Melatonin and the Gut

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ABSTRACT:
Significant quantities of melatonin are made in the human digestive tract. Melatonin has multiple effects on digestion and is important in maintaining normal digestive function. It may have clinical use in treating a range of gastrointestinal disorders including GERD, gastric ulceration, pancreatitis, liver fibrosis, irritable bowel syndrome and ulcerative colitis. Clinicians are encouraged to consider using melatonin as an adjunct in treating these conditions.
Keywords: melatonin, gastrointestinal tract, ulcerative colitis, pancreatitis, GERD, irritable bowel syndrome.

Many of the therapeutic options available to the naturopathic physician today are far from the simple cures of our professional forefathers. Although the basic premise of our practices should be centered on stimulating the vis medicatrix naturae, I find myself turning more and more to supplementing or replacing biological elements that are rendered in short supply as a result of our modern lifestyle. An excellent example is the hormone cholecalciferol, vitamin D-3. Living where we do and spending as much time indoors as we do, taking supplemental vitamin D-3 makes sense. Of late, I have begun to wonder if we should not see melatonin in a similar light as vitamin D-3, as a hormone required for health but of which deficiency is common due to lifestyle. At this point we have little clinical experience in using melatonin except to induce sleep and as an adjunctive treatment for cancer. This article focuses on the therapeutic potential of using melatonin to treat diseases of the digestive tract.

Melatonin plays a significant role in regulating the digestive tract and this should come as no surprise. Most people report a clear circadian rhythm to their bowel habits and melatonin is the clock that controls circadian rhythms. Levels of melatonin increase with darkness and drop again with light; this is how our body knows it is night or day.

The brain is not the only source of melatonin in the body, the digestive tract also makes melatonin. Lerner and co-workers discovered melatonin in the bovine pineal gland more than half a century ago, back in 1958. Sixteen years later, in 1974, the Russians, Raikhlin and Kvetnoi, isolated melatonin from the human appendix. In 1977 GA Bubenik and colleagues at the University of Guelph, Ontario, Canada, detected melatonin in the mucous membrane of the gastrointestinal tract (GIT). Melatonin is made in the GIT by the enteroendocrine cells that line the digestive tract. The gut does not need or depend on the brain for melatonin. It makes its own. If you cut out the pineal gland of a rat, it drastically decreases blood melatonin levels yet the melatonin levels in the gut remain unchanged. We will assume the same holds true in people: nobody is volunteering to play the rat in a similar human trial.

Oral doses of l-tryptophan increase blood levels of melatonin. This happens even in animals that have had their pineal glands removed. The l-tryptophan is converted to melatonin in the

gastrointestinal tract (GIT) rather than the brain. We should acknowledge that the commonly held concept that l-tryptophan is converted to serotonin may not be accurate. Serotonin is an intermediary on the pathway between l-tryptophan and melatonin and not the end of the road.

Diagram of l-tryptophan conversion pathways:
http://upload.wikimedia.org/wikipedia/en/0/0b/Tryptophan_metabolism.png

L-tryptophan can take one of two pathways in the body; one path leads to production of niacin, the other pathway leads to production of first serotonin and then melatonin.

The factors that control which pathway the l-trytophan takes are only now being explored. Stress, disease, malignancy, active immune activity and pesticides all create changes in rate of conversion. Chronic immune activation pushes tryptophan toward niacin production, to the point that low l-tryptophan serum levels are found in certain conditions like cancer:

"Low serum/plasma tryptophan concentration is observed in infectious, autoimmune, and malignant diseases and disorders that involve cellular (Th1-type) immune activation as well as during pregnancy due to accelerated tryptophan conversion."

In these chronic states where flow is directed toward making niacin, low tryptophan may lead to low serotonin levels and presumably low melatonin levels. This supports the use of melatonin with cancer but it also suggests that we should consider melatonin in other conditions besides cancer.

Mild stress increases melatonin production. A 2009 study reports that 2 hours of restraint, used to trigger a mild stress response, increases melatonin production. The stress was classified as mild because the subjects did not develop bleeding ulcers.

Although several insecticides have been shown to increase melatonin production including, parathion, carbaryl, and lindane, it would not be appropriate to suggest these chemicals as a treatment for insomnia.

Rate of conversion from serotonin to melatonin is variable so typically we choose to use melatonin itself rather than l-tryptophan in order to increase gut melatonin levels. L-tryptophan certainly has a reputation as being useful to treat insomnia and the obvious explanation would be that it increases serum melatonin levels.

Eating food triggers melatonin production by the GIT, some of which enters the blood stream. Fasting also increases gut melatonin production. Eating after a period of fasting will also create a surge in melatonin. That postprandial drowsiness that many of us were taught was the result of an 'alkaline wave' in the blood secondary to stomach acid neutralization in the gut, might after all just be a spike in blood melatonin levels.

The pineal gland produces a spike in melatonin at night in the dark, but during the day, the gut maintains the baseline levels of melatonin. There is a lot more melatonin in the GIT than in the blood. Melatonin concentrations in the GIT tissues are 10 to 100 times higher than in

blood. According to Huether's 1994 calculations the GIT contains 400 to 500 times more melatonin than the pineal gland.

