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MELATONIN AND SEROTONIN EFFECTS ON GASTROINTESTINAL MOTILITY

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The gastrointestinal tract represents the most important extra pineal source of melatonin. Presence of melatonin (M) suggests that this hormone is somehow involved in digestive pathophysiology. Release of GI melatonin from serotonin - rich enterochromaffin EC cells of the GI mucosa suggest close antagonistic relationship with serotonin (S) and seem to be related to periodicity of food intake. Food deprivation resulted in an increase of tissue and plasma concentrations of M. Its also act as an autocrine and paracrine hormone affecting not only epithelium and immune system but also smooth muscle of the digestive tract. Low doses M improve gastrointestinal transit and affect MMC. M reinforce MMCs cyclic pattern but inhibits spiking bowel activity. Pharmacological doses of M delay gastric emptying via mechanisms that involve CCK2 and 5HT3 receptors. M released in response to lipid infusion exerts a modulatory influence that decreases the inhibitory effects of the ileal brake on gastric emptying. On isolated bowel S induces dose dependent increase in tone and reduction in amplitude of contraction which is affected by M. M reduced the tone but not amplitude or frequency of contraction. M is a promising therapeutic agent for IBS with activities independent of its effects on sleep, anxiety or depression. Since of its unique properties M could be considered for prevention or treatment of colorectal cancer, ulcerative colitis, gastric ulcers and irritable bowel syndrome.

Key words: *melatonin, serotonin, gastrointestinal motility*

MELATONIN AND GASTROINTESTINAL TRACT

Gastrointestinal motility is organized by the multifactor system based on the electromechanical and pharmaco-mechanical coupling. There are a great number of locally released factors from the gut that modulate motility and secretion. These factors can be classified according to main activity: inhibition or stimulation of the

gastrointestinal motility. Most of these hormones are well recognized but there is still a group of substances which require attention. Among them is the pineal hormone - melatonin. Melatonin is synthesized and secreted during the dark phase of the day in all species. Melatonin secretion is related to the length of the night: The longer dark phase contribute to the longer the duration of its secretion (1). This hormone seems to play an important role in modulation of gastrointestinal functions reflecting the cyclic pattern of food intake. Melatonin is indoloamine synthesized in the pinealocytes from tryptophan and serotonin is most direct precursor. Both hormones influence gastrointestinal motility by selective receptors expressed on the smooth muscles and myenteric plexus cells of gastrointestinal tract. The main source of these hormones in gastrointestinal tract (GIT) are APUD cells. The basal mechanism underlying the gastrointestinal smooth muscle contraction is the cyclic generation of the electrical current. The myoelectric activity of gastrointestinal tract consists of two kinds of potentials: slow wave and spike activity organized in myoelectric migrating complex (MMC). Interstitial Cajal's pacesetter cells (ICC) are under influence of internal and external autonomic nerves (2). ICC generates cyclic membrane potential changes called the basic electrical rhythm (BER) or the slow wave and determine bowel motility. The slow wave derives mainly from type IC-M pacemaker cells located in the external sheath of duodenal muscular layer and propagates aborally. This propagation is supported by IC-DMP cells located between the longitudinal and circular muscle layers (3).

Study of Kasimay *at al.* indicated that melatonin action is mediated by CCK2 and 5-HT₃ receptors and delay of gastric emptying. From this study appears that exogenous melatonin inhibits gastric motility in part by activating sympathetic neurons as well. These findings documented the relationship between serotonin and its derivative melatonin suggesting that high doses of melatonin inhibit gastric motility by interacting with serotonin receptors present on the vagal afferent fibers and inducing vago-vagal inhibitory reflexes (4).

