EDITORIAL

FACTORS ADVERSELY INFLUENCING NEURODEVELOPMENT

T.C. THEOHARIDES[1,2,3,4], M. KAVALIOTI[5] and R. MARTINOTTI[6]

[1]Laboratory of Molecular Immunopharmacology and Drug Discovery, Department of Immunology, Tufts University School of Medicine, Boston. MA, USA; [2]Sackler School of Graduate Biomedical Sciences, Tufts University School of Medicine, Boston, MA, USA; [3]Department of Internal Medicine, Tufts University School of Medicine and Tufts Medical Center, Boston, MA, USA; [4]Department of Internal Medicine, Tufts University School of Medicine and Tufts Medical Center, Boston, MA, USA; [5]Graduate Program in Education, Lesley University, Cambridge, MA, USA; [6]Casa di Cura Villa San Marco, Ascoli Piceno, Italy

Received September 6, 2019 – Accepted October 4, 2019

Neurodevelopment has been studied extensively, especially in respect to abuse, anoxia, nutritional status and prematurity/low birth weight. However, less attention has been paid to innate and environmental factors, as well as to inflammatory conditions that may adversely affect neurodevelopment and learning in children. These include heavy metals, herbicides and polyvinyl chlorides (PVCs), mycotoxins, viral infections and Lyme disease-associated pathogens, as well as number of conditions such as chronic inflammatory response syndrome (CIRS) and Mast cell activation syndrome (MCAS). Early recognition of factors/conditions that could interfere with neurodevelopment is critical. Corrective actions, including the use of some unique natural flavonoids, could have lasting beneficial results.

There has been an unexplained increase in children with neurodevelopmental and learning problems (1, 2). Neurodevelopment has been studied extensively. More recently, atopic diseases (3) such as allergies (4, 5), asthma (6), and atopic eczema (7) have been significantly associated with behavioral and learning difficulties, including attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). Emotional stress (8, 9) both prenatally (10, 11), as well as in children (12, 13) has also been associated with increased risk of a child developing ADHD or ASD.

Less attention has been paid to innate and environmental factors, as well as inflammatory conditions that may adversely affect neurodevelopment and learning in children (14, 15). These include heavy metals, herbicides and polyvinyl chlorides (PVCs) (Table I), as well as a variety of inflammatory conditions (Table II) such as mold, Lyme disease, viral infections and especially chronic inflammatory response syndrome (CIRS) and mast cell activation syndrome (MCAS).

Recent evidence indicates that inflammation of the brain (8, 16), due to activation of microglia (17, 18) may be involved in neurodevelopment and in the pathogenesis of neuropsychiatric disorders (19, 20) but the reasons are still unknown. We reported that the peptides corticotropin-releasing hormone (CRH)

Key words: autism, brain, mast cells, flavonoids, inflammation, learning, neurodevelopment

Corresponding Author:
Theoharis C. Theoharides, MS, MPhil, PhD, MD
Department of Immunology,
Tufts University School of Medicine,
136 Harrison Avenue, Suite 304,
Boston, MA 02111, USA
Tel.: +1 617 636 6866 - Fax: +1 617 636 2456
e-mail: theoharis.theoharides@tufts.edu

0393-974X (2019)

Table I. *Factors adversely influencing neurodevelopment.*

- Electromagnetic waves
- Heavy metals
  - ✓ Aluminum
  - ✓ Arsenate
  - ✓ Lead
  - ✓ Mercury
- Herbicides
  - ✓ Atrazine
  - ✓ Glyphosate
- Inflammatory cytokines
  - ✓ IL-6, IL-31, IL-33, TNF
- Mitochondrial DNA
- Mycotoxins
  - ✓ Ochratoxin A
- Neuroendocrine disruptors
  - ✓ Polyphenols
  - ✓ Xenoestrogens
  - ✓ Bipsphenol A
  - ✓ Polyvinyl chloride
- Neuropeptides
  - ✓ Neurotensin
  - ✓ Substance P
- Neurotransmitters
  - ✓ Aspartate
  - ✓ Glutamate
  - ✓ Histamine
- Pathogens
  - ✓ Babesia
  - ✓ Bartonella
  - ✓ Borrelia
  - ✓ CMV
  - ✓ EBV
  - ✓ Fungi
- Reactive Oxygen Species
- Toxins
- Venoms
- Xenobiotics

