

## AMAZING PAPERS IN NEUROSCIENCE

# Introduction to the Hypothalamic-Pituitary-Adrenal Axis: Healthy and Dysregulated Stress Responses, Developmental Stress and Neurodegeneration

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Neurohormone systems, which regulate the maintenance of homeostasis and allostasis during stress, are a fundamental subject in the understanding of neuroendocrine function. One neuroendocrine system, the hypothalamic-pituitary-adrenal axis (HPA), is crucial for stress management. Study of the HPA-axis illustrates a mélange of interactions between different physiological systems to ensure survival, longevity, development and homeostatic maintenance. While some stress is important for healthy development, chronic stress has pathological consequences. It is important that neuroscience students have a robust

understanding of the HPA axis and a comprehension of the long-term negative physiological effects of stress. The three papers discussed here provide both an understanding and a greater context of the pervasive effects of chronic stress outside of the typical peripheral physiological responses usually discussed, such as heart and respiration rates. They clarify the effects of stress on the brain and neuroendocrine systems.

*Key words: acute stress, chronic stress, Hypothalamic-pituitary-adrenal axis (HPA), neurodegeneration, aging, neuroendocrinology*

The stressful conditions one experiences during development can have significant and long-reaching effects on their ability to react and cope with environmental, physical or mental disruptions to homeostasis. The hypothalamic-pituitary-adrenal axis (HPA) is the main stress response system. It is the neuroendocrine link between perceived stress and physiological reactions to stress (Breedlove and Watson, 2013). The primary function of the activated HPA axis is to release glucocorticoids that activate short-term physiological responses to stress. While some stress is necessary for salubrious development and aging, when an individual exists in a chronic state of stress their ability to cope is compromised by dysregulation of HPA-axis and other peripheral physiological functions. The acute stress response is initiated by short-term stressors and enables short-term behavioral and physiological coping mechanisms. Whereas, the effects of long-term chronic stress may manifest not only in an overall decline in fitness or immune health, but also in neurodegenerative brain disease linked to HPA-axis dysregulation (Esch et al., 2002). The three publications reviewed here provide an accessible introduction to the interplay between the HPA-axis, chronic stress and neurodegeneration. These papers emphasize the importance of understanding how stress activates the HPA-axis, the advantages of short-term activation, and the deleterious effects of long-term HPA-axis activation on neurological and immune function (especially during developmental periods). They illustrate that through feedback, acute and chronic stress can affect the ability of the HPA-axis to cope with future stress.

The first publication of note is a review by Monaghan and Spencer (2014). In this paper, they outline the immediate physiological and behavioral advantages and repercussions of acute stress and describe the pathway by which the HPA axis regulates the glucocorticoid corticosterone and its corresponding physiological effects. The review emphasizes the importance of stress related neural

programming during developmental and seasonal periods, where physiological tolerances for stress may shift. Specifically, Monaghan and Spencer (2014) discuss why animals may experience shifted stress tolerances, how coping mechanisms are based on the timing and duration of stress, and the ability of the acute stress response to restore homeostasis. They also discuss how specific levels of acute or chronic stress affects an animal's survival, and thus, acts as a selective evolutionary pressure. This review emphasizes the importance of behavioral, developmental and time dependent contexts when studying stress. The review explains that although two individuals may experience the same type of stress, it could have widely variable effects based on the developmental period and timescale in which the individual experiences the stress. When tolerances for stress change seasonally, the degree of effort required to restore homeostasis changes, and this can result in a greater allostatic load (accumulation of stressful experiences).

In a second notable research article, Spencer et al. (2008) used an innovative and novel avian model of early postnatal stress to provide the first direct evidence that postnatal stress affects glucocorticoid programming of the acute (HPA) stress response. Increased corticosterone levels were shown to exaggerate and prolong zebra finch stress responses. Spencer et al. (2008) provided a novel model preparation to explore the role of glucocorticoids in determining adult phenotypes: the zebra finch. Using a zebra finch model eliminates the complication of maternal corticosterone transfer through lactation. This approach cleverly overcomes a confounding factor associated with the previous mammalian model. Rather than modify or over manipulate the mammalian model, they establish the basis for a superior one. In doing so, they illustrate the impact of chronic stress during crucial early life development and its long-lasting consequences. This research article expands upon the first review by illustrating that the timing of stress

during development can alter the HPA-axis and the ability to maintain homeostasis and day-to-day functions.

