Decreased Mitochondrial Function and Increased Brain Inflammation in Bipolar Disorder and Other Neuropsychiatric Diseases

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A recent review article by Konradi and coworkers[1] summarized the results of gene expression studies based on analysis of the entire mRNA pool (transcriptome) of brains from patients with bipolar disorder. The transcriptome differs from the genome because it can be shaped by environmental influences. The authors concluded that clusters of genes (*a*) for energy production were down-regulated, (*b*) for immune responses were up-regulated, and (*c*) for oligodendrocyte function were mostly down-regulated (Fig. 1). They compared these general outcomes with similar available data from other authors for major depressive disorder and schizophrenia and concluded that there was significant overlap, making it impossible to identify a specific profile unique for bipolar disorder.

Konradi and coworkers reviewed 7 published studies between 2003 and 2009 using brain material and 4 studies using peripheral tissue from patients with bipolar disorder. These studies did not all examine the same clusters. Only 3 of the 7 studies using brain tissue investigated "markers of energy function"; of these, 2 reported significant decrease, whereas 1 study reported an increase. Only 3 of the 7 studies using brain tissue investigated expression of genes associated with immune response, and all 3 reported significant increase. Only 1 study investigated the expression of oligodendrocyte markers and found decreased expression of some but increased level of others.

Four studies using peripheral tissues were reviewed; of these, 2 studies showed decreased expression of genes regulating energy production, and only 1 study investigated genes associated with immune responses and reported significantly increased expression. No particular gene was singled out for discussion. However, the authors proposed that the transcriptome changes observed may be the early stage of an autoimmune process that is more dramatic, but similar to changes in the neuroinflammatory disease multiple sclerosis (MS).

The authors correctly discussed a number of limitations in the articles reviewed. These included the postmortem nature of the tissues that could have introduced changes related to cell death, the difference in time period between death and tissue preservation, difference in the cause of death, the possible effect of any other comorbid conditions and/or treatment, lack of information on use of tobacco or recreational drugs, and the lack of "controls." In addition, the mean age of most patients was 48 ± 30 years, which introduces a possible contribution of advanced age. Finally, the number of patients whose brains were analyzed varied considerably from 8 to 35.

The role of inflammation, especially proinflammatory cytokines, in neuropsychiatric diseases was long suspected,[2,3] but these recent results certainly provide new robust evidence. The findings about decreased energy production may be quite significant. For instance, recent publications reported decreased mitochondrial function in as many as 60% of patients with autism,[4–6] a neuropsychiatric developmental disorder showing many similarities with schizophrenia.[7] In addition, the brains of autistic patients had evidence of neuroinflammation.[8–11]

We recently showed that serum of autistic patients has high levels of mitochondrial DNA[12] known to stimulate autoinflammatory reactions.[13] Neurotensin, a peptide first isolated from the brain, has also been implicated in the pathogenesis of depression and schizophrenia,[14] is elevated in the serum of autistic children, and can stimulate mast cells.[15] Mast cells are involved in inflammation[16] and were recently reported to undergo mitochondrial fission and translocation during degranulation to the cell surface[17] with subsequent release of ATP and mitochondrial DNA.[18] ATP is considered by some a universal "alarm" signal from cells under stress, can affect neighboring cells,[19] and can sustain

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ISSN: 0271-0749
DOI: 10.1097/JCP.0b013e318239c190

