JURA

BHSc Research Symposium • October 2012 • Vol. 2, No. 2

Alterations in mTOR signaling in the genetic BTBR mouse model of autism spectrum disorder

Mariam Narous, Jong M. Rho

Abstract

Autism spectrum disorder (ASD) is a neurodevelopmental condition affecting approximately 1% of children in the general population[1]. Tuberous sclerosis complex (TSC) – a neurocutaneous disorder characterized by multi-system involvement, notably epilepsy – is highly co-morbid with ASD[2]. Previous studies have suggested that the presence of cortical tubers in the temporal lobe and the early onset of seizures are risk factors for ASD. However, the mechanisms underlying the association between TSC and ASD remain elusive. One potential molecular explanation involves the mTOR signaling pathway[3]. Disruptions in the mTOR pathway, which have been implicated in studies of TSC, may explain in part susceptibility to and pathogenesis of ASD. The primary purpose of this study was to examine the mTOR signaling pathway in the BTBR T+ tf/J mouse model of ASD[4]. The ketogenic diet (KD) – a non-pharmacological treatment for medically refractory epilepsy known to down-regulate mTOR signaling – was administered to a group of BTBR mice to evaluate whether it might reverse protein expression changes in the mTOR pathway[5]. Using western blot analysis, we measured the expression of biomarkers in the mTOR pathway. Phosphorylated mTOR levels were significantly (50%) reduced in BTBR mice, and levels of upstream pAMPK were two-fold higher in these animals compared to B6 controls. BTBR mice showed a significant (40%) reduction in the downstream markers pS6 and p4EBP1. Collectively, the protein levels determined for both upstream and downstream biomarkers were consistent with an overall down-regulation of mTOR signaling. Unexpectedly, the KD did not alter the aberrant expression of mTOR signaling proteins in BTBR mice. Contrary to expectations based on mechanistic speculation, we demonstrated an overall down-regulation of mTOR signaling in autistic BTBR mice. These findings suggest that decreased mTOR activity may be either a cause or consequence of the principal mechanisms underlying the autistic phenotype of BTBR mice.

References

1. Karmali, M. A., Petric, M., Lim, C., Fleming, P. C. & Steele, B. T. (1983). Escherichia coli cytotoxin, haemolytic-uraemic syndrome, and haemorrhagic colitis. Lancet 2, 1299-1300.

2. Fraser, M. E., Fujinaga, M., Cherney, M. M., Melton-Celsa, A. R., Twiddy, E. M., O'Brien, A. D. & James, M. N. (2004). Structure of Shiga toxin type 2 (Stx2) from Escherichia coli O157:H7. J Biol Chem 279, 27511-27517.

3. Zeng, L., Rensing, N. R., and Wong, M. (2009). Developing antiepileptogenic drugs for acquired epilepsy: Targeting the mammalian target of rapamycin (mTOR) pathway. Molecular and Cellular Pharmacology, 1(3):124-129.

4. McFarlane, H. G., Kusek, G. K., Yang, M., Phoenix, J. L., Bolivar, V. J., and Crawley, J. N. (2008). Autism-like behavioral phenotypes in BTBR T+tf/J mice. Genes, Brain and Behavior, 7(2):152-163.

5. McDaniel, S. S., Rensing, N. R., Thio, L. L., Yamada, K. A., and Wong, M. (2011). The ketogenic diet inhibits the mammalian target of rapamycin (mTOR) pathway. Epilepsia, 52(3):e7-e11.