REVIEW

Sympathoadrenal system and immune system in the regulation of adrenocortical function

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Common textbooks of endocrinology envisage the adrenal cortex and the adrenal medulla as two functionally separate systems that are regulated independently from one another. Even worse, the mononuclear cells that are present within the normal human adrenal gland have been largely neglected or regarded as innocent bystanders. In this review we would like to draw attention to the close morphological and functional interplay between these systems and to propagate the notion that there is a meaningful cross-talk between the sympathico chromaffin system, the hypothalamus-pituitary-adrenocortical axis and the immune system at the level of the peripheral gland.

Morphological evidence for an interaction between the adrenal medulla and the adrenal cortex

The location of chromaffin cells within the adrenal cortex has been described in different species (1, 2), including humans (3). We were able to provide evidence, via specific immunostaining of chromaffin cells with antibodies to synaptophysin or chromogranin A, that in all these species, including humans, rays of such cells extend from the medulla right through the cortex and may sometimes even show up as small islets within the zona glomerulosa (Fig. 1). Vice versa, specific immunostaining of cortical cells with antibodies to 17α-hydroxylase, an enzyme relevant to steroid hormone synthesis, showed that cortical cells are located within the adrenal medulla where they may appear as small cell clusters isolated from the cortex.

On the electron microscopic level, chromaffin cells are characterized by their dense-cored catecholamine-containing vesicles, while adrenocortical cells can be recognized by their typical mitochondria with tubulovesicular cristae and ample smooth endoplasmic reticulum. Ultrastructural analyses of the contact zones in all three zones of the adrenal cortex revealed that cortical and chromaffin cells were opposed to each other without separation by connective tissue or interstitium (1, 3). In addition, we succeeded in recording the exact moment of a chromaffin vesicles’ exocytosis from a chromaffin cell that was in direct contact with a zona glomerulosa cell (4).

Physiological consequences of the close anatomical co-localization of chromaffin and cortical cells

Increasing evidence exists for a neural influence on adrenocortical functions such as diurnal variations in adrenal steroidogenesis (5, 6), adrenocortical growth (7), and on adrenocortical sensitivity to adrenocorticotropic hormone (ACTH) (8, 9). In addition, in pigs, isolated perfused adrenal glands with intact splanchnic innervation steroidogenesis could be stimulated independently from the hypothalamus-pituitary-adrenal (HPA) axis by electrical activation of the sympathoadrenal system (10–13). This sympathetic regulation of adrenocortical function could be described as the neuroadrenocortical axis (for a review, see Ref. 14).

Different conceivable pathways exist for how the neural stimulation could reach the adrenal cortex. This neuroendocrine regulation could be based upon the depletion of transmitters or neuropeptides from nerve endings in the adrenal cortex, because these nerves originate at least partly in the adrenal medulla (15, 16). However, adrenomedullary chromaffin cells themselves, in addition to catecholamines, produce a whole series of neuropeptides and transmitters that are able to influence adrenocortical steroid production. Some have stimulatory effects like vasoactive intestinal polypeptide (VIP) (11, 17–24), galanin (25, 26), vasopressin and oxytocin (27–35), neuropeptide Y (NPY) (36–38), substance P (39), neurenomed N (36, 40), and serotonin (41–53). Other peptides such as atrial natriuretic peptide (44–50), calcitonin gene-related peptide (51, 52), dynorphin (53), somatostatin (54) and enkephalins (55), which have been identified in chromaffin cells, exert an inhibitory influence upon steroidogenesis.

The main secretory products from the adrenal medulla following stimulation of the splanchnic nerves, however, are adrenaline and noradrenaline. These catecholamines stimulate corticosteroid secretion from the intact perfused organ (10, 12) as well as from adrenocortical cells in primary culture (56–60). This stimulation involves accumulation of all four steroid hydroxylase mRNAs (14, 56, 57). As the blood flow within the adrenal gland is directed centripetally from the cortex to the medulla (61),
secretory products released by chromaffin cells should influence steroidogenesis in the adrenal cortex in a paracrine manner. It can be assumed that the basis of this interaction is formed by the extensive cellular contacts between cortical and chromaffin cells found in mammals, including humans.

