

HPA Axis and the Adrenal Hormones



Hypothalamus
Corticotropin releasing hormone (CRH) is synthesized by neuroendocrine neurons in the paraventricular nucleus (PVN) of the hypothalamus. CRH is released into the hypophyseal portal circulation supplying the anterior pituitary gland.



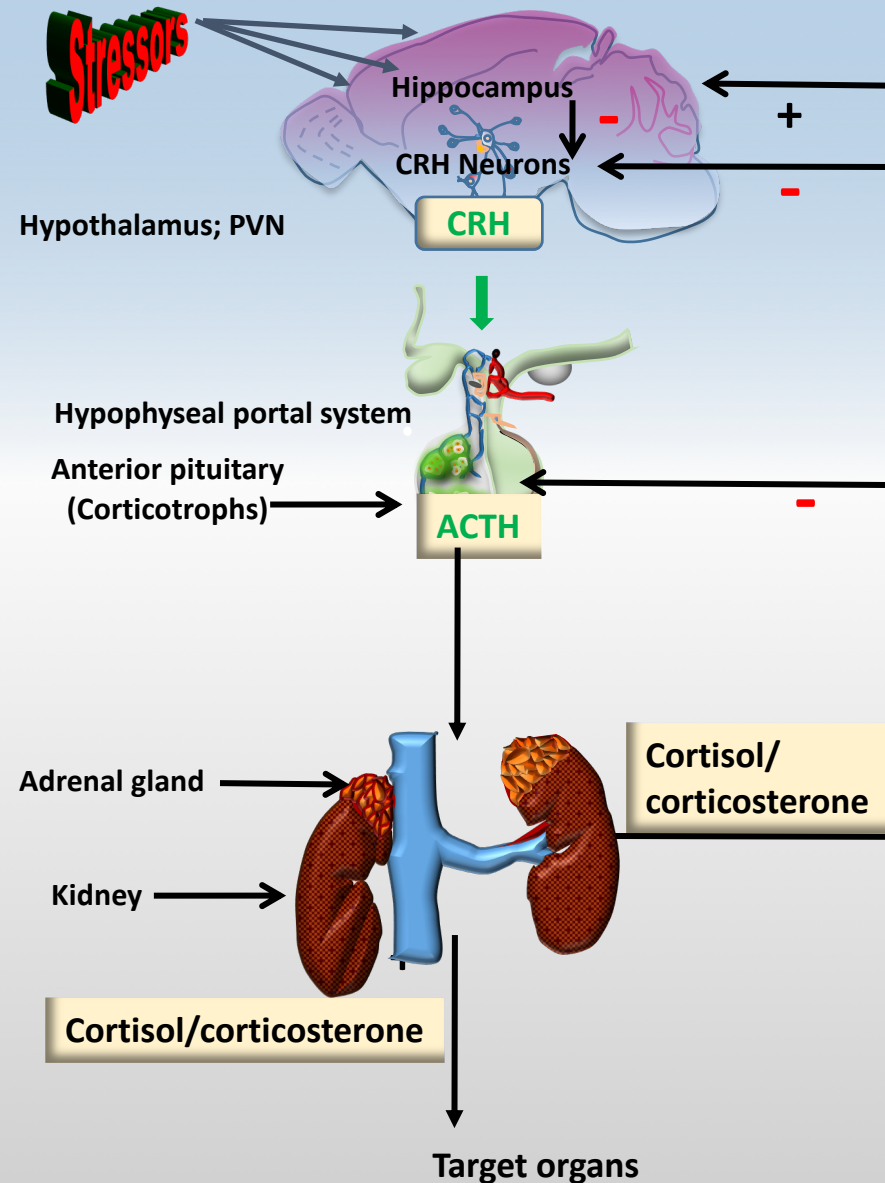
Pituitary
In the anterior pituitary, CRH binds to CRH-R1 receptors on corticotrophs to stimulate adrenocorticotrophic hormone (ACTH) secretion. ACTH is cleaved proteolytically from a complex precursor protein, pro-opiomelanocortin (POMC).



Adrenal gland
ACTH selectively activates the melanocortin 2 receptor (MCR2) in the zona fasciculata of the adrenal gland cortex. The adrenal cortex responds to ACTH stimulation by increasing synthesis of enzymes involved in the metabolism of the steroid hormone precursor, cholesterol, to glucocorticoids (cortisol or corticosterone). Other hormones produced by the adrenal cortex include progesterone, DHEA and the mineralocorticoid, aldosterone.



Target organs
Glucocorticoids bind to glucocorticoid receptors (GR) and mineralocorticoid receptors in numerous target tissues. Through GR, their principal action is to increase blood sugar through gluconeogenesis. Glucocorticoids also inhibit digestion, reproduction and immune function. In brain, they modulate stress-related behaviors and negative feedback to CRH neurons.



The HPA axis is a principal component of the stress response and homeostasis. It is activated by stress, whether psychogenic or physical. Its main secretory hormone, cortisol, is beneficial in the short term and is part of the ‘fight or flight’ response to allow homeostasis in face of environmental perturbations. However, chronically elevated levels can be detrimental and increase disease risk. In addition, when elevated during development, glucocorticoids can program long term changes in physiology which can result in increased disease risk in adulthood. This is one component of the Developmental Origins of Health and Disease (DOHaD) hypothesis.

Dr. Handa has spent a significant part of his academic career studying the HPA axis and the effects of stress on brain function. His studies show sex differences in the HPA axis, interactions between the HPG axis and stress responsivity. He has also evaluated the long-term consequences of prenatal exposure to glucocorticoids and stress on adult metabolism and autonomic function.

Dr. Cooper has evaluated the role of HPA activation on gonadal function in animals treated with chemicals capable of affecting both the HPA and HPG axis. Drs. Breckenridge, Handa and Foradori, as associate of QS³, have similarly explored effects of chemicals on adrenal gland function.

Let the experts at QS³ assist you in interpreting the toxicological effects of your chemical on the effects of HPA axis activation and its consequences for subsequent development.