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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (4): Irritable bowel syndrome

Melatonin for the treatment of irritable bowel syndrome

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Abstract

Irritable bowel syndrome (IBS) is a common disorder characterized by recurrent abdominal pain or discomfort, in combination with disturbed bowel habits in the absence of identifiable organic cause. Melatonin (N-acetyl-5-methoxytryptamine) is a hormone produced by the pineal gland and also large number by enterochromaffin cells of the digestive mucosa. Melatonin plays an important part in gastrointestinal physiology which includes regulation of gastrointestinal motility, local anti-inflammatory reaction as well as moderation of visceral sensation. Melatonin is commonly given orally. It is categorized by the United States Food and Drug Administration as a dietary supplement. Melatonin treatment has an extremely wide margin of safety though it may cause minor adverse effects, such as headache, rash and nightmares. Melatonin was touted as a potential effective candidate for IBS treatment. Putative role of melatonin in IBS treatment include analgesic effects, regulator of gastrointestinal motility and sensation to sleep promoter. Placebo-controlled studies in melatonin suffered from heterogeneity in methodology. Most studies utilized 3 mg at bedtime as the standard dose of trial. However, all studies had consistently showed improvement in abdominal pain, some showed improvement in quality of life of IBS patients. Melatonin is a relatively safe drug that possesses potential in treating IBS. Future studies should focus on melatonin effect on gut mobility as well as its central nervous system effect to elucidate its role in IBS patients.

Key words: Melatonin; Irritable bowel syndrome; Pain; Sleep; Analgesia

Core tip: Irritable bowel syndrome (IBS) is a common disorder associated with significant disability and high social cost. This is partly due to lack of effective treatment with low side effects. Melatonin is a drug that was postulated to be a potential useful arsenal in battling IBS. Its role in analgesia has been recognized in several other fields of medicine. Several well-designed placebo-controlled trials in IBS patients had consistently showed improvement of abdominal pain when taking 3 mg of melatonin with no serious side effect. Future studies should examine the long term effect of Melatonin as well as its effect on central nervous system and gut motility.

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INTRODUCTION

Irritable bowel syndrome (IBS) is a common disorder characterized by recurrent abdominal pain or discomfort, in combination with disturbed bowel habits in the absence of identifiable organic cause. It is associated with significant disability and health care costs. In the West,

the prevalence of IBS in the community is reported to be between 10%-20%[1-3]. In Asia, we have also seen a steady rise of IBS in the community. In Singapore, prevalence of IBS was reported to be 2.3%[4] in 1998, by the Manning criteria, and 8.6% in 2004 (as defined by the Rome Ⅱ criteria)[5]. In addition, a recent study has shown that the disease burden extends beyond the patient and has significant impact on the spouse or family members as well, with burden proportionally increasing with IBS severity[6], underscoring the need for effective treatment of the patient's symptoms.

Traditionally, IBS is treated with a combination of treatment modality, from antispasmodic, psychopharmacological treatment like tricyclic antidepressant to mindfulness therapy like hypnotherapy. Newer drugs such as linaclotide, prucalopride, tegaserod and lubiprostone[7] have given hope to clinicians treating the many disabling symptoms of IBS. However, worry about potential side effects, the need for long-term medication and high drug costs have been a deterrent for many IBS patients. Melatonin is one of the drug that was identified as potentially useful in IBS especially for pain symptom as well as bowel motility in constipation predominant IBS.

Melatonin (N-acetyl-5-methoxytryptamine), a hormone produced by the pineal gland, has been studied as a potential treatment of circadian rhythm sleep disorders, cancer, immune disorders, cardiovascular diseases and insomnia[8,9]. The melatonin signal chemically regulates the sleep-wake cycle by causing drowsiness and lowering body temperature[10]. The gastrointestinal tract is another large source of endogenous melatonin.

MELATONIN IN GASTROINTESTINAL TRACT

Melatonin is produced by enterochromaffin cells of the digestive mucosa. There is higher concentration of melatonin in the gastrointestinal tract than the blood or the pineal gland. The finding that the concentration of melatonin in the gastrointestinal tissues surpasses that in the blood by 10-100 times[11] suggests that melatonin may play an important role in the digestive system. Circadian variation of gastrointestinal (GI) melatonin does not appear to be controlled by photoperiodicity (like the pineal gland), but by eating and food composition. A sharp increase in the content of melatonin in GI tract tissue and circulation in response to food intake was reported in volunteers[12,13]. Melatonin played several pivotal local intestinal functions: (1) Regulation of GI motility: Melatonin exerts both excitatory and inhibitory effects on gut smooth muscles. The precise mechanism through which melatonin regulates gastrointestinal motility is still not very clear. Small doses of melatonin accelerated the intestinal transit in rats, while high doses reversed this effect[14]. In one study focusing on gastric emptying, melatonin partially inhibited gastric motility by activating sympathetic neurons. In the stomach, melatonin also reduces nitrergic myenteric innervation[15]; (2) Anti-Inflammatory Reaction: It increases natural killer cell activity and Th2 cell mediated immune responses[16]. Melatonin was shown to reduce the severity of intestinal inflammatory pathologies such as colitis in animal models[17]. Melatonin had also been shown to scavenge reactive oxygen species and inhibit macrophage by suppressing proinflammatory gents including inducible nitric oxide synthase and cyclooxygenase-2[18-20]; and (3) Moderation of Visceral Sensation: Melatonin may also be involved in mediating gut visceral sensation because patients with functional abdominal pain are reported to have a lower urinary excretion of 6-sulphatoxy melatonin and to exhibit a circadian rhythm of lower amplitude compared with healthy controls[21].

