CHAPTER 1

Pituitary Gland Therapies

1.1 CUSHING'S DISEASE

1.1.1 Pasireotide

1.1.1.1 Physiology

The Hypothalamic–Pituitary–Adrenal Axis

The hypothalamic–pituitary–adrenal (HPA) axis influences cortisol regulation through a complex balancing act between stimulatory and inhibitory factors. *Corticotrophin-releasing hormone* (CRH), produced in the paraventricular nucleus of the hypothalamus, is transmitted by the hypophyseal portal venous system to corticotroph cells in the anterior pituitary gland [1]. CRH subsequently binds to corticotrophin-releasing hormone type 1 receptor (CRH-R1) on the surface of corticotrophs. As a result, ACTH is released from secretory vesicles in corticotrophs. It should be noted that *Arginine vasopressin* (AVP) further potentiates the anterior pituitary effects of CRH by acting on its cognate Vasopressin subtype 1b receptor (V1b-R) present on corticotrophs. Additionally, CRH promotes the expression of the pro-opiomelanocortin (POMC) gene in the anterior pituitary gland, a process that also increases adrenocorticotropin hormone (ACTH) production as well [2] (see Section 3.1.1).

Subsequently, ACTH binds to the melanocortin-2 receptor (MCR-2) on cells present in the zona fasciculata of the adrenal cortex, leading to increased cortisol synthesis [3]. Adrenal-derived cortisol inhibits the secretion of POMC and ACTH by anterior pituitary corticotrophs through a negative feedback loop [4]. Additional negative feedback inhibition of CRH and AVP synthesis by cortisol occurs at the level of the hypothalamic paraventricular nucleus [5] (see Figure 1.1).

Normal and adenomatous corticotrophs express two subclasses of somatostatin receptors (SSR), namely somatostatin receptor subtype 2 (SSR_2) and somatostatin receptor subtype 5 (SSR_5). Somatostatin, a hypothalamic peptide, inhibits ACTH production through an inhibitory pathway regulated by circulating cortisol. Indeed, SSR_2 receptors are easily downregulated by cortisol, compared to SSR_5 (more resistant to negative feedback by cortisol). As a consequence, SSR_2 receptor modulators (e.g. octreotide) are less effective in Cushing's disease compared to SSR_5 modulators (e.g. pasireotide) [6].

Hypothalamic and pituitary processes: CRH is released under trophic stimulation by various factors, including catecholamines, angiotensin II, serotonin, stress, and cytokines [7]. On the contrary, GABA inhibits CRH release and ultimately ACTH production [8]. CRH from the hypothalamus stimulates anterior pituitary corticotrophs to release their preformed ACTH from secretory vesicles (fast response). Furthermore, CRH increases POMC gene expression by anterior pituitary corticotrophs (slow response).

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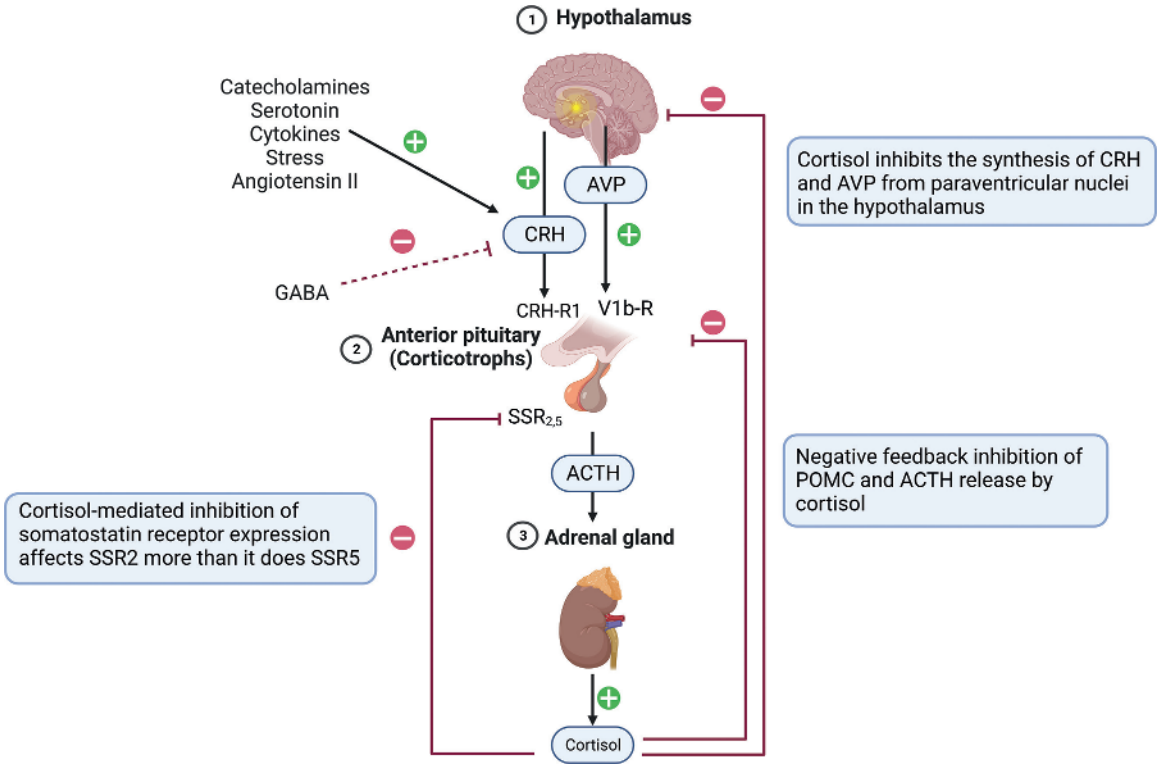

FIGURE 1.1 Schematic representation of the HPA axis, highlighting critical stimulatory and inhibitory feedback loops.

Furthermore, AVP binds to V1b receptors on corticotrophs which further enhances the action of CRH at the level of the anterior pituitary gland [2]. Activation of dopamine D2 receptors (D2Rs) present on corticotroph cells by hypothalamic-derived dopamine inhibits ACTH synthesis and release *(not shown)* [9]. *Adrenal cortex processes:* The binding of ACTH to the MCR-2 receptors present on cells in the zona fasciculata promotes the synthesis of cortisol from cholesterol [3]. *Feedback* Loops Negative feedback inhibition of POMC and ACTH release is mediated by adrenal-derived cortisol [4]. Furthermore, cortisol inhibits the synthesis of CRH and AVP from paraventricular nuclei in the hypothalamus [5]. Cortisol-mediated inhibition of somatostatin receptor expression on corticotrophs affects SSR2 more than it does SSR5 [6]. + = shows stimulatory factors and feedback loops, and − = shows inhibitory factors and feedback loops.

1.1.1.2 Mechanism of Action

Pasireotide is a *near pan-somatostatin* receptor analog because it binds to four of the five isoforms of the somatostatin receptor family, namely (SSR_1, SSR_2, SSR_3, and SSR_5). Indeed, pasireotide binds to the SSR_5 receptor subtype more avidly than the other SSR, thus its demonstrable efficacy in Cushing's disease. Corticotroph tumors in the anterior pituitary gland express more SSR_5 receptors than other somatostatin receptor subtypes. Furthermore, cortisol's negative feedback inhibition of somatostatin receptor expression by corticotrophs tends to impact SSR_2 receptors more than the SSR_5 receptor subtype. Due to its affinity for SSR_5 receptors, pasireotide is an ideal therapeutic option for Cushing's disease [10]. Also, see Figure 1.1.

1.1.1.3 Practice Guide

Pasireotide *(Signifor)* causes *hyperglycemia*, *gastrointestinal discomfort*, and *cholelithiasis*. The reported prevalence of hyperglycemia in clinical trials involving patients with Cushing's disease who received pasireotide ranged from 68.4% to 73% [11]. Therefore, it is reasonable to screen for diabetes before and during treatment with pasireotide [12]. Incretin mimetics, metformin, or insulin are preferred for treating pasireotide-mediated hyperglycemia [13]. The proposed mechanisms of pasireotide-mediated hyperglycemia are shown in Table 1.1.

Somatostatin inhibits both hepatic biliary secretions and contraction of the wall of the gallbladder in normal physiology. As a result, patients exposed to

TABLE 1.1 Pathophysiological basis of pasireotide-mediated hyperglycemia.

Hormone	Effects of pasireotide
Insulin	The binding of pasireotide to SSR_5 receptors present on beta cells inhibits pancreatic insulin release [11].
Glucagon	The activation of SSR_2 receptors present on pancreatic alpha cells leads to the inhibition of pancreatic glucagon release. In essence, the reduced affinity of pasireotide for the SSR_2 receptor subtype promotes glucagon-mediated hyperglycemia [11].
Incretins	Pasireotide, through intestinal somatostatin receptors, inhibits the release of the glucagon-like peptide 1(GLP-1) and the glucose-dependent insulinotropic peptide (GIP) from K and L cells, respectively [14, 15]. See Section 4.1.7 for the role of incretins in insulin secretion.

Source: Adapted from refs. [11, 14, 15].

somatostatin analogs (SSAs) are predisposed to forming gallstones [16].

The typical dose range for immediate-release pasireotide is 0.3–0.9 mg (300–900 mcg) as a subcutaneous injection (thigh, upper arm, or abdomen) twice daily. A long-acting release (LAR) formulation is administered once a month (10–30 mg) intramuscularly as a depot injection by a health worker [13]. In practice, the LAR formulation is introduced after patients have demonstrated a response to immediate-release pasireotide.

Clinical Trial Evidence

SSR_5 receptors are abundant in corticotroph tumors, as has been previously mentioned. The *Pasireotide B2305 Study group* trial investigated the efficacy of pasireotide, a SSA with a profound affinity for the SSR_5 receptor, in reducing corticotroph tumor growth [17].

Key Message

Pasireotide led to a halving of median urinary-free cortisol levels in a cohort of patients with confirmed Cushing's disease (persistent, recurrent, or newly diagnosed).

The B2305 pasireotide study group evaluated the efficacy of pasireotide in Cushing's disease. In this pivotal phase 3 trial, 162 subjects with persistent, recurrent, or newly diagnosed Cushing's disease (not considered suitable candidates for transsphenoidal surgery) with urinary-free cortisol (UFC) levels 1.5 times the upper limit of the normal reference range were randomized to subcutaneous pasireotide 600 mcg ($n = 82$) or 900 mcg ($n = 80$), twice daily. The primary outcome was UFC levels below or at the upper limit of the normal reference range. There was approximately a 50% reduction in median UFC levels in the second month of the study, and UFC levels stabilized through to the end of the study for all participants [17].

1.1.2 Retinoic Acid

1.1.2.1 Physiology

Regulation of Corticotroph Physiology by Retinoic Acid

The normal corticotroph cell has a POMC promoter gene, which is critical in POMC synthesis and eventual ACTH secretion. In normal physiology, there are retinoid-sensitive mediators (transcription factors) required for the activation of the POMC promoter gene, namely, *activator protein 1* (AP-1) and *nuclear receptor 77* (Nur77). Retinoic acid (RA), by binding to its nuclear RA receptors inhibits AP-1 and Nur77 expression, thus preventing the activation of the POMC promoter gene [18, 19]. It should be noted that *chicken ovoalbumin upstream promoter transcription factor 1* (COUP-TF1) protects AP-1 and Nur77 from direct inactivation by RA [20]. See Figure 1.2.

The reduced expression of the "*protective transcription factor,*" COUP-TF1 by some corticotroph tumor cells makes RA a reasonable therapeutic option in Cushing's disease [18, 20].

1.1.2.2 Mechanism of Action

RA reduces cortisol synthesis in subjects with Cushings disease through various observed mechanistic pathways.

1. RA reduces the synthesis of ACTH and POMC in corticotroph tumors [20]. This was reviewed earlier.
2. In addition, RA has direct tumoricidal effects on corticotroph tumors [20].

