

# Glucose Metabolism Dysfunction in Children with Autism?

**Dr. AJ Russo<sup>1\*</sup>, Dr. Albert Mensah<sup>2</sup> and Dr. Judith Bowman<sup>2</sup>**

<sup>1</sup>Visiting Assistant Professor of Biology, Drew University, Madison, NJ and Research Director, Mensah Medical Center, Warrenville, Illinois, USA

<sup>2</sup>Mensah Medical Center, Warrenville, Illinois, USA

**\*Corresponding Author:** Dr. AJ Russo, Visiting Assistant Professor of Biology, Drew University, Madison, NJ and Research Director, Mensah Medical Center, Warrenville, Illinois, USA.

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### Abstract

Based on our research and the research of others, in this review, we are suggesting that Akt may act upon many substrates, including the inactivation of GSK-3 $\alpha$ . Decreased levels of Akt may result in lower inactivation and, therefore, higher levels of GSK-3 $\alpha$ . The resulting increase in glycogen synthase activity (which forms more glycogen from glucose) lowers glucose availability. We are suggesting that the resulting hypoglycemia may be associated with the etiology of autism.

**Keywords:** *Glucose Metabolism Dysfunction; Children; Autism; GSK-3 $\alpha$*

Intracellular pathways are cascades of enzymatic reactions which activate enzymes through phosphorylation. This, in turn, activates substrates, turning them into active enzymes. These pathway enzymes then activate other substrates, and so on, until products, such as transcription factors are formed which interact with DNA, stimulating translation (protein production). This influences functions such as cell growth, apoptosis, and cell differentiation.

The orchestration of the action of intracellular pathways starts with growth factors and other signaling molecules which attach specifically to their respective membrane receptors. Those membrane proteins often become (or interact with) active intracellular enzymes which then begin the cascade of reactions.

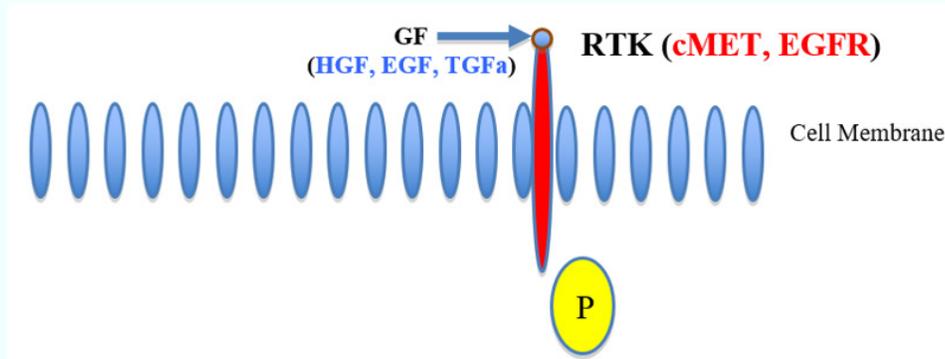
Our lab has focused on two intracellular pathways of these enzymes, the mitogen-activated protein kinase (MAPK) and protein Kinase B (Akt) pathways, which may be dysfunctional in autism and therefore may play a role in the etiology of the disease. There are many signaling proteins and receptors which initiate these pathways. We have focused on epidermal growth factor (EGF)/epidermal growth factor receptor (EGFR) and the hepatocyte growth factor (HGF)/tyrosine-protein kinase Met (cMET) growth factor/receptors.

Recently, our lab used immunoarrays to measure the concentration of 17 intracellular kinases from 26 autistic children and 12 age and gender similar neurotypical controls. We found that levels of one of these proteins, phosphorylated GSK3 $\alpha$ , were significantly higher in the autistic group [1].

This report, based on our research and the research of others, provides evidence and promotes a hypothesis that the EGF/TGF- $\alpha$ /EGFR, or alternately the TNF- $\alpha$  receptor/Akt/mTOR/GSK3 $\alpha$  results in increased GSK3 $\alpha$ , and increased GSK3 $\alpha$  suggests a dysfunction in glucose metabolism in individuals with autism.

