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Gut microbiota modulates diurnal secretion of glucocorticoids

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Abstract

A new study has identified the sophisticated communication between the gut microbiota and intestinal epithelial cells that controls diurnal variations in the secretion of corticosteroids in mice. The absence of gut bacteria disrupts this communication and contributes to hypertriglyceridaemia, hyperglycaemia and insulin resistance.

Mammals are born germ-free but immediately encounter microbes that they develop a lifelong symbiotic relationship with. The gut supplies bacteria with nutrients, and the microbiota increases the digestive capacity of the gut, provides the host with essential nutrients, and protects the host against potential pathogens.¹ A critical factor in this successful mutualism is the emergence of adaptive immunity. Bacteria express microbe-associated molecular patterns, which are recognized by pattern-recognition receptors such as Toll-like receptors (TLRs) by the host. This interaction activates immune-cell responses and is crucial in the development of a durable immune system and in the prevention of inflammation. Intestinal epithelial cells (IECs) are critical to provide a physical barrier between the host and the gut microbiota, as well as a doorway for communication between the two. A recent study by Mukherji *et al.* provides molecular insights into the microbial–host interactions that might be important in the regulation of circadian rhythms in IECs.²

Several physiologic and behavioural activities have circadian rhythms that are controlled centrally by the suprachiasmatic nuclei (SCN) in the brain. The SCN is synchronized to daily light–dark changes by optic signals delivered by the retinohypothalamic tract. The optic signals are translated into molecular events, which result in temporal expression of the core clock genes.^{3–5} Normal circadian metabolism is ensured by a rhythmic and tightly coordinated expression of genes that encode regulators and metabolic enzymes. This control requires a complex regulatory network with feedback loops and transcriptional regulators, including the proteins encoded by the core clock genes *Clock* and *Arntl* (also known as *Bmal1*) as well as the activator nuclear receptor ROR- α (encoded by *Rora*) and a repressor called NR1D1 (encoded by *Nr1d1*), which is also known as Rev-erbA- α .^{4,5} The circadian signals from the SCN are transmitted to other tissues via hormones and serum factors that are not well-understood. In addition to the SCN, clock genes are expressed in peripheral

Competing interests

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tissues, and their expression is probably influenced by food and body temperature.³ Thus, as opposed to the SCN where circadian rhythms are affected mainly by the light, peripheral clock genes integrate several neuronal, hormonal, metabolic, environmental and biochemical cues to maintain their rhythmicity.^{3,6}

Glucocorticoids, such as cortisol (in humans) and corticosterone (in rodents), are steroid hormones that have a critical role in metabolism and immune regulation. Corticosterone secretion exhibits diurnal variations and is mainly controlled by the hypothalamus-pituitary-adrenal axis. However, IECs have also been shown to synthesize corticosterones.⁷

Mukherji *et al.* studied the effect of the gut microbiota on the circadian regulation of the secretion of corticosterone by ileal IECs in mice.² The gut microbiota secretes several products that affect the physiology of IECs, for example, by helping with the differentiation and proliferation of epithelial cells.¹ Mukherji and colleagues show that the interaction between bacterial products and TLRs expressed on IECs results in decreased expression of peroxisome proliferator-activated receptor α (PPAR- α), which is encoded by *Ppara* (Figure 1). Hence, under normal conditions, the expression of *Ppara* in IECs is low. However, when mice are treated with antimicrobial agents or kept in germ-free conditions, TLRs are not activated by bacterial products, which results in increased expression of *Ppara*. Increased levels of PPAR- α interfere with the normal circadian regulation of corticosterone synthesis by the IECs by increasing the expression of NR1D1. When levels of NR1D1 are high, this repressor reduces the expression of the gene encoding nuclear factor interleukin-3-regulated protein (*Nfil3*; also known as *E4bp4*). Low levels of *Nfil3* result in increased and sustained synthesis of corticosterone throughout the day.

A sustained increased secretion of corticosterone affects metabolism and contributes to hyperglycaemia, hypertriglyceridaemia, insulin resistance and high levels of fatty acids, which are seen in mice chronically treated with antibiotics or kept in a germ-free environment.² Constant low expression of *Rora* and high expression of *Nr1d1* in germ-free mice leads to a continuous low concentration of *Arntl*, which in turn disrupts the circadian rhythms.²

The study by Mukherji *et al.* highlights several novel features related to the circadian regulation of cellular physiology such as the synthesis of corticosterone. The study provides evidence that bacterial products influence the cellular circadian variations, and it explains some of the molecular pathways that might be regulated by the exposure of IECs to bacterial products. Mukherji and colleagues explain how high levels of PPAR- α disrupt circadian rhythms by upregulating NR1D1. Future studies might identify molecular inputs that disrupt circadian mechanisms in peripheral tissues. The overproduction of corticosterone by ileal IECs could have profound effects on physiology and metabolism in mice, although the corticosterone from IECs contributes considerably less to the plasma concentration than the corticosterone secretion regulated by the hypothalamus–pituitary–adrenal axis. Although glucocorticoids can reset circadian clocks in cultured cells,⁸ the experiments by Mukherji *et al.* in the absence of bacteria provide a molecular mechanism that could reset the cellular circadian clocks when TLRs are inactive. Corticosterone produced in IECs could synchronize circadian rhythms in the IECs.

The study by Mukherji and co-workers opens up several novel questions. The authors discuss that noncircadian production of bacterial products could transmit their signal because of circadian expression of receptors such as TLRs. Secretion of bacterial products might also be rhythmic; after all, bacteria in the intestine are exposed to food in a rhythmic manner just like IECs. This theory can be tested by assessing changes in the bacterial populations or concentrations of bacterial products in the intestinal lumen after providing animals with food only for short periods of time over several days.

IECs consist of several types of differentiated cells, such as enterocytes, goblet cells and enteroendocrine cells. Further studies could investigate which type of cells respond to the bacterial products and produce corticosterones. Another question to address is how the IECs respond to bacterial products when circadian rhythms are disrupted by factors such as sleep deprivation, jetlag or a high-fat diet. Furthermore, how corticosterone produced by ileal IECs only affects the ileum but not the colon is unclear. Yet, deregulation of corticosterone synthesis by IECs affects whole-body metabolism, which causes hypertriglyceridaemia, insulin resistance and hyperglycaemia. It will be interesting to see whether agents that re-synchronize production of corticosterone by IECs could be used to treat diabetes mellitus.

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Figure 1.

Regulation of corticosterone synthesis by intestinal epithelial cells in normal and germ-free mice. Bacteria activate TLRs, which leads to low levels of *Ppara*. The expression of *Nfil3*, *Arntl* and *Rora* is high at time ZT0 in the circadian cycle. By contrast, *Nr1d1* levels are low, which results in low levels of corticosterone. Under germ-free conditions, TLRs are not activated, which leads to high, sustained expression of *Ppara*, continuous high expression of *Nr1d1* and disruption of the circadian cycle and thus increased synthesis of corticosterones. Abbreviations: ZT0, 0600 h; ZT8, 1400 h; ZT12, 1800 h.