The mammalian adrenal gland is a highly vascular organ. In the rat adrenal gland, glucocorticoid secretion is closely linked to the blood flow rate through the adrenal gland (62, 63). Evidence exists that adrenal blood flow may be regulated in part by neuropeptides like VIP, substance P, NPY, neurotensin and enkephalins released from the capsular region of the adrenal gland in response to splanchic nerve stimulation (64). Therefore, in addition to a direct effect, these adrenal neuropeptides may influence adrenocortical function indirectly by regulating adrenal vasculature.

In summary, the sympathetic innervation of the adrenal gland not only stimulates the release of catecholamines from the medulla but in addition regulates steroidogenesis within the adrenal cortex either through secretagogues released from nerve endings within the cortex or from adrenal medullary chromaffin cells. The two tissues are closely interwoven, which could be the prerequisite for a paracrine interaction.

The immune-endoctrine axis at the level of the adrenal gland

The interaction between the immune system and the HPA axis has been studied extensively since the pioneering work of Besedovsky and Sorkin (65). It is now well known that the immune system influences the activity of the HPA axis by stimulating the secretion of corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) at the level of the hypothalamus and the pituitary, respectively (for a review, see Refs. 66–69). However, increasing evidence exists for a local regulatory effect of the immune system on adrenal function.

Cytokines locally influence adrenal function

Cytokines are soluble peptides released from immune

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**Fig. 1.** Paraffin section of porcine adrenal immunostained for synaptophysin. The medullary cells are stained, whereas the cortex shows no staining. Cortical and medullary tissues are closely interwoven. Chromaffin cells occur in all three zones of the cortex and spread in the subcapsular area of the zona glomerulosa (× 100). Reproduced from: Bornstein SR, Ehrhart-Bornstein M, Scherbaum WA, Pfeiffer EF, Holst JJ. Effects of splanchic nerve stimulation on the adrenal cortex may be mediated by chromaffin cells in a paracrine manner. Endocrinology 1990;127:900–6. © The Endocrine Society.
cells. Despite their effects within the immune system, they can directly influence different target tissues, including the adrenal cortex.

Interleukin 1 (IL-1) is the term for two polypeptides (IL-1α and IL-1β) with a wide spectrum of inflammatory, metabolic, hematopoietic and immunological properties (70). A direct effect of IL-1 on adrenal steroidogenesis has been demonstrated in different animal models. Interleukin 1 stimulates the release of corticosteroids from in situ perfused rat adrenal glands (71), in hypophysectomized rats (72) and from rat (73, 74) and bovine (75) adrenal cells in primary culture. Controversial data exist on how the stimulatory effect of IL-1 is transmitted to the adrenal cortex. Three possibilities are discussed: the involvement of prostaglandins (71, 75); an extrapituitary, probably intradrenal, CRH/ACTH system (72); via catecholamines released from the medulla (73, 74).

The pleiotropic cytokine interleukin 6 (IL-6) is known to be involved in the regulation of hematopoiesis, immune responses and acute phase reactions (76). Interleukin 6 on its own and in synergism with ACTH stimulates the release of corticosterone from rat adrenocortical cells (77). In humans, IL-6 activates the HPA axis by stimulating the release of cortisol and ACTH. Interestingly, after long-term application of IL-6, ACTH plasma levels decrease whereas IL-6 still leads to a significant stimulation of cortisol release, suggesting a direct effect of IL-6 on the adrenal cortex (78). In addition, IL-6 stimulates corticosteroid release from human adrenocortical cells in primary culture, exerting its most prominent effect on the release of adrenal adrogens (unpubl. obs.).