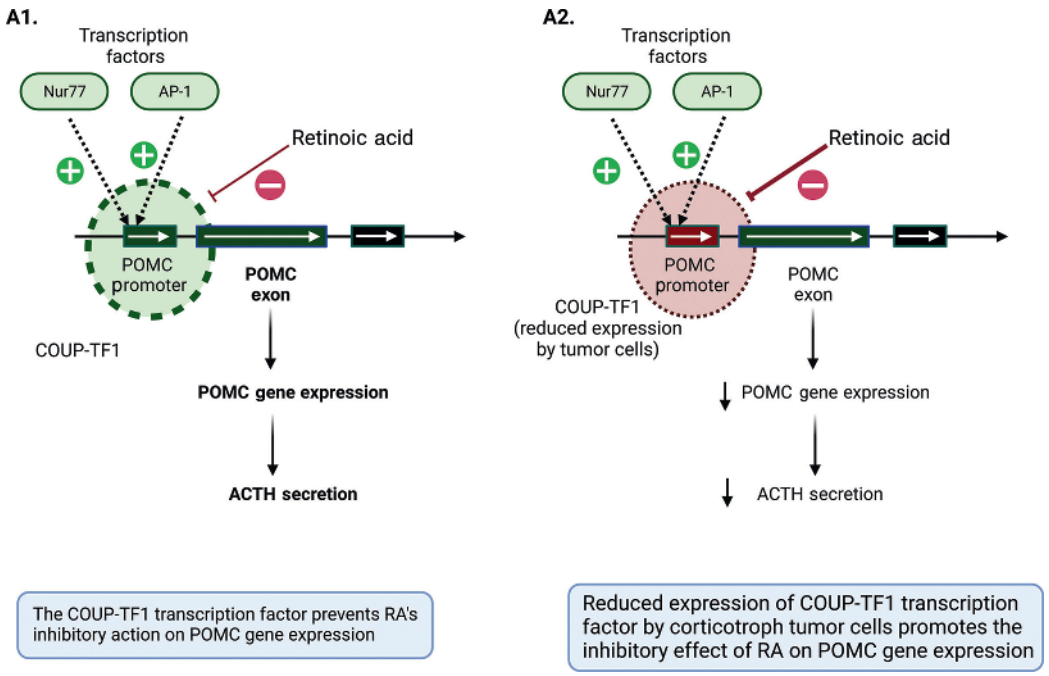

FIGURE 1.2 The role of retinoic acid in anterior corticotroph pathophysiology. AP-1 and Nur77 are critical transcription factors required for activation of the POMC promoter gene in a corticotroph cell. The COUP-TF1 transcription factor prevents RA's inhibitory action on both AP-1 and Nur77, allowing POMC transcription and ACTH secretion to proceed in normal physiology *(image A1)* [18, p. 11]. On the contrary, corticotroph tumors have a reduced expression of COUP-TF1, which allows RA to inhibit AP-1 and Nur77 (critical mediators of POMC promoter gene activation) *(image A2)* [20]. *The thickness of the dashed circle = degree of expression of COUP-TF1. Adapted and modified from Pecori GF et al.* [20].

3. RA reduces adrenal cortisol production through its antiproliferative effects on hyperplastic adrenocortical cells [20].
4. RA also downregulates the expression of the MCR-2 by adrenal cells (see Figure 1.1, [21]).

1.1.2.3 Practice Guide

- RA is teratogenic and should be used with extra caution in women of reproductive age group. Other reported side effects of RA include photosensitivity and mucositis [22].
- RA receptor activation increases the cortisol suppressive effects of dopaminergic agonists (DAs). Combining RA and DA is a suggested therapeutic option in patients with Cushing's disease [23].

Clinical Trial Evidence

The first proof-of-concept study of RA in humans with Cushing's disease was carried out in 7 subjects, with a variable decrease in UFC levels ranging from 22 to 73% [20]. A recent open-label prospective trial evaluated the safety and efficacy of isotretinoin (13-cis RA isomer) in patients with persistent or recurrent Cushing's disease [24].

Key Message

Retinoic acid (a new treatment approach) was associated with a greater than 50% reduction in urinary-free cortisol levels compared to baseline in this small study. Retinoic acid is a potential therapeutic option in patients with persistent or recurrent Cushings disease.

In this single-arm open-label prospective study over a 12-month period, 16 patients with persistent or recurrent Cushings disease after transsphenoidal surgery were treated with isotretinoin monotherapy. All subjects received 20 mg of oral isotretinoin once daily. This was increased by 20 mg every 4 weeks to a maximum dose of 80 mg once daily. The primary outcome was defined as normalization of UFC or > 50% reduction in UFC. At the end of the study, four patients

(25%) had sustained normalization of UFC [24]. The expression of COUP-TF1 (determinant of response to RA) by pituitary corticotrophs was not assessed in this study. This may explain the low response rate observed in the study (see Figure 1.2).

1.1.3 Dopaminergic Agonists

1.1.3.1 Physiology

The Hypothalamic–Pituitary–Adrenal Axis

Refer to Figure 1.1 to review the effects of hypothalamic-derived dopamine on ACTH-producing corticotrophs.

1.1.3.2 Mechanism of Action

Although approximately 80% of corticotroph adenomas express D2 receptors, they have relatively low D2 receptor density, making DAs a less favorable therapeutic option [25]. Bromocriptine and cabergoline reduce cortisol production by binding to D2 receptors present on corticotrophs; however, they are not as effective as SSAs [9].

1.1.3.3 Practice Guide

- Patients taking DAs exhibit an *"escape phenomenon,"* which is characterized by up to a third of patients who previously responded experiencing rebound hypercortisolemia [25].
- Cabergoline is associated with valvular heart disease, especially in patients exposed to doses close to the upper limit of the acceptable dose range [26]. Therefore, serial echocardiograms are reasonable in patients who are taking high doses of cabergoline [26] or are exposed to a cumulatively high lifetime dose [27].
- Common side effects of DAs include postural dizziness, nausea, and headaches [28].
- In contrast to the lower dose range of 0.5–2.0 mg/week of cabergoline used in prolactinomas [29], a much higher dose range between 2.5 and 5 mg/week is required to treat CD [30, 31]. See Section 1.3.1

Clinical Trial Evidence

In this study, the long-term effects of cabergoline therapy in patients with Cushing's disease were explored [32].

Key Message

A third of patients with Cushing's disease treated with cabergoline achieved either normalization or a significant reduction in urinary-free cortisol levels.

This single-arm, retrospective study assessed the efficacy of cabergoline in Cushing's disease. A total of 30 patients received oral cabergoline 0.5–1.0 mg/week, uptitrated weekly. The primary outcome was defined as normalization of UFC levels or > 50% reduction in UFC (this occurred in 36.6% of subjects) [32].

1.1.4 Steroidogenesis Inhibitors

1.1.4.1 Physiology

Adrenal Steroidogenesis

Review of adrenal steroidogenesis (see Section 3.1.1). The role of various adrenal steroidogenic inhibitors, such as ketoconazole, metyrapone, and mitotane in Cushing's syndrome, is shown in Figure 1.3 [37].

1.1.4.2 Mechanism of Action

See Figure 1.3 for a summary of various enzymatic targets of steroidogenic inhibitor therapies. The mechanism of action of metyrapone, mitotane, ketoconazole, and the recently approved steroidogenesis inhibitor, osilodrostat, will be reviewed next.

Metyrapone: Metyrapone has a pyridine moiety, which allows it to alter the activity of 11beta-hydroxylase (critical in the final step of cortisol synthesis). Other metyrapone-inhibited steroidogenic enzymes include the 17 alpha-hydroxylase(17α-OH) and 18-hydroxylase enzymes (less potent inhibition) [36].

Mitotane: Mitotane has both *"adrenolytic"* (adrenal cell death) and *"adrenostatic"* (enzymatic inhibition) properties. Mitotane is a chemotherapeutic agent with a diphenylmethane moiety that causes mitochondrial dysfunction, lysis, and necrosis. Mitotane, as stated earlier, exerts its "adrenostatic" function by inhibiting the side-chain cleavage enzyme, 11beta hydroxylase, and 3βHSD [36].

Ketoconazole: Ketoconazole has an imidazole group (confers its antifungal properties) with demonstrable inhibitory effects on various steroidogenesis enzymes (in particular, the side

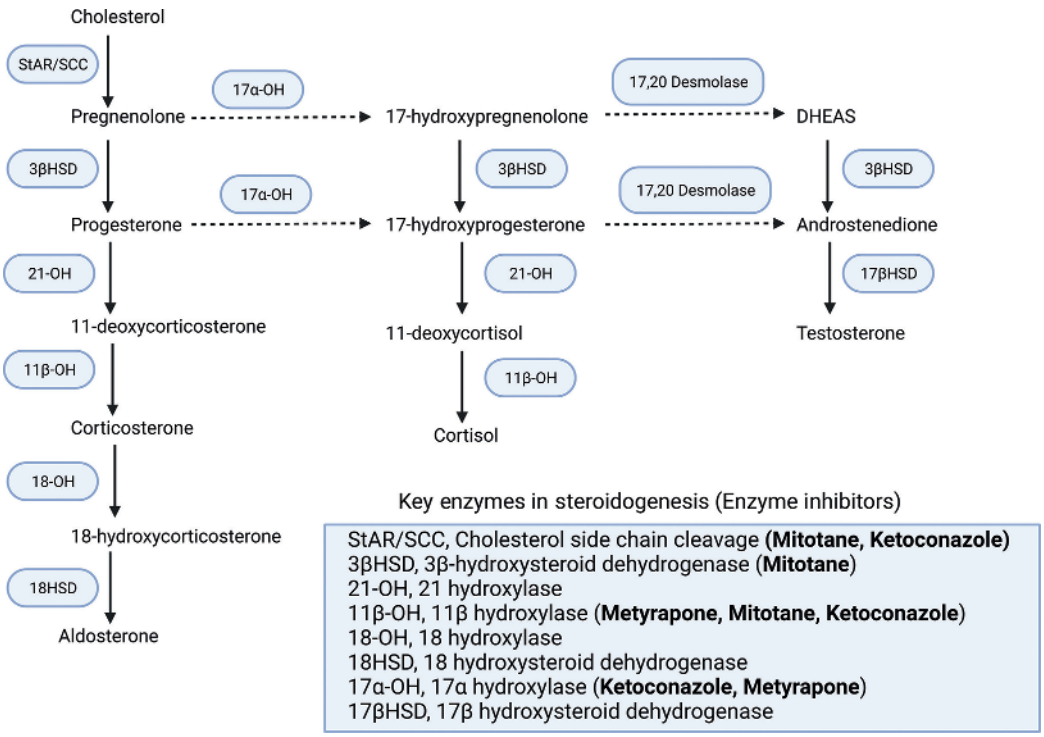

FIGURE 1.3 Schematic representation of adrenal steroidogenesis pathways and the site of action of various enzyme inhibitors. *Metyrapone* primarily inhibits 11 beta-hydroxylase activity (11β-OH), which results in reduced cortisol production of cortisol [33]. Consequently, there is an accumulation of intermediate mineralocorticoid precursors (11-DOC) [34] and a shunting of progesterone and pregnenolone to androgen production [35]. *Mitotane* inhibits various adrenal steroidogenic enzymes, including the side chain cleavage enzyme complex(StAR/SCC), 11beta hydroxylase(11β-OH), and 3βHSD [36]. *Ketoconazole* similarly inhibits various steroidogenic enzymes, including the side chain cleavage enzyme complex, 17alpha hydroxylase (17α-OH), and 11β-OH enzymes [36]. *Source*: Adapted from ref. [37].

chain cleavage complex, 17 alpha-hydroxylase and 11 beta-hydroxylase) in the adrenal cortex and gonads [36].

Osilodrostat: Osilodrostat, like metyrapone, inhibits 11-beta hydroxylase activity in the adrenal cortex. However, unlike metyrapone, osilodrostat has a relatively higher potency and a shorter plasma half-life; thus, it can be administered less frequently (two times daily instead of four times daily) [38].

1.1.4.3 Practice Guide

In practice, these agents are slowly titrated to achieve normal serum cortisol, which can be monitored using late-night salivary cortisol or 24-hour UFC. Overt hypoadrenalism is an inadvertent complication that should be anticipated in patients taking steroidogenesis inhibitors [13].

Metyrapone: Hypokalemia is a known complication of metyrapone treatment due to the accumulation of intermediate steroids with intrinsic mineralocorticoid activity (for example, 11-DOC). Therefore, close monitoring of serum potassium is therefore required [35]. Furthermore, hirsutism (shunting of proximal steroids into androgenic precursors), hypertension, and edema (mineralocorticoid effects of 11-deoxycorticosterone) can occur in patients on metyrapone. Unlike ketoconazole, metyrapone is comparatively safer in pregnancy [39].

