Chapter 3
Cell Signaling Within Endocrine Glands: Thyroid, Parathyroids and Adrenal Glands

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Abstract Despite the fact that there can be argued that no single cell in the human body can be devoid of molecular tools that fit into the broad definition of an endocrine function, some organs are primarily dedicated to hormone secretion and are therefore designated endocrine glands. Under regulation by pituitary gland (reviewed on the previous chapter), three peripheral organs are exclusively devoted to endocrine functions: the thyroid, the parathyroid and the adrenal glands. This Chapter on endocrine system will cover the signaling pathways implied in these three organs, with identification of their particular and shared features.

Keywords Endocrine system · Signaling pathways · Thyroid gland · Parathyroid gland · Adrenal gland

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J. V. Silva et al. (eds.), *Tissue-Specific Cell Signaling*,
https://doi.org/10.1007/978-3-030-44436-5_3

Abbreviations

17βHSD5	17β-hydroxysteroid dehydrogenase
1α,25(OH)2D	1α,25-dihydroxyvitamin D
2-AG	2-arachidonoylglycerol
$[Ca^{2+}]_i$	Intracellular calcium concentration
$[Ca^{2+}]_e$	Extracellular ionized calcium concentration
$[(PO_4)^{3-}]_e$	Phosphate serum concentration
AA	Arachidonic acid
AADC	L-aromatic amino acid decarboxylase
AC	Adenylate cyclase
Ach	Acetylcholine
ACTH	Adrenocorticotropic hormone
ANG I	Angiotensin I
ANG II	Angiotensin II
AT1R	Angiotensin II receptor type 1
ATF	Activating transcription factor
ATP	Adenosine triphosphate
CaMK	Calmodulin-dependent protein kinases
CaMKII	Calmodulin-dependent protein kinase II
cAMP	Cyclic 3′,5′-adenosine monophosphate
CaSR	Calcium-sensing receptor
CREB	cAMP response element binding
CRH	Corticotropin-releasing hormone
CT	Calcitonin
CYB5A	Cytochrome B5A
CYP11A1	Cholesterol side chain cleavage enzyme
CYP11B1	11β-hydroxylase
CYP11B2	Aldosterone synthase
CYP17A1	17α-Hydroxylase
CYP21A2	21α-hydroxylase
DA	Dopamine
DAG	Diacylglycerol
DBH	Dopamine β-hydroxylase
DHEA	Dehydroepiandrosterone
DHEA-S	Dehydroepiandrosterone sulfate
Epi	Epinephrine
ERK	Extracellular signal-regulated kinase
FGF23	Fibroblast growth factor 23
GH	Growth hormone
GR	Glucocorticoid receptor
Hh	Hedgehog signaling pathway
HPA	Hypothalamic-pituitary-adrenal axis
HSL	Hormone-sensitive lipase

IP3	Inositol 1,4,5-triphosphate
LDL	Low-density lipoproteins
LO	Lipoxygenase
MAG	Monoacylglycerol lipase
MC2R	Melanocortin receptor 2
MAPK	Mitogen-activated protein kinase
MCT8	Monocarboxylate transporter 8
NCoR	Nuclear receptor co-repressor
NE	Norepinephrine
NIS	Sodium-iodide symporter
NO	Nitric oxide
PI3K	Phosphoinositide-3-kinase
PIP2	Phosphatidylinositol 4,5-bisphosphate
PNMT	Phenylethanolamine N-methyltransferase
PKA	Protein kinase A
PKC	Protein kinase C
PLA2	Phospholipase A2
PLC	Phospholipase C
PLD	Phospholipase D
$(PO_4)^{3-}$	Phosphate
PRL	Prolactin
PTH	Parathormone
PTHrP	Parathyroid hormone-related protein
SF1	Steroidogenic factor 1
Shh	Sonic hedgehog
StAR	Steroidogenic acute regulatory protein
SULT2A1	Sulfotransferase 2A1
T3	Triiodothyronine
T4	Thyroxine
TG	Thyroglobulin
THSR	Thyroid-stimulating hormone receptor
TPO	Thyroid peroxidase
TRH	Thyrotropin-releasing hormone
TRHR1	Thyrotropin-releasing hormone receptor 1
TSH	Thyroid-stimulating hormone
TSHR	Thyroid-stimulating hormone receptor
VMAT1	Vesicular monoamine transporter 1
VGCC	Voltage-gated Ca^{2+} channels

3.1 Introduction

There can be no argue that there is no single cell in the human body devoid of functionalities that could fit in this broad definition of an endocrine function, some cell types present a specific histological endocrine differentiation and are primarily committed to synthesize and secrete hormones. Endocrine differentiated cells can be found either scattered, isolated or in cell aggregates in organs pertaining to different physiological systems, such as endocrine cells along the gastro-intestinal system which comprise part of the "diffuse endocrine system", or in alternative can be organized in endocrine tissues within organs that are dedicated to the secretion of specific hormones, also known as endocrine glands. Hormones can be classified according to three different molecular classes based on their chemical structure: peptide hormones, which include proteins and polypeptides; steroids, which are lipid-derived hormones and amino acid-derived, namely tyrosine derived hormones [1].

The focus of this chapter will be to describe the signaling pathways so far identified in the three peripheral glands of the endocrine system, namely within thyroid, parathyroid and adrenal gland.

3.2 Thyroid Gland

The thyroid is an endocrine gland located in the anterior part of the lower neck [2]. The functional unit of the gland is the thyroid follicle that consists of a central core of colloid surrounded by an epithelium with a single layer of follicular cells (Fig. 3.1). In the thyroid gland parenchyma there are two predominant cell types: the epithelial follicular cells, which are the vast majority of thyroid tissue cells [3] and the parafollicular cells, also known as C cells that reside in the periphery of the follicle [3, 4].

3.2.1 Follicular Cells

Thyroid follicular cells are the ones responsible for the synthesis and secretion of thyroid hormones thyroxine (T4) and triiodothyronine (T3). The most important regulator of thyroid hormones synthesis is the thyroid-stimulating hormone (TSH) secreted by the anterior pituitary gland under the influence of the hypothalamic thyrotropin-releasing hormone (TRH). TSH is very sensitive to small fluctuations in serum thyroid hormones levels [5]. Besides that, as iodine is a limiting substrate for thyroid hormone synthesis, dietary iodine availability is also an important regulatory factor [6].

