Dig Dis Sci (2015) 60:819–821
DOI 10.1007/s10620-015-3598-8

EDITORIAL

Association of Serotonin Transporter Promoter Polymorphism (5HTTLPR) with Microscopic Colitis and Ulcerative Colitis: Time to Be AsSERTive?

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Received: 12 February 2015 / Accepted: 17 February 2015 / Published online: 3 March 2015

Serotonin (5-hydroxytryptamine; 5-HT) is a bioamine neurotransmitter classically recognized for its importance in central nervous system (CNS) functions. Nevertheless, most of the body's serotonin is peripherally located, with over 95 % of the body's 5-HT produced in the intestine, where it modulates motility and secretion [1]. Intestinal 5-HT has also been demonstrated to play a major role in enteric nervous system development, intestinal epithelial homeostasis, and the modulation of intestinal inflammation [2–5]. Despite the recognition that intestinal inflammatory diseases such as ulcerative colitis (UC) can have strong genetic components [6], genetic polymorphisms linked with serotonin have not been associated with these disease states. In this issue of *Digestive Diseases and Sciences*, Sikander et al. [7] conducted the first prospective case–control study to demonstrate that there may be a potential association between polymorphisms in the 5-HT transporter (5-HTT) gene-linked polymorphic region (5-HTTLPR) of the serotonin transporter (SERT) gene promoter and the intestinal inflammatory diseases UC and microscopic colitis (MC).

In the intestine, 5-HT is produced by two different isoforms of the same biosynthetic enzyme, tryptophan hydroxylase (TPH). The vast majority (90 %) of 5-HT is produced by TPH1 in the enterochromaffin (EC) cells (and mast cells in rodents). The remainder is synthesized by TPH2 in enteric neurons [8]. TPH2 is also located in the neurons of the CNS. Under normal conditions, SERT terminates the action of released intestinal 5-HT via uptake into mucosal enterocytes and serotonergic neurons. The remaining 5-HT diffuses into the systemic circulation where it is taken up primarily by platelets which also contain SERT. Because 5-HT does not cross the blood–brain barrier, virtually all 5-HT present in blood is synthesized in the intestine [1, 9, 10]. Further, because platelets do not contain the synthetic machinery necessary to produce 5-HT (TPH), all platelet 5-HT is the result of SERT-mediated uptake. SERT is thus essential for intestinal and blood 5-HT homeostasis. The expression of SERT is regulated in part by a polymorphism in the 5-HTTLPR which has two predominant variant alleles: a short (S) allele and long (L) allele. The S allele is associated with reduced transcriptional efficiency and lower functional expression of SERT relative to the L allele [11]. It is therefore possible that intestinal and platelet 5-HT levels would be abnormal in individuals harboring an S allele.

Abnormal concentrations of 5-HT could affect an individual's predisposition to or severity of intestinal inflammatory disease. Human studies have revealed a potential role for mucosal 5-HT in intestinal inflammation. Increased enteric 5-HT concentrations are present in patients with Crohn's disease (CD), UC and MC [12–14]. This elevation is associated with significantly increased EC cell numbers and decreased SERT transcription in some studies [15, 16]. Studies have been conflicting, however, in UC where decreased amounts of mucosal 5-HT, TPH1 and SERT immunoreactivity and decreased EC cell numbers have also been observed [16].

Murine models have further supported the contribution of 5-HT toward intestinal inflammation. Mice that lack SERT, and thus have an increase in available intestinal 5-HT, develop more severe colitis when induced by trinitrobenzene sulfonic acid (TNBS) [17]. These mice also

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develop a more severe spontaneous colitis that arises as a result of interleukin (IL)-10 deletion [18]. Mice that do not produce intestinal mucosal 5-HT because they lack TPH1 are resistant to dinitrobenzene sulfonic acid-induced colitis [19]. Mice or guinea pigs with TNBS-induced colitis also demonstrate SERT downregulation and an increase in EC cell number and/or 5-HT release [9, 20–22].