Table II. *Conditions adversely affecting neurodevelopment.*

- Abuse
- Allergies
- Anoxia
- Anxiety disorder
- Asthma
- Attention deficit hyperactivity disorder
- Atopic dermatitis (eczema)
- Avitaminosis
- Chronic inflammatory response syndrome
- Cyclic vomiting syndrome
- Food intolerance
- Hyperthermia
- Hypothyroidism
- Idiopathic urticaria
- Maternal deprivation
- Mastocytosis
- Mast cell activation syndrome
- Multiple chemical sensitivity syndrome
- Neglect
- Non-IgE food allergy
- Nutrition (poor)
- Pediatric acute neuropsychiatric syndrome
- Rhinosinusitis

and neurotensin (NT) are increased in the serum of patients with ASD (21, 22), and can activate human microglia to secrete the pro-inflammatory cytokine IL-1β and chemokine CXCL8 IL-8 (22). These molecules may be produced inside the brain or enter the brain through a disrupted blood-brain barrier (BBB), documented in psychiatric disorders (23) and in ASD (24), due to molecules such as histamine released from brain mast cells (25). Mast cells can stimulate microglia (26) via histamine (27), leading to secretion of pro-inflammatory mediators.

Histamine is secreted from activated mast cells in atopic diseases and mastocytosis (28), but is also found in many foods such as cheese, fermented milk and alcoholic products, nectarines, ripe fruits, sardines, sauerkraut, spinach, spices and tuna. Levels of histamine can build up in patients who have reduced activity of the histamine degrading enzyme diamine oxidase (DAO). Both the activity and the gene expression of DAO can be tested, and DAO can be administered as a dietary supplement that would reduce histamine levels in the intestine. This

approach is complimentary to giving antihistamines, preferably rupatadine (not available in the US, but can be compounded) because it can also inhibit mast cell and eosinophil activation (29) since these cell types are stimulated especially in children exposed to mold (30). However, it should be noted that high doses of antihistamines could interfere with learning and motivation (31).

Natural flavonoids are increasingly discussed as therapeutic agents for neurodegenerative disorders (32, 33). Especially, luteolin (5,7,3´,4´-tetrahydroxyflavone) has potent anti-oxidant, anti-inflammatory (34, 35), anti-allergic (36), and neuroprotective (34) actions including significant improvement of children with ASD (37, 38). The purest (>87%) luteolin, with the greatest oral absorption due to its liposomal formulation in olive kernel extact, is found in the dietary supplements BrainGain®, NeuroProtek®, and Purelut®; a new product will combine luteolin with Ashwagandha, which has anti-anxiety properties (39). We recently showed that the structurally-related methoxyluteolin (5,7,3´,4´-tetramethoxyflavone) is more potent than luteolin (22, 40) and has even better oral absorption (41) but to date has beem formulated only in the anti-inflammatory skin lotion GentleDerm® (42).

Addressing offending conditions and/or minimizing the detrimental effects of suspect molecules as early as possible is of great importance in improving neurodevelopment, cognition and learning in children.

DISCLOSURE**:** TCT is the inventor of US patents No. 7,906,153; No. 8,268,365 and No. 9,050,275 for the treatment of neuroinflammatory conditions.

