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The Relationship Between Daytime Salivary Melatonin and Gastrointestinal Symptoms in Young Adults Seeking Psychiatric Care

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ABSTRACT

Objective: The pathophysiology of irritable bowel syndrome (IBS) is not completely understood, although we do know that patients with IBS have a high prevalence of psychiatric comorbidity (mainly depression and anxiety disorders). Melatonin, produced in the gastrointestinal tract, influences gut motility. Psychiatric conditions are associated with circadian disturbances in peripheral melatonin levels. This study aimed to investigate associations between daytime salivary melatonin and gastrointestinal symptoms in young adult psychiatric patients.

Methods: Ninety-six patients (86% women), aged 18–25 years (M (SD) = 21 (2)), seeking psychiatric care with primarily anxiety disorders, affective disorders, or both were included in the study. Total scores from the Gastrointestinal Symptoms Rating Scale - IBS were compared with salivary melatonin measured at three time points (30 minutes after waking up, at 11:00 hours and 30 minutes after lunch) during the waking hours of 1 day.

Results: After adjustment for potential confounders, melatonin levels in saliva 30 minutes after lunch remained significantly correlated to the total Gastrointestinal Symptoms Rating Scale - IBS score after correction for multiple testing (B = 0.016, SE = 0.006, p = .015, q = 0.045). In a post hoc analysis, symptoms of gastrointestinal pain and bloating contributed most to this association.

Conclusions: In young adult psychiatric patients, salivary melatonin levels after lunch are associated with gastrointestinal symptoms, which is consistent with the proposed effect of elevated levels of gastrointestinal melatonin on gut motility. This result suggests a link between IBS symptoms and regulation of melatonin in patients with psychiatric disorders.

Key words: depression, human, irritable bowel syndrome, melatonin, mental health.

INTRODUCTION

Melatonin is a neuroendocrine hormone known to regulate sleep and circadian rhythm. During the dark hours, melatonin in plasma is mainly of pineal origin, whereas during the day, because the production and secretion of melatonin in the pineal gland are effectively inhibited by light, circulating levels of melatonin are believed to be of peripheral origin (1). The enterochromaffin (EC) cells are neuroendocrine cells located throughout the gastrointestinal (GI) tract that produce and secrete serotonin and melatonin—two enzymatic steps away from each other. EC cells are thus a major source of melatonin in the GI tract and the amount may greatly surpass the amount of melatonin in the pineal gland (1,2).

Melatonin affects GI motility via membrane receptors that include melatonin (MT1 and MT2) and serotonin (5-HT) receptors (3). Both MT1 and MT2 are expressed in several cell types throughout the GI tract, with the highest levels in the large intestine (4). Melatonin induces contraction of cultured gastric smooth muscle cells, likely via MT1 receptor signaling given that this effect is blocked with a nonselective MT1/MT2 antagonist but not with a MT2-specific antagonist (5). Binding of melatonin to 5-HT4 receptors can cause smooth muscle relaxation, whereas stimulation of 5-HT3 receptors may result in smooth muscle contraction (3). Melatonin may also influence gut smooth muscle via the inhibition of nicotinic receptor channels regulating smooth muscle contraction (3). Furthermore, melatonin can inhibit the activity of the serotonin transporter (6). The reported effects of melatonin on GI motility seem to be dose dependent, because administration of pharmacological doses of melatonin seems to decrease motility and increase colonic transit time,

BMI = body mass index, **EC** = enterochromaffin, **GI** = gastrointestinal, **GSRS** = Gastrointestinal Symptoms Rating Scale, **IBS** = irritable bowel syndrome, **IQR** = interquartile range, **MADRS-S** = Montgomery Åsberg Depression Rating Scale–Self-Assessment, **OC** = oral contraceptives, **OR** = odds ratio, **SNRI** = serotonin-noradrenaline reuptake inhibitors, **SSRI** = selective serotonin reuptake inhibitors

SDC Supplemental Content

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Received for publication March 21, 2018; revision received September 17, 2018.

