GLUCOCORTICOIDS AND BRAIN

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Contents

Summary

Glucocorticoid hormones are involved in the response of the living organisms to stress. Some of these hormone actions are adaptive and protective, whereas other effects are associated with damage and dysregulation. The diversity of effects is a reflection of the multiple functions of glucocorticoid secretions and the different modes of control of adrenocortical activity via hypothalamus and pituitary, as well as the separate roles which the two types of intracellular glucocorticoid receptors play. In addition to genomic effects, non-genomic actions of glucocorticoids at the membrane level have been recognized. The response of the brain to changes in the environment is one of the principal actions of glucocorticoids. Thus, for each primary response of neurotransmitter system to stress, a delayed counter-regulatory action of glucocorticoids exists at the level of a neurotransmitter receptor or second-messenger system. On the other hand, glucocorticoids mediate pathological effects on the brain, which are associated with transient ischemia, aging, and stress. This chapter discusses the involvements of glucocorticoids in pathophysiology of affective illness as well as in both individual and stress-induced vulnerability to drug effects.

1. Introduction

Virtually any challenge to homeostasis will stimulate secretion of glucocorticoids (corticosterone in some rodents e.g. rat and mouse, and cortisol in most other mammals, including humans) (see *Stress and Coping*). These hormones have a maintenance or permissive action and modify the flow of metabolic energy from lipids and proteins in muscle, fat, and other tissues to carbohydrates as available energy resource for brain and heart during stress. On the other hand, glucocorticoids prevent over-reaction of defense mechanisms to stress. Metaphorically, M. Tausk compared the action of

glucocorticoids with protection against “water damage caused by the fire brigade”. Inflammatory and immune, cardiovascular, and central responses to noxious stimuli would themselves become damaging if left uncontrolled by glucocorticoids (Figure1). While glucocorticoids may be good to control the stress response, chronically elevated levels of glucocorticoids may act deleteriously.

Hypercorticism has been shown to lead to immunosuppression, muscle atrophy, osteoporosis and disturbances in mood and mental performance. Since these symptoms characterize the aging process as well, high glucocorticoid levels are thought to be related to brain aging and age-related neuropathology.

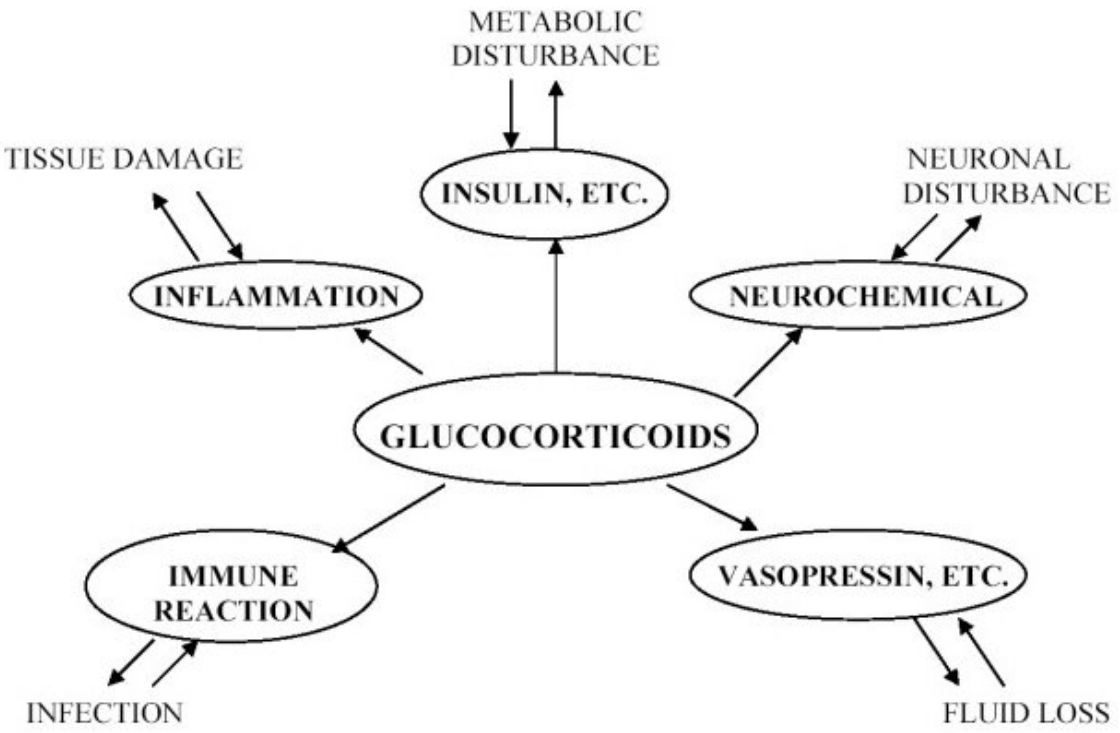

Figure 1. Schematic representation of glucocorticoid action in response to stress.

