

Development of the Cerebral Cortex: XII. Stress and Brain Development: I

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Too much stress is not good. The acute stress of evading a predator is life-saving. However, waiting to hear about whether a grant is funded or tenure is awarded are examples of sustained stressors that often cause adverse effects. Stress is one of the primary reasons for referrals to psychiatrists.

While the stress response is vital for our survival, too much stress has deleterious effects on many aspects of our physiology, including immune responses, the cardiovascular system, and our reproductive abilities. It is less well appreciated that excessive stress also compromises the nervous system. In this column, we review the mechanisms by which stress impairs neuronal function and contributes to brain aging and cognitive impairment.

The effects of stress are mediated by several molecules, including the glucocorticoid hormone, hydrocortisone. Hydrocortisone is synthesized in the cortex of the adrenal gland, where it is released into the blood stream. Similar to most steroid hormones, hydrocortisone is a water-insoluble molecule, and this fact leads to several important differences between this family of signaling proteins and the growth factors that were recently discussed.

Steroid hormones exert much longer-lasting responses than do peptide hormones, growth factors, or neurotransmitters. To become soluble in the bloodstream and other extracellular fluids, most hormones bind to specific carrier molecules that help to transport them throughout the body. Water-insoluble

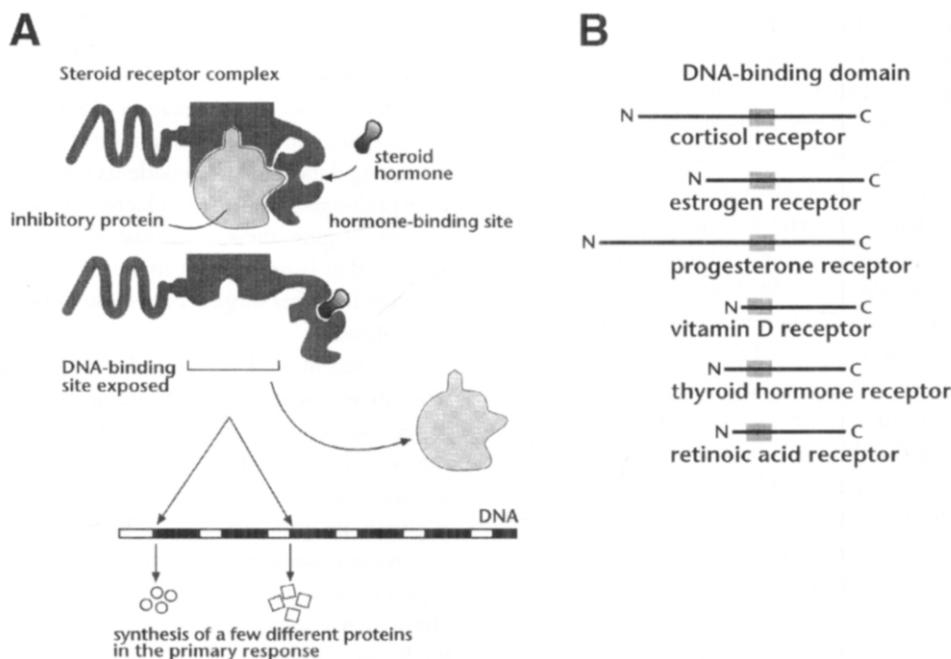


Fig. 1 Steroid hormone receptors are transcription factors. Normally, these receptors are present in an inactive state in either the cytosol or nucleus of cells. The lack of activity is due to a protein that binds to them and inhibits them. This regulatory protein is displaced when a steroid hormone associates with its receptor. A DNA-binding domain is thus exposed and has access to specific nucleotide sequences within the promoter regions of a number of genes. The transcription of these genes is termed the primary response of the hormone. As some of the newly synthesized proteins are themselves transcription factors, a secondary delayed response results in the transcription of additional genes initiated by these transcription factors. In this way, the cell produces a group of proteins that is needed at that moment in response to stress.

signaling molecules generally persist in the bloodstream for greater lengths of time than do the water-soluble factors, which are removed or metabolized within minutes of being released. The effects of growth factors or neurotransmitters disappear within seconds or milliseconds. In contrast, hormones such as hydrocortisone persist in the blood for hours, while the thyroid hormones last even longer and their actions persist for days.