Mitotane: Mitotane is lipophilic and, as a result, is stored in a large repository of adipose tissue. This increases the drug's half-life, leading to a delay in its onset of action. Most importantly, the dose of mitotane required to treat Cushing's disease is much lower than the large tumoricidal dose used to treat adrenocortical carcinomas [40]. Mitotane has teratogenic effects and due to its large volume of distribution (stored in adipose tissue), it should be discontinued for at least five years before potential conception [41].

Ketoconazole: Ketoconazole is the recommended first-line medical therapy for nonpregnant adults with confirmed endogenous hypercortisolemia. It is an FDA category C drug and may interfere with androgen-dependent development of the sex organs of an unborn male baby. Despite these apparent antiandrogenic effects, it has been inadvertently used in expectant mothers without overt deleterious fetal effects [39, 41]. Side effects encountered in routine practice include *gynecomastia*, hepatic injury, *male hypogonadism*, and gastrointestinal discomfort. *Electrolyte imbalance* is usually due to either uncontrolled hypercortisolemia (mineralocorticoid receptor activation by cortisol) or hypoadrenalism [42].

Osilodrostat (isturisa): The most common adverse drug events include nausea, headaches, and the clinical effects of either the accumulation of precursor adrenal hormones or overt hypocortisolemia (adrenal insufficiency). Osilodrostat has clinical utility in persistent and recurrent Cushing's disease [43].

Clinical Trial Evidence

This was a retrospective study to evaluate the efficacy of mitotane in Cushing's disease. Seventy-six consecutive patients with proven Cushing's disease reporting to a single facility were followed for a median period of 6.7 months (95% CI of 5.2–8.2 months). The patients received mitotane at a total daily dose of 4 g in three divided doses. Gradual de-escalation to a minimally tolerable dose needed to maintain remission was allowed during the study. There was no placebo or active comparator arm. The primary outcome was defined as Cushing's disease (normalization of 24 hours of UFC). This occurred in 72% of patients [40].

Key Message

Mitotane leads to biochemical amelioration of Cushing's disease (normalization of 24-hour urinary-free cortisol) in more than 70% of patients at doses much lower than required for the treatment of adrenal carcinoma.

Pathophysiology Pearl

The cortisol-to-cortisone shunt

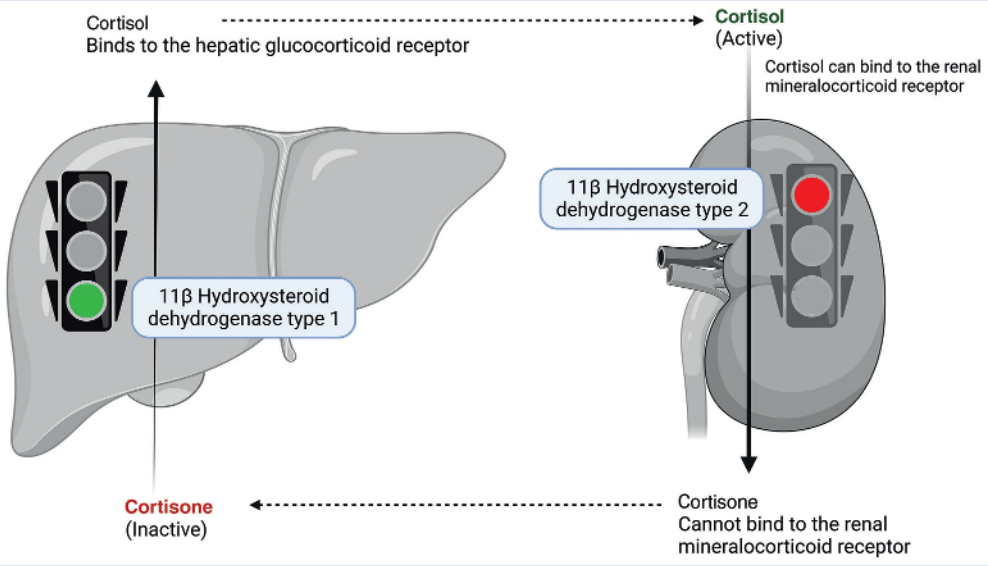

FIGURE 1.4 The cortisol-to-cortisone shunt and the role of two isoforms of 11 beta-hydroxysteroid dehydrogenase (11β-HSD) enzymes. Cortisol and aldosterone bind to the nonselective renal mineralocorticoid receptor under normal physiologic conditions [44]. The 11-beta hydroxysteroid dehydrogenase type 2 (11β-HSD2) isoform converts cortisol to cortisone, thus protecting the renal MCR from direct activation by cortisol. The 11 beta-hydroxysteroid dehydrogenase type 1 (11β-HSD1) isoform converts inactive cortisone to cortisol [45].

Clinical Pearl

Ketoconazole-induced apparent mineralocorticoid excess

There is a reported case of *apparent mineralocorticoid excess* (AME) in a patient treated with ketoconazole. The patient developed hypokalemia and hypertension in a manner that simulated a *"non-glucocorticoid-mediated"* AME. Unlike *metyrapone*, which mainly inhibits 11-beta hydroxylase (not to be confused with 11β-HSD), *ketoconazole* inhibits 11-beta hydroxylase and proximal side-chain cleavage enzymes (see Figure 1.3). This conventionally results in a *relatively lower* concentration of 11-Deoxycorticosterone (a potent mineralocorticoid) in patients treated with ketoconazole compared to metyrapone. Therefore, hypertension and hypokalemia may be inadvertently attributed to refractory hypercortisolemia (effects of excess cortisol overwhelming 11β-HSD2 and activating the renal MCR) rather than accumulation of DOC (see Figure 1.4). In this scenario, an increase in the dose of ketoconazole due to the presumed uncontrolled hypercortisolemia would exacerbate hypertension and hypokalemia (mineralocorticoid effects of DOC). Although DOC-mediated hypertension is more common in patients treated with metyrapone, this rare case report highlights the possibility of ketoconazole-mediated **hypertension** due to DOC accumulation of DOC in Cushing's syndrome [42].

1.1.5 Mifepristone

1.1.5.1 Physiology

Glucocorticoid Receptor Physiology

There are two isoforms of the glucocorticoid receptor (GR), namely, the GRα and GRβ glucocorticoid receptor. The GRα isoform is the proverbial "classic glucocorticoid receptor" in the cytosol, while the GRβ isoform resides in the nucleus. The GRβ receptor exerts a mainly modulatory role by inhibiting the function of GRα [46]. Figure 1.5 shows the mechanism of action of cortisol in normal physiology.

1.1.5.2 Mechanism of Action

Mifepristone, also known as *RU486* (Roussel-Uclaf 38 486), has antiglucocorticoid and anti-progesterone effects. RU486 binds to the *ligand-binding domain* (LBD) of the cytosolic glucocorticoid receptor without directly promoting its downstream effects, such as activation of hormone response elements and transcription factors involved in glucocorticoid-mediated gene function [49].

1.1.5.3 Practice Guide

- Patients taking mifepristone *(Korlym)* may develop significant hypercortisolemia (with elevated ACTH levels), which can increase their risk of *hypokalemia and hypertension (cortisol activating renal MCR)* [50]. Antiprogestin effects predispose female patients to *endometrial hyperplasia (unopposed estrogen action)*.
- Monitor patients for symptoms and signs of adrenal insufficiency. It is worth noting that cortisol levels are unreliable in patients on mifepristone. Indeed, patients may be "adrenally insufficient" despite high cortisol levels (blockade of the GR) [51].
- Mifepristone is approved by the FDA of the United States (Food and Drug Administration) to manage endogenous hypercortisolemia associated with hyperglycemia [52]. Glycemic control improves in up to 60% of patients treated with mifepristone. Thus, doses of antihyperglycemic agents may need to be adjusted [53].
- It is also an abortifacient due to its antiprogesterone effects. Table 1.2 shows the therapeutic sites of action of medical-directed therapies of Cushing's disease.

Clinical Trial Evidence

The Study of the Efficacy and Safety of Mifepristone in the Treatment of Endogenous Cushing's Syndrome (SEISMIC) and its extension sub-study assessed the effects of long-term mifepristone on neuroimaging findings in patients with Cushing's disease [55].

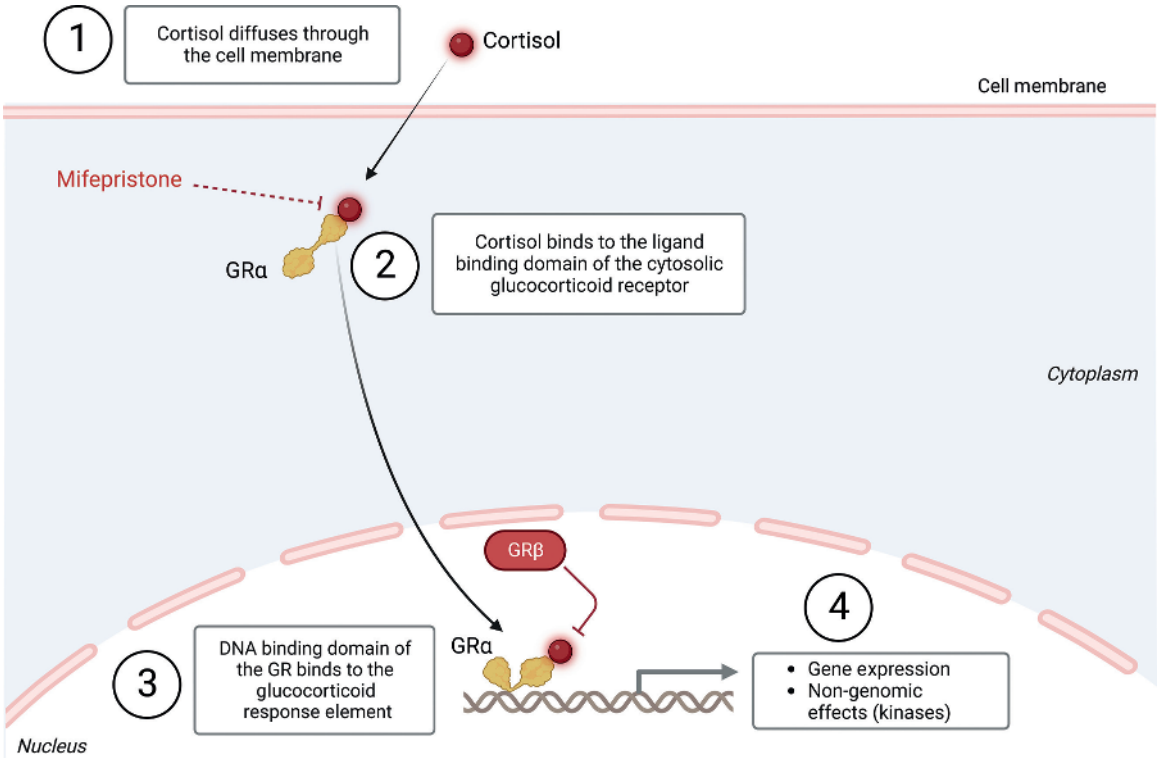

FIGURE 1.5 Glucocorticoid receptor physiology. Cortisol (glucocorticoid), a steroid hormone, diffuses through the plasma membrane to bind to the ligand-binding domain (LBD) of the cytosolic glucocorticoid receptor *(Step 1)*. The hormone–receptor complex undergoes a conformational change and is then translocated from the cytosol into the nucleus to exert its genomic effects *(step 2)*. The glucocorticoid receptor's DNA binding domain (DBD) binds to its assigned hormone response sequence, the Glucocorticoid Response Element (GRE), to exert its intranuclear effects. This leads to the activation of transcription factors, which can activate or inactivate gene expression [46, 47]. Glucocorticoids may also exert nongenomic effects through various kinases *(step 3)*. This typically occurs minutes after ligand–receptor interaction in the cytosol [46]. The nongenomic effects of glucocorticoids include inflammatory and noninflammatory processes (calcium mobilization and muscle function) [48]. GRβ inhibits the intranuclear effects of GRα [46]. *Source*: Adapted from ref. [46].

