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Hypothalamic–pituitary–adrenal function during health, major surgery, and critical illness

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Key points

- The circadian rhythm of the hypothalamic–pituitary–adrenal (HPA) axis is composed of 45–60 min pulses of cortisol, known as an ultradian rhythm.
- The corresponding pulsatility in cortisol-receptor binding is important for normal functioning with varying effects on gene transcription.
- Cortisol-binding globulin acts as a reservoir and effectively delivers free cortisol to inflammatory sites.
- The value of point assessments of HPA axis function in the intensive care unit is therefore probably of minimal use other than to diagnose *absolute* deficiency.

The basic constituents of the hypothalamic–pituitary–adrenal (HPA) axis will be familiar to most physicians because the 'stress response' is seen after any significant illness, injury, or surgery. However, this article seeks to highlight the substantial advances in understanding that have been made in the last decade and how these may alter treatment and guide future research.

The HPA pathway

A simple schematic of the HPA axis can be seen in Figure 1.[1] The paraventricular nucleus (PVN) of the hypothalamus is the 'control centre' of the HPA axis. It receives input from multiple other centres:

Suprachiasmatic nucleus: the body's 'biological clock' provides diurnal information, modulating inhibitory gain to the PVN, resulting in low activation during periods of sleep, increasing in anticipation of awakening and peaking in the morning, the basis of the circadian rhythm.

Brainstem nuclei: delivers information from physiological changes such as hypotension or inflammation.

Limbic region: provides stimulation from cognitive or emotional stressors.

Sympathetic/sensory: in addition to higher centre inputs at the hypothalamus, there is also extensive sensory and sympathetic innervation to the end target, the adrenal glands, via the splanchnic nerves. Both cholinergic pre-ganglionic and catecholaminergic post-ganglionic sympathetic fibres synapse at the adrenal gland and appear to sensitize it to adrenocorticotrophic hormone (ACTH), increasing cortisol release. This is probably an indirect effect—vasodilation leads to a higher adrenal blood flow which in turn means more cortisol output. Furthermore, the adrenal gland has autonomous clock genes exerting additional circadian control on steroidogenesis and ACTH sensitivity. This effect may be modulated directly by light and possibly via splanchnic innervation.

The PVN contains two types of neuroendocrine cells:

Magnocellular neurones synthesize arginine vasopressin (AVP—also known as anti-diuretic hormone, ADH), which is then transported to the posterior pituitary (an embryological down-growth from the hypothalamus), for storage and subsequent release.

Parvocellular neurones synthesize corticotrophin-releasing hormone (CRH), which is secreted from the median eminence of the hypothalamus into the hypophyseal portal

