GENETIC POLYMORPHISM OF SERT RECEPTORS

CRISTINA HOȚOLEANU, R. POPP, DAN L. DUMITRAȘCU

2nd Medical Department, University of Medicine and Pharmacy „Iuliu Haţieganu" Cluj-Napoca, Romania

Abstract

Irritable bowel syndrome (IBS) has a complex pathogenesis. It has been suspected that genetic factors may be involve in the presentation of the disease and on the response to therapy. Among suggested factors, polymorphisms in the promoter region of serotonin transporter (SERT) may play a role. This is a review of the available data on the polymorphism of the serotonin transporter. Data of an own pilot study is also presented, showing long allele association with IBS-C type (predominant constipation).

Keywords: irritable bowel syndrome, serotonin-receptor.

Irritable bowel syndrome (IBS) is a complex disorder with multiple pathogenetic mechanisms. Although no specific gene has been identified in association with IBS, polymorphisms in the promoter region of serotonin transporter (SERT) may play a role in IBS pathology.

Serotonin (5-HT) is a paracrine messenger used by enterochromaffin cells, which function as sensory transducers. It is involved in intestinal peristalsis and secretion. At the gastrointestinal level serotonin activates at least 5 types of receptors, influencing intestinal peristalsis, secretion and signaling in the brain-gut axis.

The removal from its sites of action is mediated by serotonin reuptake transporter (SERT or 5-HTT). An increased 5-HT release in the bowel may result in diarrhea, nausea, vomiting. 5-HT acting at 5-HT4 receptors increases the release of transmitters from their terminals and from other terminals in prokinetic reflex pathways. Signaling to the central nervous system and the activation of myenteric intrinsic primary afferent neurones is 5-HT3 mediated. In patients with IBS, stimulation of 5-HT type 3 receptors may lead to cramps, diarrhea, bowel contractions.

The practical consequence is the use of 5-HT3 antagonists and 5-HT4 agonists for gastrointestinal symptoms treatment. 5-HT3 antagonists decrease the intensity of several manifestations (nausea, vomiting) associated with chemotherapy and bowel discomfort in irritable bowel syndrome; 5-HT3 antagonists tend to produce constipation and this effect should be considered before prescription. In contrast, 5-HT4 agonists, such as tegaserod, are effective in the treatment of irritable bowel syndrome with constipation. They do not stimulate nociceptive extrinsic nerves nor initiate peristaltic and secretory reflexes. They enhance the release of transmitters in prokinetic pathways. When all the signalling by 5-HT is over, the action is ended by uptake into enterocytes or neurones, which is mediated by the serotonin reuptake transporter. In inflammatory states, serotonergic signalling is diminished at mucosa level.

A recent meta-analysis focused on the assessment of efficacy and tolerability of tegaserod in IBS and chronic constipation in adults and adolescents aged 12 years and above, using MEDLINE 1966-December 2006 and EMBASE 1980 to December 2006. The authors found a significant improvement of the gastrointestinal symptoms in C-IBS, during the last 4 weeks of treatment with both tegaserod 12 mg and 4 mg doses compared with placebo. The responder rate for this endpoint was also higher for the first 4 weeks of treatment with tegaserod 12 mg. Tegaserod significantly improves the bowel habit for both doses. Effects of tegaserod on bloating, stool consistency, and straining were not consistent across the studies. The authors concluded that tegaserod appears to improve the overall symptomatology of IBS, and the frequency of bowel movements in C-IBS. A study (published in 2010) shows the significant improvement of the quality of life and symptoms in C-IBS by using 6 mg. tegaserod daily. Another study (from 2008) shows the benefits of tegaserod in both C-IBS and mixed-IBS. Concluding all these results, tegaserod has been approved for treatment of irritable bowel syndrome (IBS) with constipation in women and for chronic constipation in men and women.

The 5-HT(3) antagonists, granisetron and ondansetron, are useful for nausea associated with cancer chemotherapy. Alosetron is used for the treatment of IBS with diarrhea; according to FDA- it should be used for cases refractory at other therapy. Other drugs include tricyclic antidepressants and serotonin selective reuptake inhibitors for IBS therapy.

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Adresa pentru corespondenţă: ddumitrascu@umfcluj.ro

Several studies showed association between SERT polymorphisms located in the promoter region (5-HTTLPR) and IBS; some authors found this association predominantly in women. Polymorphisms in the promoter region of the SERT gene affect its efficiency.

Although a matter of debate, recent studies show a strong significant association between SERT-P deletion genotype and diarrhea predominant IBS phenotype whereas the SERT-P insertion was not significantly associated with IBS. However, other studies identified a significant higher incidence of SERT-P insertion genotype in constipation predominant IBS type (C-IBS).

Current data show controversial results, depending upon the race and criteria used for IBS diagnosis.

Several Chinese studies show a lower response at tegaserod in C- IBS with insertion SERT-P genotype comparatively to deletion genotype.

The differences regarding the response at tegaserod in C-IBS patients may be explained by genetic factors, such as SERT-P polymorphisms: the insertion SERT-P genotype is associated with a poor response, as it was previously shown, as well as a low improvement regarding the stool frequency, stool consistency and sensation of bowel complete evacuation.

Other studies show the absence of the association between SERT-P polymorphisms and IBS- the authors found the same prevalence of these polymorphisms in both IBS and healthy subjects. However, they noticed the tendency to constipation of the patients with insertion SERT-P genotype.

Several authors investigated possible associations between these polymorphisms and several psychological traits in IBS, based upon the biopsychosocial model of IBS. Patients who were homozygous for the short allele of 5-HTTLPR (deletion genotype SERT-P) presented a significantly higher risk for depression. No association was found between genotype and anxiety, suicidal ideation or general psychological distress, according to this recent Italian study. In this study the authors concluded that *deletion genotype SERT-P* is significantly associated with an increased pain sensation and increased rectal compliance.

Therapeutic agents targeting altered 5-HT signaling may provide an effective alternative of the treatment for patients with IBS. The adjustment of the long term therapy should take into consideration the depression also, possible associated with a SERT genotype.

We performed a case control study to establish the associations of the functional polymorphism represented by insertion, respectively deletion of 44 base pairs in the 5- polymorphic region SERT (5-HTTLPR) with the IBS subtypes and main phychological traits.

We enrolled 2 groups, one with 20 patients with IBS (10 with constipation and 10 with diarrhea), and another one, with 16 sex- and aged- matched controls. The genetic analyses were made using PCR; depression and anxiety were assessed using BDI and STAI respectively.

We found a significant association of long allele genotype (resulting from insertion) with IBS with constipation: 6 cases versus 1 in control group and 2 in IBS with diarrhea. No significant association was found between 2 sexes.

No significant association was found between deletion genotype and IBS with diarrhea subtype (3 cases versus 2 in IBS with constipation and 2 in control group). Both groups of IBS showed similar scores for anxiety, depression.

We concluded that although a significant association between long allele genotype and IBS with constipation, no others associations were found between other subtype of IBS, respectively depression and anxiety.

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