Ann. N.Y. Acad. Sci. ISSN 0077-8923

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Issue: Annals *Reports*
COMMENTARY

Biological plausibility of the gut–brain axis in autism

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Organic abnormalities with neuroinflammatory and psychiatric consequences involving abnormal kynurenine and purine metabolism, neurotransmitter and cytokine imbalances, and altered levels of nutrients and metabolites are noted in autism, and many of these abnormalities—specifically including increased intestinal permeability, microbial metabolites, and heightened serum levels of endotoxin—originate from the gut.

Keywords: gut–brain axis; autism; metabolites

In their recent review, Sherwin *et al.*[1] discuss, among many other issues, the relationship of the gut microbiome–brain axis with autism under a section subtitled "Microbiota-based therapies for the treatment of autism: hype or hope?" Sherwin *et al.*[1] largely discuss preclinical data, citing only the 2017 open-label study by Kang *et al.*[2] that used a sequence of oral vancomycin, omeprazole, polyethylene glycol laxative, and standardized human fecal microbiota transplant to produce clinical benefit in subjects with autism.

Readers will likely benefit from learning of additional relevant clinical studies, including the publication by Sandler *et al.*[3] showing the alleviation of autistic manifestations following treatment with oral vancomycin, as well as case reports showing positive impact of various antimicrobial therapies (metronidazole, ketoconazole, and amoxicillin) in patients with autism.[4,5] Autistic patients have been shown to have gut dysbiosis with yeast as well as *Clostridia* species,[6] the latter being a group of bacteria noted for their production of neurotoxic substances. International researchers have consistently demonstrated that autistic subjects have heighted production of 3-(3-hydroxyphenyl)-3-hydroxypropionic acid (HPHPA), an abnormal phenylalanine metabolite of *Clostridia* in the gastrointestinal tract.[7,8] HPHPA reportedly interferes with the conversion of dopamine to norepinephrine; reduction of HPHPA following antimicrobial therapy correlates with clinical improvement, thereby supporting biological plausibility of a clinically important microbiome–mind relationship.[9]

Also consistently reported by research groups is elevated fecal production of p-cresol in autistic subjects;[10–12] p-cresol can be produced by microbial degradation of tyrosine and—similarly to HPHPA—interferes with the conversion of dopamine to norepinephrine via covalent inactivation of dopamine beta-hydroxylase.[13,14] The fact that HPHPA and p-cresol are produced in the gastrointestinal tract and are measurable in urine provides evidence of their systemic absorption and distribution; in autism, gut dysfunction correlates with elevated urinary p-cresol, which correlates with behavioral abnormalities and autism severity.[15] Relatively elevated dopamine and reduced norepinephrine are consistent with monoamine models of psychopathology, and evidence supports a role of dopaminergic dysfunction in autism.[16] Furthermore, elevated dopamine is converted to aminochrome,[17] which promotes mitochondrial dysfunction and forms adducts that compromise neuronal structure and function, thereby further contributing to neuropsychopathology.[18]

Additional abnormalities with neuroinflammatory and psychiatric consequences involving abnormal kynurenine and purine metabolism,

doi: 10.1111/nyas.13516

cytokine imbalances, and altered levels of nutrients and metabolites are also noted in autism, and many of these abnormalities—specifically including increased intestinal permeability, microbial metabolites, and heightened serum levels of endotoxin—originate from the gut.[19,20] Autism, like nearly all noncommunicable diseases, shows the evidence of genetic risk and predisposition; however, human studies have not identified causal genetic variants for major neuroinflammatory characteristics in autism, thereby suggesting that these are secondary or reactive in nature.[21] Indeed, the biomedical literature is robust in its demonstration of the heterogeneity of the autistic phenotype and the potent contribution of epigenetic, (neuro)inflammatory, microbial, and toxicological factors.[22]

Competing interests

The author declares no competing interests.

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