DOI: 10.1097/PSY.0000000000000644

whereas melatonin in lower concentrations seems to increase motility and decrease colonic transit time (3,7–10). EC cells also produce serotonin and a recent review highlights the complexity of its role in regulating GI motility (11). Increased serotonin signaling has been shown in the gut in patients with irritable bowel syndrome (IBS), including increased levels of serotonin in plasma, (12) and may contribute to the changed motility and sensation in IBS (13). At physiological levels, melatonin most likely acts as an antagonist of serotonin in regulating gut motility (10).

IBS is a functional bowel disorder in which the main symptoms consist of abdominal pain and altered stool consistency and frequency. IBS patients often exhibit greater postprandial abdominal pain, discomfort, urge, and greater colonic motility (gastrocolic reflex), as well as increased stress response and visceral hypersensitivity compared with healthy controls (14). Functional imaging of IBS patients has shown abnormalities in areas of the brain involved in pain and arousal states (anterior cingulate cortex and the amygdalae) (15). Four possible IBS subtypes include IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), mixed IBS (IBS-M), and unsubtyped IBS (IBS-U), depending on the predominant stool pattern (16,17). The pathogenesis and pathophysiology of IBS are poorly understood. Low-grade inflammation and disturbances in the brain-gut axis that affect afferent signaling and central processing of nociceptive signals have been proposed to play a role (18–20). In a prospective, community-based study, GI infection as well as predisposing factors (e.g., female sex, vulnerability to diarrhea under stress, illness anxiety, and somatic symptom burden) were found to predict the development of IBS (21). Sex hormones have been suggested to have a potential mechanism in sex differences (3,22,23).

Evidence for a role of abnormalities in serotonin metabolism in IBS has been reported (24). Some suggest that IBS patients with diarrhea might have reduced serotonin reuptake and those with IBS with constipation might have impaired release of serotonin (24,25). There is also evidence of decreased melatonin metabolites in IBS-D versus IBS-C and healthy controls (26).

A high prevalence of psychiatric comorbidity—predominantly major depression and anxiety—has been reported in patients with IBS (27). One study found that depression and generalized anxiety disorder comorbidity is linked to increased symptom severity in patients with IBS (28), whereas another study showed that patients in remission from depression have no more IBS symptoms than controls (29). Sleep disorders are also prevalent in IBS patients (26,30–33), possibly mediated by alterations in tryptophan metabolism (26,30–32).

Although causality has been difficult to establish (whether psychopathology is predisposing for IBS or vice versa), there is evidence that in some patients, functional GI symptoms arise first and that mood disorders develop later, suggesting that primary gut disturbances might be the underlying driver of the mood disorder in at least a subgroup of patients (24). Subgrouping IBS patients based on a combination of GI symptoms and psychological and extraintestinal somatic symptoms common in IBS has been suggested for both clinical management and research (34). One study proposed that the IBS-C might be associated with higher levels of anxiety and depression (35); however, other studies have found no differences between IBS symptom subtypes in this regard (36).

Studies of melatonin administration in patients with IBS have reported ameliorated abdominal pain and reduced rectal pain threshold, as well as improvements in overall IBS scores and quality of life when melatonin was given orally in the evening (37–39). However, no improvement in sleep disturbances was seen in IBS patients with melatonin treatment (38,39).

We recently described the expression of melatonin in EC cells in both normal human GI tract (4) and in tumors derived from these cells (40). Patients with high tumor expression of melatonin reported less diarrhea and high daytime plasma levels of melatonin were associated with nausea (40). Considering the known actions on GI motility, high local accumulation of melatonin in the GI tract could be expected to dampen gut motor activity, whereas a more moderate rise in local melatonin likely would increase motor activity. Although there is large variability in melatonin levels between individuals, the normal melatonin rhythm is very stable over time in a given individual, rather like a hormonal fingerprint (41). Melatonin in saliva is correlated to melatonin in serum (42). Our group has previously demonstrated that levels of melatonin in saliva are highly variable, with low levels at bedtime associated with higher severity of depressive symptoms (43). The present study is conducted on data from the same cohort of young adult psychiatric patients.