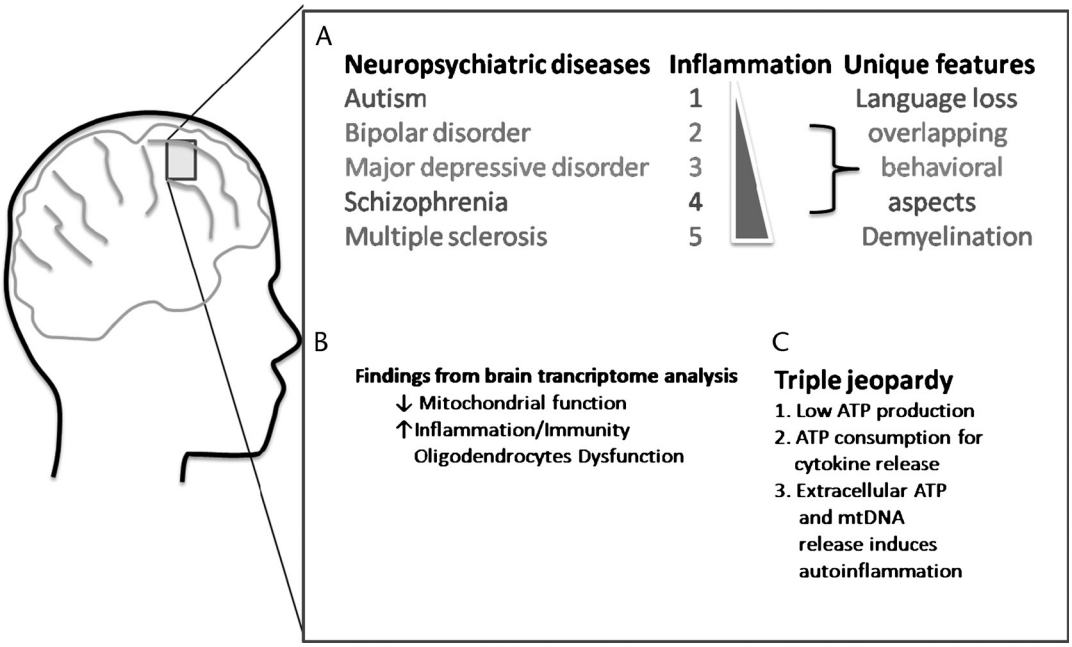

FIGURE 1. Diagrammatic representation of (A) the possible association between the recent transcriptome findings and neuropsychiatric diseases; (B) transcriptome changes consistent with down-regulation of genes involved in mitochondrial function and ATP production, up-regulation of genes involved in inflammation and immunity, and dysfunction of genes involved in oligodendrocyte activities; and (C) proposed ''triple jeopardy'' due to (1) low ATP production, (2) shift of part of the ATP to support synthesis and release of proinflammatory cytokines, and (3) part is extracellular ATP release leading to autoinflammation.

inflammation through mast cell activation.[20] In fact, mitochondrial DNA was shown to be secreted from neuroblastoma cells inside membrane-enclosed exosomes.[21] All these findings, taken together, may constitute a "triple jeopardy" for the brain: (*a*) decreased mitochondrial ATP production, (*b*) further reduction by diversion of ATP to support proinflammatory, and (*c*) extracellular ATP and mitochondrial DNA release, which can stimulate autoimmune/autoinflammatory reactions.

These results point to the need for new treatment approaches addressing neuroinflammation. A number of articles have reported that certain nonsteroidal anti-inflammatory drugs, such as celecoxib, may be useful in bipolar disorders[22] and depression.[23] However, it should be noted that recent evidence indicated that nonsteroidal anti-inflammatory drugs could actually decrease the effectiveness of selective serotonin reuptake inhibitors.[24] Another option may be to select natural flavonoids[25] such as those found in artichoke, chamomile, and chrysanthemum.[26] For instance, the flavone luteolin has potent antioxidant, free radical scavenger, anti-inflammatory, and mast cell inhibitory activity.[27] In addition, luteolin inhibits microglia interleukin 6 release,[28,29] as well as mimics the activity of brain-derived neurotrophic factor.[30] Luteolin also inhibits autistic-like behavior in mice[14] and has antidepressant effects.[31] We had previously reported that luteolin also blocks mast cell–dependent stimulation of activated T cells,[32] as well as activated peripheral blood mononuclear cells from patients with MS.[33] These findings led to the proposal that luteolin may be a novel treatment of MS.[34]

In conclusion, there is no doubt that the available evidence indicates brain mitochondrial dysfunction and heightened immune response in neuropsychiatric diseases. However, it is still hard to understand how in certain cases these changes affect mostly the behavior, whereas in others they lead to loss of speech (autism) or demyelination and mostly neurological problems (MS). Nevertheless, new anti-inflammatory molecules may be useful for the treatment of neuroinflammation in neuropsychiatric disorders, especially if administered in formulations that permit sufficient oral absorption and brain uptake.

AUTHOR DISCLOSURE INFORMATION

Dr Theoharides is the inventor of US patent no. 7,906,153 for the treatment of multiple sclerosis, and US patent application no. 11/214,831 for the treatment of brain inflammatory disorders, as well as the dietary supplement Brain Gain (US registration no. 3,518,791). Drs Zhang and Conti have no conflicts of interest to report.

REFERENCES

1. Konradi C, Sillivan SE, Clay HB. Mitochondria, oligodendrocytes and inflammation in bipolar disorder: evidence from transcriptome studies points to intriguing parallels with multiple sclerosis [published online ahead of print]. *Neurobiol Dis*. 2011.
2. Theoharides TC, Weinkauf C, Conti P. Brain cytokines and neuropsychiatric disorders. *J Clin Psychopharmacol*. 2004;24:577–581.
3. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biol Psychiatry*. 2009;65:732–741.
4. Giulivi C, Zhang YF, Omanska-Klusek A, et al. Mitochondrial dysfunction in autism. *JAMA*. 2010;304:2389–2396.
5. Palmieri L, Persico AM. Mitochondrial dysfunction in autism spectrum disorders: cause or effect? *Biochim Biophys Acta*. 2010;1797:1130–1137.
6. Frye RE, Rossignol DA. Mitochondrial dysfunction can connect the diverse medical symptoms associated with autism spectrum disorders. *Pediatr Res*. 2011;69:41R–47R.

