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Endocrinology of Stress

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When an animal detects a stressor, it initiates a stress response. The physiological aspects of this stress response are mediated through two endocrine systems. The catecholamine hormones epinephrine and norepinephrine are released from the adrenal medulla very rapidly and have numerous effects on behavior, metabolism, and the cardiovascular system. This is commonly termed the Fight-or-Flight response. On a longer time scale, the glucocorticoid hormones are released from the adrenal cortex. They interact with intracellular receptors and initiate gene transcription. This production of new proteins means that glucocorticoids have a delayed, but more sustained, effect than the catecholamines. The glucocorticoids orchestrate a wide array of responses to the stressor. They have direct effects on behavior, metabolism and energy trafficking, reproduction, growth, and the immune system. The sum total of these responses is designed to help the animal survive a short-term stressful stimulus. However, under conditions of long-term stress, the glucocorticoid-mediated effects become maladaptive and can lead to disease.

Stress, as originally coined by Selye (1946), has been the subject of study for decades. It became quickly apparent that the term “stress” actually encompasses three related topics: changes/stimuli from the environment that cause “stress” (subsequently called stressors); the physiological and psychological responses to those stimuli (subsequently called the stress response); and the diseases that result from an overstimulation of the physiological and psychological responses (subsequently called chronic stress effects). Research has focused on all three of these concepts. An enormous amount is now known about what stimuli elicit which physiological and psychological responses. We also know many of the mechanisms whereby various hormonal mediators compromise organ, tissue, and cellular function (Fink, 2007). This paper will provide a brief overview of what is known about the endocrine responses to stressors. The following general information is broadly known and widely presented. Most of the information comes from the following sources (McEwen & Goodman, 2001; Nelson, 2005; Norman & Litwack, 1997; Norris, 2007; Sapolsky, Romero, & Munck, 2000) and interested readers should consult them for more detail. Specific information and individual studies are cited independently.

Although there are many hormones that have been identified as playing a role in the vertebrate stress response, two categories of hormones are thought to form the central components of the endocrine response. These are the catecholamines, epinephrine and norepinephrine (also known as adrenalin and noradrenalin) and the glucocorticoids. Together, these hormones help to orchestrate the body’s stress response. How they do so is presented below.

Catecholamine Responses

The catecholamines are a class of hormones consisting of a 6-carbon ring with a carbon side chain. The type of side chain determines the type of catecholamine and provides biological specificity. The two most important catecholamines in the stress response are epinephrine (Epi) and norepinephrine (Norepi). The catecholamines bind to specific membrane-bound G-protein receptors. When bound, these receptors initiate an intracellular cAMP signaling pathway that rapidly activates cellular responses. The speed at which these responses are activated provides the foundation for many of the catecholamine effects.

The suite of responses mediated by Epi and Norepi are commonly called the Fight-or-Flight response because they have immediate effects on increasing the readiness and activity of the animal. Upon detection of a stressor, Epi and Norepi are released by both the adrenal medulla and nerve terminals of the sympathetic nervous system. These hormones are produced beforehand and stored in secretory vesicles. Consequently, release of Epi and Norepi occurs rapidly after detection of a stressor. When coupled to the rapid activation of cellular processes through their receptors in target tissues, Epi and Norepi activate organism-level responses within seconds of detecting a stressor.

Epi and Norepi activate a number of responses, including: decreasing visceral activity and shutting down digestion; increasing visual acuity; increasing brain blood flow and arousal; increasing gas exchange efficiency in the lungs; breaking down glycogen to release glucose stores; inducing vasodilation in muscles; inducing vasoconstriction in the periphery; increasing heart rate; and inducing piloerection. This suite of responses comprises the classic Fight-or-Flight response and is designed to help the animal survive an acute threat such as an attack by a predator or conspecific competitor. They not only activate beneficial responses such as increasing alertness and providing energy to muscles, but also inhibit processes, such as digestion, that can be superfluous during an acute emergency.

Glucocorticoid Responses

Glucocorticoids are a class of steroid hormones consisting of a 4-ring carbon backbone with different hydroxyl groups and carbon side chains attached at various places around the rings. The particular side chain and where it is attached determines which steroid it is, and provides specificity for the various steroid receptors. All steroids share common precursors and common synthetic pathways and are interconverted, so that both the classic steroid hormones (e.g., testosterone) and their intermediates (that can also have biological activity) can be found both in tissues and in the blood. However, the primary steroids released in response to a stressor are the glucocorticoids (GCs): cortisol and corticosterone. Most species rely primarily upon either cortisol (e.g. fish and most mammals, including humans and marine mammals) or corticosterone (e.g. birds, reptiles, amphibians, and some rodents), although both can be found in most species and some species rely upon a

mix of the two (e.g. some rodent species). Both hormones bind to the same receptors and appear to have identical functions in their respective species.