Here, we examine the relationship between saliva-melatonin levels measured at three time points per individual for 1 day and self-reported GI symptoms in young adult patients primarily experiencing anxiety and affective disorders. Given the knowledge of melatonin's actions in the GI tract, we hypothesize that IBS symptoms are correlated to daytime melatonin levels in saliva.

MATERIAL AND METHODS

The study was reviewed and approved by the Regional Ethics Committee in Uppsala (Dnr 2012/81 Dnr 2012/81/1 and 2013/219) and all patients signed an informed consent.

Patient Samples

Patients in the study were part of "Uppsala Psychiatry Patient Samples," a project designed to collect biological material from patients seeking psychiatric care at the Department of General Psychiatry, Uppsala University Hospital, Sweden. Patients from 18–25 years of age, who met the criteria for any psychiatric diagnosis (mainly affective and anxiety disorders), according to the DSM-IV, were asked to participate in the study. The cohort is described in detail elsewhere (44). The patients in this study were recruited from January 2013 to May 2014. In general, the patients in the cohort were somatically healthy; however, one patient reported celiac disease, one reported rheumatoid arthritis, but none reported inflammatory bowel disease or any other inflammatory disorder.

The self-rating version of the Montgomery-Åsberg Depression Rating Scale Self-Assessment (MADRS-S) (45–47) was used to estimate depressive symptoms. The MADRS-S contains nine questions rated on a six-point (0–6) Likert-like scale, with an overall score ranging from 0 to 54.

The Swedish translation of the Gastrointestinal Symptom Rating Scale for IBS (GSRS-IBS) was used to evaluate GI symptoms. The GSRS was originally developed to evaluate treatment for IBS and peptic ulcer disease. The GSRS-IBS differs from the GSRS as to how the questions and the answer scale are constructed. The GSRS-IBS comprises 13 items addressing only IBS symptoms that occurred in the past week (48). Symptoms were rated on a seven-point (1–7) Likert-like scale, scored from 1 (no symptoms) to 7 (very severe symptoms). The total score could range from 13 to 91 points. The GSRS questions are grouped into the following five categories: pain syndrome (question 1 and 2), bloating syndrome (question 3, 4, and 13), constipation syndrome (question 5 and 8), diarrhea syndrome (question 6, 7, 9, and 10) and satiety (question 11 and 12).

In addition to the GSRS-IBS, patients filled out questionnaires for sociodemographics, medical history, and heredity; all questions are identical

to those used in LifeGene (http://www.lifegene.se) and EpiHealth (http://www.epihealth.se). One item from the following question was used in this study. "How likely are you to slumber or fall asleep in the following situation: just after eating lunch (without alcohol), - as opposed to just feeling tired? It relates to your usual way of living lately. Use the following scale to select the most suitable number for each situation: 0 = would never sleep, 1 = slight risk of sleep, 2 = moderate risk of sleep, and 3 = high risk of sleep."

This study is a subgroup of a previously described cohort (43). Because the GSRS-IBS questionnaire was added at a later date to the Uppsala Psychiatry Patient Samples protocol, the period of the current study is different. For this study, 621 consecutive patients were eligible to participate and 264 (42.5%) consented. Saliva sampling was completed by 102 (38.6%) of these patients. Six patients were omitted because they did not fulfill criteria for any DSM-IV Axis 1 diagnosis. The present study included patients for which both GSRS-IBS scores and saliva were available (n = 96).

Saliva Collection and Analysis

Data were available from saliva samples at six time points during the waking hours of one day: when waking up, 30 minutes after waking up but before breakfast, at 11.00 hours, 30 minutes after lunch, at 22.00 hours and just before going to bed. The three time points representing daytime measurements (30 minutes after waking up but before breakfast, at 11.00 hours and 30 minutes after lunch) were selected for analysis in this study. Participants were carefully instructed and received written guidance on the method of sample collection. Saliva was collected using inert polymer cylindrical swabs (10 × 30 mm), which were then placed in a storage tube (swabs and tubes from Salimetrics Europe Ltd, Suffolk, United Kingdom) and kept in the refrigerator until delivery to the laboratory within 48 hours. Participants were instructed not to eat or drink 30 minutes before sampling. The participants documented collection times. To ensure compliance, the research assistant verified collection times and sampling method with the patient upon receipt (samples not collected as instructed were excluded). Of maximally 288 (3 × 96) hormone measurements, 9 (3%) were missing because of mistakes in saliva sampling or insufficient saliva volume.