In the lower gastrointestinal tract melatonin helps regulate peristalsis. It cancels out serotonin's spasmodic effect on the intestine and restores peristalsis. Pretreatment with melatonin prevents serotonin induced spasm. This shows up when measuring bowel transit times (BTT). Serotonin speeds things up, that is shortens BTT. Adding melatonin slows things back down, lengthening BTT. Small doses of melatonin though, by relaxing serotonin spasms, also aid motility. Melatonin slows things down if they move too fast and speed them up if too slow. If you like big words, call melatonin a 'peristaltic modulator.' These properties make melatonin a possible treatment for treating irritable bowel syndrome.

Pereira and de Souza brought the idea of using melatonin to treat reflux disease to our attention in an article published in the Journal of Pineal Research in May 2006. They told the case of a 64 year-old woman whose GERD symptoms responded favorably to a formula containing 6 mg of melatonin plus several amino acids and vitamins. In October 2006, the same journal published a paper by Pereira comparing the action of this melatonin formula against omeprazole. Pereira gave the melatonin containing supplement to 176 patients and 20 mg doses of omeprazole to another 175 patients. All 176 patients who received the melatonin supplements "reported a complete regression of symptoms after 40 days of treatment." Only 115 subjects (66%) of the omeprazole patients reported similar improvement. These results are almost too good to be believable. The formula for the mixture used in this research in no secret, Pereira lists it in the text of his paper. It is surprising that some enterprising supplement manufacturer isn't selling it.

Melatonin inhibits nitric oxide production and this prevents relaxation of the lower esophageal sphincter (LES) and this may explain how melatonin prevents reflux.

A 2006 paper reported on night time melatonin levels in people with upper digestive tract disorders. Blood melatonin levels were measured in 24 patients with nonerosive esophageal reflux disease (NERD), 25 with gastroesophageal reflux disease (GERD), 34 with duodenal ulcer disease (DUD), 36 with functional dyspepsia (FD) and in 30 healthy people used as controls. Patients with GERD or DUD made less melatonin than the healthy subjects (27.2 and 25.5 vs 34.7 pg/ml). Those patients with the non-erosive diseases, NERD or FD had the highest levels of melatonin(43.2 and 42.4 pg/ml). High melatonin appears protective to the mucosal tissues of the upper digestive tract.

In a 2007 study 60 people diagnosed with either Epigastric Pain Syndrome (EPS) or Postprandial Disorders Syndrome (PDS) were given 5 mg of melatonin nightly for 6 weeks. The concentration of nitric oxide metabolites in gastric juice was measured in the test subjects and in 25 healthy control subjects. Nitric oxide levels were lower in the healthy subjects, 6.8 versus 11.0 and 9.3 in EPS and PDS patients respectively.
After treatment with melatonin levels dropped to 8.2 and 6.9 respectively.

Note that the GERD clinical trial was 40 days in length and this last one was 6 weeks long. It is useful to point this out to patients and tell them not to expect effect for 6 weeks.

The common assumption that people get heart burn at night because they are horizontal and gravity no longer holds the food down may need to be rethought. Nighttime lighting may lower melatonin secretion and allow the LES sphincter to relax inappropriately. This may partly explain why reflux worsens at night.

It's not just gut smooth muscles that are affected by melatonin. Perhaps we should be using melatonin during labor. Research dating back to the 1960s and 1970 reports that melatonin relaxes smooth muscles in the reproductive tract. Melatonin has a synergistic effect with oxytocin in triggering more coordinated and more forceful uterine contractions and so may be of use in labor and delivery. Melatonin also appears to moderate placental function for the better. Although some sources suggest melatonin is contraindicated during pregnancy, I have been unable to locate the reason. Instead, recent publications suggest it may be beneficial

Melatonin is often referred to as an antioxidant. It's reported to be twice as effective as vitamin E. Melatonin prevents the damage caused by ischemia and reperfusion of gut mucosa.

Melatonin may be useful in treating a range of diseases of the digestive tract. Melatonin may be of therapeutic benefit in treating infections, bacterial, fungal or viral, in the mouth. It may be useful for healing tooth extractions, periodontal diseases and oral cancers. One option might be to add melatonin to the toothpaste one uses at bedtime.

Melatonin may be of use in treating gastric ulcers. If you torture a rat by waterboarding it or as the journals describe it, 'stress a restrained rat by water immersion,' the rat rapidly develops gastric ulcerations. These ulcers bleed more during the daytime and start to heal at night. If you destroy the rat's pineal gland so it can't make night time melatonin, the ulcers rapidly worsen and do not heal even at night. One possible explanation for this action is that melatonin relaxes smooth muscles in the intestinal tract and increases mucosal blood flow.
Melatonin may be useful for treating pancreatitis. It stimulates amylase secretion by the pancreas and it protects the pancreas from damage. These, "… beneficial effects of melatonin … on acute pancreatitis could be related to the ability of melatonin to scavenge the free radicals, to activate antioxidative enzymes and to modulate the cytokine production." In animal models of pancreatitis, melatonin not only protects against damage but also moderates the effects of the disease. In a rat study, melatonin reduced pancreatic damage by decreasing TNF-alpha levels.
Melatonin moderates bowel transit time and so may be useful for treating irritable bowel disease. In a small clinical trial of 18 patients in 2007, each patient received either 3 mg of melatonin or a placebo for 8 weeks. Those receiving melatonin significantly improved overall IBS score (45% vs. 16.66%). The improvement in Quality of Life score was 43.63% in melatonin group and 14.64% in placebo group. Though a small group to gather data from, the improvements are significant.

