Editorial

Melatonin: A potent antioxidant agent with anti-inflammatory and anti-apoptotic effects that might be useful in the treatment of IBD patients

A. Triantafillidis[1], J.K. Triantafillidis[2]

INTRODUCTION

Inflammatory bowel disease [Crohn's disease and ulcerative colitis], is a chronic relapsing disorder of great significance for both society and patients as well. The exact pathogenesis of the disease is not fully understood, although interaction between immune factors, genetic suspectibility and the environment seem to be the most important ones.

Melatonin (5-methoxy-N-acetyltryptamine), a derivative of the essential amino acid tryptophan, is an indolamine hormone secreted throughout the day. This hormonal molecule is produced mainly in the pineal gland although various other tissues including the gastrointestinal tract are sites of production. Melatonin is an agent that promotes sleep produced mainly at night. It is secreted in the retina, salivary glands, thyroid, liver and intestine, thus playing a fundamental role in the neuroimmuno- endocrine system of the organism. In the intestine, locally synthesized melatonin is released by enterochromaffin cells in much larger amounts than in the pineal gland. Melatonin has a circadian entrainment and is excreted in the bile participating in the entero-hepatic circulation.

Mechanism of action

The mechanisms of the protective effects of melatonin have not been fully elucidated. Melatonin seems to participate in various defence mechanisms against colonic inflammatory processes because; it improves the gut blood flow, stimulates the immune system, preserves the important endogenous antioxidant reserve of GSH, prevents lysosomal enzyme disruption, reduces the levels of TNF-α, inhibits the enhanced myeloperoxidase activity, decreases the free radical levels, reduces the bacterial translocation levels and induces the apoptotic processes, thus reducing the extent of colonic damage.[1]

Key words: Melatonin, inflammatory bowel disease, ulcerative colitis, Crohn's disease, treatment

[1]Pharmacist, University of Athens, [2]Prof of Medicine, Saint Panteleimon General Hospital, Nicea, Greece

Author for correspondence:

Aikaterini Triantafillidis, Iera Odos 354, 12461, Haidari, Athens, Greece, e-mail: jkt@vodafone.net.gr

Stimulation of the immune system

Melatonin can protect gastrointestinal mucosa against damage by stimulating the immune system and fostering microcirculation and epithelial regeneration[2,3]. Although there is no direct evidence that the effect of melatonin on the immune response is enhanced in the gastrointestinal tract, indirect evidence indicates that administration of melatonin in rats significantly increases the number and size of Peyer's patches.

Decrease of free radical levels

A growing body of data indicates that oxygen-derived free radicals and nitrogen species could act as mediators of the disruption of the intestinal barrier in IBD. The involvement of melatonin in oxygen radical pathophysiology has been confirmed in various colitis models. Because reactive oxygen species seem to play a significant role in the pathogenesis of ulcerative colitis, melatonin may explain its protective effect because of its antioxidant effect. Melatonin also decreases free radical levels by stumilating the activities of enzymes involved in antioxidative defense.[4]

It has been shown in the TNBS model of experimental colitis that the extent of mucosal damage index and histology score, and the levels of myeloperoxidase malondi-

adehyde and nitric oxide were higher than in the control group and that melatonin ameliorated these parameters. The stimulation of lipopolysaccharide increases the level of nitric oxide and myeloperoxidase, malondiadehyde and melatonin reduces the level of malondiadehyde and nitric oxide. On the other hand, in the colonocyte oxidative injury model melatonin reverses the oxidative injury considerably. So, in the TNBS model of colitis, melatonin could control inflammation both *in vivo* and *in vitro*. The protective effect of melatonin in the acetic acid and TNBS model of colitis is probably mediated via local inhibition of iNOS and COX-2 expression in colonic mucosa.[5]

Reduction of Tumor Necrosis Factor-alpha (TNF-α) levels

TNF-α is a very important cytokine produced mainly by activated monocytes and macrophages. It has been shown experimentally that melatonin prevents circulatory failure in rats with endotoxemia by inhibiting the release of TNF-α[6]. Worledge *et al*[7] reported that administration of TNF-a antibodies can effectively treat experimental rat colitis. Triantafillidis et al[8] also showed that subcutaneous administration of infliximab (the chimeric antibody against TNF-α) can successfully ameliorate experimental colitis in rats.

Several data indicate that Matrix metalloproteinases play an important role in the pathogenesis of colitis. Melatonin reduced pro metalloproteinases-9 and metalloproteinases-2 activities that were induced in the colon of rats with experimental colitis. Reduced metalloproteinases-9 and metalloproteinases-2 activities were associated with reduced expression of TNF-alpha.[9] It seems that melatonin's ability to ameliorate DNBS-induced colitis in rats is related to a reduction in pro metalloproteinases-9 and metalloproteinases-2 activities and expression.

