

Antidepressants can treat inflammatory bowel disease through regulation of the nuclear factor- κ B/nitric oxide pathway and inhibition of cytokine production: A hypothesis

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treatment and attenuation of development of IBD in adjusted doses.

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Abstract

Inflammatory bowel disease (IBD) is a group of inflammatory disorders mainly affecting the colon and small intestine. The main types of IBD are Crohn's disease (CD) and ulcerative colitis (UC). UC is restricted to the large intestine whereas CD can affect any part of the gastrointestinal tract. Treating this disorder depends on the form and level of severity. Common treatment involves an anti-inflammatory drug, such as mesalazine, and an immunosuppressant, such as prednisone. Several signaling pathways, including nuclear factor (NF)- κ B and nitric oxide (NO), and genetic and environmental factors are believed to play an important role in IBD. Amitriptyline is a commonly used antidepressant with known anti-inflammatory activities. Amitriptyline also acts on the NF- κ B/NO pathway or cytokine production. Therefore, we hypothesize that antidepressants like amitriptyline can be pioneered and considered effective as an innovative and effective therapeutic in the

INTRODUCTION

While inflammatory bowel disease (IBD) is regarded as an idiopathic disease, it is believed to result from inappropriate and ongoing activation of the mucosal immune system driven by the presence of normal luminal flora^[1,2]. This abnormal response is presumably facilitated by defects in both the barrier function of the intestinal epithelium and the mucosal immune system^[1,2]. An unknown factor is also believed to trigger the immune system to produce an inflammatory reaction, leading to symptoms such as bloody diarrhea, abdominal cramps and anemia which jeopardize the patient's quality of life. Given the high number of individuals affected by IBD with respect to its demographic, socioeconomic,

occupational and geographical distribution and because of its discomfort, an unknown factor is also believed to trigger the immune system to produce an inflammatory reaction, leading to symptoms such as bloody diarrhea, abdominal cramps and anemia which jeopardize the patient's quality of life^[3,4]. Treatments include anti-inflammatory drugs, immune suppressors, antibiotics, pain relievers and surgery as a last line of treatment^[4].

One form of treatment considered over the years is the use of antidepressants in IBD^[5]. Further disorders treated by amitriptyline include diarrhea^[6] and fibromyalgia^[7], among others. Because of the ability of generating reactive oxygen species (ROS) and subsequent irreversible serious mitochondrial damage, as well as inhibiting antioxidants in tumor cells, amitriptyline can be used as a promising new drug to be tested for anti cancer therapy^[8]. This subject also suggests another beneficial effect of amitriptyline in the suppression/attenuation of risk of gastrointestinal cancers. Furthermore, anti-inflammatory properties of antidepressants, including imipramine, amitriptyline and clomipramine, have been investigated in studies^[9,10].

Repeated antidepressant administration has effects on production of pro-inflammatory cytokines, including interleukin (IL)-1 β , IL-10, IL-4 and tumor necrosis factor α (TNF- α)^[11,12]. The increased production of them in the intestinal mucosa is believed to be a significant factor in the pathophysiology of IBD and inflammatory diseases^[11,13]. A transcription factor is the other promotion factor which is regulated with nuclear factor (NF)- κ B. Furthermore, NF- κ B plays a key role in regulating the immune response and inflammatory cytokine production^[14]. It is quickly released from its cytoplasmic inhibitor (I κ B) and, following transmigration into the nucleus, binds to DNA response elements in gene promoter regions. It has been shown that there is increased activation of NF- κ B in lamina propria mononuclear cells from IBD patients which may be involved in the regulation of the inflammatory response^[14]. Therefore, inhibiting NF- κ B may represent one important mechanism by which antidepressant like amitriptyline like amitriptyline exert an anti-inflammatory effect in IBD.

HYPOTHESIS

Here, we hypothesize that the anti-inflammatory properties of amitriptyline can be explored in the treatment of IBD. Studies have pointed to the anti-inflammatory actions of antidepressants such as amitriptyline. Amitriptyline is used to treat symptoms of IBD but its use as an anti-inflammatory agent has not gained much consideration for the treatment of IBD. By acting on the NF- κ B pathway, amitriptyline may exert anti-inflammatory actions. Therefore, our hypothesis concludes that by determining a dose, much lower than that used in depression, amitriptyline can be used as an anti-inflammatory agent for the treatment of IBD.

CONCLUSION

Amitriptyline is an antidepressant drug which is widely used for the treatment of IBD and gastrointestinal disorders^[5,15]. It is effective for treating psychological and somatic symptoms in patients suffering from IBD^[15]. Furthermore, other studies have shown the anti-inflammatory effects of antidepressants by different mechanisms^[16,17]. Amitriptyline also acts on α_1 -adrenoceptors to produce anti-inflammatory effects^[16]. Due to its effects on the inhibitory cytokine IL-10, amitriptyline has been reported to suppress neuroinflammation^[18]. Furthermore, antidepressants have anti-inflammatory effects by considerably decreasing the production of nitric oxide (NO) and TNF- α in microglia and astrocyte cultures at mRNA levels^[17]. Furthermore, they can inhibit the degradation of I κ B, nuclear translocation of the p65 subunit of NF- κ B. Therefore, NF- κ B cannot translocate into the nucleus to bind with DNA to promote the expression of gene regions^[18]. Antidepressants also can inhibit the phosphorylation of p38 mitogen-activated protein kinase in the lipopolysaccharide-stimulated microglia cells^[17]. This phosphorylation can also induce the associated inflammatory gene expression to produce the proinflammatory cytokines and NO, which may be attenuated or inhibited by the antidepressants^[18]. NO can also induce ROS and therefore can increase the intestinal damage and, with the cytokine production, prolong the development of IBD. Based on these studies, the NF- κ B pathway has been considered to play an important role in the inflammatory process. Therefore, we hypothesize that antidepressant like amitriptyline, by modulating this pathway, may be more effective for treating and suppressing the development of IBD through its anti-inflammatory actions.

Anti-inflammatory drugs, such as sulfasalazine, mesalamine and corticosteroids, are currently being used as the first line of treatment in IBD. Amitriptyline is used in treating IBD for other reasons. It has been suggested that psychological co-morbidities with antidepressants can help manage IBD^[15]. Amitriptyline has side effects due to its anticholinergic activity, including weight gain, changes in appetite and muscle stiffness. Other side effects include seizures, mania and psychosis^[17]. These side effects, however, are very rare and the two main side effects of antidepressants are drowsiness and dry mouth^[18]. However, given the fact that a much lower dose will possibly be used to exert an anti-inflammatory action on IBD, these side effects may be very minimal. Therefore, by adjusting the dose to suit the anti-inflammatory effects of antidepressants on IBD, they can be used as an effective anti-inflammatory drugs for the treatment of IBD.

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