Key Message

Although mifepristone causes an increase in ACTH among patients with Cushing's disease, it does not significantly increase the size of the pituitary tumor.

The SEISMIC trial was an open-label, multicenter prospective study that evaluated the effects of mifepristone on tumor size and ACTH levels in Cushing's disease over a 24-week period. Subjects received a starting dose of oral mifepristone (300 mg) once daily, steadily increasing to a maximum daily dose of 1200 mg. The primary outcome was defined as a change in ACTH (compared to baseline) and MRI changes (volumetric changes in tumor size). 72% of the subjects had a twofold increase in ACTH compared

TABLE 1.2 Summary of therapeutic targets in Cushing's disease.

Therapy	The primary site of action
Pasireotide	Anterior pituitary gland (SSR_1, SSR_2, SSR_3, and SSR_5 receptors)
Retinoic acid	Anterior pituitary gland (Retinoic acid receptors)
Cabergoline	Anterior pituitary gland (Dopaminergic receptors)
Ketoconazole	Adrenal steroidogenesis inhibitor
Metyrapone	Adrenal steroidogenesis inhibitor
Mitotane	Adrenal steroidogenesis inhibitor
Mifepristone	Glucocorticoid receptor antagonist

Source: Adapted from Hinojosa-Amaya et al. [54].

to baseline. ACTH returned to baseline after discontinuing RU486. Tumor progression and regression occurred in two and three subjects, respectively. This was not statistically significant. In fact, there was no evidence that mifepristone predisposes patients to accelerated pituitary tumor growth [55].

In conclusion, there are novel therapies for Cushing's disease which are currently in development. These include cyclin-dependent kinase 2 (CDK2) modulators (*Roscovitine*), epidermal growth factor receptor (EGFR) inhibitors (Gefitinib), and GR antagonists (*Relacorilant*), to mention a few [54].

Concepts to Ponder Over

Will octreotide, an SSR2 agonist, be a suitable therapeutic option in patients with Nelson syndrome?

Nelson syndrome (NS) may occur after bilateral adrenalectomy in patients with Cushing's disease. NS is characterized by corticotroph tumor expansion and elevated levels of ACTH. However, the underlying pathophysiology of this condition remains unclear at this time [56]. The loss of negative feedback inhibition of cortisol on tumorous corticotroph cells inadvertently leads to their proliferation. Patients may develop hyperpigmentation involving the skin and mucous membranes due to elevated levels of ACTH [57].

It should be noted that cortisol inhibits SSR on corticotroph cells. SSR_2 receptors are preferentially inhibited to a higher degree than SSR_5 receptors [6]. In NS, the lack of cortisol-mediated downregulation of SSR_2 receptors makes SSAs, which bind to this receptor subtype, a reasonable therapeutic option. Although octreotide is less effective in treating Cushing's disease, it has a role in Nelson's syndrome [56, 58].

How does cabergoline (a dopaminergic agonist) cause cardiac valvulopathy?

Compared to bromocriptine, cabergoline is associated with a higher risk of cardiac valvulopathy. The reported cardiac effects of cabergoline include the thickening of the *chordae tendineae* and cardiac valves [59]. The binding of cabergoline to $5HT_{2B}$ *receptors* in the endocardium leads to valvulopathy. The predilection of cabergoline-induced valvulopathy for the tricuspid valve may be due to the disproportionately high amount of this receptor subtype in the right side of the heart [27].

1.2 ACROMEGALY

1.2.1 Somatostatin Analogs

1.2.1.1 Physiology

The role of somatostatin in the regulation of growth hormone.

Growth hormone-releasing hormone (GHRH) is a peptide hormone composed of 44 amino acids synthesized in the arcuate nucleus of the hypothalamus. GHRH is secreted in a pulsatile fashion and is carried from the hypothalamus to the anterior pituitary gland through the hypothalamo-hypophyseal vessels. By binding to receptors on the surface of anterior pituitary somatotrophs, GHRH stimulates gene transcription, translation, and the eventual release of *growth hormone* (GH) from their secretory vesicles. *Somatostatin* (also known as somatostatin receptor inhibitory factor, SRIF), on the other hand, blocks the release of GH by somatotrophs by acting on somatostatin receptors (primarily SSR_2 receptors) [60]. *Ghrelin* (derived from gastric oxyntic cells) is a GH secretagogue that exhibits its effects by acting on hypothalamic GHRH cells in the median eminence [61]. GH and insulin-like growth factor 1 (IGF-1) provide additional negative feedback inhibition of GH secretion (see Figure 1.6). Refer to Table 1.3 for a summary of the various physiological factors which regulate growth hormone secretion.

GH binds to the extracellular component of the hepatic GH receptor (GH-R) and induces a series of intracellular processes required for the transcription and translation of specific genes that encode IGF-1, *IGF-binding protein 3* (IGFBP3), and an *acid-labile subunit* (ALS) [68–70]. These products of GH action at the level of the liver form a ternary complex in circulation that influences the ability of IGF-1 to bind its peripheral insulin-like growth factor 1 receptor (IGF-1R). Indeed, post-translational modification of IGFBP3 (e.g. glycosylation, phosphorylation) is an essential determinant of IGF-1's ability

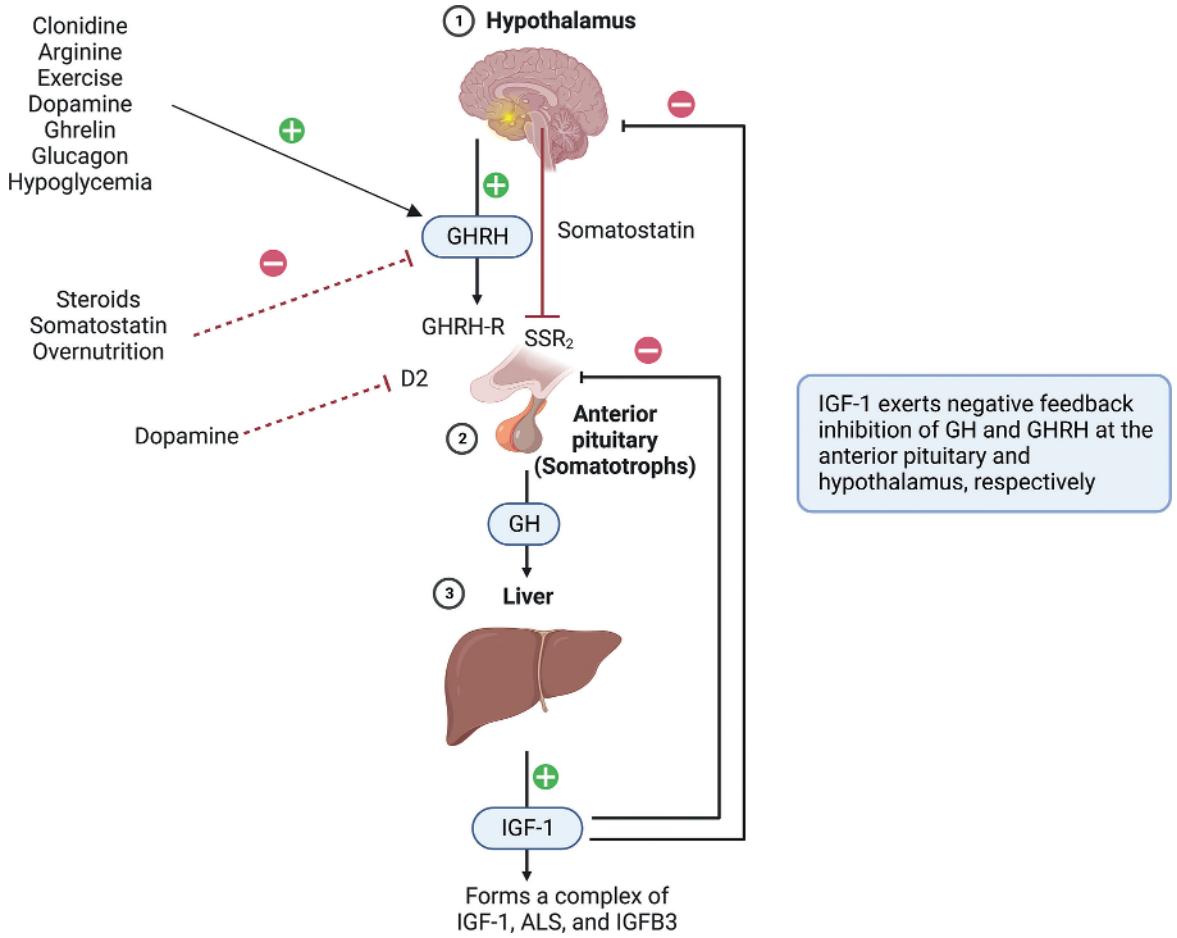

FIGURE 1.6 The growth hormone and insulin-like growth factor 1 axis. Hypothalamic-derived GHRH binds to GHRH-R on anterior pituitary somatotrophs and consequently mediates their secretion of GH. Binding of GH to GH-R in the liver promotes the synthesis of IGF-1, ALS, and IGFB3 – a complex that determines the circulating half-life and, therefore, peripheral effects of IGF-1. IGF-1 exerts negative feedback inhibition of GH and GHRH in the anterior pituitary and hypothalamus, respectively. GH exerts negative feedback inhibitory effects on its production at the level of the anterior pituitary gland. Somatostatin inhibits the release of growth hormone by somatotrophs. Important co-inhibitory and co-stimulatory factors influencing net GH secretion are shown *(negative and positive signs)*. *Source*: Adapted from ref. [62].

TABLE 1.3 Regulators of GH.

Promotes GH secretion	Inhibits GH secretion
Arginine [63]	Overnutrition [64]
Clonidine [63]	Glucocorticoids (high doses) [65]
Estrogen[a] [66]	Somatostatin [60]
Hypoglycemia, Glucagon [67]	
L-dopa [63]	
Exercise [63]	

[a] This effect is route-dependent, with the oral route causing an increase in GH and a paradoxically low IGF-1. Transdermal estrogen does not produce this effect [66].
Source: Adapted from refs. [60, 63–67].

to bind to IGF-1R. For example, *glycosylation* of IGFBP3 increases the ability of IGF-1 to bind to IGF-1R. *Deglycosylation*, on the other hand, impairs ligand-to-receptor binding [62]. The consequences of GH action are widely accepted as pivotal for macronutrient metabolism (carbohydrate, lipid, and protein) and cellular growth [71].

1.2.1.2 Mechanism of Action

SSAs activate SSR on somatotroph tumor cells and thus inhibit their production of GH and, consequently, hepatic IGF-1. There is evidence that SSAs also lead to a reduction in the size of GH-secreting tumors [72, 73].

1.2.1.3 Practice Guide

SSAs approved in the United States for the treatment of acromegaly include octreotide (short release), octreotide long-acting release (Sandostatin LAR), and lanreotide (Somatuline). A few practice pearls were shared earlier in Section 1.1.1 (use of pasireotide in Cushing's disease).

- A hallmark side effect of pasireotide is *hyperglycemia*. The risk of hyperglycemia is disproportionately higher among patients with diabetes or prediabetes; it is reasonable to screen for hyperglycemia before and during treatment [74].
- First-generation SSAs (for example, lanreotide and octreotide) have a higher affinity for SSR2 than the SSR5 isoform of the somatostatin receptor [75]. Pasireotide, on the other hand, has a greater affinity for the SSR5 receptor subtype. Tumor response is influenced by the density of specific histological SSR subtypes (e.g. sparsely vs. densely granulated growth hormone-secreting tumors) [76]. This is clinically relevant since it can influence the effectiveness of selected therapies. For example, sparsely granulated somatotroph tumors tend to express SSR5 receptors (pasireotide). Densely granulated somatotrophs, on the other hand, express the SSR2 subtype (octreotide) predominantly [76–78].
- SSAs are associated with an increased risk of cholelithiasis and diarrhea [79].
- Monitoring response to therapy – IGF-1 should normalize to the age and sex-specific reference range for IGF-1. Furthermore, GH should be suppressed to a nadir of <1 ng/mL or < 0.4 ng/mL (for newer and more sensitive GH assays) after an oral glucose load with 75 g of anhydrous glucose (Oral glucose tolerance test).