REFERENCES

1. Leigh JP, Du J. Brief report: forecasting the economic burden of autism in 2015 and 2025 in the United States. J Autism Dev Disord 2015; 12:4135-39.
2. Centers for Disease Control and Prevention. CDC estimates 1 in 59 children has been identified with autism spectrum disorder. 4-30-2018. https://www.cdc.gov/features/new-autism-data/index.html.
3. Theoharides TC, Tsilioni I, Patel AB, Doyle R. Atopic diseases and inflammation of the brain in the pathogenesis of autism spectrum disorders. Transl Psychiatry 2016; 6(6):e844.
4. Lyall K, Van de WJ, Ashwood P, Hertz-Picciotto I. Asthma and allergies in children with autism spectrum disorders: results from the CHARGE Study. Autism Res 2015; 8(5):567-74.
5. Liao TC, Lien YT, Wang S, Huang SL, Chen CY. Comorbidity of atopic disorders with autism spectrum disorder and attention deficit/hyperactivity disorder. J Pediatr 2016; 171:248-55.
6. Kotey S, Ertel K, Whitcomb B. Co-occurrence of autism and asthma in a nationally-representative sample of children in the United States. J Autism Dev Disord 2014; 44(12):3083-88.
7. Billeci L, Tonacci A, Tartarisco G, Ruta L, Pioggia G, Gangemi S. Association between atopic dermatitis and autism spectrum disorders: a systematic review. Am J Clin Dermatol 2015; 16(5):371-88.
8. Angelidou A, Asadi S, Alysandratos KD, Karagkouni A, Kourembanas S, Theoharides TC. Perinatal stress, brain inflammation and risk of autism-Review and proposal. BMC Pediatr 2012; 12(1):89.
9. Theoharides TC, Kavalioti M. Effect of stress on learning and motivation-relevance to autism spectrum disorder. Int J Immunopath Pharmacol 2019; 33:2058738419856760
10. Beversdorf DQ, Manning SE, Hillier A, et al. Timing of prenatal stressors and autism. J Autism Dev Disord 2005; 35(4):471-78.
11. Ronald A, Pennell CE, Whitehouse AJ. Prenatal maternal stress associated with ADHD and autistic traits in early childhood. Front Psychol 2010; 1:223.
12. Rodgers J, Glod M, Connolly B, McConachie H. The relationship between anxiety and repetitive behaviours in autism spectrum disorder. J Autism Dev Disord 2012; 42(11):2404-9.
13. van Steensel FJ, Bogels SM, Perrin S. Anxiety disorders in children and adolescents with autistic spectrum disorders: a meta-analysis. Clin Child Fam Psychol Rev 2011; 14(3):302-17.
14. Ratnaseelan AM, Tsilioni I, Theoharides TC. Effects of mycotoxins on neuropsychiatric symptoms and immune processes. Clin Ther 2018; 40(6):903-17.
15. Rossignol DA, Frye RE. Evidence linking oxidative stress, mitochondrial dysfunction, and inflammation