7. Volkmar FR, Cohen DJ. Comorbid association of autism and schizophrenia. *Am J Psychiatry.* 1991;148:1705–1707.
8. Enstrom AM, Van de Water JA, Ashwood P. Autoimmunity in autism. *Curr Opin Investig Drugs*. 2009;10:463–473.
9. Theoharides TC, Kempuraj D, Redwood L. Autism: an emerging 'neuroimmune disorder' in search of therapy. *Exp Opin Pharmacother.* 2009;10:2127–2143.
10. Goines P, Van de WJ. The immune system's role in the biology of autism. *Curr Opin Neurol*. 2010;23:111–117.
11. Wills S, Cabanlit M, Bennett J, et al. Detection of autoantibodies to neural cells of the cerebellum in the plasma of subjects with autism spectrum disorders. *Brain Behav Immun*. 2009;23:64–74.
12. Zhang B, Angelidou A, Alysandratos KD, et al. Mitochondrial DNA and anti-mitochondrial antibodies in serum of autistic children. *J Neuroinflammation*. 2010;7:80.
13. Zhang Q, Raoof M, Chen Y, et al. Circulating mitochondrial DAMPs cause inflammatory responses to injury. *Nature*. 2010;464:104–107.
14. Parker-Athill E, Luo D, Bailey A, et al. Flavonoids, a prenatal prophylaxis via targeting JAK2/STAT3 signaling to oppose IL-6/MIA associated autism. *J Neuroimmunol*. 2009;217:20–27.
15. Angelidou A, Francis K, Vasiadi M, et al. Neurotensin is increased in serum of young children with autistic disorder. *J Neuroinflammation*. 2010;7:48.
16. Theoharides TC, Alysandratos KD, Angelidou A, et al. Mast cells and inflammation [published online ahead of print]. *Biochim Biophys Acta*. 2010.
17. Zhang B, Alysandratos KD, Angelidou A, et al. Human mast cell degranulation and preformed TNF secretion require mitochondrial translocation to exocytosis sites: relevance to atopic dermatitis. *J Allergy Clin Immunol*. 2011;127(6):1522.e8–1531.e8.
18. Zhang B, Alysandratos KD, Angelidou A, et al. TNF secretion from human mast cells is regulated by mitochondrial dynamics and mitochondrial uncoupling protein 2 (UCP2). *J Immunol*. 2010;184:11.
19. Corriden R, Insel PA. Basal release of ATP: an autocrine-paracrine mechanism for cell regulation. *Sci Signal*. 2010;3(104):re1.
20. von zur MF, Eckstein F, Penner R. Guanosine 5′-[beta-thio]triphosphate selectively activates calcium signaling in mast cells. *Proc Natl Acad Sci U S A*. 1991;88:926–930.
21. Guescini M, Genedani S, Stocchi V, et al. Astrocytes and glioblastoma cells release exosomes carrying mtDNA. *J Neural Transm*. 2010;117:1–4.
22. Nery FG, Monkul ES, Hatch JP, et al. Celecoxib as an adjunct in the treatment of depressive or mixed episodes of bipolar disorder: a double-blind, randomized, placebo-controlled study. *Hum Psychopharmacol*. 2008;23:87–94.
23. Davis A, Gilhooley M, Agius M. Using non-steroidal anti-inflammatory drugs in the treatment of depression. *Psychiatr Danub.* 2010;22(suppl 1):S49–S52.
24. Theoharides TC, Asadi S, Weng Z, et al. Serotonin-selective reuptake inhibitors and nonsteroidal anti-inflammatory drugs—important considerations of adverse interactions especially for the treatment of myalgic encephalomyelitis/chronic fatigue syndrome. *J Clin Psychopharmacol*. 2011;31:403–405.
25. Middleton E Jr, Kandaswami C, Theoharides TC. The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease, and cancer. *Pharmacol Rev.* 2000;52(4):673–751.
26. Harnly JM, Doherty RF, Beecher GR, et al. Flavonoid content of U.S. fruits, vegetables, and nuts. *J Agric Food Chem*. 2006;54:9966–9977.
27. Kimata M, Shichijo M, Miura T, et al. Effects of luteolin, quercetin and baicalein on immunoglobulin E-mediated mediator release from human cultured mast cells. *Clin Exp Allergy.* 2000;30:501–508.
28. 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 U S A*. 2008;105:7534–7539.
29. Meyer U, Feldon J, Dammann O. Schizophrenia and autism: both shared and disorder-specific pathogenesis via perinatal inflammation? *Pediatr Res*. 2011;69:26R–33R.
30. Jang SW, Liu X, Yepes M, et al. A selective TrkB agonist with potent neurotrophic activities by 7,8-dihydroxyflavone. *Proc Natl Acad Sci U S A*. 2010;107:2687–2692.
31. Ishisaka M, Kakefuda K, Yamauchi M, et al. Luteolin shows an antidepressant-like effect via suppressing endoplasmic reticulum stress. *Biol Pharm Bull*. 2011;34:1481–1486.
32. Kempuraj D, Tagen M, Iliopoulou BP, et al. Luteolin inhibits myelin basic protein-induced human mast cell activation and mast cell dependent stimulation of Jurkat T cells. *Br J Pharmacol*. 2008;155:1076–1084.
33. Sternberg Z, Chadha K, Lieberman A, et al. Immunomodulatory responses of peripheral blood mononuclear cells from multiple sclerosis patients upon in vitro incubation with the flavonoid luteolin: additive effects of IFN-beta. *J Neuroinflammation*. 2009;6:28.
34. Theoharides TC. Luteolin as a therapeutic option for multiple sclerosis. *J Neuroinflammation*. 2009;6:29.