



Circadian rhythm and its potential influence on gut motility

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The gastrointestinal system exhibits circadian fluctuations in activity that are under control of central and peripheral mechanisms. Disturbance of such rhythms may be associated with symptoms like constipation. Available evidence shows that stimulant laxatives such as bisacodyl can act synchronized on circadian colonic fluctuations helping to restore physiological gut rhythms.

Circadian rhythms make us go to bed and to wake up at certain times. They also regulate fundamental biological processes such as diurnal variation of blood pressure control and airway resistance. Such rhythms have strong therapeutic impact, for instance, the recommendation to administer oral glucocorticoids early in the morning to synchronize with endogenous cortisol peaks. Anybody having taken long-distance flights covering multiple time zones may have experienced jet lag as a classic symptom of disturbed circadian rhythm, and perhaps also constipation within the first days upon arrival. The latter, also known as ‘traveler’s constipation’ [3] exemplarily shows how circadian rhythms may affect gastrointestinal (GI) functions. A recent systematic review discusses how disruption of circadian rhythms can affect GI functions, the underlying mechanisms and their implications for pathologies such as constipation and irritable bowel syndrome [1].

Circadian rhythms of the gut are orchestrated by an interaction between central and peripheral clocks: the suprachiasmatic nucleus (SCN), acting as the central circadian pacemaker, and organ-specific peripheral clocks. The SCN resets itself using light signals (Fig. 1) and resets the clocks in peripheral organs, subsequently influencing circadian patterns of expression of specific genes e.g. regulating gut function. Besides, the GI system is further influenced by local cues such as nutrient availability or behavioral factors such as sleep/wake cycles (Fig. 1) [1, 2]. The SCN and peripheral core molecular clocks oscillate in a 24-hour rhythm and are responsible for the periodic activity of various segments and transit along the GI tract. Morning awakening or meals, respectively hormones such as motilin, ghrelin, gastrin or serotonin can enhance colonic motility, while sleep is known to strongly inhibit both propagating and non-propagating

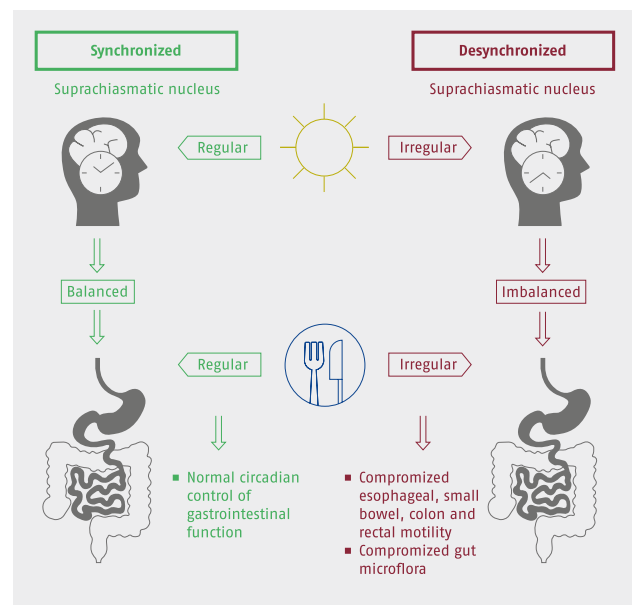


Fig. 1. Normal and disrupted circadian control of the gastrointestinal tract. Reproduced with permission from [1].

contractions [1]. As a result, the GI system is in a resting state at night, rapidly activated at the time of awakening and then exhibits increased activity throughout the day. However, if inner clocks are desynchronized gut function can be negatively affected, e.g., during Ramadan fasting – causing a shift to nighttime eating when the gut is in a resting state – an increase in constipation was observed [1].

Disrupted circadian rhythm can contribute to the GI disorders such as constipation including ‘traveler’s constipation’ and may also apply to the much larger group of

people working night shifts on a regular base. Furthermore, a role of altered circadian rhythms has been discussed for constipation related to irritable bowel syndrome (IBS) and neurodegenerative diseases. This raises questions on how circadian rhythms can be leveraged by therapeutic interventions to promote GI functioning. Theoretically, this could be achieved by directly addressing the circadian rhythm, for instance by administering melatonin, and some studies suggest certain dosing regimens of melatonin being beneficial in inflammatory bowel disease [1]. Another approach is the application of oral laxatives which facilitate morning evacuation in constipated patients. This will help to restore the disturbed/dysfunctional circadian rhythm of the gut. According to several studies [1], stimulant laxatives acting synchronized with the circadian rhythm help to restore natural circadian gut functionality: bisacodyl when taken at night, mimics the naturally occurring circadian rhythm promoting peristalsis and secretion of fluid in the gut resulting in a bowel movement in the morning.

Taken together, these data demonstrate that disrupted circadian rhythms may be an important contributing factor to conditions such as constipation. Interventions restoring natural rhythms, including certain laxatives, may promote GI health. However, further studies are required to substantiate the beneficial effects of laxatives on circadian rhythms in the gut.

Literature

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