Stress Adaptation and the Resilience of Youth: Fact or Fiction?

The young are resilient! This age-old adage refers to the ability of the young to adapt to changing stress in the environment. The origin of these stressors can be physical (pollution, nutrient status, infections) or psychological (trauma, parenting, home environment). Resilience is the ability to adapt to a changing environment, and this adaptive stress response (also known as allostasis) is crucial for survival. Every organism—plants, animals, humans—have developed a number of mechanisms to adapt to these stressors to ensure growth, survival, and reproduction. Our ability to adapt is controlled by both nature (genetic predisposition, epigenetics) and nurture (prenatal/early life and/or later life experiences). Of these, genetic variations or mutations are “hard-wired” into our DNA and are not affected as we age. Conversely, environmental stressors have a long-lasting effect on our ability to adapt, depending on the intensity of the stressor and the stage of life at which they are experienced. These stressors are sensed by the brain and are translated into a series of epigenetic changes in multiple tissues, activation of hypothalamic-pituitary-adrenal (HPA) axis, and structural changes in specific brain regions.

How then does aging affect the stress response? Two parallel hypotheses exist. One common theory of stress adaptation is that, as we age, the hormonal and epigenetic changes that are protective in youth (allostasis) become maladaptive later in life due to alterations in the body and the brain that accumulate over time. This cumulative allostatic load, whether it is oxidative stress, corticosteroids, or infectious agents, renders the individual less able to mount an additional adaptive stress response, leading to vulnerability instead of resilience (4). An example of this process is the age-associated decrease in immune function that renders an older individual more susceptible to chronic disease through decreases in adaptive and innate immunity (3). In this theory, youth are resilient since they have not yet reached allostatic overload and the adaptation to stress is beneficial.

The second theory of age-related stress adaptation is that early life experiences cause epigenetic changes that underlie a “predictive” adaptive response. Within this context, the importance of the perinatal environment on adaptation and aging is an emerging area of investigation. Adverse perinatal circumstances can be brought on by a wide variety of different factors, including toxicological exposures (both prenatal and postnatal), maternal psychological stress (generating high cortisol levels), nutritional deprivation or excess, and direct stress (acute restraint or neglect). Emerging evidence suggests that stressors that occur at vulnerable times during development have greater and more enduring effects than stressors that occur later in life (5). The resilient fetus is able to adapt its metabolism to a hostile environment, but often these adaptations become irreversible and even pathological. The best described adverse phenomenon is dysregulation of the maternal HPA, causing release of glucocorticoids and exposure of the fetus. Persistently high levels of maternal glucocorticoids have been linked to development of metabolic, cardiovascular, and psychiatric disorders in the offspring. Furthermore, these disorders in the offspring can be linked to epigenetic changes, which were influenced by maternal responses. These epigenetic changes (DNA methylation, histone modification, non-coding RNA) are essential for normal development but are also subject to regulation by environmental stimuli and provide a crucial “molecular memory” to translate past stressful events into changes in gene expression, the HPA, neuronal circuitry, and future behaviors (5). One example of this phenomena was originally observed in humans, in which nutritional deprivation in utero predicted an adaptive stress response to nutrient-scarce postnatal environment and a “thrifty phenotype” as an adult (1). This phenotype, however, increases the risk of obesity, metabolic syndrome, and hypertension. Moreover, adaption to hypoxia in rodents causes altered DNA methylation in the germ line, whereas intrauterine growth restriction in rodents is associated with changes in histone modification and chromatin remodeling, and altered brain structure in the amygdala, hippocampus, and frontal cortex. Within this context, the resilience of youth would be considered transient and permit survival to adulthood but predispose the adult to be more vulnerable to later life stressors. One must keep in mind, however, that interventions such as exercise (the real polypill) (2), diet, and pharmacological therapy can attenuate this early life imprinting and lead to a more physiological adaptive stress response and healthy aging.

In summary, the physical and mental health that we enjoy results from life-long stress adaptations that are dictated by genetic predisposition, prenatal/early life environmental stressors that lead to biological embedding of brain structures, and neurohormonal responses that impact our ability to respond to stress as adults. Although the processes of epigenetic changes and neuronal plasticity were once thought to be permanent, they are now proven to be amenable to positive environmental changes. Therefore, we may one day celebrate the resilience of the elderly!

References