Reduction of bacterial translocation and induction of apoptosis

Melatonin could exert protective effects on colonic inflammation via reduction of bacterial translocation. Melatonin attenuates bacterial translocation and apoptosis as it could be supported by the lower serum levels of TNF-a and endotoxin, and the reduced colonic tissue oxidative stress and caspase levels in experimental models.

In colitis, the frequency of apoptosis is considerably increased and loss of epithelial cells appears to occur mainly due to apoptosis. In an experimental study of colitis in rats it was shown that colonic caspase-3 activity was significantly higher in the TNBS model compared to the control group and treatment with melatonin significantly decreased the caspase-3 activity. Again it was found that melatonin inhibits hepatic caspase-3 activities and attenuates DNA fragmentation in D-galactosamine-lipopolysaccharid-treated mice.[10] The available data indicate that the protective effects of melatonin against TNBS- induced colitis might be, at least in part, mediated by its anti-apoptotic effects.[11] Other data indicate that melatonin may exert therapeutic activity in IBD through its ability to inhibit NF-kappaB dependent induction of MAdCAM-1.[12]

However, in an experimental model of colitis it was shown that short-term administration of melatonin is protective while in the long term it negatively influences evolution of inflammatory colitis; therefore, the immunostimulatory effect of melatonin in some situations when given chronically, such as during inflammatory bowel disease could have negative consequences.[13]

Possible therapeutic application in human IBD

Melatonin certainly plays an important role in regulating epithelial functions as well as significant anti-inflammatory and anti-apoptotic effects. Melatonin reduces bacterial translocation and its anti-apoptotic effect and therefore it can reduce the extent of mucosal damage. It seems that melatonin could exert a beneficial role in human IBD through reduction of the TNF-a levels. However, further studies are required to clarify whether melatonin is an effective and above all safe therapy for human IBD.

REFERENCES

1. Nosálová V, Zeman M, Cerná S, Navarová J, Zakálová M. Protective effect of melatonin in acetic acid induced colitis in rats. J Pineal Res 2007;42:364-370.
2. Terry PD, Villinger F, Bubenik GA, Sitaraman SV. Melatonin and ulcerative colitis: Evidence, biological mechanisms, and future research. Inflamm Bowel Dis 2008 Jul 14. [Epub ahead of print]
3. Konturek SJ, Konturek PC, Brzozowska I, et al. Localization and biological activities of melatonin in intact and diseased gastrointestinal tract (GIT). J Physiol Pharmacol. 2007; 58:381-405.
4. Mei Q, Xu JM, Xiang L, Hu YM, Hu XP, Xu ZW. Change of nitric oxide in experimental colitis and its inhibition by melatonin in vivo and in vitro. Postgrad Med J 2005; 81:667-672.
5. Dong WG, Mei Q, Yu JP, Xu JM, Xiang L, Xu Y. Effects of melatonin on the expression of iNOS and COX-2 in rat models of colitis. World J Gastroenterol. 2003; 9:1307-1311.
6. Wu CC, Chiao CW, Hsiao G, Chen A, Yen MH. Melatonin prevents endotoxin-induced circulatory failure in rats. J Pineal Res 2001;30:147-156.
7. Worledge KL, Godiska R, Barrett TA, Kink JA. Oral administration of avian tumor necrosis factor antibodies effec-

tively treats experimental colitis in rats. Dig Dis Sci 2000; 45:2298-2305.
8. Triantafillidis JK, A. Papalois, A. Parassi, et al. Favorable response to subcutaneous administration of Infliximab in experimental colitis in rats. World J Gastroenterol 2005; 11:6843-6847.
9. Esposito E, Mazzon E, Riccardi L, Caminiti R, Meli R, Cuzzocrea S. Matrix metalloproteinase-9 and metalloproteinase-2 activity and expression is reduced by melatonin during experimental colitis. J Pineal Res 2008; 45:166-173.
10. Wang H, Xu DX, Lv JW, Ning H, Wei W. Melatonin attenuates lipopolysaccharide (LPS)-induced apoptotic liver damage in D-galactosamine-sensitized mice. Toxicology 2007; 237:49-57
11. Akcan A, Kucuk C, Sozuer E, Esel D, Akyildiz H, Akgun H, Muhtaroglu S, Aritas Y. Melatonin reduces bacterial translocation and apoptosis in trinitrobenzene sulphonic acid-induced colitis of rats. World J Gastroenterol 2008; 14:918-924.
12. Sasaki M, Jordan P, Joh T, Itoh M, Jenkins M, Pavlick K, Minagar A, Alexander SJ. Melatonin reduces TNF-a induced expression of MAdCAM-1 via inhibition of NF-kappaB. BMC Gastroenterol 2002; 2:9.
13. Marquez E, Sánchez-Fidalgo S, Calvo JR, la de Lastra CA, Motilva V. Acutely administered melatonin is beneficial while chronic melatonin treatment aggravates the evolution of TNBS-induced colitis. J Pineal Res 2006; 40:48-55.