OPEN ACCESS Freely available online

Journal of Clinical Trials

Commentary

Commentary on Treating Impulsivity with Probiotics in Adults (PROBIA): Study Protocol of a Multicenter, Double-blind, Randomized, Placebo-Controlled Trial

Gara Arteaga-Henríquez[1,2*], J Antoni Ramos-Quiroga[1,2,3,4]

[1]Department of Psychiatric Genetics Unit, Vall d'Hebron Research Institute (VHIR), Barcelona, Catalonia, Spain;[2]Department of Psychiatry, Hospital Universitari Vall d'Hebron, Barcelona, Catalonia, Spain;[3]Department of Network Research Centre on Mental Health (CIBERSAM), Barcelona, Catalonia, Spain;[4]Department of Psychiatry and Legal Medicine, Universitat Autònoma de Barcelona, Barcelona, Catalonia, Spain

STUDY DESCRIPTION

Should psychiatric symptoms start to be treated with bacteria? The manuscript on the first randomized placebo-controlled trial determining the effects of supplementation with synbiotics on reducing impulsive and compulsive behavior in a sample of patients diagnosed with attention deficit and hyperactivity disorder (ADHD) and/or borderline personality disorder (BDP) raises the question of a central implication of the brain-immune-gut axis on, at least, a subgroup of mental disorders. Furthermore, it points into the necessity of designing new evidence-based therapeutic approaches for the management of still difficult-to-treat symptoms as for example, impulsivity.

Although sparse, recent evidence has suggested an association between immune imbalances and several psychiatric disorders, such as ADHDT [1-3]. However, studies searching for immunological markers in subjects with ADHD have not provided conclusive findings, likely due to small sample sizes and a high heterogeneity among the biological markers searched for. An increasing number of studies have shown a strong association between immune/allergic disorders (e.g. psoriasis, type 1 diabetes, asthma, and inflammatory bowel disease) and the risk of developing ADHD [4-6]. Interestingly, all the above-mentioned disorders share a common immune background, i.e. an imbalance in the Th17/Treg axis [7,8]. T helper (Th)17 cells play a role in defense against bacteria, but also on autoimmunity and on allergic diseases [9-11], with an increase in these cells predisposing to autoimmunity or allergy [12,13]. On the contrary, T regulatory (Treg) cells maintain tolerance to self-antigens and prevent from autoimmune diseases. Importantly, increasing evidence suggests that not only microglia, but also T cell activity (and especially Th17 and Treg cells activity), might be needed for a proper brain development and function of important brain areas playing a role in mood, behavior and cognition, such as the hippocampus [14].

Recent reports have reported a regulatory action of the gut microbiota on the Th17/Treg axis by (among other factors), the production of serotonin, dopamine and/or noradrenaline precursors [15]. Thus, gut dysbiosis has not only been related to inflammatory conditions such as inflammatory bowel disease, but also, to neuropsychiatric conditions such as ADHD [16] Furthermore, recent studies have shown that, many agents used for the treatment of ADHD such as desipramine and/or bupropion [17,18]) might exert their action by correcting immune imbalances (such as Th17/Treg axis abnormalities). In addition, recent findings suggest immunomodulatory and anti-inflammatory properties of probiotics [19], possibly by selectively targeting Th 17 cell lineages [20].

To sum up, although evidence supports the implication of the brain-immune-gut axis in mental disorders, the studies conducted so far have not identified which factors may play a causal role. More studies addressing how the microbiota interacts with the immune system and the brain are urgently needed to address this issue with important diagnostic and therapeutic implications.

FUNDING

The project under which the study is being performed is sponsored by the European Commission and funded by the European Union's Horizon 2020 research and innovation program under grant agreement no. 728018. The sponsors and funders played no part in study design; collection, management, analysis, and interpretation of the data; writing of the report; or the decision to submit the report for publication.

REFERENCES

1. Misener VL, Schachar R, Ickowicz A, Malone M, Roberts W, Tannock R, et al. Replication test for association of the IL-1 receptor antagonist gene, IL1RN, with attention-deficit/hyperactivity disorder. Neuropsychobiology. 2004;50:231-234.

