



# Insulin signaling and autism

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Autism and autism spectrum disorders (ASDs) are thought to be caused mostly by genetic factors with an additional contribution from unidentified environmental risk factors. Identifying these environmental risk factors could improve both prevention and development of therapeutics, but the nature of these factors is not well understood.

Clues to the identification of one environmental risk factor come from studies of a specific set of genetic diseases in which the frequency of autism or ASD is significantly increased. These diseases include tuberous sclerosis (40–50% of afflicted individuals have autism), type 1 Neurofibromatosis (a several-fold increase in frequency of autism in afflicted individuals), and autism with macrocephaly (Mansheim, 1979; Gillberg and Forsell, 1984; Goffin et al., 2001). As has been noted previously by several others (for example, see Kelleher and Bear, 2008), the genes affected in these disorders, *Tsc1/Tsc2*, *Nf1*, and *PTEN*, respectively, each encode inhibitors of a specific signaling pathway called the PI3K/Tor pathway (Hay and Sonenberg, 2004). *Nf1* encodes a Ras GTPase activator protein, which reduces the ability of Ras to activate the lipid kinase PI3K (Xu et al., 1990; Rodriguez-Viciana et al., 1994). *PTEN* encodes a lipid phosphatase that opposes the effects of PI3K. *Tsc1/Tsc2* encode pathway inhibitors that are negatively regulated by PI3K activity (Manning et al., 2002). One effect of PI3K/Tor activity is increased mRNA translation, which is mediated by activation of the translation initiation activator eIF-4E. This observation is of interest because a fourth disease gene that increases the frequency of autism, Fragile X, encodes a translational inhibitor that might oppose the effects of eIF-4E (Brown et al., 1982; see **Figure 1**). Thus, mutations in any of these four genes both increase mRNA translation and increase the incidence of autism.

Other evidence supports the idea that hyperactivation of the PI3K/Tor pathway causes autism and ASD. Recently, Neves-Pereira et al. (2009) suggested that translocations or point mutations that

hyperactivate eIF-4E are causal for autism. In addition, studies of copy-number variants associated with autism revealed that hyperactivated PI3K variants were found in numbers far in excess of those expected by chance (Serajee et al., 2003; Cuscó et al., 2009).

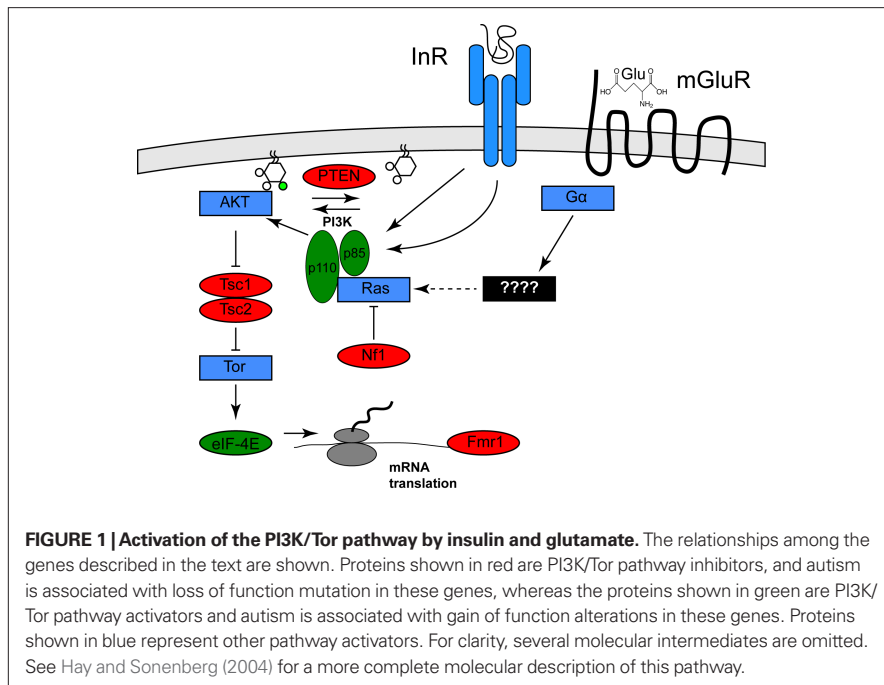
In neurons, the PI3K/Tor signaling pathway affects a form of synaptic plasticity that has been implicated in autism (Bear et al., 2004). This form of synaptic plasticity is called long term depression (LTD) mediated by metabotropic glutamate receptors (mGluR), which are G protein coupled receptors for which glutamate is ligand. The best characterized example of mGluR-LTD occurs at the synapse between the Schaffer collaterals and CA1 pyramidal cells of the hippocampus. At this synapse, mGluR-LTD induction requires dendritic protein synthesis (Huber et al., 2001), activation of both PI3K and Tor (Hou and Klann, 2004), and ultimately internalization of AMPA-type glutamate receptors (Snyder et al., 2001). In addition, loss of *Fmr1*, the protein affected in Fragile X, increases the magnitude of mGluR-LTD (Huber et al., 2002; Waung and Huber, 2009) suggesting that *Fmr1* normally functions to inhibit LTD by inhibiting translation of specific dendritic messages. These observations and others have led to the proposal that at least some of the deficits in autism might reflect increased sensitivity to mGluR-LTD induction (Bear et al., 2004; Kelleher and Bear, 2008) as a consequence of hyperactivation of the PI3K/Tor pathway.