Melatonin might be a candidate for IBS treatment based on the following considerations: (1) melatonin has analgesic effects which may help to alleviate abdominal pain and influence the sensation of abdominal distention in IBS patients; (2) melatonin has regulatory effects on gastrointestinal tract motility and sensation which may improve the bowel habits and alleviate abdominal pain or distention in IBS patients; (3) melatonin could have a sleep promoting effect which may useful to treat the sleep disturbance of IBS patients; and (4) melatonin has mood regulation and anti-stress effects which could help alleviate the abnormal psychological parameters observed in IBS patients. Thus, we believe that melatonin might serve the several aspects of IBS treatment strategy because it targets not only the psychological component, *i.e.*, stress, anxiety, depression and sleep disorder but also the peripheral elements of abnormal bowel sensation and motility. Below we examine the possible mechanisms of melatonin in the treatment of IBS.

PHARMACOLOGY OF MELATONIN

Melatonin is commonly given orally though it also can be given *via* intravenous, intranasal or transbuccal routes. Melatonin is readily absorbed when it is administered *via* any route. It crosses all morphophysiological barriers, *e.g.*, blood-brain barrier and placenta, with ease.

The absorption and bioavailability of melatonin varies widely. When given by mouth, peak melatonin concentration occurs within an hour and serum half-life is approximately 35-50 min[22]. Because of its fast clearance, regular melatonin formulations can produce physiological levels for only 2-4 h[23]. The typical dose range in studies of melatonin's effects on sleep disturbance has been between 0.3-5 mg, with 2-3 mg commonly being used. Ingested melatonin that did not undergo first-pass metabolism in the liver is eventually metabolized, mainly in the liver. After conjugation with sulfuric or glucuronic acid, it is excreted by the kidneys. A single night-time dose is cleared by the following morning. Legal availability of melatonin varies in different countries from over the counter in United States to prescription only in other countries. It is categorized by the United States Food and Drug Administration as a dietary supplement. Melatonin treatment has an extremely wide margin of safety though

it may cause minor adverse effects, such as headache, rash and nightmares. Studies of human subjects given varying doses of melatonin (1-6.6 g/d) for 30-45 d did not reveal abnormalities at the end of the test period except drowsiness[24,25]. However, in a placebo-controlled trial using 3-6 mg of melatonin for eight weeks on IBS women, drowsiness only happened in a minority of participants and there was no difference between the groups[26,27]. Lu *et al*[26] also showed that baseline saliva melatonin levels were lower in IBS compare to normal control and oral melatonin supplement was able to increase the level of melatonin in the saliva.

WHAT ARE THE PUTATIVE SITES OF ACTION OF MELATONIN IN IBS?

Sleep promoter

Besides the bowel symptoms, sleep disturbance is commonly observed in patients with IBS, it being reported to occur in 26%-55% of IBS patients[28-30]. Although the cause and effect association is not clear, there is some evidence supporting the "bad bowels cause bad dream" hypothesis[31-36] including the finding that IBS patients have more frequent rapid eye movement (REM) sleep - a sleep phase that is characterized by arousal - than non-REM sleep[37,38]. IBS patients were also found to have higher rapid eye movement latency[34,39]. IBS patients with sleep dysfunction were also found to have abnormal physiological threshold of pelvic muscles. IBS patients had a significantly lower threshold volume for urge and anal sphincter pressure for maximal squeeze as compared with those without sleep dysfunction[40].

It has been suggested that melatonin has a sleep promoting effects by cueing circadian rhythms and thus indirectly promoting sleep[41]. In addition, melatonin was also suggested to have a role in direct promotion of sleep[42]. Currently, there is a general agreement that melatonin is probably not a direct soporific or hypnotic compound[43]. Rather, the most commonly proposed mechanism for melatonin to induce sleepiness relates to its effects on the circadian clock, *i.e.*, it "opens the sleep gate"[44] and also it slightly reduces body temperature which promotes sleep[45]. Clinical trials in healthy volunteers have shown that exogenous melatonin accelerates sleepiness probably *via* thermoregulatory mechanisms[46]. Melatonin has these effects over a wide range of doses, ranging from physiological (250 μg) to pharmacological (1-10 mg) levels[40]. Besides the above effects of melatonin on sleep in healthy subject or animals, many clinical trials and reviews have shown that melatonin may exert sleep promoting effect in a number of circadian rhythm sleep disorders[20,47-49].