The frequency of the slow wave determines the motor activity of the smooth muscles. The pacemaker region of the intestine is located in duodenal bulb close to pylorus is independent from the gastric electrical activity pacesetter. The frequency and velocity of the slow waves are the highest in the region of duodenal pacemaker and decreases caudally (3, 5). In the rat the duodenal slow wave frequency ranges from 20 to 40 cycles per minute and it has higher amplitude and longer plateau than in the jejunum. The BER amplitude varies from -55 to -35 mV (6). This electrical activity is influenced by a great number of the paracrine and neurocrine factors and is used as an indicator of gastro duodenal coordination. Melatonin in the fasted state induces dramatic reduction of the irregular spike activity (ISA) on the entire intestine including phase III of the MMC. Periodicity of MMC length decreased by 50%. Unfortunately frequency of slow waves were not calculated in this study (70), those effects of melatonin on myoelectric activity provide strong evidence that melatonin relaxes the bowel by acting mostly on phasic contractions.

Interdigestive motility is organized in migrating myoelectric complex MMC. A meal abolishes MMC changing it to irregular activity. The gastrointestinal tract motility depends on a dark-light cycle. Namely, motility is more activated during daylight than during dark period.

It is well known the role of melatonin in regulation of the biologic cycles. The dark triggers release of this hormone from the pineal gland during the night time but during the day a significant source of it seems to be gastrointestinal tissue. The gut is rich in melatonin and in some species melatonin concentration in gastrointestinal tissue surpasses the blood level up to 100 times (8). Melatonin is synthesized in enterochromaffin cells of the gut and its release most likely depends on periodicity of the food intake (9). The latest reports provided data that melatonin plays an important role in regulation of the gastrointestinal motility. This thesis confirmed the fact that postprandial motor response is shorter in the dark phase than light phase and this effect can be reversed by melatonin antagonist (10).

Merle *et al.* Suggested that endogenous melatonin act on pre and postprandial intestinal motility at night and this effect has been observed with exogenously administered hormone as well. Additionally, they found, that melatonin reinforce cyclic pattern of MMC but inhibit occurrence of irregular spike activity (7). Melatonin seems to interact with CCK in some motility aspects. Melatonin was found to reduce the duration of CCK stimulatory effects on gastrointestinal smooth muscle (10). Those authors speculate that melatonin is released to the lumen of proximal bowel in response to food intake and travels to the distal part. This may explain why the MMC pattern first reappears in the distal part of the bowel in the end period of satiety. Present reports although are inconsistent in the matter of the melatonin role on the gut motility. The report of Martín *et al.* suggests that melatonin release induced by lipid infusion alleviate inhibitory effect of lipid related ileal break. This suggests that melatonin plays modulatory role on the gastric emptying (11). These results correspond partially with reports of Drago *et al.* They found that small doses of melatonin accelerates the intestinal transit in rats. High doses reversed stimulatory effects of lower doses of melatonin. These results indicate that melatonin effect might be mediated by intestinal melatonin receptors. Moreover, administered intraperitoneally melatonin increased intestinal myoelectrical activity but its parameters change were not given. This effect was reversed by luzindole - melatonin competitive receptor antagonist and seems to be mediated by peripheral receptors (12).

MELATONIN AND SEROTONIN ANTAGONISM

Acceleration of intestinal transit by melatonin was previously described by the group of Bubenik *et al.* They tested the interaction of melatonin and serotonin and found that serotonin induced decrease of the food transit was partially blocked by melatonin. In this interesting study melatonin *in vitro* reduced the tone of gut

muscles and counteracted the tonic effects of serotonin. They proposed the hypothesis of counterbalancing system of melatonin and serotonin in regulation of gut activity (13, 14). Lee and Pang suggest that melatonin has direct effect on bowel functions it decrease serotonin induced gut contraction, alleviates serotonin induced gastric mucosal flow and inhibits proliferation of epithelium (15). The protective role of melatonin against damage induced by stress, ischemia-reperfusion injury is well documented. This action is mediated by limitation of the free radical activity and stimulation of mucosal renewal and prostaglandin release.