Glucocorticoid secretion is driven both by external and internal events, as well as by the biological clock, so the fact that these hormones influence brain function is not surprising. Glucocorticoids alter food intake, and modulate behavior and blood pressure. These compounds alter neurotransmitter systems of the brain, often in a biphasic and dose-dependent manner, which involves modulation of biosynthesis of transmitter or modulation of the transmitter receptors.

A variety of neuropeptide systems also regulated by glucocorticoids, including corticotropin-releasing hormone (CRH), vasopressin, angiotensinogen, neuropeptide Y, and enkephalin. Finally, glucocorticoids exacerbate the destructive effects of excitatory amino acids on pyramidal neurons in the hippocampus, while protecting neurons of the dentate gyrus from destruction.

2. Action Mechanisms of Glucocorticoids

Glucocorticoids, like other steroid hormones, may affect nerve cell function via a gene-mediated mechanism of action. The steroid hormone binds to an intracellular receptor, the steroid-receptor complex then interacts with specific sequences within a DNA-promotor region, and this results in a subsequent alteration of gene expression in the target cell. These genes encode the synthesis of neuropeptide precursors, enzymes involved in transmitter synthesis and intermediary metabolism, and proteins underlying transmitter signaling. The genomic action of glucocorticoids is slow in onset and long-lasting. In addition to their intracellular receptor-mediated effects, glucocorticoids and their metabolites also have fast but relatively short acting membrane effects on neuronal excitability. They may explain hypnotic, anesthetic, anticonvulsant, and anxiolytic action of glucocorticoids in the brain.

Thus, glucocorticoid action in the brain affects neurotransmission both via intracellular steroid receptors and gene-mediated events. Its metabolites may modulate neurotransmitter action via membrane-associated neurotransmitter receptors (see Figure2).

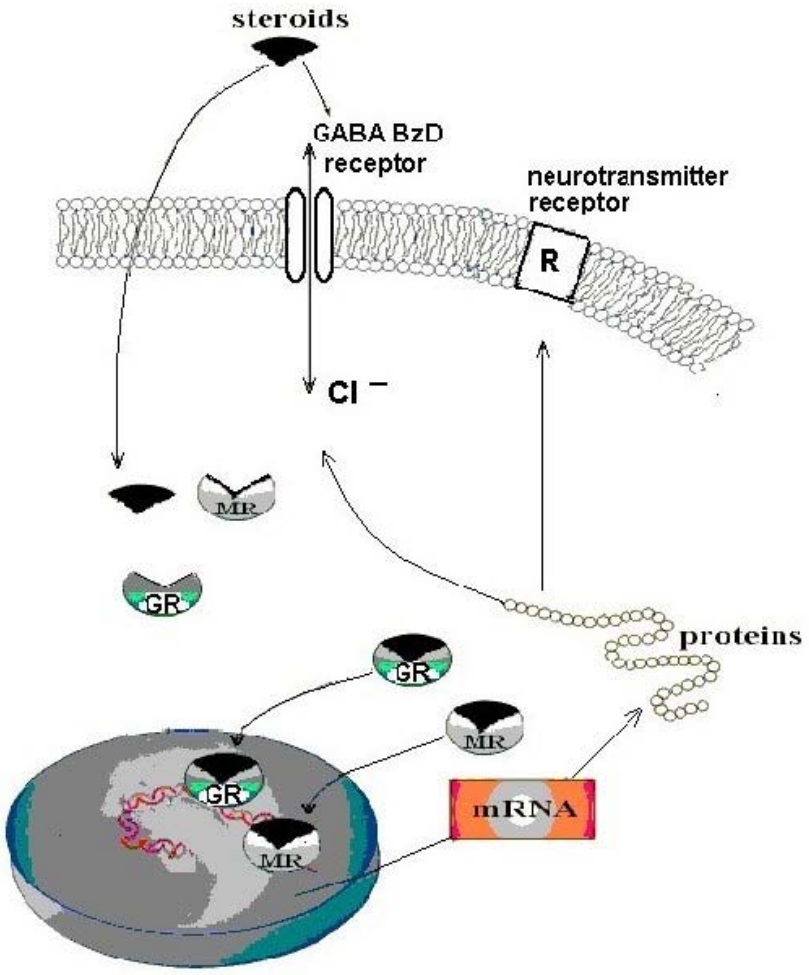

Figure 2. Steroid hormone action at the level of the genome and at the membrane level.