How do the steroid hormones mediate their varied responses? For each hormone, a specific receptor exists within the cell. It is important to note one fundamental difference, however, between the steroid hormones and the other signaling molecules. The receptors for growth factors and neurotransmitters lie on the outer surface of the cell and directly bind their ligand. The neurotransmitter dopamine, for example, is released at the presynaptic terminal, diffuses across the synaptic cleft, and binds directly to its receptor on the postsynaptic membrane.

In contrast, the receptors for steroid hormones do not lie on the surface of the cell, but rather are concentrated inside the cell. Most hormones are synthesized from cholesterol and are able to diffuse across the lipid plasma membrane. Once inside the cell, the various hormones bind to their respective receptors. Many of the receptors, such as those for hydrocortisone, are found enriched in the soluble compartment of the cell, termed the cytosol. Others, such as the receptors for retinoic acid, are enriched in the nucleus.

How is a signal generated after a hormone binds to its receptor? The majority of occupied steroid hormone receptors act as classic transcription factors. Transcription factors control the amount of various proteins present in the cell by regulating whether or not a particular gene is transcribed. Receptors for hormones have several amino acid domains that allow them to function as signaling proteins (Fig. 1). In their inactive state, hormone receptors bind an inhibitory protein, and this complex of proteins masks the DNA-binding domain. The inhibitory protein is released when the hormone binds to a second domain, and the release of the inhibitory protein results in a change in the shape of the receptor. The DNA-binding domain is now exposed and the receptor is able to interact with specific DNA sequences within the promoter region of genes within the nucleus. In this way, hormone receptors initiate the transcription of genes required by the cell at that moment.

Most hormones exert their effects in two stages. Initially, the hormone receptor induces the transcription of a small number of genes. This effect usually occurs within 30 minutes and is known as the primary hormonal response. However, as many of the genes that are transcribed during this initial phase are themselves transcription factors, a cascade of transcription is initiated. The newly synthesized proteins activate additional genes in a delayed or secondary hormonal response. A single

hormone, therefore, can initiate a complex pattern of gene expression.

A further level of transcriptional control arises from the fact that many genes require the presence of several different transcriptional proteins before they are activated. Depending on the combination of gene regulatory proteins that are present within the cell, a hormone will activate different proteins and thereby elicit different responses. This has the effect of varying the response of different cells to the same hormone.

So far, we have discussed the mechanisms by which steroid hormones exert their signals. A great deal of work has been done to determine the effects of stress and the effects of glucocorticoids on neuronal functioning. The short-term consequence of excessive amounts of glucocorticoids or stress is actual atrophy of dendritic processes. The damage appears to be most prevalent on pyramidal neurons in the CA3 region of the hippocampus, a region that is vital for many cognitive skills including memory. This atrophy is reversible. Remove the stress or hormone, and dendritic processes gradually grow back. After long-term stress, however, neurons begin to die.

Although much of the earlier work was conducted in rodents, the experimental design has now been extended to primates. Stressful situations or prolonged exposure to glucocorticoids leads initially to hippocampal dendritic atrophy and eventually to the destruction of neurons. Collectively, the rodent studies suggest that the extent of exposure to stress or to the glucocorticoids over the lifetime correlates directly with the degree of hippocampal decay in old age. Obviously, it is not possible to conduct these studies in humans. However, some intriguing data come from patients with Cushing disease, who have prolonged exposure to glucocorticoids. On magnetic resonance imaging, these individuals show selective hippocampal atrophy that is reflected in impaired memory. These findings are reversible after surgical correction of the cause of the hypercortisolism.

More recent work has extended these findings. Amounts of stress or glucocorticoids that are not of sufficient magnitude to lead to neuronal atrophy or neuronal death still put neurons at enhanced risk of damage by a second insult. Exposure to excessive amounts of excitatory amino acids (EAAs), such as glutamate or kainate acid, is known to be harmful, causing seizures and damage to the hippocampus. When animals are exposed to small but persistent amounts of stress or high physiological levels of glucocorticoids, the damage caused by the EAAs is augmented.

The hippocampus is particularly vulnerable. This probably relates to its being the most glutamatergic region of the brain because of its role in plasticity during learning. This accounts for its atypical vulnerability to a number of necrotic insults, including seizures or global ischemia. Finally, there is also a very high concentration of glucocorticoid receptors in the hippocampus.

WEB SITES OF INTEREST

<http://www.neurosci.pharm.utoledo.edu/MBC3320/Lecture21.html>
<http://www2.mrc-lmb.cam.ac.uk/brochure/Schwabe, J.html>
<http://flybase.bio.indiana.edu/.data/allied-data/interactive-fly/gene/uspirc2b.htm>
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