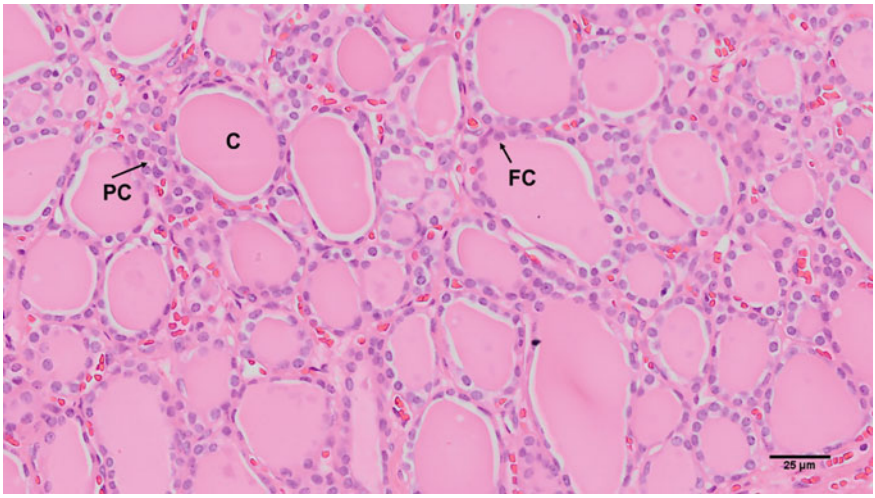

Fig. 3.1 Human thyroid gland stained by hematoxylin and eosin (H&E) (200x); C—Colloid, FC—Follicular cells, PC—Parafollicular cells

3.2.1.1 Regulation of Thyroid Hormones Synthesis by TSH

TSH is the main physiological hormone implicated in thyroid function regulation. TSH acts on the follicular thyroid cell by activating the TSH receptor (TSHR), a member of the glycoprotein G coupled-receptor family (Fig. 3.2) [7]. TSHR is located at the basolateral membrane of thyroid follicular cells and mediates the activation of two regulatory pathways: cyclic 3′,5′-adenosine monophosphate (cAMP) and phospholipase C (PLC) cascades [8, 9]. This dual-activation is rendered by the ability of TSHR being capable to interact with all Gα subtypes, in particular with the Gs and Gq subtypes [10, 11].

After TSH-mediated receptor activation TSHR couples predominantly to Gs [12, 13]. Gs activation then leads to cAMP production that binds to the regulatory subunit of protein kinase A (PKA), releasing and activating its catalytic subunit. Activated PKA regulates the iodine uptake and the transcription of genes involved in thyroid hormone production: sodium-iodide symporter (NIS), thyroglobulin (TG) and thyroid peroxidase (TPO) [4, 9, 14].

In the PLC cascade, the TSHR activation causes the activation of Gq protein that stimulates PLC [8, 9]. PLC hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP2) into diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP3). IP3 binds to its endoplasmic reticulum receptors, which act as channels for the release of the Ca^{2+} stored in this organelle. Increased intracellular calcium concentration $[Ca^{2+}]_i$ is followed by an increase of Ca^{2+} from the extracellular medium. In thyroid cells, Ca^{2+} activates calmodulin-dependent protein kinases (CaMK) that regulate the iodide apical efflux, H_2O_2 generation through Dual oxidase 2 (DUOX-2) activation, TG iodination and constitutive activation of nitric oxide (NO) synthase [9, 12, 15]. In

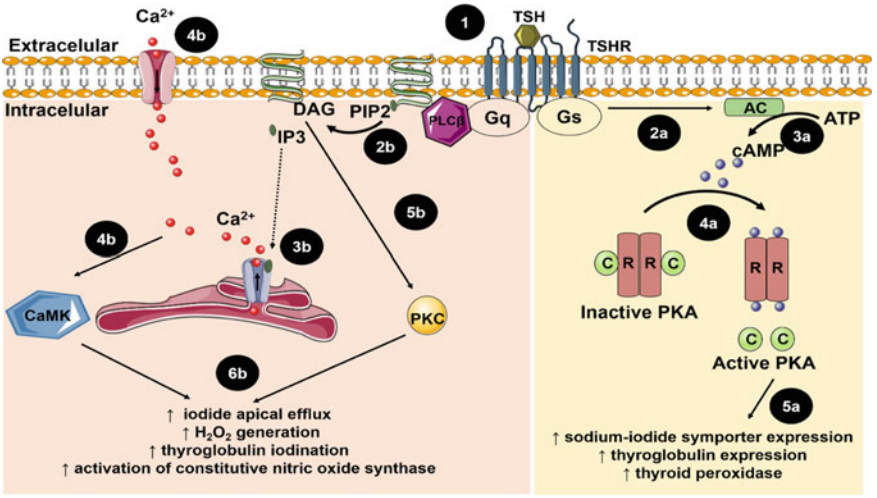

Fig. 3.2 Signaling pathways activated by thyroid stimulating hormone (TSH) in thyroid follicular cells. (1) TSH binds to the thyroid stimulating hormone receptor (THSR), activating two Gα protein subtypes: Gs and Gq. These proteins activate two different regulatory pathways: cAMP and phospholipase-C (PLC) pathways, respectively. cAMP pathway: (2a) Gs activates adenylate cyclase (AC); (3a) AC converts adenosine triphosphate (ATP) to cAMP; (4a) cAMP binds to the regulatory subunits (R) of protein kinase A (PKA), releasing and activating the catalytic subunits (C) of this protein (5a) Activated PKA activates transcription of genes involved in the thyroid hormone production: sodium-iodide symporter, thyroglobulin and thyroid peroxidase. PLC pathway: (2b) Gq activation stimulates PLC that hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP2) into diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP3); (3b) IP3 binds to its endoplasmic reticulum receptors releasing the Ca^{2+} stored in this organelle; (4b) Increased intracellular Ca^{2+} is followed by an increase of Ca^{2+} from the extracellular medium and calmodulin-dependent protein kinases (CaMK) activation; (5b) DAG activates the protein kinase C (PKC); (6b) PLC pathway, through CaMK and PKC activation, regulate the iodide apical efflux, H_2O_2 generation, thyroglobulin iodination and constitutive activation of nitric oxide synthase. *Notes* Dotted arrows depict particles movement

addition, DAG, the other molecule that results from PIP2 hydrolysis, is responsible for the activation of protein kinase C (PKC) which in turn activates protein kinase D (PKD) that enhances iodination and also activates the transcription of genes involved in the thyroid hormone production, such as DUOX-2 [4, 16, 17].

A cross-signaling between PIP2 and cAMP cascades has been reported. The activation of CAMK through the PIP2 cascade inhibits cAMP accumulation and thus the cAMP cascade. Besides that, the PKC activation enhances cAMP response to TSH [4, 18].

3.2.1.2 Regulation of Thyroid Hormones Synthesis by Iodine

Iodine is the main substrate used by thyroid follicular cells for the synthesis of thyroid hormones [6]. The thyroid gland has the capacity to maintain synthesis and secretion of thyroid hormones when iodine availability becomes scarce by shifting the synthesis of hormones from T4 to T3, which synthesis requires less iodine besides being more potent [19].

In contrast, iodide excess decreases the thyroid response to TSH, thus inhibiting the thyroid hormones secretion. This phenomenon, known as the Wolff–Chaikoff effect, was first described in 1948 by Wolff and Chaikoff after the observation that rats exposed to high amounts of iodide, presented decreased levels of organic form of iodide [20]. Although the molecular mechanisms underlying the acute Wolff–Chaikoff effect are not completely understood, some studies reported that iodide is able to inhibit the first steps of both TSH regulatory pathways, cAMP and PLC pathways, inhibiting the downstream effects and thus the thyroid hormones secretion [21–24]. In normal physiological conditions, iodide-mediated thyroid function inhibition is transient and this phenomenon is termed "Wolff-Chaikoff effect adaptation", which can be explained by the downregulation of the NIS and thus inhibition of iodide transport into the thyroid follicular cells [21].

