

Melatonin and the Gut: The Untold Connection by **Ron Mariotti, ND and Eric Yarnell, ND, RH(AHG)**

Melatonin is a hormone critical to regulation of circadian rhythm, primarily in the suprachiasmatic nucleus of the hypothalamus. It is found in all life forms from algae to humans. Though it was previously believed that the pineal gland was the main source of melatonin, newer research has shown this to be false. The roles and function of melatonin are in fact clearly even broader than previously believed and may need to be cast in a whole new light in view of emerging research.

Gut vs. Brain Melatonin

In animals including humans, gastrointestinal (GI) tissue produces 400 times more melatonin than is found in the pineal gland.¹ It is also produced in the retina to a lesser extent. The concept that melatonin isn't primarily a pineal hormone begs the question of what the real breadth of function of melatonin is.

Melatonin is a potent immunomodulator, cytoprotectant, free-radical scavenger, supporter of mitochondrial function, regulator of cyclooxygenase-2 (COX-2), and neuroprotective.² Neural melatonin seems to serve a different function from enteric melatonin. Neural melatonin acts as an endocrine hormone and is secreted into the blood stream. Enteric melatonin produced in the gut and the retina acts as a paracrine hormone.

Nevertheless, research shows one cannot simply assign a singular role to each type of melatonin. Neural melatonin does regulate circadian rhythms but it also has a significant antioxidant role throughout the organism. Enteric melatonin is capable of acting as a protective antioxidant as well as a neurotransmitter, carrying information between the gut and the brain. Local effects of enteric melatonin include the ability to increase gut motility, protect the gut mucosa from ulcer formation, and protection of the pancreas.^{1, 3-9}

Enteric Melatonin: Sources and Actions

The production site of melatonin in the gut is the enterochromaffin cells, which are also the largest source of serotonin in the body.⁸ The trigger for release is the presence of food in the stomach. Melatonin acts to regulate the production of hydrochloric acid and pepsin as well as the myoelectric activity of the gut smooth muscle cells. In the gut, enteric melatonin acts as a direct scavenger of reactive oxygen species, increases microcirculation in the area, affects bicarbonate production via a receptor mediated pathway, and affects movement of gastric contents.^{8, 10, 11} Clinically, it is proposed as a potential means of prevention and treatment of colorectal cancer, ulcerative colitis, irritable bowel syndrome (IBS), and pancreatitis.^{8 4}

In a rat model, melatonin and L-tryptophan protected the gastric mucosa from various insults.¹² In these animals the removal of the pineal gland resulted in a down regulation of COX-2 mRNA expression. When exogenous melatonin was administered COX-2 mRNA was upregulated. It was concluded that the protective action of melatonin was due to an

increase in gastric microcirculation mediated by prostaglandin E₂, which was derived from COX-2 expression. In another, related study, it was found that the removal of the pineal gland caused hyperproliferation of the small bowel crypt cells.¹³

Melatonin is also found in the bile. It is thought that in the bile it acts as an antioxidant and serves to protect the organism from the oxidative damage of the bile acids and oxidized cholesterol derivatives.⁹

Clinical Implications

IBS affects 3-5% of the population in Western countries and causes an array of symptoms including abdominal pain, bloating, and irregular and unpredictable bowel habits. Most treatments have focused on the symptoms. However, our understanding of the gut-brain-axis has increased the sophistication at which we can approach patients with this condition.

Traditional therapies, for the most part, provide temporary relief. If we are to truly affect a change in these patients, it appears we must influence the nervous system at the level of the gut. Melatonin may provide us with a means to this end. Acting via the serotonin receptors we can alter gut motility.¹⁴ Melatonin, at doses of 3 mg per day over a two week period has been found, in humans with IBS, to decrease gastrointestinal pain, stool frequency, and rectal pain with defecation.¹⁵ This dose was not found, in this study, to have any effect on sleep patterns.

The surprising finding that melatonin is primarily a gut paracrine hormone requires a broadening of our thinking about this molecule. The notion that it just alters our reactions to light/dark patterns is clearly antiquated. The use of melatonin to regulate and protect gut function presents fascinating potential for clinical application.

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