It is clear from the involvement of glucocorticoids in normal brain functions and in the adaptation to stress that these hormones play a beneficial role. Indeed, under stress, adrenalectomized animals are very vulnerable, and the adrenal steroids have long been known to play an important role in protecting the brain from endogenous catecholamines and other neurotransmitters. Their secretion is activated as a result of repeated stress. This counter-regulatory action of glucocorticoids exists at the level of a neurotransmitter receptor or second-messenger system. One example of this phenomenon involves the noradrenergic innervation of the cerebral cortex. The effect of stress is to increase noradrenergic activity; repeated stress leads to an induction of the enzyme tyrosine hydroxylase (TOH) in the locus coeruleus that projects directly to the cerebral cortex. To counteract increased noradrenergic tone during chronic stress, glucocorticoids mediate a suppression of the postsynaptic second messenger response (i.e. the activation of camp formation), which is mediated by beta adrenergic receptors. However, the effect of glucocorticoids is an indirect one, and it is mediated by an alpha-1 adrenergic receptor mechanism, which normally potentiates the beta receptor response via calcium ions. Calcium ions with calmodulin are involved in cAMP generation in nervous tissue. Calcium-calmodulin-stimulated adenylate cyclase activity is suppressed by chronic stress via a glucocorticoid-dependent mechanism in the cerebral cortex. Collectively, these actions of glucocorticoids secreted during stress are consistent with an action of stress hormones to reduce arousal mediated through the noradrenergic systems, and thereby prevent over-activation of this system.

Glucocorticoids have effects not only on the noradrenergic brain system. Serotonin actions via $5HT_{1A}$ receptors, which can be anxiogenic, are suppressed by glucocorticoids in the hippocampal formation but not in the cerebral cortex. Moreover, central actions of serotonin are attenuated by glucocorticoid treatment. The serotonin system's interactions with glucocorticoids are complicated by the fact that circulating glucocorticoids are permissive agents that acutely activate serotonin formation during stress. Thus glucocorticoids are involved in both the acute activation of a receptor system as well as chronically in the regulation of the same receptor type in the opposite direction.

Whereas the glucocorticoids in the brain act to prevent over-reactions of neurochemical systems, under some circumstances the protective mechanisms fail and damage ensues. The actions of stressors on the hippocampus illustrate the negative side of dysregulation (see section 7).

3. Corticosteroid Receptors

The genomic effects of glucocorticoids are mediated by Type I (mineralocorticoid) receptors (MR) and Type II (glucocorticoid) receptors (GR). These two receptor types are products of different genes and can coexist within the same cells. The primary structure of MR and GR is known (Figure 3). All steroid receptor molecules consist of three main functional domains: a DNA binding domain, a steroid binding domain and N-terminal domain, also referred to as the immunogenic domain. The DNA binding domain is a cysteine-rich region responsible for the formation of two "zinc-fingers", which interact directly with hormone responsive elements on the DNA promotor region of the target gene. The carboxy-terminal domain of the receptor molecule constitutes the

ligand-binding domain. Mutation studies with GR have shown that deletion or partial loss of this particular binding domain generated a permanently active receptor. Accordingly, it is thought that steroid binding takes away the inhibitory influence of the steroid-binding domain on steroid receptor-DNA interaction and subsequent transcription.