Clinical Trial Evidence

Pasireotide, a second-generation multireceptor SSA, causes a more significant biochemical improvement of acromegaly in contrast to first-generation SSAs (*octreotide* and *lanreotide*) [80, 81].

Key Message

In patients with uncontrolled acromegaly with octreotide or lanreotide, pasireotide produces a treatment response in 15–20% of patients.

The PAOLA study (*Pasireotide versus continued treatment with octreotide or lanreotide in patients with inadequately controlled acromegaly*) was a randomized, prospective, parallel-group study evaluating the safety and efficacy of pasireotide. 198 patients with uncontrolled acromegaly (GH >2.5 mcg/L and IGF > 1.3 times the age- and gender-adjusted upper limit of normal) on octreotide or lanreotide for a minimum of 6 months. Patients were randomized to pasireotide (40 or 60 mg) administered intramuscularly once every 28 days or active comparators (octreotide or lanreotide). The authors defined the primary outcome as a GH level <2.5 mcg/L and normalization of IGF-1. The primary outcome occurred in 15% (40 mg), 20% (60 mg), and 0% (octreotide/lanreotide) [80].

1.2.2 Growth Hormone Receptor Antagonists

1.2.2.1 Physiology

Growth Hormone and IGF-1 Pathway

The growth hormone receptor (GH-R) belongs to the cytokine receptor family [82] and is composed of *extracellular* (binds to its cognate ligand, that is, GH), *transmembrane,* and *cytosolic* domains [83]. See Figure 1.7 and Table 1.4.

1.2.2.2 Mechanism of Action

Pegvisomant has structural homology with endogenous GH except for the substitution of nine amino acids. *Pegylation* (the process of attaching polyethylene glycol to the protein) of GH changes its pharmacokinetic properties, making it hypoallergenic [87].

Due to its similarity to GH, Pegvisomant can occupy the GH receptor pocket, depriving the receptor of direct activation by GH. More importantly, it does not activate GHR (antagonistic action) because it induces defective dimerization of the receptor, thus preventing subsequent signal transduction pathways (JAK–STAT signaling) and eventual production of IGF-1 [88].

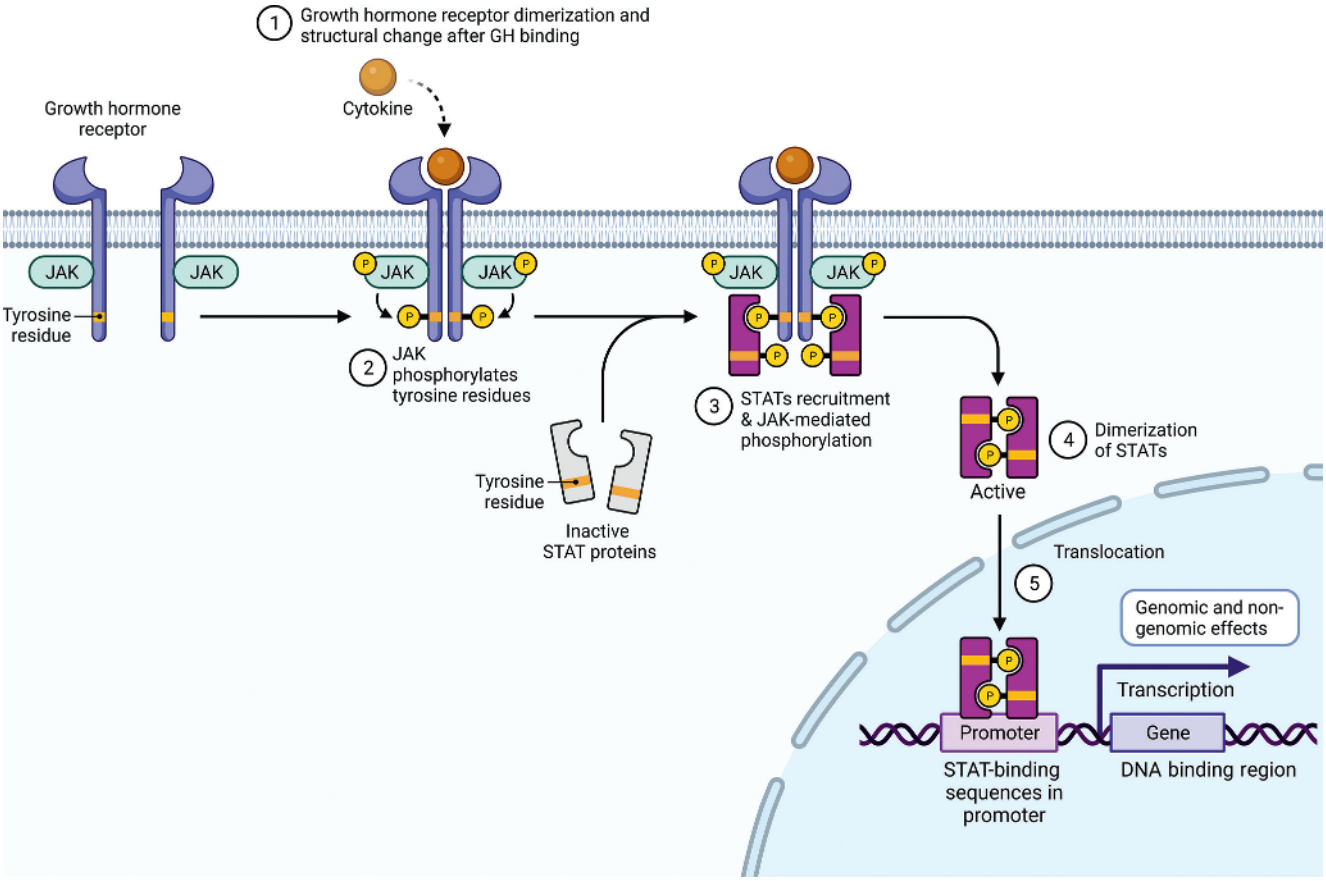

FIGURE 1.7 Growth hormone receptor and intracellular effects of GH to GHR binding. GH binds to the GH-R, leading to dimerization and consequent structural change in the receptor. This critical step initiates the *Janus-Kinase* (JAK) signal *transducer and activator of transcription* (STAT) intracellular signaling pathway. The phosphorylation of tyrosine residues in both the GHR transmembrane domain and STAT molecules is mediated by activated JAK2 tyrosine kinase [84]. There are various STAT molecules involved in specific intracellular processes. STAT5 (transcription factor), for example, is translocated from the cytoplasm to the nucleus and binds to DNA in specific DNA binding regions(DBRs) [85], which encode protein sequences [86]. Mitogen-activated protein kinase (MAPK) activation by JAK2 ultimately exerts genomic (gene expression) and non-genomic effects. GH mediates the production of IGF-1 in various tissues other than the liver, including growth plate chondrocytes, adipose tissue, and skeletal muscle [86]. *Source*: Adapted from ref. [85].

TABLE 1.4 Gene sequences encoding IGF-1 production in specific organs.

Organ	Gene sequence(s)
Liver	Socs2
Skeletal muscle	Igf1
Fat (Adipose tissue)	Fos, Jun, and Igf1
Bone (Chondrocyte)	Igf1

Socs2, suppressor of cytokine signaling 2; Igf1, insulin-like growth factor 1; Jun, proto-oncogene; Fos, proto-oncogene. Source: Adapted from Chia [86].

1.2.2.3 Practice Guide

- Pegvisomant can cause an increase in the size of GH-secreting tumors; it is thus recommended to monitor tumor size with serial pituitary MRIs [89]. Coadministration of SSAs and pegvisomant can reduce the risk of tumor re-expansion compared to pegvisomant monotherapy [90].
- Pegvisomant, a GH-R antagonist, causes an increase in GH levels, thus limiting the utility of GH assessments during monotherapy with this agent. As a result, the evaluation of treatment

response requires serial monitoring of serum IGF-1 levels [89].

- Hepatic enzyme elevation occurs during treatment and resolves after cessation of therapy. Liver function tests (LFT) should therefore be routinely monitored during treatment. Consequently, patients with unexplained elevations in LFT should not start pegvisomant [91].

Clinical Trial Evidence

The pivotal study that led to the approval of pegvisomant was published in 2000. It was a phase III study that compared various doses of pegvisomant with placebo [88]. Additional long-term safety data are available from the ACROSTUDY database. The ACROSTUDY registry is a prospective, Phase IV (post-marketing surveillance) study of patients with acromegaly treated with pegvisomant [92, 93].

Key Message

There is a low but clinically significant risk of tumor re-expansion for patients receiving *pegvisomant* monotherapy, although this should not preclude its use (ACROSTUDY).

A randomized, double-blind, placebo-controlled study comparing various doses of pegvisomant with placebo in patients with acromegaly over a 12-week study period. A total of 112 subjects with confirmed acromegaly, status-post pituitary surgery, radiation therapy, drug therapy, or treatment-naïve. Study participants were randomized to various doses of subcutaneous pegvisomant administered daily (10 mg, 15 mg, or 20 mg) or a comparable placebo. The primary outcome was defined as a mean change in IGF-1 compared to the baseline level. There was a mean decrease in IGF-1 of 4%, 26.7%, 50.1%, and 62.5% in the placebo, 10 mg,15 mg, and 20 mg, respectively. Various doses of pegvisomant compared to placebo resulted in a clinically significant decrease in IGF-1 and improved clinical features of acromegaly [88].

1.2.3 Dopaminergic Agonists

1.2.3.1 Physiology

Growth Hormone Physiology and the Role of Central Dopaminergic Pathways

The binding of dopamine to D2 receptors in either pituitary somatotrophs or lactotrophs impairs the release of GH and prolactin, respectively [94]. Additionally, dopamine impairs hypothalamic somatostatin release, increasing *GHRH secretion* [95] (See Figure 1.6).

The differential effects of dopamine on GH secretion should be appreciated in normal physiology. The effects of Dopaminergic agonists (DA) at the level of the anterior pituitary gland are more profound than its effects in the hypothalamus. The net effect is a reduction in GH secretion.

1.2.3.2 Mechanism of Action

Growth hormone-secreting tumors express D2R receptors to varying degrees, determining their response to DAs [96]. Indeed, the responsiveness of D2Rs on somatotroph tumors depends on their sensitivity and the concentration of circulating GH [97].

1.2.3.3 Practice Guide

- Cabergoline is more effective than bromocriptine and reduces tumor size in approximately 30% of patients [98]. Also, see Section 1.1.3.

Clinical Trial Evidence

There is a paucity of evidence from randomized, placebo-controlled clinical trials among patients with acromegaly treated with cabergoline [99].

Key Message

Normalization of IGF-1 occurs in a third of acromegalic patients treated with cabergoline monotherapy. There is limited information about the effects of cabergoline on tumor size. Tumor shrinkage was demonstrated in patients with high baseline levels of prolactin (PRL) and IGF-1. It is a reasonable treatment option in *somatomammotrophic tumors* (GH-PRL co-secreting tumors).

This was a meta-analysis of prospective, nonrandomized studies in patients with cabergoline-treated acromegaly. A total of 227 subjects in 15 studies with significant heterogeneity were evaluated. There was no placebo group in this study. The patients were exposed to cabergoline monotherapy at variable doses ranging from 0.3–7 mg/week. The authors defined the primary outcome as the normalization of IGF-1. The primary outcome was achieved in 34% of patients [99].

Concepts to Ponder Over

What is the effect of estrogen replacement therapy on the GH–IGF-1 axis?

There is a paradoxical effect of estrogen replacement on both GH and IGF-1; this depends on the route of administration of estrogen (oral or transdermal). The oral route leads to an increase in hepatic synthesis of growth hormone binding proteins (*first-pass effect*), which in turn bind GH avidly and somewhat attenuates its peripheral effects at the level of the liver (i.e. GH-induced IGF-1 production). This effect occurs despite an estrogen-mediated increase in pituitary GH production. It has been postulated that oral estrogen is not a GH secretagogue and that GH levels increase due to the loss of negative feedback inhibition of IGF-1 on somatotrophs [66](see Figure 1.6. To further support this hypothesis, women on transdermal estrogen replacement therapy were shown to have GH requirements much lower than those on oral estrogens. Transdermal estrogen escapes the *"hepatic first-pass effect"* and, as such, does not lead to clinically significant changes in GH-binding proteins [100]. It should be noted that women on chronic GH replacement therapy who inadvertently start oral estrogen replacement experience a decline in IGF-1 levels (*GH antagonizing effects of estrogen*), which will require an up-titration in GH doses [101, 102].