Tumor necrosis factor alpha (TNF-α) is a 17-kD polypeptide hormone that is produced by a wide variety of tissues (79). In the adrenal gland, TNF-α inhibits the angiotensin II-induced aldosterone release from rat adrenal cells (80) as well as basal and ACTH-stimulated cortisol production and P-450 enzyme expression in human fetal adrenal glands (81, 82). In cultured human fetal adrenal cells, TNF-α inhibits basal and ACTH-induced insulin-like growth factor (IGF) expression (83, 84), indicating the involvement in growth and differentiation of the fetal adrenal gland.

Transforming growth factor beta (TGF-β) describes a family of three related peptides that have a wide variety of biological activities and are produced by many tissues (85–88), including macrophages (89, 90). A number of reports concurrently demonstrated the inhibitory action of TGF-β on adrenocortical steroidogenesis in vitro (91–101) and high-affinity receptors for TGF-β have been detected on bovine adrenocortical cells (102). However, species-specific differences exist concerning the potency of TGF-β to inhibit the different steroidogenic enzymes (95). Like other inhibitory cytokines, such as TNF-α or interferon-γ, TGF-β causes a decrease in IGF-II mRNA (84) and inhibits the growth of fetal zone cells (103).

Interferons are polypeptides that interfere with viral replication in infected cells. In addition, they have a wide variety of effects in immune function (104). In the adrenal gland two members of this family seem to influence steroidogenesis. Interferon-α stimulates adrenal corticosterone secretion from rat adrenal cells in primary culture (105). In contrast, interferon-γ, similar to TNF-α, inhibits basal and ACTH-induced IGF expression in human fetal adrenal cells (83, 84), suggesting its involvement in growth and differentiation of the fetal adrenal gland.

Altogether, several cytokines that may influence adrenocortical steroidogenesis. However, it is generally accepted that plasma cytokine levels are too low to account for a direct effect on adrenal function. If secretory products of the immune system influence adrenal function, these factors should therefore be produced within the adrenal gland itself.

Cellular source and regulation of cytokines within the adrenal

Macrophages and monocytes

The adrenal cortex is extensively infiltrated by macrophages under normal conditions (106, 107) (Fig. 2). This infiltration could be the prerequisite for a local immune–adrenal interaction.

In addition to their phagocytotic functions, macrophages are able to secrete a variety of products. Upon stimulation they produce several cytokines like IL-1, IL-6, TNF-α (70) and TGF-β (89, 90) or peptides like VIP (108) that can influence adrenocortical function. Because some of these cytokines have stimulatory and others inhibitory effects on the adrenal cortex, macrophages should be able to exert both functions. In accordance, the stimulatory action of monocytes on cortisol production by cultured human adrenocortical cells through a factor different from ACTH has been reported (109). On the other hand, stimulated murine macrophages produce a factor (factors) that inhibit(s) the action of ACTH on the adrenal cortex in vitro (110, 111). Therefore, monocytes/macrophages seem to be able to up- or down-regulate adrenocortical function depending on the cytokines or peptides released. It remains to be elucidated under which conditions macrophages either stimulate or inhibit adrenocortical function.

The intra-adrenal regulatory circuit is closed by the fact that macrophages are influenced by the sympathetic system, because they have high numbers of β-receptors (112), and by an activated HPA axis. Cortisol inhibits immune function, including the secretion of cytokines by monocytes (113). The macrophage seems to be a key player in this bidirectional communication.

Lymphocytes

Lymphocytes have been reported to produce and secrete
ACTH-like substances (114), whereas the levels of extrapituitary ACTH are probably too low to account for a significant stimulation of adrenal steroidogenesis, even in response to viral infection (115). However, at least one case has been reported where ectopic ACTH production by a granulomatous mass led to Cushing’s syndrome (116). In the human adrenal gland of the elderly, infiltration by T lymphocytes seems to be a regular phenomenon (117). Therefore, these immune cells have the potential for a paracrine influence on adrenocortical function.

