al., 2012). For example, mutations of the gene for the ‘phosphatase and tensin homolog (*PTEN*)’ are associated with human cancers, extreme macrocephaly and ASDs, whose pathogeneses include disruption of metabolic regulation of mTOR signaling pathways (Buxbaum and Hof, 2012). Given the fact that mTOR signaling pathways affect an array of cellular functions, including cell cycle kinetics, cellular differentiation, cell growth, cell survival, metabolism and protein synthesis, it is not surprising that genetic variations of genes coding for upstream regulators and downstream effectors of mTORCl have been associated with ASDs (Crino, 2011; Hoeffer and Klann, 2010).

Consistent with the pathogenic role of mTORC1 overactivity, several proof of concept/proof of principle studies showed that treatment with rapamycin attenuated severity of behavioral and neuropathological findings in transgenic mouse models of TSC (Meikle et al., 2008; Sahin, 2012; Talos et al., 2012; Tsai et al., 2012). Additionally, there are data from relevant mouse models of TSC to suggest that addressing the metabolic lesion (i.e., disinhibited mTOR signaling activity) may have beneficial effects on behavior in “adolescent” mice (Ehninger, 2013; Talos et al., 2012). Because TSC is a chronic disease, an ideal strategy to dampen mTOR overactivity must be effective, safe and tolerable upon sustained long-term administration.

Increased levels of mTOR activity are found in transgenic mice with absent expression of TSC1 in cerebellar Purkinje cells; these mutant mice show deficits of social interaction, impairments of spatial memory and cerebellar abnormalities (Tsai et al., 2012). Importantly, postnatal chronic treatment with rapamycin (6 mg/kg), an inhibitor of mTORCl, improved sociability, spatial working memory, and increased the number of cerebellar Purkinje cells to levels observed in the wild type controls (Tsai et al., 2012). A recently described transgenic

knockout mouse model of TSC (*Tsc1*$^{\text{null-neuron}}$), lacks TSC1 expression in most neurons starting at embryonic day 13 and exhibits well-characterized TSC mutant phenotypes and deficits similar to those seen in patients with TSC pathology (Meikle et al., 2007, 2008). For instance, these mice develop enlarged and dysplastic neurons, and show reduced myelination and overactivation of phosphorylated-S6, a ribosomal protein located downstream of mTORCl. Importantly, postnatal treatment with rapamycin (6 mg/kg) in this model also dramatically improved the TSC phenotype (Meikle et al., 2008).

2. NMDA receptor regulates normal sociability

The NMDA receptor is an example of a highly regulated glutamategated cationic channel receptor; the receptor is a heteromeric protein complex constructed from four constituent polypeptide subunits (Millan, 2005; Millan et al., 2014). The likelihood that the binding and cooperative interaction of glutamate and the obligatory glycine co-agonist will result in channel opening depends on the unique combination of polypeptide receptor subunits (i.e., combinatorial diversity), the extent to which intracellular domains are phosphorylated, and the concentration of allosteric modulators, such as neurally active steroids and polyamines, among other factors (Deutsch et al., 2011b; Millan, 2005). Transgenic mice that have diminished expression of the obligatory NR1 NMDA receptor subunit or NMDA receptors with approximately five-fold reduced affinity for the obligatory glycine co-agonist display impaired sociability in standard paradigms (Halene et al., 2009; Labrie et al., 2008). Recently, genetically engineered mice, whose expression of the NR1 subunit is conditionally “knocked out” in parvalbumin-containing GABAergic inhibitory interneurons, showed diminished sociability, relative to their wild type littermates, confirming a regulatory role for the NMDA receptor in normal mouse sociability (Billingslea et al., 2014). Also, in the resident-intruder mouse model of social interaction, D-cycloserine (320 mg/kg), a partial glycine$_{B}$ site agonist, increased social exploration and diminished aggression in the resident mouse; importantly, the mice tested in the resident-intruder model had “normal” expression of NMDA receptors (McAllister, 1994). In summary, these data support an important role of the NMDA receptor in regulation of sociability, and suggest that targeting this receptor with agonists may improve impaired sociability in disorders, such as ASDs.