What effect does pegvisomant have on glycemic control?

GHR antagonists *improve insulin sensitivity* at the level of the liver, skeletal muscle, and adipose tissue [103]. In a GH excess state like acromegaly, *GH promotes increased lipolysis* in adipose tissue, which liberates free fatty acids (FFAs) (mediators of peripheral insulin resistance). See Figure 1.10 for the effects of GH on fat metabolism. There is a significant reduction in endogenous glucose output among patients with active acromegaly after a 4-week course of pegvisomant. Suppression of GH-induced lipolysis by pegvisomant reduces FFAs, and consequently improves peripheral insulin resistance [104].

1.3 PROLACTINOMA

1.3.1 Dopaminergic Agonists

1.3.1.1 Physiology

Regulation of Prolactin Release

Anterior pituitary lactotrophs release prolactin (a peptide hormone) under trophic stimulation by a hypothalamic-derived *prolactin-releasing factor (a putative hormone)*, *vasoactive intestinal peptide*, or *thyrotropin-releasing hormone (TRH)* [105].

Hypothalamic dopamine (tuberoinfundibular dopaminergic neuronal cells) inhibits the release of prolactin by binding to D2 receptors on anterior pituitary lactotrophs. Prolactin increases hypothalamic dopamine release by upregulating tyrosine hydroxylase activity (dopamine synthesis pathway) in tuberoinfundibular neurons, thus promoting its inhibition by dopamine [106] (Figure 1.8). A summary of the various physiological regulators of prolactin secretion is shown in Table 1.5.

Although classically associated with the function of the mammary glands, prolactin has several extramammary effects due to the presence of prolactin receptors in various tissues. There are PRL receptors (PRL-R) in pancreatic beta cells (glucose-mediated insulin release), adipose tissue (thermoregulation), and hematopoietic cells (T-cell activation), to name a few [107, 108].

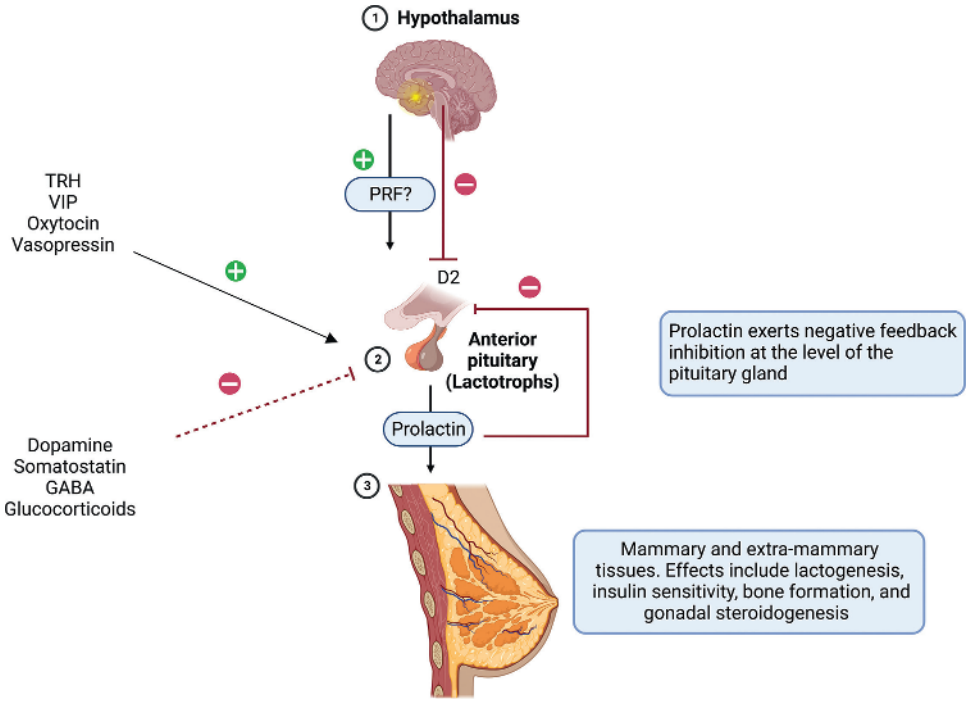

FIGURE 1.8 Schematic representation of the hypothalamic–pituitary-mammary axis. PRF is a putative (unconfirmed) hormone involved in the stimulation of PRL release by lactotrophs in the anterior pituitary gland. Hypothalamic dopamine affects prolactin release by binding and activating D2 receptors present on lactotrophs. Stimulatory and inhibitory factors involved in the regulation of PRL release are represented by + and – signs. Extramammary tissues include gonadal steroidogenesis, skeletal growth, and glucose metabolism, to mention a few.

TABLE 1.5 Regulators of prolactin secretion.

Inhibition of prolactin secretion	Stimulation of prolactin secretion
Dopamine	TRH
Somatostatin	VIP
GABA	Oxytocin
Glucocorticoids	Vasopressin

VIP, vasoactive intestinal peptide; GABA, gamma-aminobutyric acid.
Source: Adapted from Saleem et al. [106].

1.3.1.2 Mechanism of Action

DAs (cabergoline and bromocriptine), synthetic derivatives of ergots, bind to D2 receptors on the surface of pituitary lactotroph tumors and induce dopamine-mediated inhibition of prolactin synthesis and secretion. DAs also exhibit "tumoricidal properties" by promoting programmed cell death of lactotroph tumors through complex intracellular pathways that involve estrogen and neuronal dopamine transporters [109].

1.3.1.3 Practice Guide

- Patients who do not experience a *normalization of serum PRL* or a *50% reduction in tumor size* are classified as dopaminergic agonist resistant. However, no conventionally accepted dose or duration of exposure to DA is required to diagnose a patient as resistant to DA [110, 111].
- Predictors of an inadequate response to DAs include *male gender*, *macroprolactinoma*, *tumor characteristics* (cystic or hemorrhagic), *prolonged latency to euprolactinemia,* and *high PRL at baseline* [112].
- For women in the reproductive age group planning a pregnancy, the use of bromocriptine is a safer therapeutic option compared to cabergoline. This is due to the availability of more safety data for the former compared to the latter [113].
- Side effects of DA include nausea, vomiting, headaches, postural hypotension, psychotropic side effects (hallucinations, psychosis), and nasal congestion [114, 115]. The dictum "start low and go slow" helps mitigate the side effects of DA.

Cabergoline has a longer half-life, a higher affinity for D2R, and a relatively tolerable side-effect profile compared to bromocriptine [116].

- It is reasonable to screen for psychiatric disorders before initiating DAs. Compulsive gambling has been associated with cabergoline use; it is therefore important to alert patients of this potential side effect [117].

Clinical Pearl

It has been speculated that Mary Tudor, Queen Mary I of England, may have had an undiagnosed prolactinoma based on historical accounts. She experienced a myriad of symptoms, including amenorrhea (from 19 years), headaches, impaired vision, phantom pregnancy, and galactorrhea for most of her adult life [105].

Prolactin-secreting tumors are the most common hormone-secreting tumors in the pituitary gland [106], with a reported prevalence of 50 per 100,000 [107]. Medical therapy using primarily dopaminergic agonists is the mainstay of treatment. Surgery is reserved for patients with medication resistance or intolerance [108].

Clinical Trial Evidence

There was a paradigm shift from surgery to DAs for the treatment of prolactinomas in the 1970s due to the superior efficacy and safety of medical therapy compared to surgery. DAs are now widely recommended as a first-line treatment option for patients with prolactinomas. Due to advancements in transsphenoidal endoscopic procedures, surgery may be a viable option for patients. This was explored in a systematic review investigating surgery as a viable alternative first-line treatment for prolactinoma [118].

Key Message

Dopaminergic agonists remain the first-line therapeutic option in most patients with prolactinomas. However, surgery is more likely to lead to long-term remission in patients regardless of tumor size (macroprolactinoma or microprolactinoma), based on the results of this large meta-analysis.

In this meta-analysis, evaluating long-term remission rates after a dopaminergic holiday or transsphenoidal surgery, patients were grouped into medical ($n = 3564$) and surgical ($n = 1836$) arms. The primary outcome was defined as long-term (≥1 year) remission (in other words, maintenance of normal serum prolactin) after either the withdrawal of medical therapy or post-transsphenoidal surgery. The primary outcome after the dopaminergic holiday was 34% (95% CI, 26–46) and 67% (CI, 60–74) after transsphenoidal surgery [118].

1.3.2 Temozolomide

1.3.2.1 Physiology

Cellular Protective Mechanisms Against Mutagens

Endogenous and exogenous factors can promote DNA damage and inadvertently trigger a cascade of events that lead to the formation of tumors. Cells in normal physiology maintain their integrity through a variety of protective pathways such as mismatch repair, nucleotide excision repair, and methylguanine-DNA methyltransferase (MGMT) enzymatic processes [119].

1.3.2.2 Mechanism of Action

Temozolomide (TMZ) is an alkylating chemotherapeutic agent that promotes the methylation of specific residues of guanine (position O-6) and purine (positions N3 and N7) in DNA. This introduces breaks in the DNA of rapidly growing cells, such as lactotrophic tumors, leading to their apoptosis (programmed cell death) [120]. A schematic representation of the mechanism of action of temozolomide is shown in Figure 1.9.

1.3.2.3 Practice Guide

- An evaluation of *MGMT promoter methylation status* is a useful *predictive biomarker* [121] in patients with aggressive prolactinomas or carcinomas [122]. There is an inverse relationship between tumor levels of MGMT and the degree of responsiveness to TMZ [122]. However, MGMT as a biomarker is a novel approach to predict TMZ response in patients with prolactinomas. Therapeutic response after a minimum of 3 cycles of treatment performed better than tumor levels of MGMT in a large cohort of patients with pituitary tumors (including prolactinomas) [123].

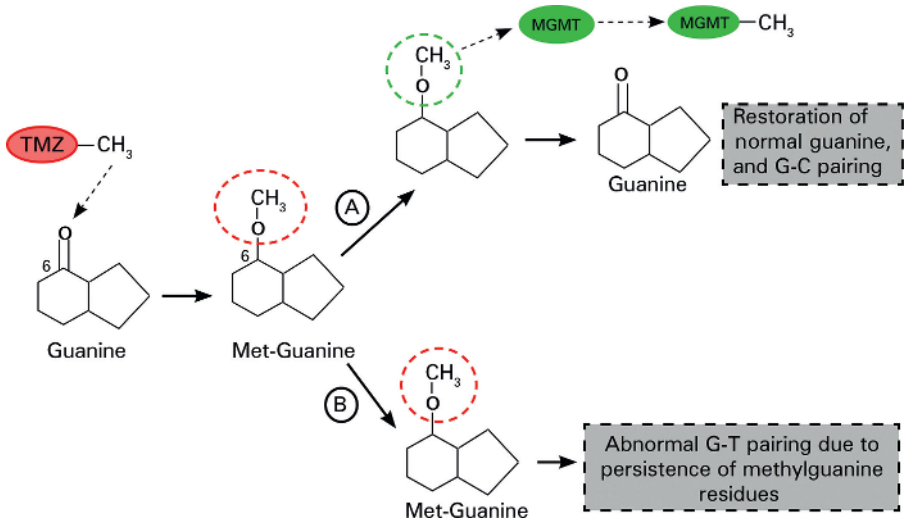

FIGURE 1.9 Schematic representation of the mechanism of action of temozolomide. TMZ promotes the methylation of guanine(G) at the number 6 carbon position, a step that leads to the formation of methylguanine residues in DNA. There is a "suicide enzyme" called methylguanine-DNA methyltransferase (MGMT), whose primary function is to remove these abnormal methyl groups, thus restoring the integrity of guanine residues in DNA *(Step A)*. This defective methylated guanine pairs with thymine (T) instead of cytosine (C) (by convention) during replication. Mismatch repair enzymes excise these **mispaired guanine-thymine** residues, although this is ultimately a futile exercise. Continuous cycles of erroneous G and T pairing and T excisions lead to irreparable DNA breaks that promote cell death *(Step B)* [120]. *Source*: Adapted from ref. [120].