Brain-gut interaction: mood enhancer

Patients with IBS often complain of a wide variety of symptoms apart from GI symptoms, which may not necessarily originate from the GIT but from central abnormal psychological conditions such as stress, anxiety and depression. Psychological distress and major life events are frequently present in IBS. The most common comorbid psychiatric disorders seen in IBS patients include anxiety disorders (panic and generalized anxiety disorder), depression, somatoform disorders and phobic disorders[50-52]. Compared with healthy controls, patients with IBS are observed to have higher scores for anxiety, depression, hostile feelings, sadness and interpersonal sensitivity[53-55]. In United States, Whitehead *et al*[56] reported a prevalence of 30.5% for depression and 15.5% for anxiety state in IBS patients. IBS symptoms are often exacerbated by psychological stress. In Hong Kong, Generalized Anxiety Disorder was five times more common among IBS patients than non-IBS control[57].

Melatonin is documented to have a possible role in regulation of mood disorders, such as anxiety and depression, both of which are often caused by certain acute or chronic stress events[52,58]. Many studies reported decreases in nocturnal melatonin concentrations in depressed patients, compared with controls[19,59]. Antidepressant therapy has been reported to restore the circadian melatonin rhythm in depressive patients[60]. It was observed that most melatonin treated women reported a general improvement in mood and a significant mitigation of depression[61]. Reduction of nocturnal melatonin peak has been observed in depressed patients in most studies and an increase in nocturnal melatonin levels has been found in patients during treatment with desipramine[52,62].

Clinical studies in IBS patients with melatonin had mixed result when it comes to depression and anxiety. Two studies in Singapore using 3 mg of melatonin showed that there was no difference in depression and anxiety score in subjects taking melatonin compared to placebo[23,63]. Another study in India showed improvement of psychological well-being and mood in the treatment group taking 3 mg of melatonin for 2 wk, however, the details of psychological parameters were not provided[24].

Antinociceptive action of melatonin

The clinical finding that patients suffering less from pain during the night when melatonin level is higher led to the suggestion that melatonin has a possible analgesic effect. This suspicion was supported by the finding that pinealectomy abolished such dark phase analgesia[64] and that it could be restored using melatonin replacement[65]. However, the mechanism of the analgesic effects of melatonin is still not clear at present. It may include complex interactions among melatonin, opioidergic system and melatonin receptors. Met-enkephalin and beta-endorphin are two endogenous opioids involved in the regulation of pain sensitivity in hypothalamus. The levels and circadian rhythmicity of these two opioids changed in rats that received pinealectomy[66,67]. This may imply that the change in the brain concentration of these endogenous opioids could be a mechanism for the mediation of the melatonin induced modulation of pain sensitivity. However, a recent study found that melatonin exerts its analgesic actions not by binding to opioid receptor subtypes but by

Table 1 Placebo-controlled studies: treatment effect of melatonin in irritable bowel syndrome patients

Ref.	Subjects (total, age, IBS Criteria)	IBS subtypes	Treatment *vs* control	Pain	Bloating/ distention	Motility	Sleep	Psycho-logical	Overall IBS score	Outcome
Song *et al*[63], 2005, Singapore	40, 20-64 years old, ROME Ⅱ IBS (with sleep disturbance)	14 IBS-C, 18 IBS-D, 8 IBS-A	20 (3 mg, bedtime, 2 wk) *vs* 20 Placebo	Yes[4]	No	No	No	No	N/A	Decreased abdominal pain and increased pain threshold
Lu *et al*[26], 2005, Singapore	17, 41+/-14 years old woman, ROME Ⅱ IBS	N/A	12 (3 mg bedtime for 8 wk) *vs* 12 Placebo	Yes[5]	Yes[5]	No[1]	No	No	N/A	Effective in improving bowel symptoms in female IBS patients
Saha *et al*[27], 2007, India	18, 18-65 years old, ROME Ⅱ IBS	N/A	9 (3 mg bedtime for 8 wk) *vs* 9 Placebo	Yes	Yes	Yes	N/A	Yes	Yes[2]	Improved overall IBS score, extracolonic score as well as QOL
Chojnacki *et al*[72], 2013, Poland	80, 48-65 years old woman, ROME Ⅲ IBS	40 IBS-C, 40 IBS-D	40 (3 mg morning, 5 mg bedtime for 6 mo) *vs* 40 placebo	N/A	N/A	Yes[3]	N/A	N/A	Yes[3]	Improved visceral pain and abdominal bloating for IBS-C patients