in the brain of individuals with autism. Front Physiol 2014; 5:150.
16. Hagberg H, Gressens P, Mallard C. Inflammation during fetal and neonatal life: implications for neurologic and neuropsychiatric disease in children and adults. Ann Neurol 2012; 71(4):444-57.
17. Gupta S, Ellis SE, Ashar FN et al. Transcriptome analysis reveals dysregulation of innate immune response genes and neuronal activity-dependent genes in autism. Nat Commun 2014; 5:5748.
18. Koyama R, Ikegaya Y. Microglia in the pathogenesis of autism spectrum disorders. Neurosci Res 2015; 100:1-5.
19. Jones KA, Thomsen C. The role of the innate immune system in psychiatric disorders. Mol Cell Neurosci 2013; 53:52-62.
20. Chavarria A, Alcocer-Varela J. Is damage in central nervous system due to inflammation? Autoimmun Rev 2004; 3:251-260.
21. Tsilioni I, Dodman N, Petra AI et al. Elevated serum neurotensin and CRH levels in children with autistic spectrum disorders and tail-chasing bull terriers with a phenotype similar to autism. Transl Psychiatry 2014; 4:e466.
22. Patel AB, Tsilioni I, Leeman SE, Theoharides TC. Neurotensin stimulates sortilin and mTOR in human microglia inhibitable by methoxyluteolin, a potential therapeutic target for autism. Proc Natl Acad Sci U S A 2016; 113:E7049-E7058.
23. Kealy J, Greene C, Campbell M. Blood-brain barrier regulation in psychiatric disorders. Neurosci Lett 2018;133664.
24. Fiorentino M, Sapone A, Senger S, et al. Blood-brain barrier and intestinal epithelial barrier alterations in autism spectrum disorders. Mol Autism 2016; 7:49.
25. Esposito P, Chandler N, Kandere-Grzybowska K, et al. Corticotropin-releasing hormone (CRH) and brain mast cells regulate blood-brain-barrier permeability induced by acute stress. J Pharmacol Exp Ther 2002; 303:1061-66.
26. Skaper SD, Giusti P, Facci L. Microglia and mast cells: two tracks on the road to neuroinflammation. FASEB J 2012; 26(8):3103-17.
27. Zhang X, Wang Y, Dong H, Xu Y, Zhang S. Induction of microglial activation by mediators released from mast cells. Cell Physiol Biochem 2016; 38(4):1520-31.
28. Theoharides TC, Tsilioni I, Ren H. Recent advances in our understanding of mast cell activation - or should it be mast cell mediator disorders? Expert Rev Clin Immunol 2019; 15(6):639-56.
29. Vasiadi M, Kalogeromitros K, Kempuraj D, et al. Rupatadine inhibits pro-inflammatory mediator secretion from human mast cells triggered by different stimuli. Int Arch Allergy Immunol 2010; 151(1):38-45.
30. Theoharides TC. Mold and immunity. Clin Ther 2018; 40(6):882-84.
31. Theoharides TC, Stewart JM. Antihistamines and mental status. J Clin Psychopharmacol 2016; 36(3):195-97.
32. Jones QR, Warford J, Rupasinghe HP, Robertson GS. Target-based selection of flavonoids for neurodegenerative disorders. Trends Pharmacol Sci 2012; 33(11):602-610.
33. Theoharides TC, Stewart JM, Hatziagelaki E, Kolaitis G. Brain "fog," inflammation and obesity: key aspects of neuropsychiatric disorders improved by luteolin. Front Neurosci 2015; 9:225.
34. Nabavi SF, Braidy N, Gortzi O, et al. Luteolin as an anti-inflammatory and neuroprotective agent: A brief review. Brain Res Bull 2015; 119(Pt A):1-11.
35. Jang S, Kelley KW, Johnson RW. Luteolin reduces IL-6 production in microglia by inhibiting JNK phosphorylation and activation of AP-1. Proc Natl Acad Sci USA 2008; 105(21):7534-39.
36. Weng Z, Patel AB, Panagiotidou S, Theoharides TC. The novel flavone tetramethoxyluteolin is a potent inhibitor of human mast cells. J Allergy Clin Immunol 2015; 135(4):1044-52.
37. Taliou A, Zintzaras E, Lykouras L, Francis K. An open-label pilot study of a formulation containing the anti-inflammatory flavonoid luteolin and its effects on behavior in children with autism spectrum disorders. Clin Ther 2013; 35(5):592-602.
38. Tsilioni I, Taliou A, Francis K, Theoharides TC. Children with autism spectrum disorders, who improved with a luteolin containing dietary formulation, show reduced serum levels of TNF and IL-6. Transl Psychiatry 2015; 5:e647.
39. Theoharides TC, Kavalioti M. Stress, inflammation and natural treatments. J Biol Regul Homeost Agents 2018; 32(6):1345-47.
40. Patel AB, Theoharides TC. Methoxyluteolin Inhibits neuropeptide-stimulated proinflammatory mediator

release via mTOR activation from human mast cells. J Pharmacol Exp Ther 2017; 361(3):462-71.
41. Walle T. Methylation of dietary flavones greatly improves their hepatic metabolic stability and intestinal absorption. Mol Pharm 2007; 4(6):826-32.
42. Theoharides TC. Tolerability and benefit of a tetramethoxyluteolin-containing skin lotion. Int J Immunopath Pharmacol 2017; 30(2):146-51.