Biochemical Analysis

Upon receipt, tubes were centrifuged and stored at −20°C until analysis. Salivary melatonin was measured with competitive ELISA (Direct Salivary Melatonin Elisa EK-DSM; Bühlmann Laboratories AG, Schönenbuch, Switzerland). Analyses were performed at the routine laboratory of the Department of Clinical Chemistry, Uppsala University Hospital, Uppsala, Sweden. The laboratory is accredited by a Swedish government authority (Swedac). Total assay variability was less than 11%. Where melatonin levels were more than 50 ng/l, limited saliva volume did not allow further dilutions. Calculations for these participants were conducted using the value 50 ng/l.

Statistics

All statistical analyses were conducted with the Statistical Package for the Social Sciences, Version 22.

Before all analyses, the continuous variables were screened for normality using the Shapiro-Wilk test of normality, $p > .05$, and for a visually estimated normal distribution (histogram, Q-Q plot, box plot). The total GSRS-IBS scores and subscales were not normally distributed. Salivary melatonin was not normally distributed, and hence, analyses were performed as nonparametric tests. Because of the skewed data distribution, the generalized linear model analysis was performed using the gamma distribution.

Generalized linear model analyses of melatonin in relation to GSRS-IBS scores were conducted for the three selected time points. The following possible confounding factors were included in all models: sex, body mass index (BMI), antidepressive medication, and oral contraception. A two-sided p value of less than .05 was considered significant. The Bonferroni method was applied to correct for multiple comparisons and was reported as q values.

RESULTS

Participant Characteristics

A total of 96 patients were included in the study (83 women, 13 men), with a mean age of 21 years (range = 18–25 years). The patients were diagnosed with current depression (n = 53), bipolar disorder (n = 24), and any anxiety disorder (n = 66) (some of the patients had more than one disorder). MADRS-S total scores ranged between 4 and 46, with a median value of 22 (Table 1 presents participant characteristics).

Melatonin Levels and Correlations to Gastrointestinal Symptoms

Salivary melatonin levels ranged from 0.5 to greater than 50 ng/l for all time points (median values are shown in Table 1). The median GSRS-IBS score was 31 (range = 13–78), with an interquartile range (IQR) of 19. For the subscales, median and IQR were the following: pain = 3 (1.5), satiety = 2 (2.5), bloating = 3 (1.6), constipation = 1.5 (2), and diarrhea = 2 (1.5).

Melatonin values at three time points (awakening +30 minutes, 11:00 hours and lunch +30 minutes) were evaluated using generalized linear models with potential confounding factors (sex, BMI, use of antidepressants, and oral contraceptives) included in the analyses. A significant relationship between melatonin values after lunch (lunch +30 min) and the total GSRS-IBS score (p = .015, q = 0.045) was found (Table 2). Post hoc exploration of the subscales showed that the association was related to the symptoms of GI pain (p = .047) and bloating (p = .033). Thereafter, these subscale symptoms were tested for associations with melatonin levels at

TABLE 1. Participant Characteristics

n (%)	96 (100)
Female, n (%)	83 (86.5)
Age, M (SD)	21.0 (2.0)
BMI, M (SD)	24.2 (5.7)
MADRS-S, median (range)	22 (4–46)
GSRS-IBS,[a] median (range)	31 (13–78)
Saliva-melatonin, median (IQR), ng/l	
Awakening +30 min	6.9 (2.7–15)
11:00	3.3 (1.8–5.8)
Lunch + 30 min	2.8 (1.8–4.7)
Diagnosis, n (%)	
Unipolar depressive disorder	53 (55.2)
Bipolar disorder	24 (25.0)
Any anxiety disorder	66 (68.8)
Medication,[b] n (%)	
SSRI/SNRI	48 (50.0)
Antipsychotics	3 (3.1)
Mood stabilizers	6 (6.3)
Oral anticonception	26 (27.1)

BMI = body mass index, GSRS-IBS = Gastrointestinal symptoms rating scale for irritable bowel syndrome, IQR = interquartile range, SSRI/SNRI = selective serotonin re-uptake inhibitors/serotonin–noradrenaline reuptake inhibitors.