3. NMDA regulation of mTOR activity

NMDA receptor activation is an important regulator of mTOR signaling activity (Huang et al., 2007) (Fig. 1). Specifically, sustained NMDA receptor activation leads to the rapid internalization of two isoforms of the cationic amino acid transporter, resulting in diminished arginine transport into cortical neurons (Huang et al., 2007). Intraneuronal concentrations of arginine are detected by ‘nutrient sensors’ that influence mTORCl activity. Thus, when intraneuronal concentrations of arginine are low, mTORCl activity is dampened, resulting in diminished rates and amounts of protein synthesis (Huang et al., 2007). Further, NMDA receptor activation regulates the duration of signaling by the phosphorylated form of extracellular signal regulated kinase 1/2 (ERK1/2), an important driver of mTORCl activity. Specifically, NMDA receptor activation leads to the calcium ion-dependent activation of calcineurin, an important phosphatase that cleaves phosphate from and, thereby, activates ‘STriatal Enriched protein tyrosine Phosphatase (STEP)’ (Fitzpatrick and Lombroso, 2011;

Paul and Connor, 2010; Paul et al., 2003). STEP is an important phosphatase enriched within anatomic brain areas that serve as important nodes within circuits necessary for sociability and cognition, including frontal cortex and hippocampus (Fitzpatrick and Lombroso, 2011). Sustained NMDA receptor activation leads to dephosphorylation of ERK1/2 by STEP, which may dampen mTOR signaling activity. As noted above, the phosphorylated form of ERK1/2 is an important driver of mTOR signaling. Thus, the data suggest that a potential mechanism contributing to the therapeutic action of NMDA receptor activation is down-regulating mTOR signaling activity; of course, future studies must confirm this hypothesis.

4. Nonsyndromic mouse models of ASDs

Unlike transgenic knockout mouse models, whose impaired sociability may be causally-related to diminished or absent expression of single major genes, the genetically-inbred Balb/c and BTBRT+ Itpr3tf/J (BTBR) mouse models are particularly interesting models of ASD because their impaired sociability may reflect subtle epistatic interactions within a network of related genes, many of which may be normal polymorphisms (Cuscó et al., 2009; Levitt and Campbell, 2009). Syndromic forms of ASD due to the effects of single major genes (e.g. tuberous sclerosis, neurofibromatosis type 1 and fragile X syndrome) occur much less commonly than nonsydromic presentations. The genetic mechanisms contributing to or underlying the impaired sociability of Balb/c and BTBR mice may more closely resemble what occurs in most presentations of ASD (Cuscó et al., 2009; Veenstra-Vanderweele et al., 2004).

The Balb/c mouse has altered endogenous tone of NMDA receptor-mediated neurotransmission as reflected in its hypersensitivity to the behavioral effects of MK-801 (dizocilpine), a noncompetitive NMDA receptor antagonist that binds to a hydrophobic channel domain of the NMDA receptor (Burket et al., 2010a; Deutsch et al., 1997, 1998). Previous data showed that Balb/c mice are more sensitive to MK-801's antagonism of electrically precipitated tonic hindlimb extension, and elicitation of irregular episodes of intense jumping behavior, termed “popping,” and circling behavior than other strains (Burket et al., 2010a; Deutsch et al., 1997, 1998). Balb/c mice also have impaired sociability and serve as an established model of ASD (Brodkin, 2007; Burket et al., 2010b; Deutsch et al., 2011a). For example, Balb/c mice show diminished locomotor activity in the presence of an enclosed and freely-behaving social stimulus mouse, relative to the outbred Swiss Webster comparator strain (Burket et al., 2010b). Also, in a standard social paradigm, Balb/c mice spend less time in the compartment containing an enclosed social stimulus mouse; spend less time exploring the enclosed social stimulus mouse; and make fewer discrete episodes of social approach, mounting and anogenital sniffing of a freely-behaving stimulus mouse, among other examples of impaired social behavior, relative to the Swiss Webster comparator strain (Jacome et al., 2011a, 2011c). Finally, although the Balb/c mouse did not differ from the comparator Swiss Webster strain in terms of time spent exploring an inanimate object and did not spend less time in the open arms of an elevated plus maze, this mouse strain differed from the comparator Swiss Webster strain in terms of decreased time spent exploring an enclosed social stimulus mouse (Jacome et al., 2011b). Thus, the Balb/c mouse displays selective reduction of social exploration, although it is not more anxious

