A Tripartite Picture of the Effect of Stress on the Brain

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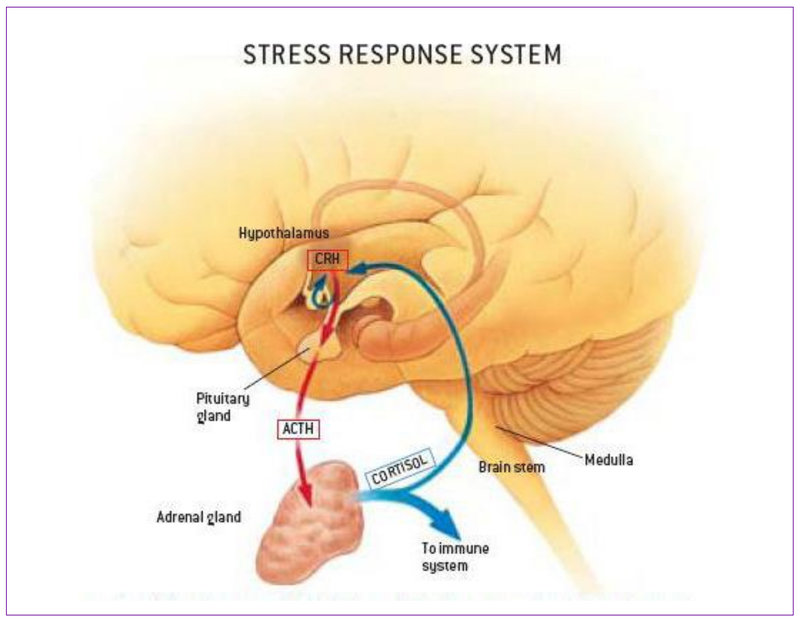
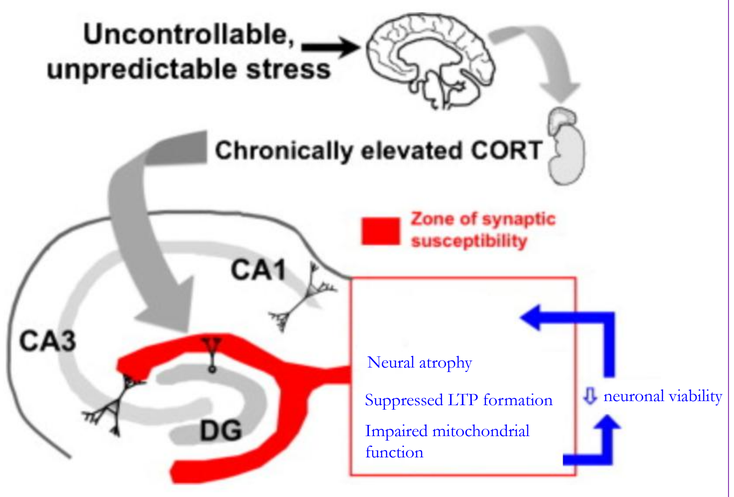
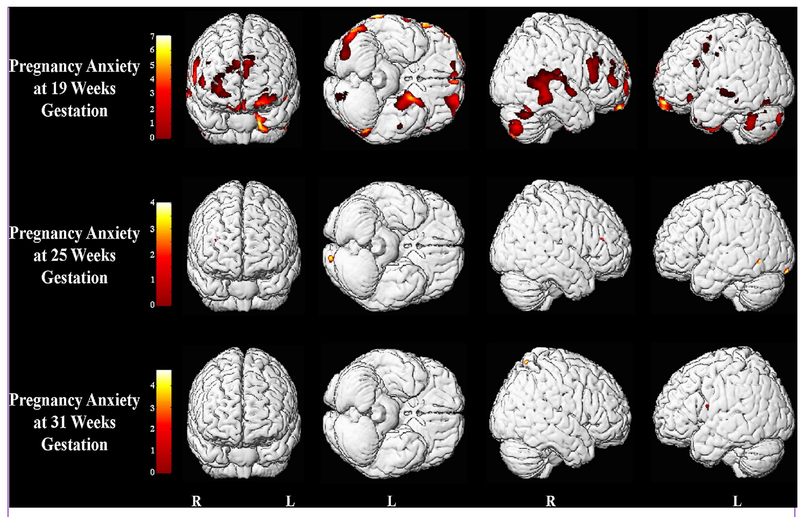






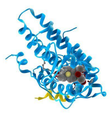
Anxiety during pregnancy is associated with reduced gray matter volume in 6-9 year-old human offspring. Buss et al, 2010

Corticosteroid levels are elevated in the body's natural response to stress. They exhibit bidirectional effects on neuronal viability, reflecting the positive and negative effects of stress on cognition. These effects are due to a cascade of complex mechanisms involving glucocorticoid receptors and mitochondrial integrity.