- TMZ, a chemotherapeutic agent, is associated with expected short-term toxicity concerns, such as nausea, emesis, and fatigue [124]. Cytopenias (hematologic toxicity), which require a dose reduction or discontinuation of therapy, are infrequent [123, 124]. Safety data after 5–8 years of exposure to TMZ are very reassuring, making it a valuable long-term salvage therapeutic option [125].

Clinical Trial Evidence

There are no published randomized trials evaluating the safety and efficacy of TMZ compared to placebo. A recent systematic review of all published case reports and case series provided valuable information on the response of dopaminergic agonist-resistant prolactinomas to TMZ [124].

Key Message

Temozolomide has a favorable side-effect profile and is a reasonable rescue therapeutic option in patients who have exhibited a suboptimal response to DAs, radiation therapy, or surgery. Approximately 75% of patients with treatment-resistant prolactinomas achieved a reduction in tumor volume and serum prolactin levels after a temozolomide trial.

This was a meta-analysis of case series and reports that evaluated the tumor response to TMZ in 42 subjects with prolactin-secreting adenoma or carcinoma. Patients with resistance to dopaminergic agonist therapy received oral TMZ dose as 150–200 mg/m^2 in 1–24 therapeutic cycles. The primary outcome was defined as a change in tumor size and hyperprolactinemia improvement. Compared to baseline, a significant reduction in tumor size and prolactin levels occurred in 76.5% and 75% of patients, respectively [124].

Concepts to Ponder Over

How does primary hypothyroidism contribute to hyperprolactinemia?

Undiagnosed primary hypothyroidism can present with significant hyperprolactinemia and pituitary gland enlargement [126, 127]. Patients with primary hypothyroidism have an upregulation of both TRH and TSH synthesis in the hypothalamus and pituitary gland, respectively [128]. TRH, a prolactin secretagogue, promotes hyperprolactinemia [105](see Figure 1.8). Anterior pituitary thyrotrope hyperplasia under the influence of TRH leads to the formation of a thyrotrope pseudotumor (diffuse enlargement of the pituitary gland).

An inadvertent "stalk effect" due to impingement of the sellar mass on the pituitary stalk disrupts the dopaminergic tracts, leading to impaired tonic inhibition of lactotrophs by dopamine.

Is there a role for SSAs in the treatment of prolactinomas?

Dopaminergic agonist-resistant prolactinomas are usually treated with surgical debulking, radiation therapy, or temozolomide [129]. As you may recall, somatostatin inhibits prolactin release (see Figure 1.8 [106]. Prolactinomas co-express SSR1 and SSR5 predominantly. The low expression of SSR_2 receptors by prolactinomas is responsible for their suboptimal response to octreotide. Pasireotide, being a multireceptor SSA, has an affinity for both SSR_1 and SSR_5 receptors, making it a viable option in the management of prolactinomas (see Section 1.1.1) [130]. There are reports of prolactinomas that have responded to pasireotide [129, 131, 132].

Clinical Pearl

Harvey Cushing was able to associate skeletal undergrowth with a putative growth factor from the anterior pituitary gland. His observations were recorded in his paper, The pituitary body and its disorders, in 1912. *"Doubtless as many cases of infantilism are due to a primary hypophyseal as to a primary thyroid insufficiency … this is particularly true for cretinoid states – may actually be due to defective hypophyseal activity"* [133]. It was not until the 1950s that growth hormone or somatotrophin was eventually extracted from the anterior pituitary gland. Purified growth hormone was initially utilized in treating short stature in pediatric patients [134]. Although the use of growth hormone in adults took several decades, its utility in a hypopituitary adult was first demonstrated by Raben in 1962 [135]. Adult growth hormone deficiency may present with isolated growth hormone deficiency or coexist with other pituitary hormone insufficiencies [102, 136].

1.4 ADULT GROWTH HORMONE INSUFFICIENCY

1.4.1 Growth Hormone

1.4.1.1 Physiology

Anabolic Effects of Growth Hormone

Basic growth hormone physiology was reviewed earlier in Section 1.2.1. GH exerts its anabolic effects in skeletal tissue, muscle, and adipose tissues [133]. The anabolic effects of growth hormone in various tissues are shown in Table 1.6.

TABLE 1.6 Anabolic effects of growth hormone.

Tissue	Effects
Skeletal tissue	1. Synthesis of type 1 collagen 2. IGF-1-mediated linear growth (stimulation of chondroblasts)
Adipose tissue	1. Promotes lipolysis by potentiating the effects on hormone-sensitive lipase (see Figure 1.10) 2. Glucose uptake
Skeletal muscle	Protein synthesis and muscle growth

Source: Adapted from Root and Root [133].

Adipocyte and Growth Hormone Physiology

There are four variants of adipocytes: brown, white, pink, and beige. This classification system is based on their location and physiological role. In this section, we review the physiology of white adipocytes and the importance of growth hormone in fat storage and mobilization. A detailed description of the physiology is covered in Chapter 7.

White adipose tissue (WAT) is primarily involved in the storage and mobilization of fatty acids. Two enzyme systems, lipoprotein lipase (LPL) and hormone-sensitive lipase (HSL), play essential roles in these energy-status-dependent tasks (Figure 1.10).

The Growth Plate and Growth Hormone Physiology

The growth plate (physis) is an anatomically distinct region composed of cartilage with three critical physiological zones in longitudinal bone growth (hypertrophic, proliferative, and resting zones) [138]. Growth hormone promotes the proliferation of chondrocytes in the resting zone. IGF-1, produced by local chondrocytes under trophic stimulation from GH *(see* Table 1.4*)*, promotes the expansion of chondrocytes in all three zones of the growth plate (Figure 1.11) [138, 139].

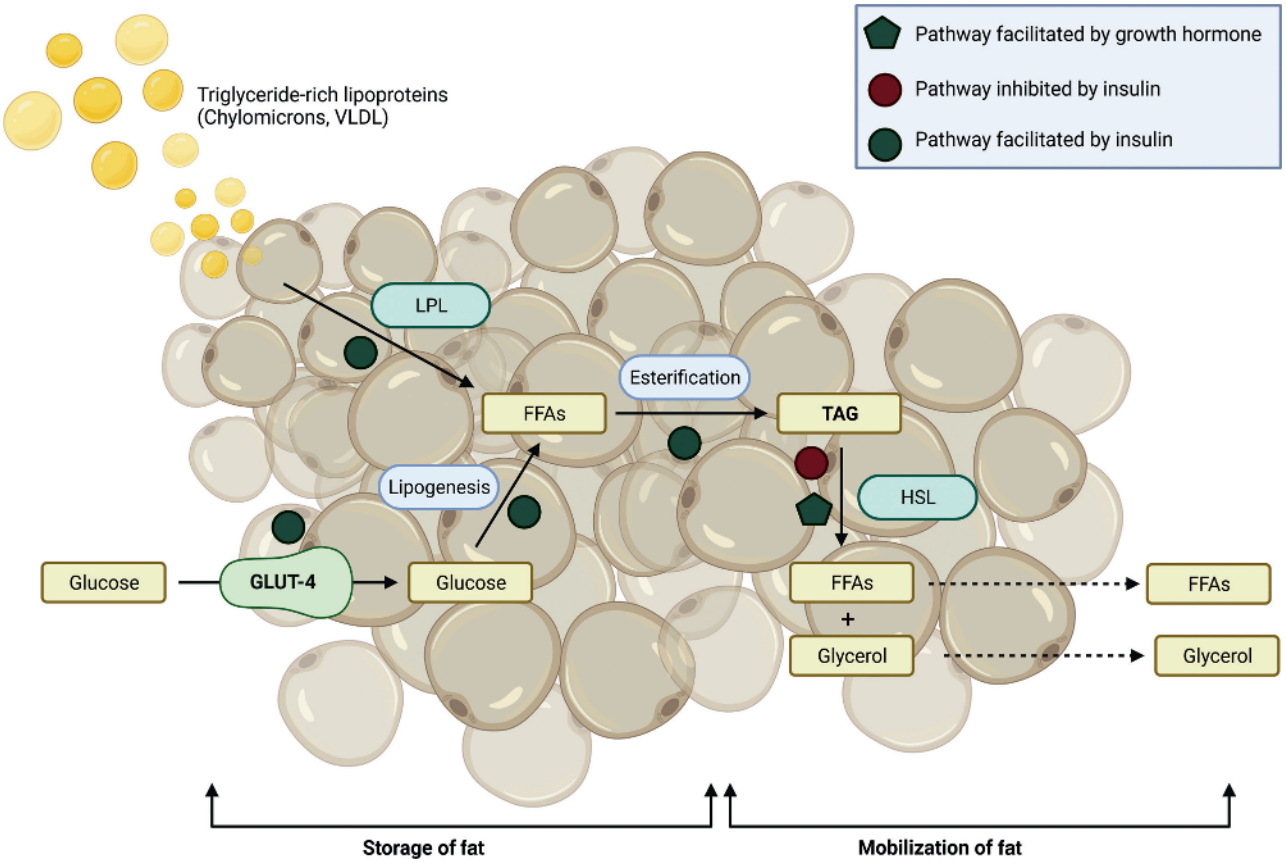

FIGURE 1.10 The regulation of fat storage and mobilization by growth hormone. Fat storage occurs in the prandial period, a process that involves the hydrolysis of triglycerides (TAG) in triglyceride-laden lipoproteins into free fatty acids (FFAs). LPL-induced storage of FFA is facilitated by insulin [134] and inhibited by growth hormone [135]. Also, glucose transporter 4 (GLUT4) transfers glucose from circulation to WAT after a meal. The conversion of glucose to FFA is also facilitated by insulin [136]. Ultimately, FFAs are esterified into TAGs. During periods of energy deficit, hormone-sensitive lipase (HSL) mediates the conversion of TAG repositories to FFA and glycerol. These, in turn, become substrates for gluconeogenesis. Growth hormone facilitates HSL-induced lipolysis of TAG into FFAs and glycerol [137]. On the contrary, insulin inhibits this fat mobilization step. + = shows stimulatory factors, − = shows inhibitory factors. *Source*: Adapted from ref. [134].

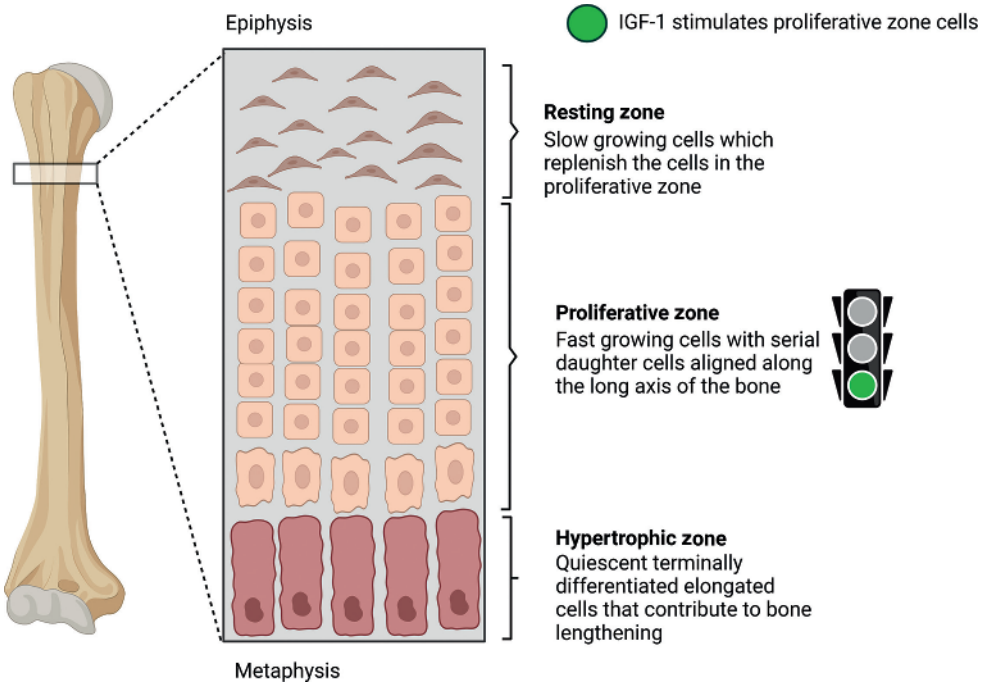

FIGURE 1.11 The configuration of the three physiologic zones of the human growth plate. Growth plates are present at the ends of tubular bones. There is a sequential arrangement of the hypertrophic, proliferative, and resting zones from the epiphyseal to the metaphyseal ends of the bone [138]. *Source*: Adapted from ref. [138].