than the comparator strain in nonsocial situations, nor does it have a diminished exploratory drive, in general (Jacome et al., 2011b). Because the Balb/c mouse is behaviorally hypersensitive to MK-801, D-cycloserine and D-serine, a partial and full glycine$_B$ agonist acting at the NMDA receptor, respectively, were investigated for their ability to improve sociability in this mouse strain. The data showed that these targeted NMDA receptor agonist interventions improved several quantitative measures of sociability in 4- and 8-week-old Balb/c mice (Deutsch et al., 2011a, 2012; Jacome et al., 2011a). Further, the C57B1/6 strain of mouse spent more time exploring D-cycloserine-treated Balb/c mice than they did exploring vehicle-treated Balb/c mice, suggesting that D-cycloserine "normalized" social signals emitted by the Balb/c strain (Benson et al., 2013). Overall, a growing body of evidence implicates the NMDA receptor in regulation of normal mouse sociability; additionally, the NMDA receptor serves as a therapeutic target for the treatment of impaired sociability in several relevant mouse models of ASD.

NMDA receptor activation affects mTOR signaling by its influence on the cascade of intracellular phosphorylations along the *Ras* and *PI3K* signal transduction pathways, upstream of mTORC1, which could serve as one of its potential mechanisms of prosocial effects (Crino, 2011; Peça and Feng, 2012; Talos et al., 2012). In addition to the Balb/c mouse, the BTBR mouse is another inbred mouse strain that models impaired sociability and stereotypic behavior displayed by persons with ASDs (McFarlane et al., 2008; Silverman et al., 2010; Wöhr et al., 2011; Yang et al., 2007). Interestingly, the BTBR mouse strain differs from at least 12 other inbred strains with respect to genetic variation of the gene encoding kynurenine 3-hydroxylase, an enzyme regulating the pool of kynurenic acid (McFarlane et al., 2008). Kynurenic acid is involved both as a ligand and part of a metabolic pathway that influences neurotransmission mediated by glutamate. Furthermore, a very recent signaling pathway analysis using quantitative proteomics to explore cortical and hippocampal tissues of aged 15 month-old male BTBR mice, compared to age and sex-matched C57B1/6 mice, showed that the mTOR signaling pathway in cortex was among "the top 10 most significantly-populated neuronally-specific" signaling pathways (Jasien et al., 2014). Also, levels of mature brain-derived neurotrophic factor (BDNF) and total TrkB receptor, a receptor tyrosine kinase on the cell surface that transduces the BDNF signal, were reduced in cortical and hippocampal tissues of aged BTBR mice, compared with C57B16 mice (Jasien et al., 2014). BDNF signal transduction is a known regulator of mTOR signaling pathways; thus, these data suggest a compensatory decreased transduction of BDNF in response to elevated and dysregulated mTOR signaling in BTBR mice. Importantly, the aged BTBR mice continued to show deficits of sociability. Of course, these provocative differences in protein abundance and, possibly, mTOR signaling between BTBR and C57B16 mice could be related primarily to their different genetic backgrounds and reflect nonspecific effects of genetic drift. In summary, there is strong support for therapeutic interrogation of glutamatergic neurotransmitter systems and mTOR signaling pathways in these two mouse models of ASDs. Since NMDA receptor activation regulates sociability and mTOR signaling activity, and the latter is upregulated in several syndromic forms of ASD, we wondered whether D-cycloserine, a pharmacological strategy for producing NMDA receptor activation, would improve sociability in the BTBR mouse model of ASD. D-Cycloserine improved sociability in the BTBR mouse, supporting the hypothesis that its

prosocial effects are mediated, at least in part, by dampening effects on mTOR signaling activity in brain (Burket et al., 2013). Specifically, a hypothesized mechanism of D-cycloserine's prosocial effects could include: inhibition of cationic amino acid transporters that are responsible for carrying arginine into the neuron, and Ca^{2+}-calcineurin-dependent activation of STEP. STEP dephosphorylates the active form of ERK1/2, regulating the duration of ERK1/2 signaling, which is a driver of mTOR signaling (Fitzpatrick and Lombroso, 2011; Paul and Connor, 2010; Paul et al., 2003). Moreover, consistent with a hypothesis of possible upregulated mTOR signaling activity in the BTBR mouse strain, rapamycin, an inhibitor of mTORCl, was shown to improve sociability in the BTBR mouse strain (Burket et al., 2014).