The release of GCs results from a hormonal cascade that begins with the detection of a stressor. Areas of the brain that interpret external and/or internal stimuli (e.g. the amygdala and hippocampus) send neuronal signals to the hypothalamus (primarily the paraventricular nucleus). The cells in the hypothalamus send axon projections to the median eminence where they terminate along capillaries of a portal blood system that connects to the anterior pituitary. Once stimulated, the hypothalamic cells release a suite of hormones into the portal blood. The most important of these hormones are corticotropin-releasing factor (CRF) and arginine vasopressin (AVP – or arginine vasotocin in non-mammalian vertebrates). (Although CRF is sometimes referred to as CRH (corticotropin releasing hormone), a recent committee addressing nomenclature proposed that CRF be adopted as the appropriate name (Hauger et al., 2003) CRF and AVP travel the short distance of the portal blood system from the base of the hypothalamus to the anterior pituitary. There they bind to receptors and stimulate the release of adrenocorticotrophic hormone (ACTH). ACTH is then released into the general circulation and travels to the adrenal cortex where it binds to its receptors and stimulates the production of steroid synthetic enzymes. GCs, like all steroids, are not stored once they are produced, so there is no functional difference between ACTH-induced production of GCs, and the release of GCs into the bloodstream. Thus, the increase in production rate results in increased GCs released into the peripheral circulation. This hormonal cascade from the hypothalamus to the adrenal via the pituitary is called the Hypothalamic-Pituitary-Adrenal (HPA) axis. Although other factors, such as gonadal steroids, cytokines, and the splanchnic nerve, can also directly or indirectly modulate GC secretion, the HPA axis is the primary pathway stimulating GC release in response to a stressor.

Once released, GCs travel in the peripheral circulation primarily bound to corticosteroid binding globulins (CBG). Steroids are highly lipophilic so that most GCs are bound to CBG, but unbound GCs increase dramatically during a stress response. Whether CBG functions primarily as a carrier to deliver GCs to their target tissues, or primarily as a buffer to moderate GC function, is currently under debate (e.g. Breuner & Orchinik, 2002). Once at the target tissue, GCs pass through the outer cell membrane and bind to an intracellular cytoplasmic receptor. Activated receptors then enter the nucleus and begin acting as transcription factors. Activated receptors bind to short stretches of DNA sequences called glucocorticoid response elements and act as promoters or inhibitors of gene transcription. Consequently, the end product of GC stimulation is either the production of new proteins or the inhibition of protein production. In addition, there is evidence that a membrane-bound receptor for GCs exist. This receptor is believed to mediate rapid behavioral effects of GCs. Along with GC's effects in response to a stressor, GCs vary in a circadian rhythm and are important in regulating normal physiological processes.

In contrast to Epi and Norepi, GCs are much slower at exerting their effects. The multiple steps of the HPA axis ensure a time lag between the onset of a stressor and the increase in blood GC concentrations. In general, increases in GC

concentrations cannot be detected in under 3-5 min (and occasionally longer for some species). When coupled with GCs' primary effect of altering gene transcription rates, the physiological impact of GCs begins to occur approximately 20-30 min after the onset of a stressor. If a stressor does not continue, negative feedback will generally start to reduce GC concentrations in 30-60 min, although because the newly produced proteins can continue to function, GCs' physiological effects can last considerably longer. Consequently, the catecholamines and the GCs dovetail to produce both an immediate and a longer-term response to stressors.

Although GCs alter gene transcription rates for an enormous number of genes, at the organismal level GCs can be classified as having five broad effects (Romero, 2004): increasing blood glucose concentrations; altering behavior; inhibiting growth; inhibiting reproduction; and modulating the immune system. This suite of effects is believed to help the animal recover from a stressor, shut down those systems that can profitably be delayed until the danger has passed, and prepare the animal for potential subsequent stressors. Each of these broad effects will be discussed briefly below.

The classic effect of GCs is to increase the blood glucose available to tissues involved in responding to a stressor. In fact, the name "glucocorticoids" was assigned to these hormones because of this important role, which takes two general forms. First, GCs increase blood glucose by converting protein to glycogen, thereby indirectly increasing glycogen break down into glucose by Epi and Norepi, and by stimulating the catabolism of protein to form new glucose in a process called gluconeogenesis. Second, GCs reduce the uptake of blood glucose by target tissues, resulting in higher blood glucose concentrations available to tissues involved in responding to stress. GCs do this by stimulating the internalization of glucose transport molecules from the cell surface of target tissues. Fewer glucose transporters result in less glucose utilization, the sum of which across multiple target tissues results in higher blood glucose concentrations. Tissues that need extra glucose to respond to the stressor (e.g. muscles) compensate for the GC effect and essentially have preferential access to the increased pool of blood glucose. The sum of these effects is that GCs orchestrate the allocation of energy stores during either prolonged stressors or after stressors have ended (Dallman et al., 1993).