Mineralocorticoid Receptor

Affinity: K_d=.3nM

- The higher affinity means MRs respond to lower physiological levels of glucocorticoids



Glucocorticoid Receptor

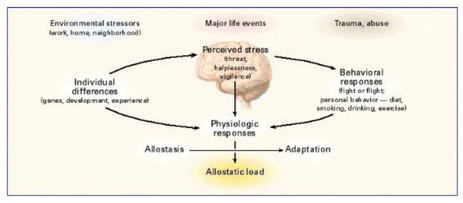
Affinity: K_d=1-5nM

-the lower affinity means GRs respond to higher levels of glucocorticoid, typically under stress

Different receptor subtypes with different binding affinities allow for an inverted "U"-shaped dose response curve, whereby high and low levels of GCs elicit a smaller response, and intermediate levels elicit a larger response.

Repeated and/or prolonged exposure to high levels of glucocorticoids result in destructive cellular processes that originate in the mitochondria.

Long-term potentiation (LTP) refers to the long-lasting enhancement in signal transmission between two neurons that result from stimulating them synchronously. As a phenomenon underlying synaptic plasticity (the ability of chemical synapses to change their strength), both short-term and chronic, toxic stress have an ability to alter this process. As memories are thought to be encoded by modification of synaptic strength, long-term potentiation is widely considered one of the major cellular mechanisms that underlie learning and memory. In a similar vein, long-term depression, in neurophysiology, is an activity-dependent reduction in the efficacy of neuronal synapses that can last for hours or longer.



The Stress Response and Development of Allostatic Load. The perception of stress is influenced by one's experiences, genetics, and behavior.

LTP and other forms of plasticity play a critical role in the hippocampus, frontal cortex and other brain areas in learning and memory function. These areas are particularly susceptible to the biodirectional effects of stress-induced glucocorticoid release. Glucocorticoid challenges have been to be unable to induce significant changes in memory function in the absence of a stress context.

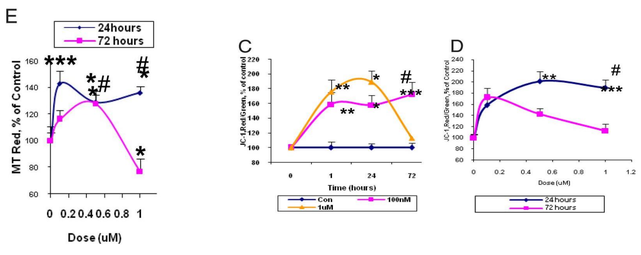
- Acute stress has the potential to either enhance or impair memory function depending on the timing and pairing of stressor and acquisition of memory task or retrieval of encoded information.

- Chronic stress however results under all circumstances in cognitive deficits regardless of the particular nature of the stressor or subset of memory function being assessed.

- Results from studies that have examined war zone survivors, breast cancer patients, and individuals diagnosed with post-traumatic stress disorder have consistently found global impairments in memory function.

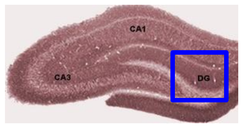
Chronic levels of stress results in persistently high levels of glucocorticoids, which have negative effects on neuronal viability. This mechanism involves mitochondrial integrity, which is mediated by a complex of activated GR receptors and the mitochondrial membrane protein Bcl-2. This protein complex controls mitochondrial stability by regulating pore formation and permeability of the outer mitochondrial membrane.

In a study of the effects of glucocorticoids on markers of mitochondrial viability, elevated levels of GCs are associated with decreased mitochondrial function, and subsequent neuronal viability.

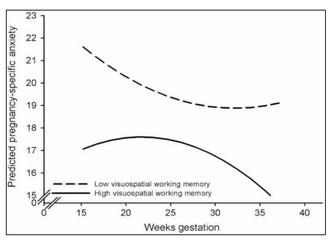


The effects of glucocorticoid levels on membrane potential and mitochondrial oxidation, respectively. (Jing Du et. Al.,2008)

It is important also to consider the hormone in question, as well as its relationship to the specified brain area. The dentate gyrus (DG) is part of the hippocampal formation, and is thought to contribute to new memories and spatial awareness and function. This area of the brain, in addition to the hippocampus (amongst other areas), has shown high activity during periods of stress in mouse models. In spite of this, under *in vitro* recording conditions, it is known that dendate gyrus neurons exhibit a significantly negative resting membrane potential. This is due to the incredibly strong GABA (an inhibitory neurotransmitter) –ergic tone the neurons in the area are subject to. Thus, researchers that used corticosterone as a paradigm for stress hormones recognized that "under those conditions, corticosterone was unable to facilitate synaptic potentiation" (Pu et al., 2007). This alludes to the fact that mechanistically, different hormones have differing effects on the central nervous system's response to stress.



While most studies of the effects of chronic stress on memory and cognition in humans have looked at adults, there is a distinct need for a better understanding of the consequences of chronic stress and adverse conditions during the prenatal period and early childhood. Preliminary results suggest that exposure to stress throughout pregnancy will result in reduced grey matter volumes and subsequently in memory function deficits in the school-aged children of stressed mothers.



High anxiety during pregnancy is associated with lower performance in a spatial working memory task in 6-9 year old human offspring. Buss et al, 2011