5. Conclusion

NMDA receptor activation may be an important regulator of mTOR signaling activity in the brain. Possible mechanisms of the dampening of mTOR signaling by NMDA receptor agonists include, internalization of specific cationic amino acid transporters in relevant areas of the brain, leading to a reduction in intraneuronal arginine concentrations and a dampening of mTOR signaling activity. Additionally, NMDA receptor activation and the opening of the associated cation channel lead to a cascade that begins with the activation of calcineurin and, ultimately, the dephosphorylation of ERK1/2, which, in turn, dampens mTOR signaling. Data from syndromic forms of ASD suggest that dampening of mTOR activity can improve core domains of ASD symptomatology, including socialization. Unfortunately, strategies for the direct inhibition of mTORCl may not be applicable for a disorder, such as ASD, whose origin is during fetal brain development and persists throughout the lifespan (e.g., rapamycin is immunosuppressive). Thus, effective pharmacotherapeutic strategies to activate the NMDA receptor may safely dampen mTOR signaling activity in brain on a long-term basis for a chronic neuropsychiatric disorder, such as ASD. Also, because the NMDA receptor is enriched in brain, NMDA receptor activation may avoid systemic effects, while targeting the social and cognitive impairments of TSC and ASDs in general. A recent translational clinical trial of D-cycloserine in adolescents and young adults with ASDs with good expressive language ability and normal to near-normal IQs reported promising results, supporting future exploration of this provocative hypothesis (Urbano et al., 2014, in press); D-cycloserine has been used as a treatment intervention and validated tool to study the activation of the NMDA receptor in a variety of neuropsychiatric disorders, including schizophrenia, obsessive compulsive disorder, and posttraumatic stress disorder (PTSD) (de Kleine et al., 2014; Difede et al., 2014; Goff, 2012; Goff et al., 2008; Scheeringa and Weems, 2014; Wilhelm et al., 2008).

Importantly, there are exciting complementary strategies for activating the NMDA receptor, in addition to administration of direct $glycine_B$ site partial and full agonists, including inhibitors of the glycine transporter type 1 (GlyT1) and allosteric modulators of the metabotropic glutamate receptor 5 (mGluR5) (Canitano, 2014; Millan et al., 2014). Stimulation of mGluR5 results in phosphorylation of the NMDA receptor and, thereby, increases its sensitivity to activation by drugs mimicking glutamate and glycine. Conceivably, some of these complementary strategies will enjoy greater precision, acting

"when and where" endogenous glycine and D-serine, are released in brain; moreover, these strategies may not be associated with receptor desensitization or potential excitotoxicity.

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Abbreviations

TSC	Tuberous Sclerosis Complex
ASD	Autism spectrum disorder
mTORCl	Mammalian target of rapamycin complex 1
Rheb	*Ras* homolog enriched in brain
mTOR	Mammalian target of rapamycin
PTEN	Phosphatase and tensin homolog
NMDA	N-methyl-D-aspartate
ERK 1/2	Extracellular signal regulated kinase 1/2
STEP	Striatal enriched protein tyrosine phosphatase
BDNF	Brain-derived neurotrophic factor
PTSD	Posttraumatic stress disorder
GlyT1	Glycine transporter type 1
mGLuR5	Metabotropic glutamate receptor 5