Correspondence to: Gara Arteaga-Henríquez, Department of Psychiatric Genetics Unit, Vall d'Hebron Research Institute (VHIR), Barcelona, Catalonia, Spain, E-mail: garteaga@vhebron.net

Received date: March 03, 2020; **Accepted date:** March 17, 2020; **Published date:** March 24, 2020

Citation: Arteaga-Henríquez G, Ramos-Quiroga JA (2020) Commentary on Treating Impulsivity with Probiotics in Adults (PROBIA): Study Protocol of a Multicenter, Double-blind, Randomized, Placebo-Controlled Trial. J Clin Trials 10:406. doi: 10.35248/2167-0870.20.10.406

2. Lasky-Su J, Neale BM, Franke B, Anney RJ, Zhou K, Maller JB, et al. Genome-wide association scan of quantitative traits for attention deficit hyperactivity disorder identifies novel associations and confirms candidate gene associations. Am J Med Genet B Neuropsychiatr Genet. 2008;147:1345-1354.
3. Oades RD, Myint AM, Dauvermann MR, Schimmelmann BG, Schwarz MJ. Attention-deficit hyperactivity disorder (ADHD) and glial integrity: An exploration of associations of cytokines and kynurenine metabolites with symptoms and attention. Behav Brain Funct. 2010;6:32.
4. Misener VL, Schachar R, Ickowicz A, Malone M, Roberts W, Tannock R, et al. Replication test for association of the IL-1 receptor antagonist gene, IL1RN, with attention-deficit/hyperactivity disorder. Neuropsychobiology. 2004;50:231-234.
5. Nielsen PR, Benros ME, Dalsgaard S. Associations Between Autoimmune Diseases and Attention-Deficit/Hyperactivity Disorder: A Nationwide Study. J Am Acad Child Adolesc Psychiatry. 2017;56:234-240.
6. Hegvik TA, Instanes JT, Haavik J, Klungsoyr K, Engeland A. Associations between attention-deficit/hyperactivity disorder and autoimmune diseases are modified by sex: A population-based cross-sectional study. Eur Child Adolesc Psychiatry. 2018;27:663-675.
7. Ryba-Stanislawowska M, Werner P, Brandt A, Mysliwiec M, Mysliwska J. Th9 and Th22 immune response in young patients with type 1 diabetes. Immunol Res. 2016;64:730-735.
8. Cosmi L, Liotta F, Maggi E, Romagnani S, Annunziato F. Th17 cells : New players in asthma pathogenesis. Allergy; 2011;66:989-998.
9. Oboki K, Ohno T, Saito H, Nakae S. Th17 and allergy. Allergol Int. 2008;57(2):121-134.
10. Meller S, Gerber PA, Kislat A, Hevezi P, Gobel T, Wiesner U, et al. Allergic sensitization to pegylated interferon-alpha results in drug eruptions. Allergy. 2015;70:775-873.
11. Patel DD, Kuchroo VK. Th17 Cell Pathway in Human Immunity: Lessons from Genetics and Therapeutic Interventions. Immunity. 2015;43:1040-1051.
12. Bettelli E, Korn T, Oukka M, Kuchroo VK. Induction and effector functions of T(H)17 cells. J Nature. 2008;453:1051-1057.
13. Angkasekwinai P, Park H, Wang YH, Wang YH, Chang SH, Corry DB, et al. Interleukin 25 promotes the initiation of proallergic type 2 responses. J Exp Med. 2007;204:1509-1517.
14. Niebling J, Rünker EA, Schallenberg S, Kretschmer K, Kempermann G. Myelin-specific T helper 17 cells promote adult hippocampal neurogenesis through indirect mechanisms. Res. 2014;3:169.
15. Dinan TG, Cryan JF. Gut instincts: microbiota as a key regulator of brain development, ageing and neurodegeneration. J Physiol. 2017;595:489–503.
16. Cenit MC, Nuevo IC, Codoñer-Franch P, Dinan TG, Sanz Y. Gut microbiota and attention deficit hyperactivity disorder: New perspectives for a challenging condition. Eur Child Adolesc Psychiatry. 2017:26:1081-1092.
17. Zhang Y, Zhen H, Yao W, Bian F, Mao X, Yang X, et al. Antidepressant drug, desipramine, alleviates allergic rhinitis by regulating Treg and Th17 cells. Int J Immunopathol Pharmacol. 2013;26:107-1015.
18. Jha MK, Minhajuddin A, Gadad BS, Greer TL, Mayes TL, Trivedi MH. Interleukin 17 selectively predicts better outcomes with bupropion-SSRI combination: Novel T cell biomarker for antidepressant medication selection. Brain Behav Immun. 2017;66:103-110.
19. Mardani F, Mahmoudi M, Esmaeli SA, Khorasani S, Tabasi N, Rastin M. In vivo study: Th1-Th17 reduction in pristane-induced systemic lupus erythematosus mice after treatment with tolerogenic Lactobacillus probiotics. J Cell Physiol. 2018;234:642–649.
20. Tanabe S. The effect of probiotics and gut microbiota on Th17 cells. Int Rev Immunol. 2013;32:511-525.