Additionally, melatonin-serotonin system is claimed by the same author to affect appetite and digestive processes by endocrine as well as paracrine effects in both the brain and the GIT (16). Melatonin was proposed to regulate pancreatic secretion and maintain the integrity of pancreas (17). The knowledge about the role of melatonin in gastrointestinal motility is still limited and requires detailed studies. In contrast serotonin role on the motility was pretty well researched. The different types of serotonin receptors are expressed on different gastrointestinal cell and enteric nerves, smooth muscle and interstitial cells of Cajal (18). Enterochromaffin cells of the epithelial cells release serotonin into the lumen and stimulate colonic motility in rats *via* selective 5HT receptors (19). Released 5-HT stimulates local enteric nervous reflexes to initiate secretion and propulsive motility. On the other hand serotonin inhibits the peristaltic reflex when injected but in contrast gut motility is stimulated when serotonin is applied locally to the serosal side of the bowel (20). Serotonergic neurons play an important role in maintaining the balance between contractile and relaxant activity of GIT smooth muscles. Expression and function of these receptors differs in animal models. Some receptors mediate relaxation, other only inhibition or activation of smooth muscles. This diversity and different mode of release makes difficult to establish correlation and clear function of serotonin in GIT (21). Serotonergic neurons participating in the neural control of gut motility are present within the enteric intramural nervous system. Some neurons of ENS can either be depolarized or others can be hyperpolarized by serotonin (20). Serotonin receptors are also present on pre and postsynaptic neurones at the level of dorsal horn of the spinal cord mediating and modulating the visceral pain (22). There is evidence that destruction of enteric serotonergic neurons disrupts the MMC: reduces BER frequency, increases its duration and decreases its propagation velocity. These data support the cellular concepts that serotonin is an important mediator which modulate and process the sensory stimulation in the intestine (*Fig. 1*) (23).

The importance of both hormones in modulating gastrointestinal motility and their interaction is still not fully elucidated. Their action seems to have the contrary effect on the motility and the end effects are dose depended. Melatonin and serotonin are also involved in the hypersensitivity processes and pain conduction (24, 25). Recent clinical reports indicate that the treatment with melatonin alleviate the clinical symptoms in the irritable bowel syndrome (26, 27)

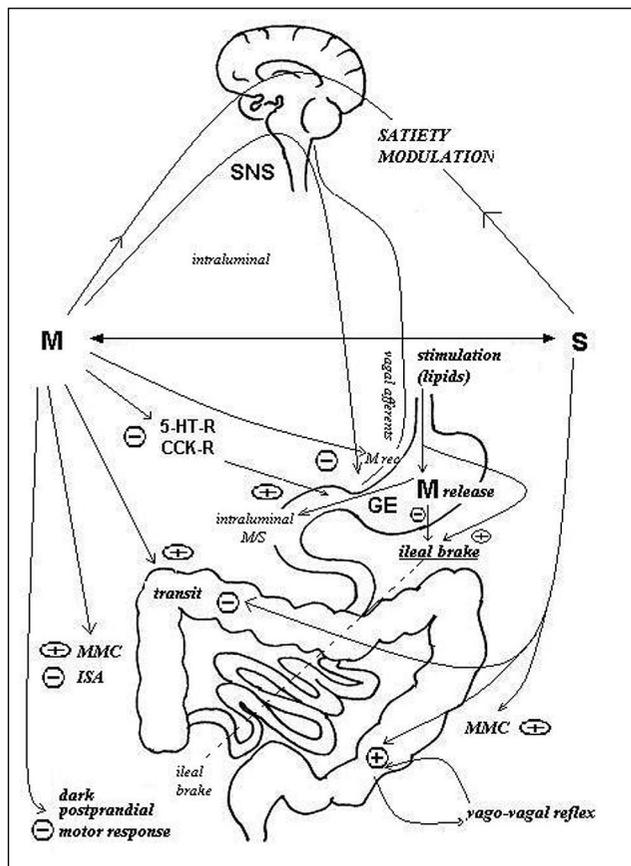


Fig.1. Schematic presentation of the melatonin-serotonin action on the gastrointestinal tract. Abbreviations: SNS - sympathetic nervous system, GE- gastric emptying.

acting along the brain-gut axis (28). The intelligent modulation of the gastrointestinal motility with melatonin/serotonin on brain-gut axis may be a key point in the treatment of patients resistant to standard therapy functional disorders of GIT. In order to introduce these promising substances into the therapeutic use, basic research for the clear recognition of their interaction and function has to be performed in the nearest future.

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