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Focused Review

Evolutionary conservation of glucocorticoids and corticotropin releasing hormone: Behavioral and physiological adaptations

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ABSTRACT

Glucocorticoids and corticotropin releasing hormone (CRH) underlie the physiology of change and adaptation. Both the steroid and peptide are quite ancient. The genes that underlie the production of these information molecules stretch back millions of years. The regulatory mechanisms of glucocorticoids have both restraining and enhancing capabilities on CRH gene expression. While restraint of CRH by glucocorticoids is a fundamental physiological feature of limiting CRH expression from over-use and exhaustion, CRH is also enhanced by glucocorticoids at both the level of extra-hypothalamic CRH sites and at the level of the placenta and fetal programming in the brain. This latter function of glucocorticoids increasing CRH gene expression underlies the physiology of change that underlies diverse adaptive functions.

1. Introduction

Diverse peptides and steroid hormones have a long evolutionary history. The focus of this review is largely about two such information molecules (glucocorticoids and corticotropin releasing hormone (CRH)) that underlie behavioral and physiological regulation; they are ancient and well expressed and are the building blocks of diverse signaling features in both the central and peripheral nervous system. Depending on where peptides are expressed, they have different functions; in the brain they are often linked to specific kinds of behaviors (Herbert and Schulkin, 2002).

One form of regulation in the brain is steroid induction of diverse information molecules (e.g., Herbert, 1993; Kalra, 1993; Fink, 1997; Pfaff, 1999). These interactions between steroid hormones and neuropeptides underlie behavioral responses; they range across vertebrates and invertebrates (Bentley, 1982; Strand, 1999).

An exaggerated emphasis has been on restraint as a primary model for steroid peptide interactions with regard to CRH and glucocorticoids. The continued evidence, both at a neural and behavioral level, is less in conformity with this view.

Two views have dominated the intellectual landscape with regard to these two hormones: first, that glucocorticoids are simply the stress hormone, second is that CRH is only restrained by glucocorticoids. There is another set of factors, namely the upregulation of CRH in several regions of the brain (and outside the brain e.g., the placenta) that impact behavior.

Thus, the first section of this paper emphasizes the evolutionary context of adrenal steroids and their diverse adaptive functions, followed by a similar description of CRH, followed by a description of the regulation of CRH by adrenal steroids. Indeed, evidence over the last 15 years suggests that one important function of the glucocorticoids is to facilitate CRH expression and not necessarily restrain CRH under diverse regulatory conditions that are broadly tied to forms of behavioral and physiological adaptation (e.g., adaptation to uncertain and fear provoking events, to parturition and birth).

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1.1. *Corticosteroids*

Corticosterone in the rat, or cortisol in humans, is a well known adrenal steroid. The ability to synthesize corticosteroids (e.g., aldosterone the other adrenal steroid and corticosterone) probably arose prior to the origin of the jawed vertebrates (hagfish and lamprey; reviewed by Denver, 1998, 2009). The ancestral glucocorticoids and its descendants were structurally pre-adapted to bind aldosterone, and thus prepared to utilize the ligand which appeared around 200 million years after the receptor (Bridgham et al., 2006). Glucocorticoid receptor phylogeny (Bridgham et al., 2006) has an ancestral profile that perhaps dates back 450 million years ago (Ortlund et al., 2007; Denver, 1998, 2009).

Tissue capable of corticosteroidogenesis is found in extant chondrichthyean fishes such as the holocephalans (ratfish) and elasmobranchs (sharks, skates, and rays). In modern bony fishes, the teleosts, cortisol is the major steroid produced by adrenocortical tissue (Bentley, 1982). A brief sketch of the evolution of glucocorticoids is depicted in Fig. 1.

Glucocorticoid function is broad with regard to their impact on regulatory behavior and physiology. Moreover, glucocorticoids vary in their effects during seasonal variation, in droughts, and in predictability for the allocation of food resources and other metabolic requirements (Wingfield, 2004; Buttemer et al., 1991; Landys et al., 2006). One idea here is that molecules may not change during evolution, but that their use does.