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We have found several growth factors (Receptor Tyrosine Kinases-RTKs) and their receptors which may be involved in the etiology of autism.



**Figure 1:** Here an RTK (Receptor Tyrosine Kinase), such as EGF (Epithelial Growth Factor), HGF (Hepatocyte Growth Factor), Transforming Growth Factor alpha (TGF $\alpha$ ) or Transforming Growth Factor beta-1 (TGF $\beta$ 1) attach specifically to its membrane bound receptor Epidermal Growth Factor Receptor (EGFR), Receptor tyrosine-protein kinase erbB-3 (ErbB3 or HER3) or Hepatocyte Growth Factor Receptor (MET) interacts with its receptor which, when activated, becomes a RTK (Receptor Tyrosine Kinase) (either cMET - tyrosine-protein kinase Met or EGFR - Epidermal Growth Factor Receptor).

With regard to EGF and its receptor EGFR We have found that EGF is significantly low in blood plasma of individuals with autism [2]. This is supported by other labs [3].

We have recently found that two other ligands for EGFR, Transforming Growth Factor alpha (TGF $\alpha$ ) and Transforming Growth Factor beta-1 (TGF $\beta$ 1), are significantly increased in individuals with autism.

Our lab has found that EGFR is increased in individuals with autism and we suggest that low EGF may be the result of increased EGFR, because free EGF is bound to EGFR [4,5].

Another growth factor and receptor involved in the etiology of autism is HGF and its receptor cMET. Our lab has also found that HGF is also significantly decreased in autism [6].

Decreased MET function is associated with an increased risk of autism spectrum disorder (ASD) [7].

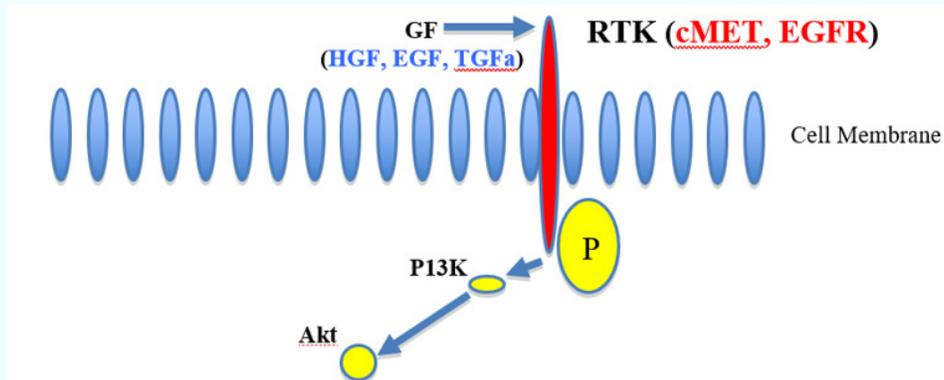
A third growth factor and receptor which may be involved in the etiology of autism is Tumor Necrosis Factor (TNF) and tumor necrosis factor receptor (TNFR). Other labs have found that TNF- $\alpha$  is also significantly increased in ASD children [8].

We have recently found, using immunoarray technology, that four different members of the Tumor Necrosis Factor Receptors are significantly higher in individuals with autism (Tumor necrosis factor receptor superfamily member 17; B-cell maturation protein; CD antigen CD269; BMCA) (Tumor necrosis factor receptor superfamily member 21; Death receptor 6-DR6; CD antigen CD358) (Tumor necrosis factor receptor superfamily member 9; 4-1BB ligand receptor; CDw137; T-cell antigen 4-1BB homolog T-cell antigen ILA; CD antigen CD137) (Tumor necrosis factor receptor superfamily member 11B; Osteoclastogenesis inhibitory factor; Osteoprotegerin; OPG).

Others have also found increased concentration of TNF receptors in individuals with autism [9].

MAPK and Akt Intracellular Pathway Proteins are also altered in autism. Our lab has found that Akt levels are decreased in individuals with autism [10]. Other researchers have also found significantly low levels of Akt in ASD individuals [11,12].