Extensive research has elucidated part of the complex interrelationship between 5-HT and the immune system. SERT and/or 5-HT receptors are expressed on many cells involved in innate and adaptive immunity, including macrophages, mast cells, dendritic cells, basophils, neutrophils, eosinophils, natural killer cells, B cells and T cells [23]. The modulation of immune cells by 5-HT can have opposing effects; immune cell activation can trigger NF-kB and/or other proinflammatory signaling pathways, thereby stimulating production of proinflammatory mediators [24]. Conversely, activation of the 5-HT7 receptor, expressed on dendritic cells, helps ameliorate chemically induced colitis [25]. The immune system likewise exerts effects on 5-HT homeostasis. The proinflammatory mediators interferon-γ and tumor necrosis factor-α decrease SERT function in colonic adenocarcinoma Caco2 cells [26]. Moreover, IL-1β and lipopolysaccharide-induced 5-HT secretion is significantly increased in EC cells derived from patients with CD compared with a control population [24].

Post-infectious irritable bowel syndrome (IBS) may represent a low-grade inflammatory state and has been associated with increased peak postprandial 5-HT release and EC cell hyperplasia [27, 28]. In investigations of SERT polymorphisms in IBS, a meta-analysis of seven studies concluded that 5-HTTPLR genotypes are unrelated to IBS, while others reported evidence of an association when patients were stratified by predominant clinical symptoms [29]. The most recent meta-analysis of 25 such studies concluded that the L/L genotype of 5-HTTLPR is associated with an increased risk of developing constipation-predominant IBS (IBS-C) [30]. 5-HTTLPR genetic polymorphisms also may provide evidence for the efficacy of serotonin-based therapies for specific subtypes of IBS. In comparison with individuals with S/S or S/L genotypes, diarrhea-predominant IBS patients with the L/L genotype demonstrated a greater response to alosetron, a 5HT3 antagonist, while IBS-C patients with the L/L genotype had less of a response to the 5HT4 agonist tegaserod [31, 32].

Sikander et al. [7] conducted a prospective case–control study in which they sought to evaluate the association between the 5-HTTLPR promoter polymorphism and serum 5-HT concentrations in UC and MC. By evaluation of the 5-HTTLPR gene polymorphism in patients categorized as active UC, UC in remission, MC or in healthy controls, the authors found that the frequency of the S/S genotype was significantly lower in patients with MC or UC in remission, relative to healthy controls. They also determined that serum 5-HT levels, as measured by ELISA, were significantly higher in individuals with MC or UC when compared to the control population. More specifically, MC patients with the L/S or S/S genotype had significantly increased serum 5-HT concentrations compared with controls with similar genotypes. Similarly, active UC patients with the S/S genotype had increased serum 5-HT concentrations compared with S/S controls. Mean 5-HT concentrations were highest in individuals expressing the S/S genotype.

This is the first study to suggest that 5-HTTLPR polymorphisms may contribute to the pathogenesis of MC and UC and that these polymorphisms may correlate with serum 5-HT concentrations. Intestinal inflammation could be initiated by the increased amount of available enteric mucosal 5-HT due to a SERT polymorphism. Individuals in this study with the S/S genotype had the highest mean 5-HT levels. It is therefore interesting that individuals with intestinal inflammatory diseases (MC or UC in remission) exhibit the S/S genotype less frequently than controls. This observation is consistent with the hypothesis that 5-HTTLPR might represent only one of the contributing factors to disease severity.

This study describes a novel association between 5-HT, genetic susceptibility variants and intestinal inflammatory disease. Future studies in the field can span into multiple directions. It may be of interest to measure concentrations of free 5-HT in plasma of individuals with intestinal inflammatory diseases. Although only ≈ 0.1 % of 5-HT released can be measured as free 5-HT [33], this pool is accessible to sites of action and receptors that may be important for intestinal serotonergic functions. It would also be interesting to evaluate whether 5-HTTLPR polymorphisms are associated with changes in other important intestinal markers of serotonin homeostasis such as TPH1, 5-HT receptors and mucosal SERT expression as well as EC cell number. Further, the observation that >50 % of the controls in this study have the S/S genotype demonstrates that the development of MC and UC is not exclusively dependent on the presence of a 5-HTTPLR polymorphism. Future studies may focus on the evaluation of the relationship between 5-HTTLPR polymorphisms and epigenetic factors as well as rare variations in SERT that have been recently discovered [34]. The current study represents an important step toward understanding the complex genetic basis of intestinal inflammatory diseases.

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