[a] GSRS-IBS scoring range 13–91.

[b] Treatment at the time of saliva sampling.

TABLE 2. Generalized Linear Models for Total GSRS Scores and Melatonin Measured 30 Minutes After Waking up, at 11:00 Hours and 30 Minutes After Lunch

	Mel Awake +30 min	Sex M/W	OCs	SSRI/SNRI	BMI
B	0.004	0.194	0.110	0.026	0.006
SE	0.0028	0.1306	0.0928	0.0836	0.0072
p	.195	.137	.235	.759	.406
	Mel 11:00 h				
B	0.005	0.213	0.103	0.036	0.007
SE	0.0059	0.1167	0.0909	0.0808	0.0071
p	.365	.068	.258	.655	.330
	Mel lunch + 30 min				
B	0.016	0.195	0.090	0.077	0.001
SE	0.0064	0.1164	0.0889	0.0783	0.0072
p	.015	.093	.312	.325	.851
q	0.045*				

Mel = melatonin, M/W = men/women, OCs = oral contraceptives, SSRI/SNRI = selective serotonin re-uptake inhibitors/serotonin-noradrenaline re-uptake inhibitors, BMI = body mass index, SE = standard error.

Potential confounding factors are included in the analysis.

* Significance at the level of $q < 0.05$ after Bonferroni correction.

the other two time points, where a significant relationship was found between GI pain ($p = .037$) and melatonin values 30 minutes after waking up (awakening +30 minutes).

Adjusting for use of antidepressant drugs did not alter the relationship between melatonin and GI symptoms. Oral contraception may also influence melatonin levels and a separate analysis of women alone is listed in Table S1, Supplemental Digital Content 1, to interpret the contribution of oral contraception to the model, http://links.lww.com/PSYMED/A520.

In another separate analysis, a correlation between reported frequency of sleeping after lunch and higher melatonin levels after lunch was revealed. This association remained after adjustment for sex, use of oral contraceptives, and use of antidepressants ($p = .028$).

DISCUSSION

This study found that higher levels of melatonin after lunch were related to increased IBS symptoms in young adults seeking psychiatric care, even after adjusting for relevant confounders. The subscales GI pain and bloating were those with the highest association to postprandial melatonin levels. In another analysis, melatonin levels in saliva after lunch correlated positively with self-reported sleepiness after meals.

The results confirm the hypothesis that daytime melatonin levels are correlated to GI symptoms as measured by the GSRS-IBS. These results are in line with some research on melatonin expression and proposed function on GI motility in animals (2,10,49–52) and with our own study on patients with neuroendocrine tumors (40). In the present study, the mechanism through which higher levels of melatonin are linked to more GI symptoms may be via decreased motility. Although this study cannot determine the source of the measured postprandial saliva melatonin, there is good cause to believe that saliva melatonin levels are reflective of those in the GI tract during the daytime. EC cells are one potential source of daytime melatonin. An increase in EC cells in patients with IBS has been described (53), and speculatively, this could increase melatonin levels, at least in a subpopulation of patients with IBS. Compellingly, a role for EC cells in psychiatric disease has also been suggested but not yet proven (54).

Our finding that melatonin is positively associated with increased bloating and GI pain contrasts with studies showing that melatonin treatment reduces pain (38,39) and administration of melatonin in postmenopausal women with IBS-C reduces bloating (55). In these studies, however, melatonin was administered at night, during fasting, or both, which does not interfere with GI processing of meals and therefore may explain the discrepant results. Indeed, the authors stated that their results suggest that melatonin probably improved IBS symptoms by modifying visceral pain perception rather than influencing gut motility, sleep pattern, or psychological well-being in patients with IBS (38). In a rat model of visceral hyperalgesia, melatonin's antinociceptive effects were demonstrated to have no effect on primary sensory afferents but did exert its effect in supraspinal areas via the central opioid system (56). Accordingly, another possibility is that the experience of symptoms in the gut may be influenced by melatonin centrally. Moreover, centrally acting melatonin may influence gut motility (e.g., through cholecystokinin-induced changes in the ileum) (57). The finding that elevated postprandial melatonin in saliva was associated with sleepiness after meals may indicate central nervous system effects.