[1]CTT significantly prolonged in control subjects. Only a trend of prolonging CTT in IBS patients; [2]Improved overall IBS score (45% *vs* 16.66%, $P < 0.05$); [3]Significant result only for IBS-C, the intensity of visceral pain and abdominal bloating had decreased in 70% of patients ($P < 0.01$) and constipation in 50% of patients ($P < 0.05$); [4]melatonin taken for two weeks significantly decreased mean abdominal pain score (2.35 *vs* 0.70; $P < 0.001$) and increased mean rectal pain threshold (8.9 *vs* 21.2 mmHg; $P < 0.001$); [5]The improvement in mean ± SD. IBS symptom score was significantly greater after treatment with melatonin (3.9 ± 2.6) than with placebo therapy (1.3 ± 4.0, $P = 0.037$ The beneficial effects of melatonin were most marked in symptoms such as abdominal plain, abdominal distension and abnormal sensation of defecation. CTT: Colonic transit time; N/A: Not available; IBS: Irritable bowel syndrome; QOL: Quality of life.

Table 2 Placebo-controlled studies: side effects of melatonin in irritable bowel syndrome patients

Ref.	Subjects (total, age, IBS criteria)	Dosage, frequency, duration	Sleepiness	GI side effect	Others
Lu *et al*[26], 2005, Singapore	17, 41+/-14 years old woman, ROME Ⅱ IBS	3 mg bedtime for 8 wk	1 × Daytime sleepiness (both treatment and placebo group)	Nil	Nil
Saha *et al*[27], 2007, India	18, 18-65 years old, ROME Ⅱ IBS	3 mg bedtime for 8 wk	1 × Drowsiness (both groups),	Nil	1 decreased libido
Chojnacki *et al*[72], 2013, Poland	80, 48-65 years old woman, ROME Ⅲ IBS	3 mg morning, 5 mg bedtime for 6 mo	Nil	Nil	2 fatigue, 1 vertigo

IBS: Irritable bowel syndrome; GI: Gastrointestinal.

binding to its own receptors and increasing the release of beta-endorphin[68]. Another study also showed that of the three other subtypes of melatonin receptors identified, *i.e.*, Mel1, Mel2 and Mel3, only Mel2 receptor is involved in the analgesic activity of melatonin[69]. Importantly, this anti-nociceptive effect may be unrelated to and independent of the sleep-inducing effects of melatonin, as was demonstrated in the study by Song *et al*[63], where melatonin was found to increase rectal pain thresholds but had no significant effect on sleep. Human studies have shown that melatonin is a hormone with potential therapeutic use for treatment of diseases with pain. Melatonin was documented to be effective in treating many types of headache, such as chronic cluster headache and migraines[70,71].

All these evidence support the belief that melatonin is involved in the modulation of pain and has analgesic effects. However, its potential as a therapeutic agent for treatment of diseases with pain still needs to be further investigated.

Outcomes in placebo-controlled studies

Placebo-controlled studies in melatonin suffered from heterogeneity in methodology (Table 1). Most studies utilized 3 mg at bedtime as the standard dose of trial. The duration of investigation also differ from 2 wk to 6 mo. Chojnacki *et al*[72] used a twice a day dosing in their study with 3 mg in the morning and 5 mg at night for 6 mo. However, there was no increased sleepiness or gastrointestinal side effects reported (Table 2). There was a variety of outcome measures from overall IBS score to quality of life. Lu *et al*[73] examined the effect of melatonin on colonic transit time (CTT) and found that melatonin increased CTT in both control and IBS patients, but only the result in control subjects was significant statistically. In other hand, Chojnacki *et al*[72] showed that with 6 mo treatment with melatonin, 50% of IBS-C patients showed improvement of constipation. However, all studies had consistently showed improvement in abdominal pain for IBS patients. Song *et al*[63] also reported increase of rectal pain threshold after 2 wk of melatonin treatment. Finally, Saha *et al*[27] showed that the overall improvement in quality of life score was 43.63% in melatonin group and 14.64% in placebo group.

CONCLUSION AND THE FUTURE FOR MELATONIN IN IBS

It is still unclear how melatonin may be useful and its mode of action in IBS patients. Current available evi-

dence showed that it is likely to be useful in battling the pain and increasing pain threshold in IBS patients. Different dosing as well as treatment period of melatonin should be studied. Melatonin is a relatively safe drug that possesses potential in treating IBS. Its attractiveness also stem from its relative low cost to the patients. Future studies should focus on melatonin effect on gut mobility especially in IBS-C patients as well as its true central nervous system effect in view of high placebo rate often observed in IBS patients.

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