GCs are known to alter behavior, but how they alter behavior depends upon the context in which the stressor is presented. Specific behavioral changes are difficult to predict. Although there has been an enormous amount of research on GCs' behavioral effects in the laboratory, recent research has also included studies of wild animals in their native habitats. For example, studies have shown that GCs can induce migratory activity in birds (Silverin, 1997). Depending upon the environmental context, GCs can promote a behavioral strategy of hiding and waiting out a stressor, or promote a behavioral strategy of abandoning an area and fleeing the stressor (Wingfield & Ramenofsky, 1997). The mechanisms for how GCs alter behavior are currently unknown and an active area of research, but may involve a novel membrane-bound G-protein receptor that induces rapid behavioral

effects. GCs can also induce long-term behavioral changes by having a direct effect on memory formation and consolidation in the brain.

GCs inhibit growth by blocking the secretion of growth hormone from the pituitary, decreasing the sensitivity of target cells to growth hormone, and inhibiting protein synthesis (related to GC-stimulated gluconeogenesis from protein catabolism mentioned above) (Sapolsky, 1992). This is a transient effect during acute stress responses and, because growth is a long-term process, appears to have little impact on the overall growth of the animal. Prolonged exposure to GCs, however, can result in observable inhibition of growth. In humans, the syndrome is called psychosocial dwarfism (Green, Campbell, & David, 1984). Inhibition of growth is believed to be an example of GCs shifting resources away from processes that can be postponed in order to use those resources to cope with an emergency.

GCs also inhibit reproduction (Wingfield & Romero, 2001). Vertebrate reproduction is regulated with a hormonal cascade that is similar to the HPA axis. The hypothalamus releases gonadotropin releasing hormone (GnRH), which causes the pituitary to release leutenizing and follicle-stimulating hormones (LH and FSH), which in turn stimulate gamete formation and reproductive steroid production (e.g. testosterone and estradiol) by the gonads. GCs suppress this pathway in several ways: by inhibiting GnRH release, reducing pituitary sensitivity to GnRH, and reducing the sensitivity of gonads to LH. Furthermore, GCs can reorient behavior away from reproduction. Similar to the effects on growth, GCs' effects on reproduction have little impact over the short-term, but long-term stress can cause complete reproductive shutdown. Stress has even been implicated as a factor in human infertility (Homan., Davies, & Norman, 2007; Wischmann, 2003). GCs' effects on reproduction are thought to be another example of allocating resources preferentially during an emergency.

Interestingly, the reproductive system can become resistant to inhibition by GCs in some reproductive contexts. For example, if GCs allocate resources away from reproduction, and thereby reduce individual fitness (i.e. successful production of offspring), the benefit of the reproductive system ignoring the GC signal may outweigh the cost of not responding to the stressor. In semelparous species (those that breed once and then die) such as some salmon species and several Australian marsupial rodents, death occurs in all individuals (or all individuals of one sex) shortly after breeding. The proximate cause of death is extremely high levels of GCs that catabolize essential proteins (reviewed in Wingfield & Romero, 2001). Reproduction in these animals clearly continues despite elevated GCs. Furthermore, GCs do not inhibit reproduction in many short-lived species and in older individuals, and in dominant individuals in some species where the dominant individual has a limited period with access to mates (Wingfield & Sapolsky, 2003). Consequently, susceptibility to GC-induced inhibition of reproduction is highly specific depending on the importance of continuing to reproduce in the presence of stress which may vary depending upon age, sex, stage of the breeding cycle, etc.

Finally, GCs have a broad inhibitory effect on the immune system (Spencer, Kalman, & Dhabhar, 2001). This has made GCs very important clinically and they are widely prescribed as drugs. GCs have a number of effects

on the immune system including: inhibiting the synthesis, release, and efficacy of cytokines (immune system proteins); inhibiting antigen presentation through reduced major histocompatibility complex (MHC) expression; reducing the activation and proliferation of T cells, B cells, and macrophages; lowering the circulating levels of lymphocytes; reducing lymphocyte chemotaxis; reducing the number of phagocytic cells at inflammation sites; stimulating atrophy of the thymus; and triggering the death of immature T and B cells. All of these effects lead to immunosuppression, especially with long-term GC exposure. There is some evidence, however, that GCs might enhance immune function in the short-term (Dhabhar, 2006; Dhabhar & McEwen, 1999). The reason GCs have such powerful immunosuppressive effects is not entirely clear, but it has been proposed as a mechanism to prevent overactivation of the immune system that could lead to autoimmune diseases.

Conclusion

The large suite of catecholamine and GC responses is believed to be essential in surviving stressors. Clearly, the lack of Epi and Norepi release, i.e. the Fight-or-Flight response, would be devastating during a predatory attack. Similarly, animals that lack GCs are unable to mount an effective stress response and quickly die (Darlington, Chew, Ha, Keil, & Dallman, 1990). All three hormones serve to orchestrate an organism's effective response to stressors in order to promote survival.

On the other hand, long-term or chronic release of these hormones can be detrimental. Repeated or constant activation of the Fight-or-Flight response can lead to cardiovascular disease. Similarly, individuals exposed to long-term or chronic GCs suffer from a number of diseases including diabetes, depression, psychosocial dwarfism, reproductive dysfunction, and immune suppression. Consequently, responses to acute stressors generally enhance fitness, but long-term exposure can decrease fitness. Clearly, successful long-term survival requires balancing acute release while minimizing chronic exposure.

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