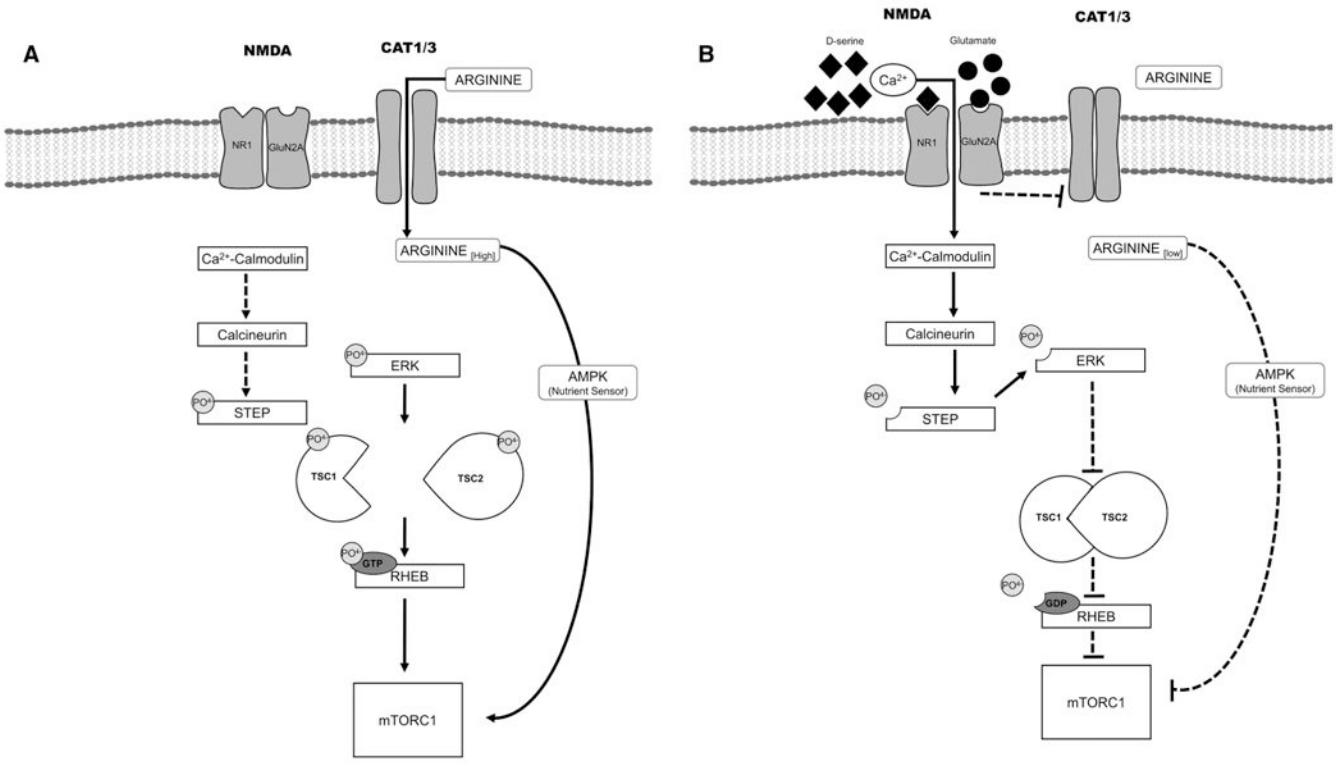

Fig. 1.

The figure is a cartoon depiction of hypothesized mechanisms by which NMDA receptor activation dampens mTOR signaling and, thereby, improves socialization in several syndromic (e.g., Tuberous Sclerosis Complex) and nonsyndromic forms of autism spectrum disorders. Panel A depicts heightened mTOR signaling activity in several syndromic and nonsyndromic forms of autism spectrum disorders, whereas Panel B depicts two possible consequences of NMDA receptor activation. NMDA receptor activation (Panel B) decreases the activity of specific cationic amino acid transporters (CAT 1/3) responsible for arginine uptake into the neuron. Arginine is detected by nutrient sensors, which contribute to regulation of mTOR signaling activity; lowered intraneuronal concentrations of arginine lead to dampening of mTOR signaling activity. NMDA receptor activation (Panel B) also leads to the Ca^{2+}-dependent activation of calcineurin, a phosphatase that activates STEP, which, in turn, dephosphorylates and inactivates ERK1/2. Phosphorylated ERK1/2 is a major driver of mTOR signaling activity. NMDA receptor activation may be preferred to direct inhibition of mTORC1 in disorders requiring chronic, even lifelong, treatment, such as autism spectrum disorders (see text for additional derails).