3.2.1.3 Synthesis and Secretion of Thyroid Hormones

Thyroid hormones synthesis requires two precursors: iodide and TG (Fig. 3.3). First step consists in the transport of iodide into the follicular cell, via NIS. NIS activity is dependent on the Na^+ gradient created by the Na^+/K^+-ATPase [25, 26]. Through the intracellular electrochemical gradient, iodide goes to the apical surface of the cell and is then transported into the colloid mainly through pendrin channels [26, 27]. Iodine is then oxidized by the enzyme TPO in the presence of hydrogen peroxide, which is generated by a NADPH oxidase, the enzyme DUOX2 [28, 29]. In addition, TG, a hormone containing about 120 tyrosine residues is synthesized on ribosomes, glycosylated in the endoplasmic reticulum, translocated to the Golgi apparatus and packaged in secretory vesicles, which is excreted into the colloid by exocytose [30].

In a process that is also catalyzed by TPO, oxidized iodide is then bounded to the tyrosyl residues of TG to form monoiodotyrosine (MIT) or diiodotyrosine (DIT), containing one or two iodine molecules, respectively [31, 32]. MIT and DIT are then combined to form T3 and T4, which in turn contain respectively three or four iodine molecules. Colloid, consisting of a reservoir of iodinated TG containing the thyroid hormones is engulfed in vesicles, by pinocytosis and internalized into the follicular cells. Then the vesicles are digested by lysosomes, which generates T4 and T3 to be released into the bloodstream, via monocarboxylate transporter 8 (MCT8) [33]. In contrast, MIT and DIT are retained in the cell and deiodinated by the iodotyrosine dehalogenase 1. Iodine is then recycled for further thyroid hormone synthesis [34, 35].

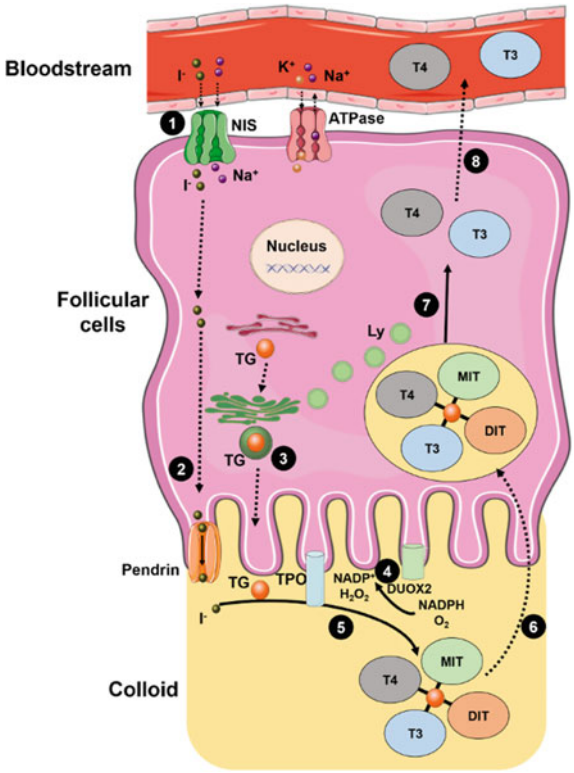

Fig. 3.3 Synthesis and secretion of thyroid hormones by the thyroid follicular cell. (1) Iodide enters the follicular cell, via sodium-iodide symporter (NIS); (2) iodide (I^-) goes to the apical surface of the cell, where it is transported to the colloid mainly through pendrin channels; (3) thyroglobulin (TG) is produced and excreted to the colloid, by exocytose; (4) DUOX2 produce hydrogen peroxide (H_2O_2); (5) In the presence of H_2O_2, thyroid peroxidase (TPO) oxides iodide and attaches it to TG to form monoiodotyrosine (MIT) or diiodotyrosine (DIT), then MIT and DIT combine to form thyroxine (T4) and triiodothyronine (T3); (6) TG complex is then internalized into the follicular cell and form intracellular vesicles; (7) vesicles are digested by lysosomes (Ly), which generates T4 and T3; (8) T3 and T4 are released into the bloodstream. Notes: Dotted arrows depict particles movement

3.2.2 Parafollicular Cells

Parafollicular cells are present in the interfollicular connective tissue stroma of the thyroid gland. Contrarily to follicular cells that arise from the endoderm, parafollicular cells derive from the neural crest cells and belong to the neuroendocrine system [2]. Parafollicular cells secrete calcitonin (CT) hormone, which participates in the regulation of Ca^{2+} homeostasis, although having a minor role [36].

3.2.2.1 Synthesis and Secretion of Calcitonin

CT is secreted in response to increased extracellular $[Ca^{2+}]_e$, through the activation of the calcium-sensing receptor (CaSR), a class C G-protein-coupled receptor [37–39]. Ca^{2+}-CaSR interaction activates Gq/11 protein that in turn stimulates PLC. PLC hydrolyzes PIP2 into DAG and IP3. IP3 acutely increases $[Ca^{2+}]_i$ levels, in a similar process as previously described for the follicular cell, which initiates the processes of CT release from the secretory vesicles into the bloodstream [19, 40]. Besides that, DAG activates PKC that regulates the transcription of key genes for Ca^{2+} homeostasis, such as CaSR and the gene that encodes CT and CT gene-related peptide [41, 42]. Contrarily to what occurs with other CaSR responsive cells, such as parathyroid cells, CaSR-mediated CT release from thyroid parafollicular cells seems to occur independently of extracellular signal-regulated kinase (ERK) 1/2 signaling activation and cAMP synthesis suppression [42, 43].

In addition to Ca^{2+}, some gastro-intestinal hormones, including glucagon, gastrin and cholecystokinin were also demonstrated to carry the ability of stimulating CT release from parafollicular cells [36, 44].

The physiological effects of CT consist in decreasing blood Ca^{2+} levels through inhibition of the osteoclast activity in the bones, inhibition of Ca^{2+} reabsorption by renal tubuli and inhibition of Ca^{2+} absorption in the intestine [36].

3.3 Parathyroid Glands

The human parathyroid glands are most often four ovoid infra centimetric glands located behind each pole of the lateral lobes of the thyroid gland, although anatomical variations in the number and location of the parathyroid glands can frequently occur [2].

The parathyroid tissue is comprised of two functional cell lines, the chief cells and the oxyphil cells. Chief cells are the predominant parathyroid cell type, which are responsible for synthesis and secretion of parathormone (PTH). The function of oxyphil cells remains controversial, despite recent evidence suggesting that these cells result from chief cells deactivation to preserve the PTH secreting potential, in addition to secreting parathyroid hormone-related protein (PTHrP) [45].

3.3.1 PTH Actions

PTH is a key player in Ca^{2+} homeostasis, along with 1α,25-dihydroxyvitamin D [$1\alpha,25(OH)_2D$] and fibroblast growth factor 23 (FGF23). PTH interacts with membrane-specific receptors on target organs, predominantly on kidney and bone to increase circulating Ca^{2+} levels [46].

In the kidney, PTH-mediated Ca^{2+} reabsorption in the distal convoluted tubule ensures a thigh control over Ca^{2+} urinary excretion, despite the majority of filtered Ca^{2+} being reabsorbed along with sodium in the proximal convoluted tubule [47]. Additionally, PTH downregulates sodium-phosphate cotransporters and inhibits sodium–hydrogen antiporter in the proximal convoluted tubule, ultimately leading to decreased reabsorption of phosphate ($(PO_4)^{3-}$) and bicarbonate, respectively [48]. Still in the kidney, PTH activates the 25-hydroxyvitamin D3-1α-hydroxylase gene promoter, the enzyme responsible for the conversion of calcifediol (25-hydroxycholecalciferol) into 1α,25(OH)2D [49]. In turn, 1α,25(OH)2D mediates dietary Ca^{2+} absorption by intestinal mucosa, with PTH ultimately promoting the alimentary Ca^{2+} absorption [50].

In the bone, PTH enhances bone turnover, leading to bone mineral matrix reabsorption that results in the release of Ca^{2+} and $(PO_4)^{3-}$ into circulation [51], in addition to stimulate new bone formation [52].

3.3.2 PTH Biosynthesis

The *PTH* gene is located on chromosome 11 that when transcribed yields pre-pro-PTH, the PTH precursor [53]. Pre-pro-PTH consists of 115-amino-acids containing the mature PTH (1-84) sequence along with a 6-amino-acid pro-hormone sequence and a 25-amino-acids signal ("pre") sequence at its N-terminus [54]. Mature PTH is stored in vesicles and granules, which are secreted into the extra-cellular fluid in the presence of low circulating calcium levels [55]. Moreover, PTH is co-stored in granules along with cathepsin B and H [56], capable of degrading PTH into C-terminus PTH fragments that hold no action over PTH/PTHrP receptors, which are selectively secreted under conditions of hypercalcemia rather than mature PTH(1-84) [55].

3.3.3 PTH Secretion and Its Regulation

The most important regulator of PTH secretion is the negative feedback loop elicited by extracellular ionized Ca^{2+} concentrations ($[Ca^{2+}]_e$) [57].

In parathyroid cells, an increase in $[Ca^{2+}]_i$ reduces the fusion of preformed PTH storage vesicles with the cytosolic membrane, thus suppressing PTH secretion, instead of stimulating hormonal secretion as commonly observed in the other endocrine glands [58], although the mechanisms that underlie this phenomena are still poorly characterized [59].

$[Ca^{2+}]_e$ binds to the seven-loop transmembrane CaSR on the extracellular membrane of parathyroid chief cells, which is coupled to Gq and Gi proteins [57]. Gq activates PLC that increases the formation of IP3 and DAG from PIP2. In turn, IP3 induces Ca^{2+} mobilization from intracellular reticular storages, thus increasing

$[Ca^{2+}]_i$ [60]. High $[Ca^{2+}]_i$ activates Ca^{2+}-dependent K^+ channels, which lead to cytoplasmic membrane hyperpolarization [61] that ultimately suppresses the fusion of PTH vesicles with the membrane and exocytosis [62]. Moreover, increased $[Ca^{2+}]_i$ indirectly activates PLA2 and PLD through PKC activation [63]. DAG is converted by DAG lipase into 2-arachidonoylglycerol (2-AG) that is then hydrolyzed into arachidonic acid (AA) by monoacylglycerol lipase (MAG). AA is also produced by PLA2 that becomes activated in the presence of elevated $[Ca^{2+}]_e$ and is ultimately modified by cyclooxygenase, lipoxygenase (LO) and epoxygenase (cytochrome P450) [64]. LO products from AA metabolism are strong inhibitors of PTH secretion when CaSR is activated by high $[Ca^{2+}]_e$ [65, 66]. Moreover, Gi activation suppresses magnesium-mediated adenylate cyclase (AC) activity, thus reducing adenosine triphosphate (ATP) conversion into cAMP [67, 68]. As cAMP is a known mediator for PTH secretion [69], reduction of intracellular cAMP arises as an additional pathway leading to Ca^{2+}-induced PTH secretion suppression (Fig. 3.4) [46].

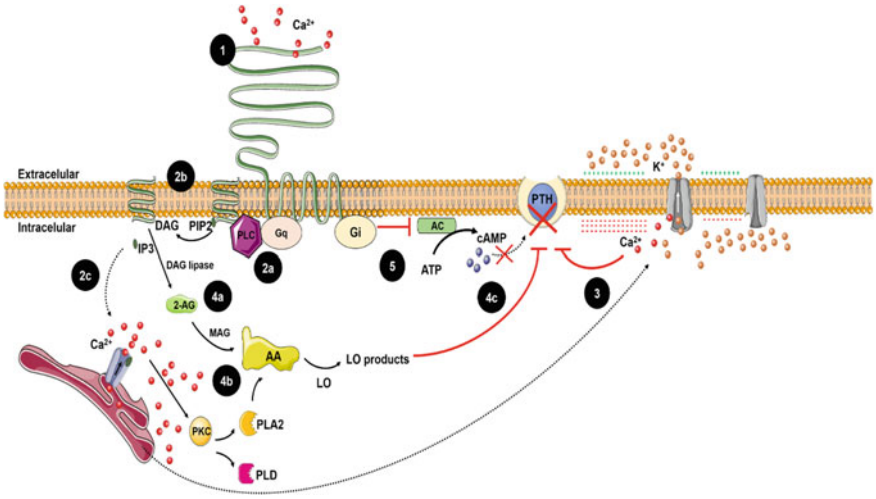

Fig. 3.4 Suppression of PTH secretion by hypercalcemia. (1) Circulating free calcium binds calcium-sensing receptor on parathyroid cell membrane, activating its subunits Gq and Gi; (2a) Gq activates phospholipase-C (PLC); (2b) PLC hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP2) into diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP3); (2c) IP3 induces calcium (Ca^{2+}) release from the endoplasmic reticulum. (3) In turn, high intracellular Ca^{2+} concentrations activate calcium-dependent potassium (K^+) channels, which determines K^+ outflow and consequently membrane hyperpolarization, suppressing membrane fusion and PTH exocytosis; (4a) Via DAG lipase and monoacylglycerol lipase (MAG), DAG is converted into 2-arachidonoylglycerol (2-AG) and arachidonic acid (AA), respectively; (4b) additionally, via protein kinase C (PKC), increased intracellular Ca^{2+} levels lead to phospholipases D and A2 activation (PLD and PLA2), also resulting in increased AA formation; (4c) AA is converted by lipoxygenase (LO) and its products also suppress PTH release; (5) lastly, subunit Gi inhibits adenylate cyclase (AC), suppressing cAMP pathway. Together, these pathways suppress PTH secretion and parathyroid cell proliferation, ultimately reducing PTH circulating levels in conditions in hypercalcemia. *Notes* Red lines represent inhibitory pathways and dotted arrows depict particles movement

Aside from $[Ca^{2+}]_e$, other molecules are involved in PTH synthesis and secretion. $1\alpha,25(OH)_2D$ extracellular levels contribute to regulate PTH secretion by inhibiting *PTH* gene transcription and parathyroid proliferation, in a Ca^{2+}-independent fashion [70, 71]. Additionally, hypermagnesemia is also able to suppress PTH secretion [69, 72], while hypomagnesemia displays more complex effects [73].

Moreover, calmodulin, a Ca^{2+}-binding protein shared by most eukaryotic cells, and calmodulin-dependent protein kinase II (CaMKII) both found in human parathyroid cells, also seem to play a role in regulating calcium homeostasis and PTH secretion [74]. While the role of calmodulin in human parathyroid cells is apparently not directly implied in Ca^{2+}-mediated PTH secretion, levels of active CaMKII decrease in the presence of high $[Ca^{2+}]_e$ ultimately leading to decreased PTH secretion [74].

Lastly, FGF23 decreases PTH secretion and PTH mRNA levels probably through mitogen-activated protein kinase (MAPK)/ERK pathway activation, in a feedback loop between bone and parathyroid glands [75].

PTH secretion is stimulated by low circulating calcium levels, which lead to increased levels of mRNA coding pre-pro-PTH probably by increasing mRNA stability [76]. High phosphate serum concentration $[(PO_4)^{3-}]_e$, decrease AA levels also leading to PTH secretion [77]. However, even in the presence of high $[(PO_4)^{3-}]_e$, PTH secretion is suppressed by high $[Ca^{2+}]_i$ [78].

3.4 Adrenal Gland

The adrenal glands are a pair of endocrine organs located above the superior pole of each kidney in the retroperitoneal space. Each gland has two distinct parts: an outer region, near the adrenal capsule, designated adrenal cortex that comprises 80% of the adrenal gland mass, and an inner region, so called adrenal medulla [79]. The adrenal cortex and medulla are separate tissues that have different embryological origin and distinct morphological and functional characteristics [2].

In order to accomplish the physiological roles attributed to the adrenal glands, these rely on a rich arterial blood supply derived from three different branches of the abdominal aorta: inferior phrenic artery, middle adrenal artery and renal artery. The arterial blood enters in the adrenal gland through the capsule and flows centripetally through the adrenal cortex into the medulla [80].

3.4.1 Adrenal Cortex

The adrenal cortex is responsible for the adrenal steroid production and it is divided into three distinct morphological layers with different functionality. The layers are the glomerulosa, the fasciculata and the reticularis layers (Fig. 3.5). These three layers present specific enzymatic features that are needed for the production of different steroid hormones [79, 81].

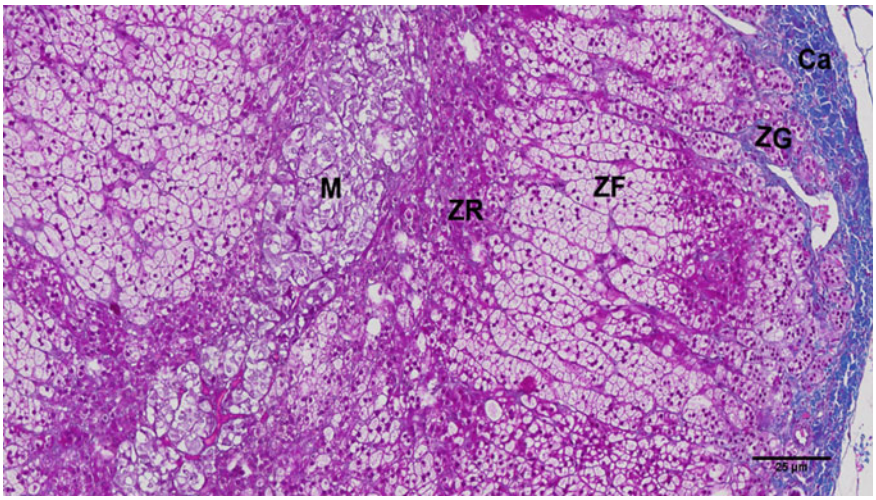

Fig. 3.5 Human adrenal gland stained by Masson tricromium (100x); Ca—Capsule; ZG—Zona glomerulosa; ZF—Zona fasciculata; ZR—Zona reticularis; M—Medulla

3.4.1.1 Steroidogenesis

Adrenocortical steroid hormones are essential in the processes of body homeostasis. Cholesterol is the common precursor of all steroid hormones and is mostly (80%) obtained from the plasma low-density lipoproteins (LDL) [81, 82]. Besides that, de novo cholesterol synthesis from acetate can also occur in steroidogenic tissues [83]. Cholesterol uptake by steroidogenic cells is performed through receptors-mediated endocytosis and the number of receptors expressed by the cells depend on the presence of stimulus for steroid production [84].

Briefly, after cellular uptake, cytoplasmic cholesterol is transferred from the outer to the inner membrane of the mitochondria, by the steroidogenic acute regulatory protein (StAR) [85]. Once in the mitochondria, cholesterol is hydroxylated twice and cleaved by the cholesterol side chain cleavage enzyme (CYP11A1) to generate pregnenolone [86] (Fig. 3.6). After leaving the mitochondria, pregnenolone is oxidized and isomerized to form progesterone. From this step of the steroidogenic cascade, due to zone-specific enzyme expression, steroidogenesis differs among the different adrenal cortex layers [86, 87]. At the glomerulosa, progesterone is converted into 11-deoxycorticosterone and transferred back into the mitochondria and is successively hydroxylated by aldosterone synthase (CYP11B2) enzyme to originate aldosterone [88]. At the fasciculata, 17α-hydroxylase (CYP17A1) converts pregnenolone into 17α-hydroxypregnenolone, which is then oxidized to 17α-hydroxyprogesterone and afterwards hydroxylated by 21α-hydroxylase (CYP21A2) to originate 11-deoxycortisol. At this point, 11-deoxycortisol reenters into the mitochondria to be converted by 11β-hydroxylase (CYP11B1) into cortisol [87, 89].

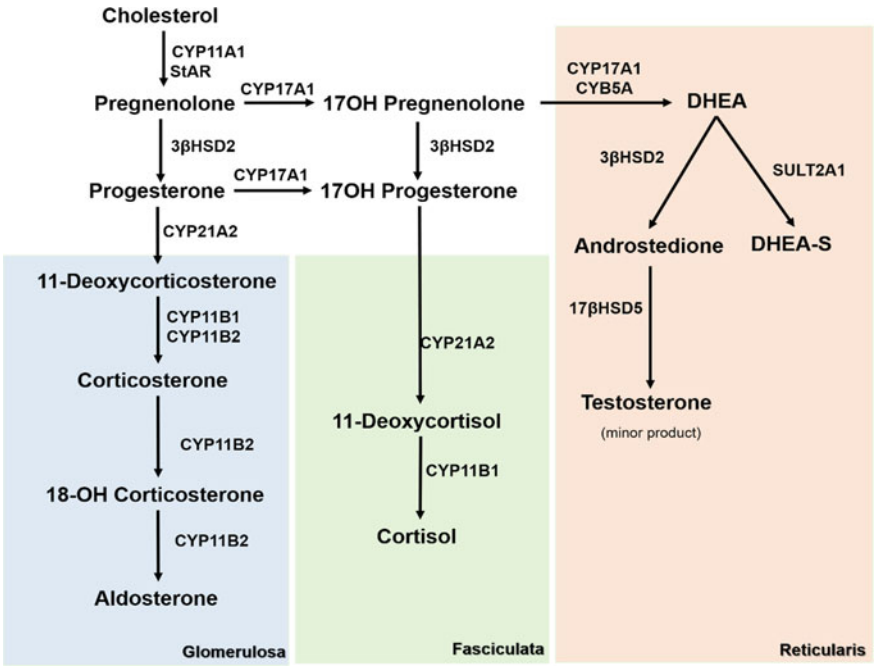

Fig. 3.6 Steroidogenesis in the different layers of the adrenal cortex. 17βHSD5—17β-hydroxysteroid dehydrogenase type 5; CYB5A—Cytochrome B5A; CYP11A1—cholesterol side chain cleavage enzyme; CYP11B1–11β-hydroxylase; CYP11B2—aldosterone synthase; CYP17A1—17α-Hydroxylase; CYP21A2–21α-hydroxylase; dehydroepiandrosterone (DHEA); dehydroepiandrosterone sulfate (DHEA-S); StAR—steroidogenic acute regulatory protein; SULT2A1—Sulfotransferase 2A1

At the zona reticularis, pregnenolone is hydroxylated by CYP17A1 to yield 17-hydroxypregnenolone and then into dehydroepiandrosterone (DHEA). Adrenal reticularis layer can also synthesize low levels of testosterone through the action of the enzyme 17β-hydroxysteroid dehydrogenase type 5 (17βHSD5) [86, 87, 90].

Due to the lipophilic properties of the steroid hormones, they are not stored in the cells, being only synthesized upon stimulation and immediately secreted [91].

3.4.1.2 Adrenocortical Stem Cells

In early studies, Ingle et al. described the regeneration of the adrenal cortex after adrenal enucleation (removal of the inner content of the adrenal gland) by only leaving the capsule and underlying subcapsular cells intact, suggesting the existence of stem/progenitor cells in the periphery of the adrenal cortex. Furthermore, this finding also corroborated the hypothesis of a centripetal migration and differentiation of the adrenal cortex, previously described [92].

The hedgehog signaling pathway (Hh) is a conserved pathway involved in adult tissue maintenance and renewal. Sonic hedgehog (Shh), an Hh family member, is present in a subpopulation of cells organized in clusters under the capsule of the adrenal gland. Lineage-tracing studies revealed that adrenocortical cells are derived from Shh positive cells, suggesting that those cells are the progenitor/stem cells of the adrenal cortex cells. Shh positive cells transduce the signal to the overlying steroidogenic factor 1 (SF1) negative cells present in the adrenal gland capsule triggering the expression of Gli1 molecule. During the adrenal development, $Gli1^+$ capsular cells migrate to the adrenal cortex and behave as stem/precursors cells, since these give rise to the $SF1^+/Shh^+$ progenitor cell pool that will lead to differentiated steroidogenic cells [93, 94].

3.4.1.3 Glomerulosa Layer

The glomerulosa layer is the outer layer of the adrenal cortex. It is the only layer that expresses CYP11B2 and thereby the single capable of synthetizing mineralocorticoids [95]. The most important and potent mineralocorticoid hormone is the aldosterone. Aldosterone is a key element of the renin-angiotensin-aldosterone system being responsible for regulating sodium homeostasis and thereby helping to control fluid volume and arterial pressure [96, 97].

Aldosterone Synthesis

The main extracellular stimuli for aldosterone synthesis are angiotensin II (ANG II) and high K^+ levels. Besides that, adrenocorticotropic hormone (ACTH) is also able to regulate aldosterone synthesis, although it has a minor contribution [88, 98].

Renin-Angiotensin-Aldosterone System

A reduction on the renal perfusion pressure leads to renin synthesis by the kidney juxtaglomerular cells. Renin is an enzyme that cleaves a protein synthesized and secreted by the liver, the angiotensinogen, to form angiotensin I (ANG I) [99]. Then, angiotensin converting enzyme (ACE) converts ANG I into ANG II [100].

In the glomerulosa cells, ANG II binds to the ANG II receptor type 1 (AT1R) which is linked to the G-protein Gq/11 that couples the receptor to its effector PLC (Fig. 3.7). PLC activation leads to the hydrolysis of PIP2 to produce DAG and IP3 [88, 101, 102]. IP3 diffuses into the cytoplasm and binds to its endoplasmic reticulum receptors, which act as channels for the release of the Ca^{2+} stored in this organelle. It results in a transient increase of the Ca^{2+} cytoplasmic concentration [88, 98]. $[Ca^{2+}]_i$ leads to the activation of CaMK [103]. The activation of different CaMK were shown to lead to different results: CaMK I is able to increase of the CYP11B2 through the activation of the transcription factors [Activating transcription factor (ATF)/cAMP

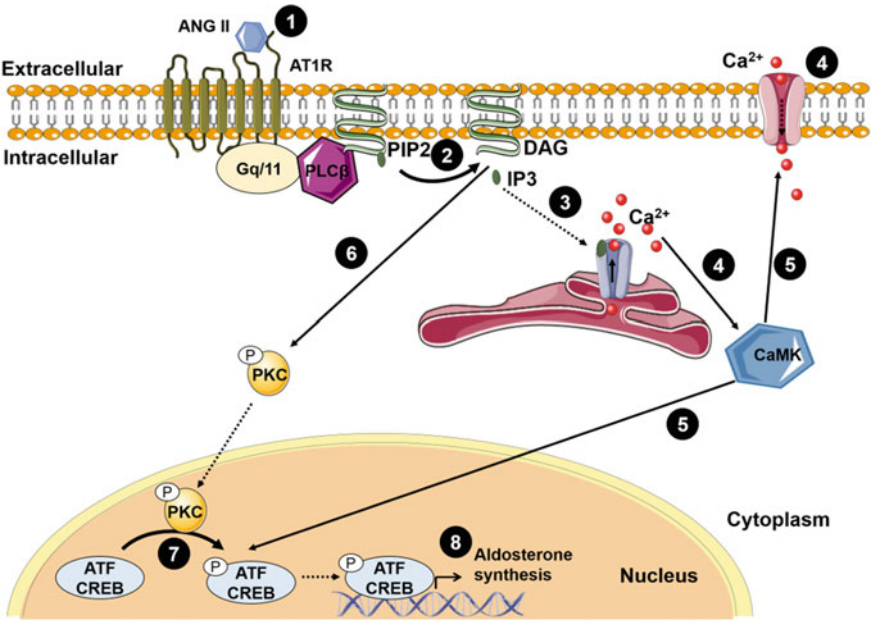

Fig. 3.7 Aldosterone synthesis regulation via angiotensin II (ANG II). (1) ANG II binds to type 1 ANG II receptor (AT1R) which is coupled to phospholipase C (PLC) through the G-protein (Gq/11); (2) PLC-β is activated and hydrolyses phosphatidylisitol 4,5-bisphosphate (PIP2) to produce diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP3); (3) IP3 diffuses into the cytoplasm and binds to its endoplasmic reticulum receptors, which act as channels for the release of the calcium (Ca^{2+}); (4) Intracellular Ca^{2+} activates the calmodulin-dependent protein kinases (CaMK); (5) CaMK activation increases the transcription of the aldosterone synthetize enzyme through the activation of the transcription factors (ATF/CREB) and also shift the voltage of the Ca^{2+} membrane channels leading to Ca^{2+} entrance; (6) Simultaneously, DAG activates the protein kinase C (PKC); (7) PKC phosphorylates and activates the transcription factors (ATF/CREB); (8) ATF/CREB activate the transcription of genes involved in aldosterone synthesis. Notes: Dotted arrows depict particles movement

response element binding (CREB)]; and CaMKII, on the other hand, shifts the voltage of the voltage-gated Ca^{2+} channels (VGCCs) leading to the enhance of Ca^{2+} influx and then increasing the aldosterone synthesis [88, 98, 103].

