Content:
Posttraumatic stress disorder (PTSD) is a psychological and physiological manifestation resulting from exposure to a significantly traumatic event and is the single anxiety disorder most experienced by Australians, affecting up to 6.4% of people aged 16-85 years of age [1]. Psychological symptoms of PTSD include recurring nightmares and distress following either reminder or memory of the traumatic event, all of which reconsolidate the feelings of fear and helplessness involved in development of the disorder [2]. Persistent PTSD also has a high rate of comorbidity with other stress-related conditions including aggression, anxiety, and depression [3]. However, unlike most other stress-related conditions, PTSD patients often present with abnormally low concentrations of the stress hormone, cortisol, while sympathetic catecholamine concentrations, responsible for the fight or flight response, are relatively high. This, coupled with the observation of elevated corticotrophin-releasing hormone (CRH) from the hypothalamus, indicate that the hypothalamic-pituitary-adrenal (HPA) axis is dysregulated in PTSD [4].

Three discrete axes mediate the response to an acute stressful situation. The sympatho-adrenal-medullary (SAM) axis via the locus coeruleus centrally, and the adrenal medulla peripherally, uses catecholaminergic signalling to enable rapid energy expenditure in order to avoid the stressor. Part of this response involves the priming the hypothalamic secretory neurons of the HPA axis. A second hypothalamic-spinal-adrenal (HSA) axis is recruited concurrently with the SAM axis and uses a direct connection between the hypothalamus and the adrenal gland to prime the adrenal cortex for secretion of stress hormones. Finally, the HPA axis releases the short-range neurotransmitter and hormone, CRH, through specialised blood vessels to the pituitary gland, resulting in the release of adrenocorticotropic hormone (ACTH) into the general circulation where it acts directly on the adrenal gland to release cortisol. These systems are subject to negative feedback at multiple levels in order to rapidly reinstate homeostasis in the absence of stressful stimuli. Evidence of this feedback system can be observed with the administration of the synthetic glucocorticoid, dexamethasone, to measure the functionality of the pituitary and adrenal glands.

Patients suffering PTSD display a hypersensitivity to glucocorticoid negative feedback, with dexamethasone significantly decreasing both ACTH and cortisol. The sensitisation of glucocorticoid receptors at least at the level of the pituitary gland is thought to be the most likely cause of this irregularity [4]. Consequently, the pituitary output of ACTH, and subsequently adrenal cortisol, is diminished, while the
hypothalamus endeavours to rectify this by increasing the output of CRH. As CRH also acts as a neurotransmitter, this affects other neural regions, most notably the locus coeruleus, which in turn maintains the SAM axis activity to increase catecholamines. Clinically, this can be observed in PTSD by monitoring the urinary output of catecholamines of which both adrenaline and noradrenaline are significantly elevated in PTSD patients. This, in combination with the characteristically low urinary output of cortisol, can be used as a reasonably specific ratio (catecholamine/cortisol) to distinguish PTSD from other neurological conditions including major depressive disorder, bipolar, and schizophrenia [5, 6].

The activity of the HPA axis normally exhibits a prominent 24-hour circadian rhythm with the circadian peak and trough occurring in the morning (waking) and evening respectively. This biological rhythm has many important functions in the timing and distribution of energy reserves in addition to regulating the availability of other hormones important for growth and reproduction. Patients suffering PTSD display a ‘flattened’ circadian secretion of cortisol, with low waking and elevated evening concentrations which overall results in a decreased cortisol output [7]. One major symptom resulting from this loss of endocrine rhythmicity is the disruption of the sleep-wake cycle, subsequently leading to insomnia, and increased incidence of emotional disturbance.

There is a higher incidence of PTSD among females, with 8.3% of Australian anxiety disorders being attributed to females aged 16-85 years old compared to the 4.6% attributed to males [1]. Although psychological reasons such as differing coping strategies are still widely debated, physiologically, females exhibit substantially higher basal and stress-responsive cortisol concentrations. This is the result of the higher HPA axis output due to the stimulatory effects of oestrogen. Increased reactivity and prolonged duration of HPA axis activity may be one explanation for the higher susceptibility of female PTSD incidence during a significant traumatic event. However, due to the large variability in the initial causative trauma, in addition to differing psychological profiles preceding trauma exposure, the development and progression of PTSD and the direct mechanisms underlying this disorder remain debateable from a neuroendocrine perspective.

References:


