Galantamine anti-colitic effect: Role of alpha-7 nicotinic acetylcholine receptor in modulating Jak/STAT3, NF-əB/HMGB1/RAGE and p-AKT/Bcl-2 pathways

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Abstract

Vagal stimulation controls systemic inflammation and modulates the immune response in different inflammatory conditions, including inflammatory bowel diseases (IBD). The released acetylcholine binds to alpha-7 nicotinic acetylcholine receptor (Ŭ7 nAChR) to suppress pro-inflammatory cytokines. This provides a new range of potential therapeutic approaches for controlling inflammatory responses. The present study aimed to assess whether galantamine (Galan) anti-inflammatory action involves Ŭ7 nAChR in a 2,4,6-trinitrobenzene sulfonic acid (TNBS) model of colitis and to estimate its possible molecular pathways. Rats were assigned into normal, TNBS, sulfasalazine (Sulfz), Galan treated (10ˌmg/kg), methyllycaconitine (MLA; 5.6ˌmg/kg), and MLAˌ+ˌGalan groups. Drugs were administered orally once per day (11 days) and colitis was induced on the 8th day. Galan reduced the TNBS-induced ulceration, colon mass index, colonic MDA, neutrophils adhesion and infiltration (ICAM-1/MPO), inflammatory mediators (NF-əB, TNF-Ŭ, HMGB1, and RAGE), while increased the anti-apoptotic pathway (p-Akt/Bcl-2). Mechanistic study revealed that Galan increased the anti-inflammatory cytokine IL-10, phosphorylated Jak2, while reduced the inflammation controller SOCS3. However, combining MLA with Galan abrogated the beneficial anti-inflammatory/anti-apoptotic signals. The results of the present study indicate that Galan anti-inflammatory/-apoptotic/ -oxidant effects originate from the stimulation of the peripheral Ŭ7 nAChR, with the involvement of the Jak2/SOCS3 signaling pathway

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