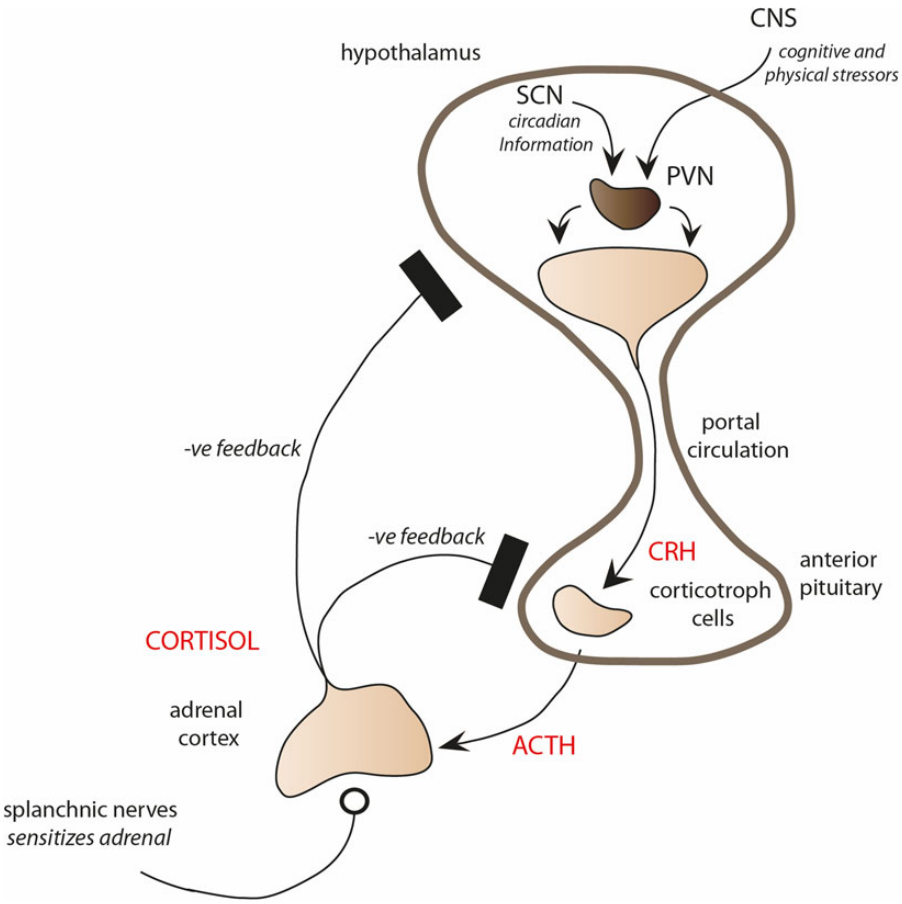

Fig 1 Basic HPA axis control. Arrows indicate positive feed-forward. Blocks indicate negative feedback. CNS, central nervous system; SCN, suprachiasmatic nucleus; PVN, paraventricular nucleus; CRH, corticotrophic-releasing hormone; ACTH, adrenocorticotrophic hormone. (Reproduced with permission from reference 1.)

circulation. CRH acts upon corticotrophs in the anterior pituitary prompting secretion of ACTH into the systemic circulation, which in turn stimulates cortisol release from the *zona fasciculata* of the adrenal cortex. Cortisol is synthesized *de novo*, secreted, and circulating free cortisol then exerts a negative feedback effect at the pituitary to reduce ACTH secretion and inhibit CRH release at the PVN. 'Normal' people under unstressed conditions normally produce the equivalent of about 20–25 mg hydrocortisone per day.

Ultradian rhythm of ACTH and cortisol

The familiar circadian rhythm of cortisol and ACTH (high in the early morning and low in the late afternoon and evening) is in fact composed of an *ultradian* rhythm of pulses lasting around 45–60 min.[2] The peaks of the circadian rhythm are generated by high amplitude pulses and the troughs by smaller pulses, or non-pulsatile activity (see Fig. 2). The term ultradian refers to any biological cycle that repeats more frequently than daily, whereas circadian rhythms follow a 1 day cycle. This pulsatility used to be considered to come from a pulse generator within the hypothalamus, but recent studies have concluded that it is more likely generated from the positive feed-*forward* from the pituitary (ACTH) and negative feed-*back* relationship from the adrenal (cortisol).[3] The driver 'pushing' the system is the hypothalamic CRH. It may be imagined on a simple level like a 'Newton's Cradle' system; where ACTH and cortisol are two balls oscillating at alternative ends and CRH is the driving force to maintain and vary propulsion.

Ultradian rhythms are relatively commonplace in neurological and other neuroendocrine pathways responsible for maintaining homeostasis. Pulsatile signalling affords many benefits including greater signal control, higher energy efficiency, and enables receptor recovery between pulses, which is essential for maintaining target responsiveness. Since pulses can vary in amplitude, duration, shape, and frequency, pulsatile signalling also transmits much greater information to the target receptor when compared with continuous signalling. This can be illustrated by comparing a colour television image (where each pixel can vary in frequency and amplitude) with that of a black and white television (where pixels may only vary in amplitude). Since the ultradian pattern of ACTH and cortisol release is relatively newly determined, much of the research seeking to accurately quantify HPA activity in health and after injury or surgery may be inaccurate due to insufficient sampling frequency.

Pulsatility is important—patients with absolute cortisol deficiency (Addison's disease), who take physiological cortisol replacement but lack the pulses, are twice as likely to die as their peers.[4] Pulses of cortisol also exhibit characteristics of an effective refractory period—the same stressor applied at different phases of the ultradian cycle appears to elicit differing magnitudes of cortisol response. An exaggerated response occurs if the stressor is applied during the increasing cortisol phase,