Cytokines produced by adrenal cells

Besides cells of the immune system, adrenal cells are also able to produce cytokines. Interleukin 1 is produced in adrenal medullary cells of the rat and it is released following cholinergic stimulation (118–120). Both IL-6 and TNF-α are produced within the steroid-producing cells in the rat zona glomerulosa. The release of IL-6 is stimulated by angiotensin II, ACTH, IL-1α, IL-1β and lipopolysaccharide (LPS). The release of TNF-α is stimulated by LPS, IL-1α and IL-1β, while ACTH inhibits its release (121–124). In contrast to rats, the expression of IL-1 (125), IL-6 (126) and TNF-α (127) in human adrenal glands has been localized to cells of the zona reticularis. Transforming growth factor β1 is synthesized by bovine adrenocortical cells (128). These cytokines produced by adrenal cells may influence adrenocortical function in an autocrine or paracrine manner.

Cytokines produced either by immune cells or by adrenal cells may be important in the fine regulation of adrenal function and its adaptation to stress. In this context it is of interest that stress stimulates the release of several cytokines, particularly IL-6, an effect that is, at least in part, mediated by adrenaline (129, 130). Therefore, the intra-adrenal immune-endocrine axis can be stimulated during stress situations in a paracrine manner via activation of the adrenal medulla.

Major histocompatibility complex (MHC)

An interesting aspect in the morphology and physiology of the adrenal gland concerns the detection of MHC class II molecules within the zona reticularis of the adrenal (131, 132). These molecules, originally thought to be restricted to some immunocompetent cells, have been found on many other epithelial cells besides the adrenal under both normal and pathological conditions. The hypothesis was raised by Bottazzo and Feldman (133), suggesting that induction of aberrant HLA-DR expression on epithelial cells is a first-step in the development of an autoimmune process. This hypothesis cannot be applied to the induction of autoimmune adrenalitis because HLA-DR, DP and DQ are expressed with zonal restriction and without finding of lymphocytic infiltration, at least in normal tissue. This is confirmed by the studies of Jackson and McNicol (131), who compared class II expression in normal adrenal glands and in Addison’s disease. They concluded that increased class II expression is due to inflammatory infiltration. A physiological role for MHC class II molecules, besides immunological function, seems possible in the adrenal gland. Some findings give support to the notion that the expression pattern of MHC class II molecules within the adrenal gland changes according to age and hormonal status. Adrenal glands of younger donors show a higher expression rate than tissues of older donors (132). Furthermore, it is pointed out in this work that, according to the theory of the functional zonation, originally MHC class II negative zona fasciculata cells could turn MHC class II positive when they change into reticularis cells and thereby alter their hormone pattern. In that respect the production of cytokines like IL-1 and TNF-α, which are able to modulate the expression of MHC class II molecules by adrenocortical cells and by intra-adrenal macrophages, may be important.

Concluding remarks

Within the adrenal gland there is communication between the sympathetic system, the immune system
and the HPA axis (Fig. 3). In contrast to the common view that an interaction of the three systems takes place only at a central level, data presented here demonstrate that an interaction and cross-talk also takes place within the peripheral gland. Besides the well-known influences of corticosteroids on adenomulary and immune functions, both systems have regulatory influences on the adrenal cortex. In addition, cytokines are produced by adrenal cells themselves, bearing the possibility for autocrine/paracrine regulations. The interactions of immune system and hormone-producing cells have been the topic of investigations on several peripheral glands. Hormone synthesis and immune function therefore seem to be connected to a considerably higher degree than previously thought.

Acknowledgments. Work done in the authors’ laboratory was supported by grants from the Deutsche Forschungsgemeinschaft (DFG grant Eh 161/1-1 to ME-B, DFG grant Bo1141/2-2 to SRB and DFG grant Schc 225/10-2 to WAS).

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