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BRAIN RESEARCH

Review

The role of glucocorticoids for spiral ganglion neuron survival

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ABSTRACT

Glucocorticoids, which are steroidal stress hormones, have a broad array of biological functions. Synthetic glucocorticoids are frequently used therapeutically for many pathologic conditions, including diseases of the inner ear; however, their exact functions in the cochlea are not completely understood. Recent work has clearly demonstrated the presence of glucocorticoid signaling pathways in the cochlea and elucidated their protective roles against noise-induced hearing loss. Furthermore, indirect evidence suggests the involvement of glucocorticoids in age-related loss of spiral ganglion neurons and extensive studies in the central nervous system demonstrate profound effects of glucocorticoids on neuronal functions. With the advancement of recent pharmacologic and genetic tools, the role of these pathways in the survival of spiral ganglion neurons after noise exposure and during aging should be revealed.

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1. The glucocorticoid signaling pathway

To survive in a challenging environment, most complex organisms have evolutionarily developed a stress response system. In humans and other vertebrates, the adrenal steroid glucocorticoids (GCs) modulate and control this system at multiple levels (see recent reviews, Kino, 2007; Viegas et al., 2008). Synthetic GCs are currently widely used to treat allergic, inflammatory, and lymphoproliferative disorders as well as hearing loss in a variety of inner ear diseases such as Meniere's disease, sudden or idiopathic hearing loss, endolymphatic hydrops, and autoimmune inner ear disease (Dodson and Sismanis, 2004; Dodson et al., 2004; McCabe, 1979; Trune et al., 2007; Wei et al., 2006). Despite their wide use, the role of GC signaling pathways in the inner ear is poorly understood.

Using cholesterol as the starting molecule, the adrenal cortex secretes three types of steroid hormones: 1) GCs (cortisol in humans and most other mammals, and corticosterone in rodents and lower vertebrates), 2) mineralocorticoids (MCs) such as aldosterone, and 3) androgens including dehydroepiandrosterone, a precursor of testosterone (Payne and Hales, 2004). The level of GCs is regulated by the secretion of adrenocorticotropic hormone from the pituitary, which in turn is regulated by arginine–vasopressin and corticotropin-releasing hormone from the hypothalamus. This regulation system is called the hypothalamic–pituitary–adrenal (HPA) axis, to which GCs can act on in a negative feedback loop (Smith and Vale, 2006). GCs, which are small hydrophobic compounds, travel in serum mostly by the carrier protein corticosteroid-binding globulin. Upon reaching target cells, GCs mediate their biological responses mainly through the glucocorticoid receptor (GR) and, in certain tissues, through the mineralocorticoid receptor (MR), which has a much higher affinity for GCs than GR. As both receptors are present in spiral ganglion neurons and other cell types in the cochlea, we will discuss the signaling pathways initiated by both GR and MR.

1.1. *GR signaling pathways*

Only one gene is known to encode GR. It is located on chromosome 5q31–q32 and produces two major GR isoforms by alternative splicing of its nine exons (Stolte et al., 2006). The GRα isoform is expressed in almost all cells and is fully functional after binding to GCs, while the GRβ isoform accounts for only 0.2–1.0% of total GR expression and does not bind GCs. Thus, we focus on the GRα isoform (simplified as GR) in the rest of this review. The structure of GR comprises of: (a) an N-terminal domain containing the transactivation function-1 (AF-1) region, (b) a highly conserved DNA-binding domain (zinc-finger motif), and (c) a C-terminal domain that binds ligands (AF-2) and also acts as a protein–protein interaction region. In the cytoplasm, the unligated GR forms a multiprotein complex with chaperone proteins (hsp90 and hsp70), immunophilin p59, co-chaperone phosphoproteins (p23 and Src), and several kinases of the mitogen-activated protein (MAP) kinase signaling pathways.

GRs can exert their effects via genomic and nongenomic pathways. In the genomic pathway (Fig. 1), the binding of GCs to GR in the cytoplasm results in GR dissociation from the multiprotein complex. GR then dimerizes and translocates

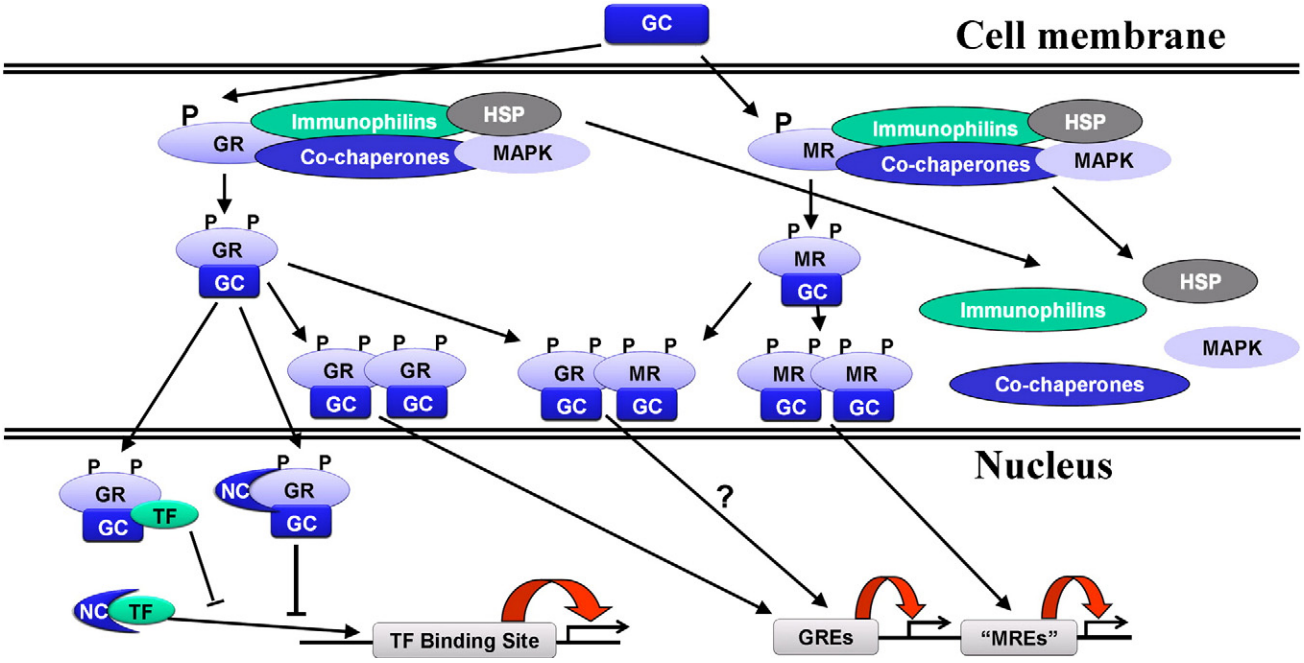

Fig. 1 – Genomic GC signaling pathways. Binding of GC to GR or MR leads to the release of immunophilins, co-chaperones, heat shock proteins (HSP), and the mitogen-activated protein kinases (MAPK). The GC–GR, GC–GR–MR, or GC–MR complex moves into the nuclei and regulates gene expression by binding to glucocorticoid response elements (GREs) or the same elements with conserved adjacent sequences preferring the GC–MR complex ("MREs"). These complexes can also regulate gene expression by interactions with other transcriptional factors (TF).