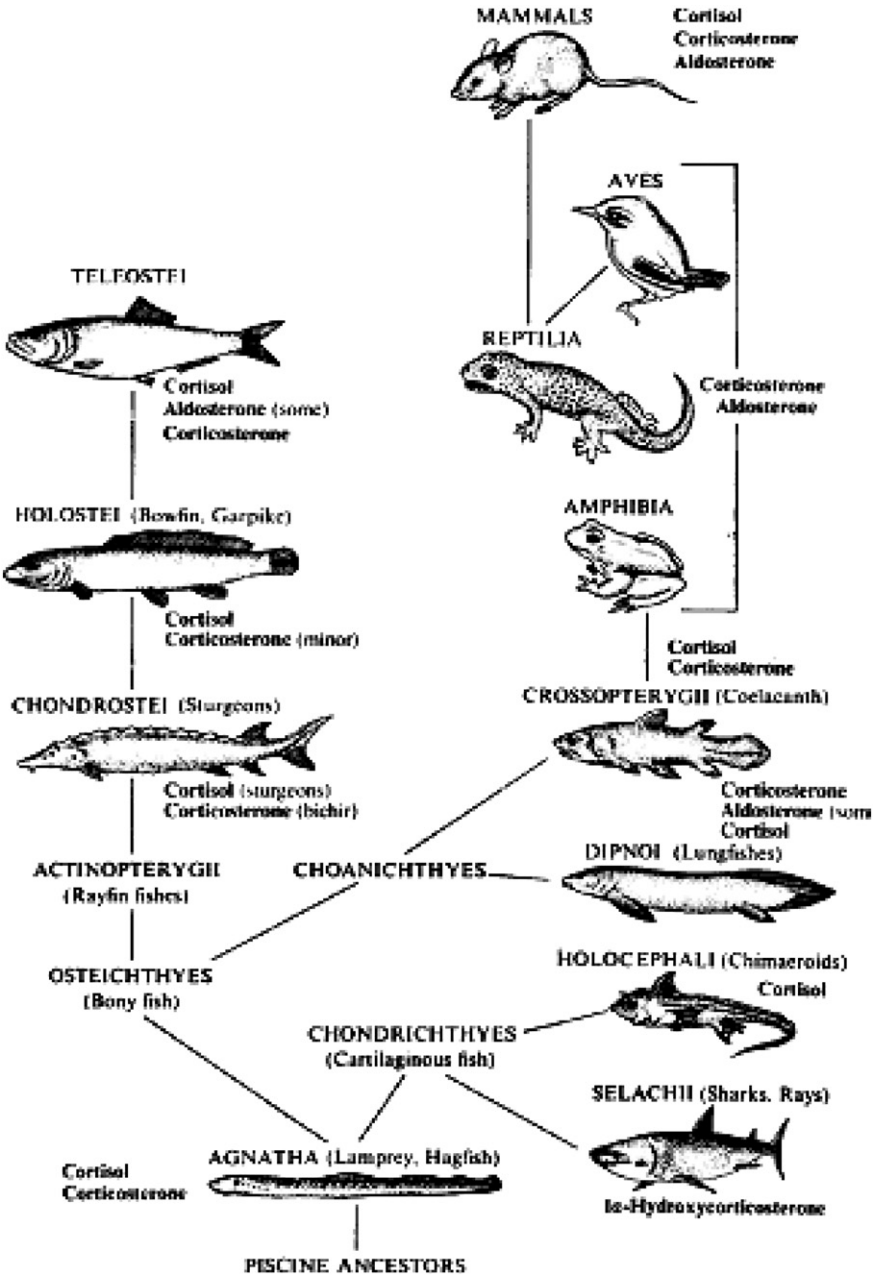

Fig. 1 – A depiction of the evolution of corticosteroids in different species (adapted from Bentley, 1982).