Reply to Letter of Peter Good

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Authors Helt, Kelley, Boorstein, Pandey, and Fein, asked authors Kinsbourne and Herbert to respond to the Good letter because of their expertise in this area. Following is Dr. Herbert's response.

The most remarkable thing about fever-associated transient improvement of core features of autism (Curran et al. 2007) is the challenge it poses to the conception of autism as trait, as static encephalopathy (Herbert 2009). What neurobiological mechanisms might underlie autism as dynamic encephalopathy? Others have advanced various models; Good proposes that in the setting of fever the free amino acid taurine may reduce astrocytic enlargement and capillary compression, thereby improving brain blood flow, and may account for clinical improvement in this context. He also proposes that ASD individuals who do not respond in this way may be taurine deficient.

One problem with pinning an explanation on any one mechanism or agent, such as taurine, is the pleiotropic web of influences of the components involved; shifts in a few parameters could lead to opposite outcomes. Good argues that fever reduces GABA and elevates taurine. GABA may be reduced by fever, but might this not reduce inhibition and cause a net increase in excitation, which if anything could increase autistic behaviors? Enlarged astrocytes would also leave more extracellular glutamate lying about, further driving

excitation. Would transient improvement of blood flow overcome this excitatory vector? Would taurine be uniquely efficacious in improving the functioning of this system?

On the other hand, taurine has a wide range of impacts; it is known to counteract many physiological problems documented or under study in ASD that could increase brain excitation, such as antioxidant effects (Oliveira et al. 2010) which counter oxidative stress (Chauhan et al. 2009; James et al. 2006), support of calcium homeostasis (Albinana et al. 2010; El Idrissi and Trenkner 2003) which may be genetically and/or environmentally compromised (Pessah and Lein 2008), protection against glutamate toxicity (Molchanova et al. 2007) which may be present in ASD again for genetic and/or environmental reasons (Rubenstein and Merzenich 2003) (Blaylock and Strunecka 2009; Harada et al. 2010), and toxicity of xenobiotics and heavy metals (Yu et al. 2007; Zhu et al. 2005) and to be protective against seizures (El Idrissi et al. 2003; Kirchner et al. 2003).

From a clinical point of view it is not necessary to have complete answers regarding the role of every component in one's model of the neurobiology of transient improvement with fever in order to test Good's taurine hypothesis. Good has risen to the challenge posed by improvement of ASD with fever by thinking in terms of measures that can be dynamical. From there it is a logical step to thinking about mechanisms amenable to intervention. Measuring taurine in children with autism while following their response to fever is one route of investigation. If taurine depletion is associated with a lack of response to fever, might it also be associated with other functional differences even in the absence of fever? Might there be other associated clinical correlates? Overall while there may be heterogeneity in the routes by which fever mediates improvement, this particular hypothesis is thought provoking and should provoke research and discerning clinical observation as well.

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References

- Albinana, E., Sacristan, S., Martin Del Rio, R., Solis, J. M., & Hernandez-Guijo, J. M. (2010). Modulation of calcium channels by taurine acting via a metabotropic-like glycine receptor. *Cellular and Molecular Neurobiology*, 30(8), 1225–1233. doi:10.1007/s10571-010-9574-0.
- Blaylock, R. L., & Strunecka, A. (2009). Immune-glutamatergic dysfunction as a central mechanism of the autism spectrum disorders. *Current Medicinal Chemistry*, 16(2), 157–170.
- Chauhan, A., Chauhan, V., & Brown, T. (Eds.). (2009). *Autism: Oxidative stress, inflammation and immune abnormalities*. Boca Raton: Taylor & Francis/CRC.
- Curran, L. K., Newschaffer, C. J., Lee, L. C., Crawford, S. O., Johnston, M. V., & Zimmerman, A. W. (2007). Behaviors associated with fever in children with autism spectrum disorders. *Pediatrics*, 120(6), e1386–1392.
- El Idrissi, A., & Trenkner, E. (2003). Taurine regulates mitochondrial calcium homeostasis. *Advances in Experimental Medicine and Biology*, 526, 527–536.
- El Idrissi, A., Messing, J., Scalia, J., & Trenkner, E. (2003). Prevention of epileptic seizures by taurine. *Advances in Experimental Medicine and Biology*, 526, 515–525.
- Harada, M., Taki, M. M., Nose, A., Kubo, H., Mori, K., Nishitani, H., et al. (2010). Non-invasive evaluation of the GABAergic/glutamatergic system in autistic patients observed by MEGA-editing proton MR spectroscopy using a clinical 3 Tesla instrument. *Journal of Autism and Developmental Disorders*.
- Herbert, M. R. (2009). *Autism: The centrality of active pathophysiology and the shift from static to chronic dynamic encephalopathy*. Taylor & Francis/CRC Press.
- James, S. J., Melnyk, S., Jernigan, S., Cleves, M. A., Halsted, C. H., Wong, D. H., et al. (2006). Metabolic endophenotype and related genotypes are associated with oxidative stress in children with autism. *American Journal of Medical Genetics. Part B: Neuropsychiatric Genetics*, 141B(8), 947–956.
- Kirchner, A., Breustedt, J., Rosche, B., Heinemann, U. F., & Schmieden, V. (2003). Effects of taurine and glycine on epileptiform activity induced by removal of Mg²⁺ in combined rat entorhinal cortex-hippocampal slices. *Epilepsia*, 44(9), 1145–1152.
- Molchanova, S. M., Oja, S. S., & Saransaari, P. (2007). Effect of taurine on the concentrations of glutamate, GABA, glutamine and alanine in the rat striatum and hippocampus. *Proceedings of the Western Pharmacology Society*, 50, 95–97.
- Oliveira, M. W., Minotto, J. B., de Oliveira, M. R., Zanotto-Filho, A., Behr, G. A., Rocha, R. F., et al. (2010). Scavenging and antioxidant potential of physiological taurine concentrations against different reactive oxygen/nitrogen species. *Pharmacological Reports*, 62(1), 185–193.
- Pessah, I. N., & Lein, P. J. (2008). *Evidence for Environmental Susceptibility in Autism: What We Need to Know About Gene x Environment Interactions: Humana*.
- Rubenstein, J. L., & Merzenich, M. M. (2003). Model of autism: increased ratio of excitation/inhibition in key neural systems. *Genes, Brain, and Behavior*, 2(5), 255–267.
- Yu, S. S., Wang, M., Li, X. M., Chen, W. H., Chen, J. T., Wang, H. L., et al. (2007). Influences of different developmental periods of taurine supplements on synaptic plasticity in hippocampal CA1 area of rats following prenatal and perinatal lead exposure. *BMC Developmental Biology*, 7, 51.
- Zhu, D. M., Wang, M., She, J. Q., Yu, K., & Ruan, D. Y. (2005). Protection by a taurine supplemented diet from lead-induced deficits of long-term potentiation/depotentiation in dentate gyrus of rats in vivo. *Neuroscience*, 134(1), 215–224.