In addition, DAG is responsible for the activation of PKC that activates the transcription factors (ATF/CREB) and thus leading to the transcription of *StAR* and *CYP11B2* [88, 104].

ANG II is also able to activate the MAPK signaling pathway, however the mechanisms are not yet completely elucidated [88]. A mechanism already described is that the binding of ANG II to AT1R activates ERK that is able to phosphorylate and activate the enzyme responsible for cleaving the cholesteryl esters to yield the cholesterol [105]. Other evidences, described that ERK can phosphorylate StAR, leading to the transport of cholesterol to the mitochondria [106, 107]. Thus, the mechanisms

through which MAPK/ERK leads to the aldosterone synthesis are ensuring the availability of cholesterol and its entrance in the mitochondria membrane in order to begin the process of steroidogenesis.

Potassium

Glomerulosa cells, respond to minor changes in the K^+ levels with the increase of aldosterone production [108]. High levels of K^+ lead to depolarization of the glomerulosa cell membrane that lead to the activation of the VGCCs and thus the influx of the Ca^{2+} [88, 109]. Increased $[Ca^{2+}]_i$ activate CaMKs and the subsequent pathways already described in the previous section.

In addition, the ability of K^+ to increase cellular cAMP levels through the Ca^{2+}-sensitive AC was also reported. cAMP activates PKA which then activates the transcription factors (ATF/CREB) and thus leading to the transcription of *StAR* and *CYP11B2* [88, 110].

ACTH

ACTH binds to melanocortin receptor 2 (MC2R) on the cytoplasmic membrane of glomerulosa cells [111]. Thus, ACTH increases cAMP concentration and activates PKA which phosphorylates and activates hormone-sensitive lipase (HSL) and StAR protein, resulting in the release of cholesterol from lipid droplets and its transportation to the inner mitochondrial membrane [88]. PKA can also activate transcription factors ATF/CREB and then induce the transcription of *StAR* and *CYP11B2* [112]. In addition, PKA stimulates the flow of Ca^{2+} ions into the glomerulosa cells and thereby increases the production of aldosterone by a mechanism involving CaMKs [113].

3.4.1.4 Fasciculate Layer

Fasciculate layer is the widest zone of the adrenal cortex. It lies under the glomerulosa layer and it is responsible for the synthesis of the glucocorticoids [114]. Cortisol is the most potent glucocorticoid in humans. Moreover, cortisol has a circadian rhythm characterized by a peak in the period before wakening and a gradual decline throughout the day [115]. In addition, cortisol secretion increases acutely in response to stressful stimuli [116, 117].

Cortisol Synthesis

Cortisol secretion is indirectly controlled by the central nervous system. The hypothalamus releases the corticotropin-releasing hormone (CRH) to the long pituitary portal

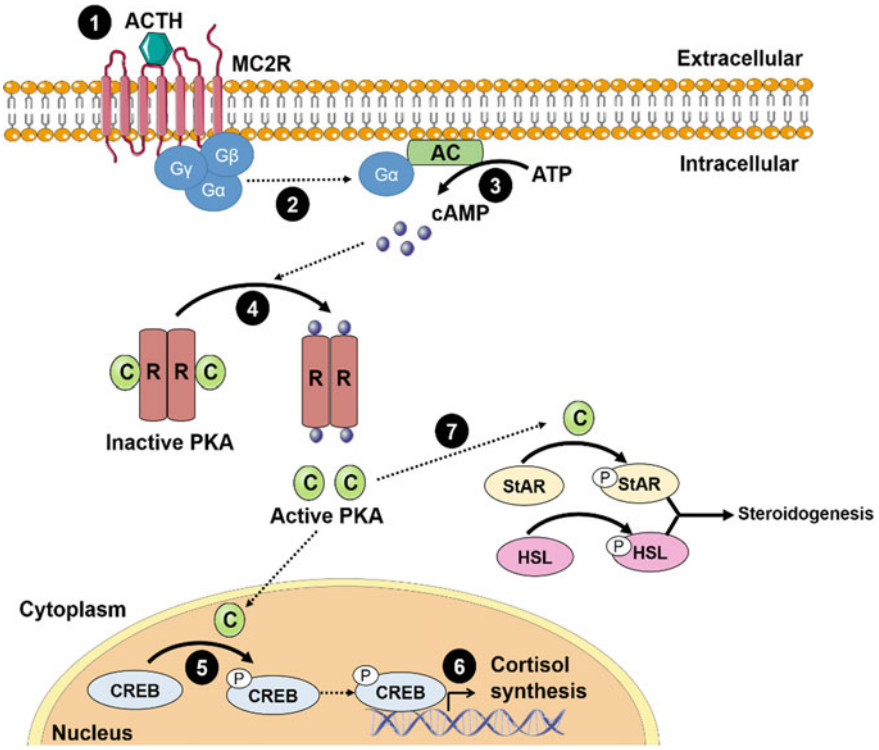

Fig. 3.8 Cortisol synthesis regulation. (1) Adrenocorticotropic hormone (ACTH) binds to the melanocortin receptor 2 (MC2R); (2) Gα subunit activate adenylate cyclase (AC); (3) AC converts adenosine triphosphate (ATP) into cyclic 3′,5′-adenosine monophosphate (cAMP); (4) cAMP binds to the regulatory subunits (R) of protein kinase A (PKA), releasing and activating the catalytic subunits (C) of this protein; (5) PKA phosphorylates the cAMP response element binding (CREB) transcription factor; (6) CREB activates the transcription of genes involved in the production of cortisol; (7) Simultaneously, PKA also phosphorylates and activates the hormone-sensitive lipase (HSL) and the steroidogenic acute regulatory protein (StAR), initiating the steroidogenesis. *Notes* Dotted arrows depict particles movement

veins. CRH binds to its membrane receptors in the anterior pituitary stimulating the release of ACTH into the blood [117]. ACTH acts on the fasciculate zone cells through the binding to the MC2R and subsequently it induces adrenocortical expansion and cortisol production [111, 118, 119].

Upon ACTH binding, the receptor undergoes conformational changes that activate AC, leading to the conversion of ATP to cAMP (Fig. 3.8) [120]. In turn, cAMP binds to the regulatory subunits of PKA, releasing and activating the catalytic subunits of this protein, which then phosphorylates the CREB transcription factor that leads to increased expression of genes involved in the production of cortisol, such as *CYP11B1* [112, 121]. Concomitantly, it also phosphorylates and activates HSL and StAR, initiating the production of cortisol, as previously described [85].

3.4.1.5 Reticularis Layer

Reticularis layer is the innermost layer of the adrenal cortex. It is located between the fasciculata layer and the adrenal medulla and it is responsible for the production of the adrenal androgens [114].

Adrenal Androgens Synthesis

Adrenal androgens synthesis is synchronized with cortisol synthesis in response to ACTH stimulation [122]. The mechanism by which ACTH stimulates androgen synthesis by adrenocortical cells is similar to the mechanism described for cortisol [123]. Like cortisol, plasma levels of DHEA, androstenedione and testosterone exhibit a circadian rhythm. On the contrary, levels of dehydroepiandrosterone sulfate (DHEA-S) do not exhibit a circadian rhythm, since this being a sulfated steroid results in a longer half-life [124, 125].

