Abstract for HYPOXEU LIVE, DRESDEN - June 9-12, 2024

Short chain fatty acids as key mediators in counteracting hypoxia dependent stress in neuronal cells

Francesco Grasselli, Laura Bonfili, Anna Maria Eleuteri

University of Camerino, School of Biosciences and Veterinary Medicine – via Gentile III da Varano – 62032 Camerino (Italy)
francescom.grasselli@studenti.unicam.it

Over the last years interest in the gut-brain connection has constantly increased, resulting in a growing attention in the yet unclear molecular mechanisms which underlie the beneficial effects of probiotics supplementation on the host health.
In this context a bidirectional relationship between hypoxia inducible factor (HIF) and the gut microbial population has been discovered. The presence of hypoxia, through the activation of HIF, is able to affect the gut microbiota composition and, on the other hand, the microbial community has been proven to modulate both the effects and the levels of HIF in *in vitro* and *in vivo* experiments [1]. In an Alzheimer's disease (AD) mouse model the administration of a probiotic formulation (SLAB51®), which strategically shifted gut microbiota composition, was able to restore cerebral HIF levels, through the reduction of prolyl hydroxylase 2 (PHD2), an enzyme involved in HIF degradation [2]. Moreover, HIF levels increased in a dose-dependent manner in human intestinal cells treated with SLAB51® lysate [3]. These findings suggest that probiotics play a role in the organism response to hypoxia being direct inducers of HIF accumulation.
Given the ability of bacteria and their metabolites to induce hypoxia it is reasonable to think that ioactive molecules that are able to pass the intestinal barrier can exert their actions in different sites, modulating HIF and subsequent downstream pathways. Among the small bioactive molecules that can pass the intestinal barrier and enter the circulation we can find different bacterial metabolites. Some of them, at given concentrations have been proven to be beneficial, and in some cases even neuroprotective [4]. In this context, great importance is given to short-chain fatty acids (SCFAs), bacterial metabolites that are able to decrease inflammation, restore insulin sensitivity and protect neurons from a series of chemical injuries [4,5].
These findings led to the idea of investigating the effects of selected bacterial metabolites on human neuronal cells in the presence of a hypoxic stimulus. In our study the SH-SY5Y cell line was challenged with cobalt chloride ($CoCl_2$), a known hypoxia and HIF inducer[6]. 24 hours prior to the induction of hypoxia, cells were pre-treated with two metabolites: sodium butyrate and sodium acetate to evaluate the effects of these molecules on HIF levels and hypoxia affected pathways. The metabolites were administered both alone or in combination, at two concentrations, and butyrate resulted as the most effective in counteracting hypoxia-dependent stress, involving a decrease in inflammatory markers and an increase in sirtuin-1 levels.

REFERENCES

[1] Pral LP, Fachi JL, Corrêa RO, Colonna M, Vinolo MAR. Hypoxia and HIF-1 as key regulators of gut microbiota and host interactions. Trends Immunol 2021;42:604–21. https://doi.org/10.1016/j.it.2021.05.004.
[2] Bonfili L, Gong C, Lombardi F, Cifone MG, Eleuteri AM. Strategic Modification of Gut Microbiota through Oral Bacteriotherapy Influences Hypoxia Inducible Factor-1α: Therapeutic Implication in Alzheimer's Disease. Int J Mol Sci 2022;23:357. https://doi.org/10.3390/ijms23010357.
[3] Lombardi F, Augello FR, Palumbo P, Bonfili L, Artone S, Altamura S, et al. Bacterial Lysate from the Multi-Strain Probiotic SLAB51 Triggers Adaptative Responses to Hypoxia in Human Caco-2 Intestinal Epithelial Cells under Normoxic Conditions and Attenuates LPS-Induced Inflammatory Response. Int J Mol Sci 2023;24:8134. https://doi.org/10.3390/ijms24098134.

[4] Sharma S, Taliyan R, Singh S. Beneficial effects of sodium butyrate in 6-OHDA induced neurotoxicity and behavioral abnormalities: Modulation of histone deacetylase activity. Behav Brain Res 2015;291:306–14. https://doi.org/10.1016/j.bbr.2015.05.052.
[5] Tran SM-S, Mohajeri MH. The Role of Gut Bacterial Metabolites in Brain Development, Aging and Disease. Nutrients 2021;13:732. https://doi.org/10.3390/nu13030732.
[6] Muñoz-Sánchez J, Chánez-Cárdenas ME. The use of cobalt chloride as a chemical hypoxia model. J Appl Toxicol 2019;39:556–70. https://doi.org/10.1002/jat.3749.