The PI3K/Tor pathway is the major intracellular effector of insulin signals, and insulin signaling is predicted to activate the PI3K/Tor pathway in a manner similar to the genetic changes described above (Scott et al., 1998). Insulin can cross the blood-brain barrier (Schwartz and Porte, 2005) and insulin receptors are present and can regulate synaptic activity in relevant portions of the brain, including the hippocampus, cerebellum, and prefrontal cortex (Zhao et al., 2004, 2006; Dou et al., 2005). Furthermore, Huang et al. (2004) reported

that insulin application evokes a LTD of synaptic activity (insulin-LTD) in the hippocampal CA1 region that is very similar mechanistically to mGluR-LTD: insulin-LTD, like mGluR-LTD, requires PI3K and Tor activity, dendritic protein synthesis, and removal of AMPA receptors from the cell surface. Thus, it appears that insulin is capable of activating the precise cellular pathway implicated in autism. For these reasons I hypothesize that insulin signaling contributes to development of autism in genetically susceptible individuals by contributing to PI3K/Tor pathway activation in neurons.

In further support of this hypothesis, Gardener et al. (2009) recently reported that in a large meta-analysis of maternal factors linked to autism, gestational diabetes was associated with the greatest increase (twofold) in incidence of autism. Although insulin does not cross the placenta, the elevation of fetal blood glucose levels as a consequence of maternal diabetes is predicted to increase fetal insulin secretion, and thus hyperactivate the fetal PI3K/Tor pathway. Another strong risk factor was advanced parental age, which may be a consequence of an age-dependent impairment of glucose tolerance short of diabetes. Furthermore, preliminary studies indicated that administration of a “ketogenic diet,” in which calories from carbohydrates are replaced with calories from fat, was therapeutic in individuals with autism and ASD (Evangelidou et al., 2003). This effect might result from the strong suppression of insulin secretion that accompanies this diet (Volek et al., 2008), which is predicted to attenuate activation of the PI3K/Tor pathway.

The incidence of gestational diabetes has recently increased (Ferrara et al., 2004), an increase that might be associated with the increased incidence in impaired glucose tolerance and hyperinsulinemia in the general population. Although the reported incidence of autism and ASD has also increased, it is not yet clear if this represents a true increase or rather a consequence of greater awareness and broader diagnostic criteria. However, if a true increase in the incidence



of autism is occurring, then this increase could be a consequence of the increased incidence in hyperinsulinemia in the general population.

Thus this hypothesis provides a mechanism for previously unexplained observations concerning the occurrence and treatment of autism as well as for any true increase in the incidence of autism and ASD that might be occurring. This hypothesis also raises new possibilities for prevention and therapeutic intervention for autism.

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