Given the connection between IBS symptoms and psychiatric morbidity, our study population would *a priori* likely exhibit more GI symptoms than healthy controls though fewer symptoms compared with a population diagnosed with IBS (29,48). All patients in this study experience psychiatric conditions, but the association between melatonin and IBS symptoms seems to be independent of a psychiatric diagnosis. A univariate association was found between the variable "any anxiety disorder (Y/N)" and postprandial melatonin but not with GSRS-IBS. Adding depressive symptoms (MADRS-S score) or any anxiety disorder (Y/N) to the model did not change the outcome (data not shown). Generally, patients with depression have been reported to have lower levels of melatonin at night compared with healthy controls (58–60). However, depressed patients are reported to have higher melatonin in saliva than healthy

controls during the daytime (61). Melatonin levels in this population are generally high; however, the current cohort consists of young individuals from the ages 18–25 years. We know that melatonin levels decrease with age, which may explain the lower levels found in samples with older adults (62).

An alternative interpretation of the results is that elevations in melatonin may be secondary to increased immune activation and low-grade inflammation. Melatonin is produced as a scavenger of free radicals and does not only neutralize reactive oxygen species but may also modulate immune response (63–68). This is a potentially important point, because both depression and IBS are linked to increased innate immune activity and oxidative stress (66,67).

This study has several limitations. First, saliva testing was conducted at home and may have differed between the participants. Extensive measures, however, were taken to reduce this risk (described elsewhere (43)). Second, inclusion of patients from the eligible patient sample was low. We have recently conducted a study examining factors that contribute to declining participation in the biobank. Major reasons for unwillingness to participate were lack of time or feeling too sick or fatigued to take part in research (unpublished manuscript). We have, additionally, examined factors that differed between patients who completed the saliva sampling as instructed versus those who did not. Patients with executive dysfunction and high impulsiveness were less likely to deliver saliva samples in accordance with the instructions (data not shown). A third limitation is that IBS symptoms are self-reported and not a verified clinical IBS diagnosis. These findings need to be verified in IBS patients. Fourth, information about the menstruation cycle distribution was not known for the time point when the GSRS-IBS was completed and could not be controlled for. Finally, because this is a cross-sectional study, information about the directionality of the correlation between melatonin in saliva and GI symptoms cannot be extracted.

CONCLUSIONS

To our knowledge, this is the first study to examine the relationship between endogenous melatonin and GI symptoms. In a cohort of young adult psychiatric patients, higher levels of melatonin in saliva after lunch are associated with increased GI symptoms, notably bloating and pain, as measured by the GSRS-IBS. Further studies are needed to determine the relationship between melatonin and GI symptoms, which may have relevance for both psychiatric patients and patients with IBS. The source of daytime melatonin in saliva, as well as the central and peripheral mechanisms linking melatonin to GI symptoms merit further investigation.

The authors thank Ulla Nordén for her excellent technical assistance. The authors also thank Professor Lisa Ekselius and Associate Professor Mats Stridsberg for fruitful scientific discussions. The authors thank Hans Arinell for excellent assistance in the statistical analysis. Sample management has been in collaboration with Uppsala Biobank.

Source of Funding and Conflicts of Interest: This work was funded by grants to JLC from Märta och Nicke Nasvells fund, Anna-Britta Gustafssons stiftelse, Stiftelsen Apotekare Hedbergs Fund, Erik, Karin och Gösta Selanders Stiftelse, and Stiftelsen Söderström-Königska sjukhemmet, The Swedish Society of Medicine and Medical Training and Research Agreement (ALF), funds of Uppsala University Hospital. The funders had no role in study design, data collection, analysis, decision to publish, or preparation of the manuscript. The authors declare no competing interests.

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