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Entitled

MODULATION OF ANTI-MICROBIAL DEFENSES IN THE GASTROINTESTINAL TRACT BY ACETYLCHOLINESTERASE INHIBITORS

by

Alreem Abdulaziz Al-Dalali Al-Mansori

Faculty Advisor

Dr. Maria J. Fernandez-Cabezudo, Department of Biochemistry and Molecular Biology

College of Medicine and Health Sciences

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Abstract

Inflammation is a crucial defense mechanism that protects the body from the effect of invading pathogens. However, the inflammatory response needs to be controlled in order to avoid systemic manifestations with serious consequences to the host. Accumulating evidence indicates that the inflammatory response is tightly regulated through immunological and neural pathways. Previously, we demonstrated that cholinergic stimulation by paraoxon, a specific and irreversible inhibitor of acetylcholinesterase (AChE), improved survival in mice following an oral infection with virulent *Salmonella enterica* serovar Typhimurium (*S. typhimurium*). However, paraoxon is an organophosphorous compound unsuited for human use. In this study, we aimed to investigate the efficiency of rivastigmine, an FDA-approved inhibitor of AChE, on murine mucosal defenses in the gastrointestinal (GI) tract against *Salmonella* infections. We show that cholinergic stimulation with rivastigmine enhanced host survival following an oral-route infection, and this correlated with lower bacterial load in systemic organs, including liver and spleen. Interestingly, while bacterial loads in systemic organs were decreased, bacterial loads were higher in intestinal content and feces compared to saline control group, suggesting enhanced bacterial shedding in the GI tract. Morphological analysis of the small intestine (ileum) showed that rivastigmine induced the degranulation of goblet cells and Paneth cells, two specialized secretory cells involved in innate immunity, and demonstrated a significant increase in the thickness of mucin layer in these mice. Immunohistochemical study of the immune population present at the intestinal mucosa revealed that rivastigmine treatment resulted in minor changes in the lymphoid population in the epithelium (intraepithelial lymphocytes or IELs) and lamina propria (LP). A comparative flowcytometric analysis of the different leukocytic populations present in the two isolated compartments of the intestinal mucosa (IEL and LP) following either paraoxon or rivastigmine treatment, demonstrated that only paraoxon induced an increase in the $CD8^+$ population in the LP. Moreover, intestinal epithelium of rivastigmine-treated mice presented a decrease in $CD8^+gdTCR^+$ cells. These findings indicate that rivastigmine-mediated cholinergic modulation increases the innate defense mechanisms at the level of the intestinal lumen, delaying the bacterial translocation from intestine to LP and systemic organs, ultimately leading to enhanced initial protection against a lethal bacterial infection. However, complete protection in this model appears to require the recruitment of professional T cells to the LP, which was only observed after treatment with irreversible AChE inhibitors, like paraoxon. The data highlight the crucial interactions between neural and immune systems that act at the GI mucosal interface to protect the host against invading pathogens.

Keywords: acetylcholinesterase inhibition, *Salmonella*, neuro-immune, intestine, mucosal barrier, goblet cells, Paneth cells, intestinal epithelium, lamina propria.