Finally, the paper of de Pablos et al. (2014) highlights the links between the HPA-axis and neurodegenerative disease influenced by chronic stress. They found that damage induced by an endotoxin in the substantia nigra was enhanced significantly in chronically stressed rats. These rats exhibited more dopaminergic neuron death than non-stressed rats because of microglial activation and upregulated inflammation. The de Pablos et al. (2014) paper builds upon the first two papers by highlighting the severe effects of chronic stress and stress response dysregulation that may predispose individuals to chronic neurodegenerative disease or exacerbate the pathogenesis of neurodegeneration. Primarily, the work of de Pablos et al. (2014) highlights the exaggerated neurodegeneration that can occur because of HPA-axis dysregulation due to chronic stress. Given the recent popularity of research into age-related brain disease and mechanical stress on the brain linked to chronic traumatic encephalopathy, this paper is very relevant.

## VALUE

These papers highlight the contrast between a healthy stress response and the dysregulated stress response. Importantly, this contrast points out the opposing roles that a single type of input can have on a neurological system just by varying the length of the input (i.e., length or timing of a stressful event). Often, inputs are described as only negative or only positive, but these papers show that the effect of a stressful stimulus on neuroendocrine function is time and development dependent. Overall, these papers supplement the textbook view of the HPA-axis by providing physiological context for research into the long-term effects of stress on the central nervous system.

Neuroendocrinology is a complex interdisciplinary field. These papers make the field accessible to a general undergraduate neuroscience audience. They delve into the background of stress by giving students the vocabulary with which to read and critically analyze information pertaining to the effects of chronic stress. The papers progress from the basic function of the acute stress response to dysregulation caused by chronic stress and the subsequent impacts on the health and disease progression of the aging brain. They facilitate a strong general understanding of stress and neuroendocrine function by raising key questions and providing context. Discussion about the assumptions and limitations of each study and methods may be prompted in the classroom.

As an aside, there are simple, relatively inexpensive and accessible cortisol (stress hormone) student activities that can complement these papers. For example, Bañuelos et al. (2017) have students quantify the human acute stress response through saliva tests that track hormone level increases accompanying thinking about a stressful event, for example, a pop quiz. Such a lab exercise would provide valuable and relevant context when juxtaposed with these papers.

Neurodegenerative disease is a hot topic and looking at it through neuroendocrine function is one way to frame the

topic for undergraduate students. Discussion of these papers would help emphasize the greater scope and context of why researchers seek to understand small portions of a specific neural system, in this case the dysregulation of the HPA-axis following chronic stress or the effects that chronic stress may have on pathogenesis of neurodegeneration. Additionally, these papers frame investigation into the HPA-axis in different ways and illustrate the importance of critical analysis using different methods.

## AUDIENCE

These three papers vary in focus and scope. Given the clarity and varied context of the texts, they are intriguing, informative and highly accessible to undergraduate neuroscience students. Typically, students would read the papers in the same order presented here. With strong emphasis placed on the first review, these papers could be a supplement or a replacement for an introduction to neuroendocrinology for college students in their junior or senior years. With heavier emphasis on the second and third papers, this trio may be used to delve deeper into long-term stress effects on neurodegenerative disease and the influence that early life stress has on development. At an advanced level (final year or masters level) these papers can promote discussion about critical analysis and evaluation of techniques and research design in small seminar-style classes. More generally, these papers may foster conversation about the development of new animal models in the study of stress and neurodegeneration. Overall, these papers represent a valuable, interesting and accessible introduction to neuroendocrine systems, specifically, the HPA-axis.

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Received March 09, 2018; revised May 23, 2018; accepted June 07, 2018.

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