We should cautiously consider melatonin for ulcerative colitis and Crohn's disease. A 2003 paper in the American Journal of Gastroenterology raised the question whether melatonin might be a useful treatment for ulcerative colitis. A 2007 study measured the urine metabolites of melatonin in 24 people with ulcerative colitis. Data showed that the metabolites were significantly higher in the UC group than in healthy controls. Higher levels of the metabolite were correlated with milder disease. This led the researchers to conclude, "Melatonin seems to

be a part of anti-inflammatory response and its high level may appease the course of UC." A 2008 report using a rat model of ulcerative colitis reports that melatonin treatment prevented the translocation of bacteria from the gut into circulation. A review of melatonin used with ulcerative colitis As of this writing Emory University is recruiting participants with ulcerative colitis for a 12 week study using 5 mg daily doses of melatonin.

http://clinicaltrials.gov/ct2/show/NCT00790478 [ClinicalTrials.gov identifier: NCT00790478]

Despite these encouraging suggestions, we should be cautious. There are two case reports, one involving a patient with Crohn's disease and a second describing a patient with ulcerative colitis that describe significant aggravation of disease when the patients took melatonin. In both cases the patients were taking the same combination of drugs, salicylazosulfapyridine, corticosteroids, and melatonin. Although these drugs all may be useful when administered separately, it may be that when administered together they provoke unwanted aggravation. For these reasons we should not administer melatonin at the same time as these other drugs are being used.
Only one paper was located that addresses whether melatonin might be useful for treating Crohn's disease. No abstract is available but the paper's title is not encouraging; "Melatonin triggers Crohn's disease symptoms." For now, avoid giving Crohn's patients melatonin.
Melatonin may be of use in diseases that cause liver fibrosis including primary biliary cirrhosis. A paper suggested this possibility in 1979. Removing the pineal gland from a lab animal precipitates the formation of fibrosis in the intestinal cavity and especially the liver. The authors went so far as to suggest, "primary biliary cirrhosis may be a pineal deficiency disease." Though an older paper, it is worth keeping in mind, especially in light of the many newer papers that tell us that melatonin protects against liver fibrosis and cirrhosis caused by carbon tetrachloride poisoning or from fatty liver.
Melatonin may be useful for patients undergoing abdominal surgery. Melatonin helps surgical incisions heal faster and prevents formation of abdominal adhesions.
Melatonin may be useful during pregnancy. Melatonin is currently listed as contraindicated during pregnancy in various references but no rationale is given. As previously mentioned, several recent reviews suggest melatonin may be beneficial during pregnancy and prevent post partum depression. Given the unwanted effects of the medications currently used to treat pregnancy related reflux disease, melatonin may someday be judged preferable.
If melatonin is beneficial for these conditions, is there evidence to suggest that incidence of these conditions correlates with melatonin levels? A major factor in melatonin suppression is night time exposure to light. For example, an Israeli study correlated breast cancer incidence with night time out door light intensity. The study judged exposure to light at night by examining night time satellite photos taken by NASA.

There is evidence suggesting gastrointestinal disease fluctuates with night time light exposure and melatonin levels. Women who work night shifts make less melatonin. People suffering from shift work sleep disorder (SWSD), the diagnostic name for complaints that stem from working either night shifts or swing shifts, have a higher than average incidence of gastrointestinal disorders. The strongest correlation is with peptic ulcer disease.
Recall that night shift workers make less melatonin. A 2003 study analyzed data from the nurse's health study and looked at risk for colon cancer in relation to frequency of working night

shifts. The study concluded, "… working a rotating night shift at least three nights per month for 15 or more years may increase the risk of colorectal cancer in women."

This information should probably change the way we treat a number of conditions. We should consider using melatonin for a list of gastrointestinal conditions, actually pretty much everything, Crohn's Disease being the only possible exception. L-tryptophan, because it is a precursor to melatonin, may also be useful. Our experience in questioning patients with digestive complaints is that a surprising percentage will also complain of sleep disorders. It is this group of patients that have both digestive and sleep complaints that may benefit from melatonin.

Moderate doses of melatonin appear adequate for treating these conditions. The GERD studies used 6 mg doses. The UC studies used doses 3 mg.

It would seem that our modern illuminated lifestyle has inadvertently caused a hormone deficiency that has long term health implications. Knowing this opens the possibility of correcting a wide range of conditions.

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