Other endocrine signals have been proposed as co-regulators of adrenal androgen secretion, such as prolactin (PRL), estrogens, prostaglandins, angiotensin, growth hormone (GH) and gonadotropins [122, 126–128]. However, its impact on androgen secretion is not considered as relevant as ACTH.

3.4.2 Adrenal Medulla

The adrenal medulla is the innermost layer of the adrenal gland and is surrounded by the adrenal cortex [129]. The adrenal medulla has an embryonic origin in the neural crest and is composed by chromaffin cells that are structurally and functionally related to postganglionic neurons of the sympathetic nervous system [2]. These cells are responsible for the production of catecholamine: DA, epinephrine (Epi) and NE [130, 131].

3.4.2.1 Adrenal Catecholamine Synthesis and Secretion

Like adrenal cortex, adrenal medulla is a key tissue involved in the physiological adaptation to stress [132]. Whenever the central nervous system perceives a stress, two key effector pathways that are activated. These include the hypothalamic-pituitary-adrenal axis (HPA), which indirectly stimulates the adrenal medulla to produce catecholamines, and the sympathetic-adrenal axis, which stimulates the adrenal medulla to secrete catecholamines, through a neural mechanism [131–133].

Due to a centripetal blood flow coming from the adrenal cortex, high levels of cortisol pass through the adrenal medulla [80, 134, 135]. As a lipophilic hormone, cortisol is able to easily cross the chromaffin cell membrane to bind the cytoplasmatic glucocorticoid receptor (GR) (Fig. 3.9). Prior to cortisol binding, GR is sequestered

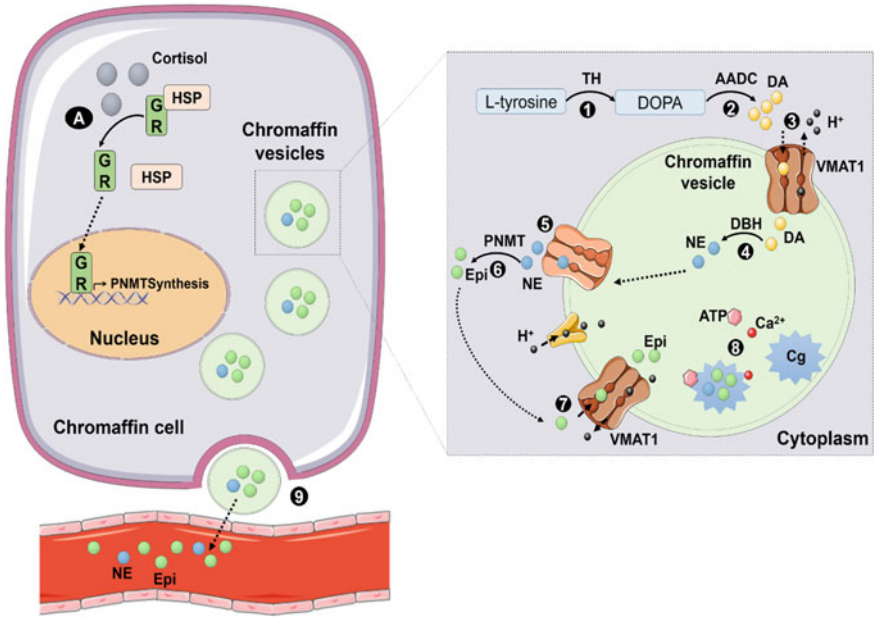

Fig. 3.9 Adrenal catecholamines synthesis and secretion. (A) cortisol crosses the chromaffin cell membrane and binds to the glucocorticoid receptor (GR). GR complex is dissociated and GR goes to the nucleus to bind in glucocorticoid response elements, activating the transcription of phenylethanolamine N-methyltransferase (PNMT); (1) Tyrosine is hydrolyzed by the enzyme tyrosine hydroxylase (TH), producing L-3,4-dihydroxyphenylalanine (L-DOPA); (2) L-DOPA is decarboxylated by the enzyme L-aromatic amino acid decarboxylase (AADC), converting it into DA; (3) DA is then incorporated in chromaffin cell vesicles through the vesicular monoamine transporter 1 (VMAT1); (4) DA is hydroxylated to produce NE by dopamine β-hydroxylase (DBH); (5) NE can be stored in the vesicles or it can goes to the cytoplasm; (6) in the cytoplasm it is methylated by PNMT to produce Epi; (7) Epi is incorporated in the chromaffin vesicle; (8) in the vesicle NE and Epi are in a complex with chromogranin (Cg), Ca^{2+} and adenosine triphosphate (ATP); (9) when stimulated by acetylcholine, the chromaffin cell membrane is depolarized and the catecholamines are released. *Notes* Dotted arrows depict particles movement

in the cytoplasm as a multiprotein complex [136]. After cortisol binding, the complex is dissociated and GR is translocated into the nucleus where it binds to glucocorticoid response elements (GRE) in the promoter regions of target genes directly or interacts with other transcription factor proteins [133, 136]. Cortisol was found to increase the transcription of genes involved in the biosynthesis of catecholamines, such as phenylethanolamine N-methyltransferase (PNMT) [131, 133, 137].

The biosynthesis of catecholamines begins with the hydroxylation of tyrosine, the catecholamines common precursor, by the enzyme tyrosine hydroxylase (TH), producing L-3,4-dihydroxyphenylalanine (L-DOPA) [133, 138]. After that, L-DOPA is decarboxylated by the enzyme L-aromatic amino acid decarboxylase (AADC), converting it into dopamine (DA) [139]. DA is then incorporated into chromaffin cell vesicles where is hydroxylated to produce NE by dopamine β-hydroxylase (DBH)

[140]. NE can be stored in the vesicles until secretion or methylated in the cytoplasm by PNMT to produce Epi [131, 141]. This last step does not occur in the adrenergic neurons as these do not express the PNMT enzyme [131], being specific of the adrenal medulla that is exposed to high levels of cortisol due to the portal nature of the adrenal circulation described above [80, 134, 135].

Catecholamines form a complex with chromogranin, ATP e Ca^{2+}, inside of the chromaffin cell vesicles until being released [137, 142]. Being only produced in the adrenal medulla, Epi is the major secretory product of the adrenal medulla [133, 134].

Opposite to catecholamines synthesis, catecholamines release is mainly mediated by the neuropeptide acetylcholine (ACh) discharge from sympathetic nerve terminals [143]. ACh binds to plasma membrane receptors on chromaffin cells and stimulates Ca^{2+}-mediated depolarization of the cell membrane [133, 144]. Then the increase of $[Ca^{2+}]_i$ levels leads to the release of catecholamines complexed with chromogranin stored in the chromaffin cell vesicles [142, 145].

3.5 Conclusion

In this chapter the key signaling pathways involved in the peripheral endocrine organs' maintenance and physiology are described. The knowledge of those pathways is essential for understanding the molecular mechanisms that might lead to endocrine disruption and disease providing important clues into multisystemic impact of endocrine physiology and pathology.

Acknowledgments The work was supported by the Foundation for Science and Technology (PTDC/MEC-ONC/31384/2017). Unit for Multidisciplinary Research in Biomedicine (UMIB) is funded by grants from FCT (UID/Multi/00215/2016 and UID/Multi/00215/2019).

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