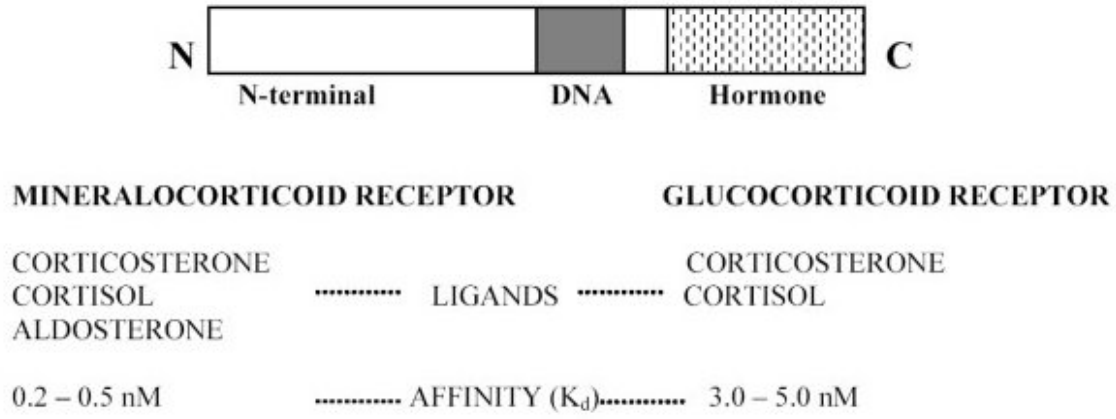

Figure 3. Domain structure of rat corticosteroid receptors.
Affinity is given for corticosterone in the rat.

MRs are present in the classical target tissues for mineralocorticoids, such as the kidney. MRs are also expressed in neurons of the limbic brain, particularly of the hippocampus. However, in spite of the structural identity of MRs in kidney and hippocampus, the MRs in hippocampus represent a pharmacologically distinct receptor type that binds the naturally occurring glucocorticoid. GR binding sites are widely distributed in neurons and glial cells throughout the brain as well as in other tissues of the body. High GR concentrations are found in the limbic system, in the parvocellular neurons of the paraventricular nucleus (PVN), and in the supra-optic nucleus of the hypothalamus. Moderate GR levels are also found in many thalamic nuclei, cortical hemispheres, and amygdala. It is important that GR and MR are capable of differentially interacting with glucocorticoids: MR binds corticosterone with a 10-fold higher affinity than GR.

Also, for many years steroids have been recognized as acting at the cell membrane level. Until recently, these effects were relegated to pharmacology because they appeared to be elicited only by high steroid concentrations in a relatively specific fashion. This perception has changed with the discovery of highly specific sites on the chloride channel of the γ-aminobutyric acid $(GABA)_A$-benzodiazepine receptor complex, which interact with physiological concentrations of natural steroids that are generated *in vivo* from naturally occurring steroid hormones. These membrane-active steroids are now referred to as "neuroactive steroids". The relevance of this mechanisms to the actions of adrenal steroids was shown by the demonstration that stress-induced secretion of glucocorticoids leads to the accumulation of THDOC, the 3α,5α-pregnane metabolite of desoxycorticosterone in blood and brain. THDOC is a potent agonist of the steroid site on the $GABA_A$-benzodiazepine receptor and potentiates the influx of chloride ions.

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Biographical Sketches

Dr. Vera Shalyapina studied at the Medical Institute Leningrad (St.-Petersburg) and received her MD in 1962. She obtained a DMSci in 1976 at Pavlov Institute of Physiology, Russian Academy of Sciences. She was appointed full professor in 1985. Dr. Shalyapina was deputy director of Pavlov Institute of Physiology RAS from 1980 to 1984 and now she is head of the laboratory of Neuroendocrinology. She

teaches experimental endocrinology and neuroendocrinology in the Medical Institute and State University of St. Petersburg. She is the author and co-author of six books and more than 280 articles in the field of endocrinology and neuroendocrinology. She is a chief of the Neuroendocrine Section of St. Petersburg's Physiological Society. Dr. Vera Shalyapina and her co-workers have discovered a number of important mechanisms in neuroendocrine regulation of adaptive behavior and hypothalamus-pituitary-adrenal axis organization. Her present research interests are in roles of corticotropin-releasing hormone in adapting the body's behavioral responses to stress.

Dr. Natalia Ordyan studied at St. Petersburg State University, Biological Department, and received her Master of Science in 1989. Since 1989 she has worked in the Pavlov Institute of Physiology, RAS, in the laboratory of Neuroendocrinology (Supervisor: prof. Vera Shalyapina). Dr. Ordyan obtained her PhD in physiology at the Russian Academy of Sciences in 1996 (she explored brain distributions of corticosteroid receptors type I and type II in high stress-reactivity rats, and rats with different behaviour strategies). Her present research work deals with the organizing effects of gonadal and adrenocortical steroids on developing mammalian brain as well as with involvement of neurosteroids in this process. Dr. Ordyan is a current Member of the Russian Physiology Society, and Member of the Russian Society of Neuroendocrinology.