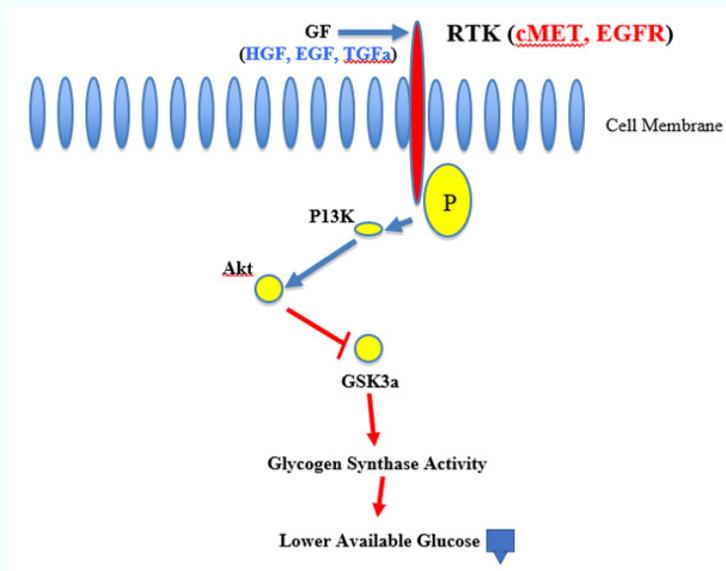
Activation of phosphatidylinositol 3-kinase (PI3-K (kinase)) results in the phosphorylation and activation of Akt [13].



**Figure 2:** EGFR phosphorylation activates EGFR which then phosphorylates P13-K activating this kinase. Activated P13-K then phosphorylates Akt.

Glycogen synthase kinase (GSK-3) is a serine/threonine kinase that phosphorylates either threonine or serine, and this phosphorylation permits a variety of biological activities, such as glycogen metabolism, cell signaling, cellular transport, and others [14].

Akt activation results in GSK-3 inhibition by phosphorylation of Ser21 in GSK-3 $\alpha$  and Ser9 in GSK-3 $\beta$  [15].



**Figure 3:** Akt may suppress the activation of many substrates including the inactivation of GSK-3. Higher than normal GSK-3a stimulates glycogen synthase activity (catalyzes the conversion of glucose into glycogen) which forms more glycogen from glucose. This lowers available glucose.

We also found a significant correlation between decreased Akt levels and high EGFR in autistic individuals. So, found that when EGFR levels are high, generally Akt levels are decreased [5].

Undernutrition results in an enhanced glycogen content which is confined to astrocytes, according to our histochemical approaches. Cortical phospho-GSK3 is also increased when an individual is undernourished. This suggests that the increased glycogen content and resultant hypoglycemia, is associated with activated GSK3-a [16].

In preterm infants, repeated blood glucose levels below 50 mg/dL may be associated with neurodevelopmental delay. Signs and symptoms of hypoglycemia are nonspecific and include jitteriness, irritability, lethargy, seizures, apnea, grunting and although uncommon, sweating, but unfortunately, hypoglycemic infants may not always be symptomatic [17].

The mechanisms by which refractory neonatal hypoglycemia (defined as sustained blood glucose < 40 mg/dl despite glucose infusion) and severe neonatal hypoglycemia (blood glucose < 25 mg/dl) increase the risk of ASD involve energy deprivation and mitochondrial dysfunction [18].

It was shown that neonatal hypoglycemia increases threefold the risk of ASD in children born at term but does not increase the risk in premature [19].

This could be explained by the fact that preterm neonates are routinely screened for hypoglycemia, but term neonates are not. So, it is possible that term neonates, with undetected hypoglycemia, could wind up with CNS damage.

In summary, based on our research and the research of others, we are suggesting that Akt may act upon many substrates, including the inactivation of GSK-3a. Decreased levels of Akt may result in lower inactivation and, therefore, higher levels of GSK-3a. The resulting increase in glycogen synthase activity (which forms more glycogen from glucose) lowers glucose availability. We are suggesting that the resulting hypoglycemia may be associated with the etiology of autism.

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