1.4.1.2 Mechanism of Action

Recombinant human GH (rhGH) with an amino acid sequence similar to endogenous 22-kDa (KDa) growth hormone [140, 141] binds to the GH receptor and promotes the downstream effects of endogenous GH [142].

1.4.1.3 Practice Guide

- Common side effects of GH replacement in adults include *myalgia*, *arthralgia*, *peripheral edema*, and *carpal tunnel syndrome*. The de-escalation of the dose of GH improves and, in some cases, leads to the amelioration of these symptoms [143]. In children on GH therapy, prepubertal breast development, slipped capital femoral epiphysis, and benign intracranial hypertension can occur [144].
- The beneficial effects of growth hormone therapy in patients with AGHD include improving lipid profiles, diastolic blood pressure, insulin sensitivity, and lean body mass to fat body mass ratio [145].

Clinical Trial Evidence

Few large, high-quality, placebo-controlled randomized clinical trials (RCTs) evaluate the safety and efficacy of growth hormone replacement therapy [146].

Key Message

Although GH replacement improves objective cardiovascular risk factors, clinical trials have yet to demonstrate a clinically significant reduction in cardiovascular events [146].

In this randomized controlled trial, 43 hypopituitary subjects with AGHD were randomized to either placebo or rhGH. The primary outcome included various surrogate cardiovascular endpoints, including visceral adiposity, insulin resistance, C-reactive protein (CRP), total cholesterol, and high-density lipoprotein. There was a reduction in high-sensitivity CRP of 38.2 vs. 18.2 (p-value = 0.03), comparing GH with placebo. There was a statistically significant increase in IGF-1 when comparing GH with placebo. Other demonstrable benefits of GH replacement included a decrease in total cholesterol and an increase in high-density lipoprotein [147].

Concepts to Ponder Over

Does GH replacement increase the risk of cancer?

A large cohort of nearly 24,000 patients treated with recombinant human GH during their pediatric years was followed up for an average of 14.8 years per patient. For patients with pediatric growth failure and no known malignancy at baseline, there was no apparent increased risk of most malignancies except for bone and bladder cancers. The incidence rates for bone and bladder cancers were 2.8 (95% confidence intervals 1.1–7.5) and 16.3 (95% confidence intervals 5.2–50.4), respectively. The risk of these new-onset malignancies was not dependent on the cumulative doses of rhGH. However, an increased signal for recurrent primary cancers was observed in patients who received GH therapy in the setting of previously treated malignancies [148].

What are the effects of growth hormone on glycemic control?

GH, a counterregulatory hormone, is expected to cause hyperglycemia in normal physiology [149]. In a long-term observational study, including more than 5000 patients deficient in growth hormone on GH replacement, the incidence of diabetes was 2.6 per 100 patient-years. The risk was significantly higher among older subjects with a high body mass index, triglyceride levels, waist circumference, or blood pressure [150]. Refer to Table 1.7 for a summary of the effects of growth hormone on glucose metabolism.

TABLE 1.7 Glycemic effects of growth hormone.

Mechanism	Glycemic effects
Inhibition of GLUT4 expression by adipose tissue	Reduced peripheral uptake of glucose by adipose tissue
Growth hormone-mediated upregulation of hormone-sensitive lipase activity in adipose tissue.[a]	Liberation of free fatty acids leads to insulin resistance (impairs post-receptor insulin signaling)

(*continued*)

TABLE 1.7 (Continued)

Mechanism	Glycemic effects
Promotion of gluconeogenesis in the liver and kidneys	Hyperglycemia in the fasting state
Growth hormone-mediated upregulation of lipoprotein lipase in skeletal muscle promotes the accumulation of FFAs in skeletal muscle.‡	Insulin resistance
GH leads to the formation of IGF-1. IGF-1 can bind peripheral insulin receptors and simulate the effects of endogenous insulin-to-insulin receptor interaction	Hypoglycemia

[a] Also see Figure 1.11 for the effects of GH on fat storage and mobilization.
Esterification of FFAs into triacylglycerides leads to the formation of intermediate products such as diacylglycerol (impairs post-receptor insulin signaling).
Source: Adapted from Kim and Park [149].

1.5 CENTRAL DIABETES INSIPIDUS

1.5.1 Desmopressin

1.5.1.1 Physiology

Antidiuretic Hormone and Regulation of Serum Osmolarity

AVP is synthesized in the nuclei of paired *hypothalamohypophyseal* neurons originating from supraoptic and paraventricular nuclei of the hypothalamus and terminating in the posterior pituitary gland [151]. Neurosecretory granules containing AVP are transported along axons that terminate in fenestrated capillaries in the neurohypophysis (posterior pituitary) [152]. The osmolarity sensing center (osmostat), located in the hypothalamus, regulates the release of AVP through relay neurons that project into the cell bodies of the supraoptic and paraventricular nuclei [153].

There is a linear relationship between plasma osmolarity and plasma AVP levels such that significant increases in plasma osmolarity cause a corresponding increase in plasma AVP [154]. In the context of dehydration, AVP, also known as antidiuretic hormone (ADH), increases water conservation at the level of the collecting duct, a process that increases urine osmolarity and leads to the restoration of normal plasma osmolarity [155] (see Figure 1.12).

1.5.1.2 Mechanism of Action

Desmopressin (1-deamino-8-D-arginine vasopressin, DDAVP) is an analog of AVP [158] with a prolonged plasma half-life of approximately 55 minutes (compared to endogenous AVP which has a half-life of 5–10 minutes) [159].

It is worth noting that substituting D-arginine for L-arginine at position 8 of the AVP amino acid chain eliminates the vasopressor effects of this synthetic analog of AVP [160]. Desmopressin promotes water conservation by binding to V2 receptors in the renal collecting ducts [158]. (See Figure 1.12). During periods of significant dehydration, the central thirst mechanism allows free water consumption, which results in the restoration of intravascular volume and osmolarity [155, 163].

Clinical Pearl

Diabetes insipidus, "tasteless urine," was distinguished from diabetes mellitus in 1674 by Thomas Willis, an English physician. Edward Schafer, a renowned physiologist, discovered the effects of a posterior pituitary extract on urine output in 1901. Paradoxically, the posterior pituitary extract increased urine output according to Schafer's experiments, although this challenged observations of the antidiuretic effects of the posterior pituitary extract on urine output in patients with diabetes insipidus.

Ernest Verney and Ernest H. Starling, in the 1920s, were finally able to demonstrate that pituitrin (posterior pituitary extract) had an antidiuretic effect (and not a diuretic effect as previously reported by Schafer) on the kidneys independent of its effects on blood pressure.

1.5.1.3 Practice Guide

- Desmopressin can be administered safely through various routes (including intravenous, subcutaneous, oral, intranasal, and intramuscular). A simple rule of thumb is to use a conversion factor of 1:10 when converting between administration routes of administration [158].

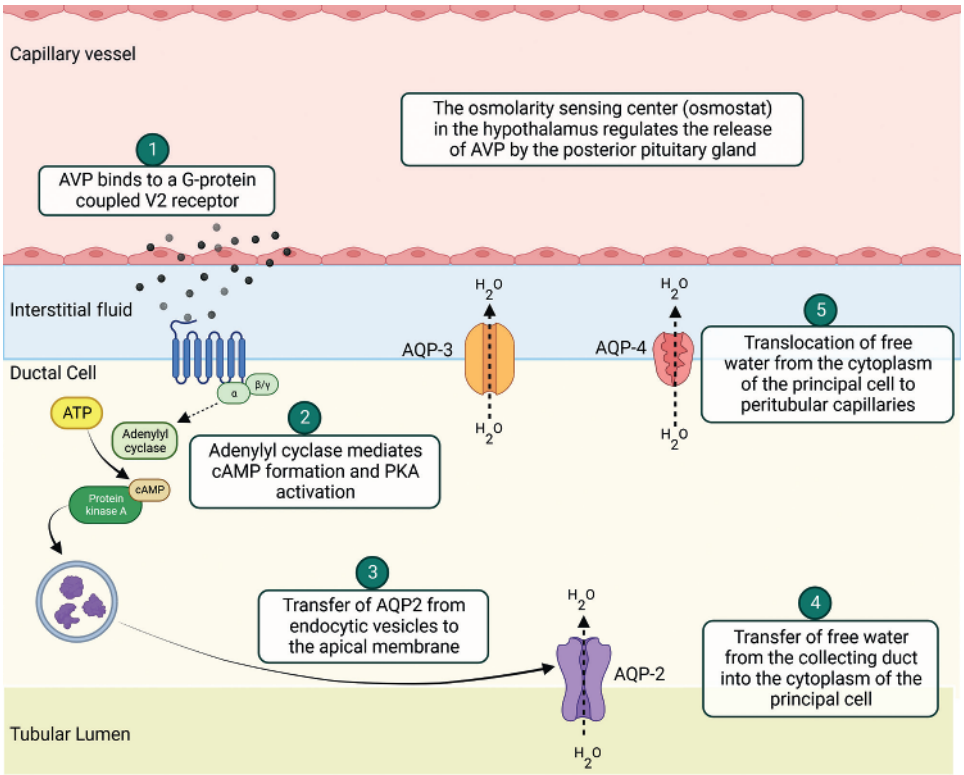

FIGURE 1.12 Schematic representation of AVP-mediated water conservation in the principal cell of the renal collecting duct. AVP binds to G-protein coupled V2 receptors on the principal cell's basolateral membrane (BM) [156]. This initiates a cascade of intracellular processes that involve adenylyl cyclase-mediated cyclic adenosine monophosphate (cAMP) production and subsequent protein kinase A (PKA) activation. Afterward, PKA will promote the release of aquaporins from endocytic vesicles. Aquaporin-2 (AQP2) released from vesicles inserts into the collecting duct apical membrane (AM). This promotes the translocation of free water from the collecting duct into the cytoplasm of the principal cell [157]. Aquaporin-3 (AQP3) and aquaporin-4 (AQP4) water channels, which are integral components (i.e. they are not released from endocytic vesicles) of the BM, facilitate the final transfer of water from the cytoplasm to the peritubular capillaries [155].

Desmopressin Conversion Via the Route of Administration

Intravenous/Subcutaneous: Intranasal: Oral = 1 mcg: 10 mcg: 100 mcg

- Coadministration of NSAIDs and desmopressin can lead to life-threatening hyponatremia [164]. In normal physiology, prostaglandin E2 (PgE_2) impairs the liberation of AQP2 from their endocytic vesicles after AVP to V2 receptor interaction. Cyclooxygenase inhibitors impair the synthesis of PgE_2, thus increasing the availability of AQP2 (water intoxication) [165].
- Consider an intermittent "DDAVP holiday" to reduce the likely risk of hyponatremia. Patients can be advised to delay the administration of a scheduled dose of DDAVP once a week until 2 or 3 successive episodes of breakthrough polyuria [166].
- Gastrointestinal peptidases denature oral desmopressin; as such, patients should be advised of the importance of taking this medication on an empty stomach or at least 90 minutes after a meal [167].
- *Pituitary adenomas* rarely present with central diabetes insipidus (CDI). Therefore, CDI in the setting of a sellar mass is more suggestive of an alternative differential diagnosis, such as craniopharyngiomas or a granulomatous process [166].

Clinical Trial Evidence

In this retrospective study, the incidence of hyponatremia in patients with CDI was evaluated between the intranasal and oral desmopressin routes of administration. Thirty-two subjects who had previously been well-controlled with stable doses of intranasal DDAVP were switched to an oral route of administration for a maximum duration of 18 months [168].

Key Message

Based on the results of this study, the frequency of significant hyponatremia (<130 mmol/L) was 4.2% when subjects were on intranasal desmopressin, compared to 1.3% when on oral desmopressin. This was statistically significant. Normal water and sodium balance are better achieved with oral DDAVP compared to intranasally administered DDAVP [168].

Pathophysiology Pearl

Conditions masquerading as diabetes insipidus

- Gestational diabetes insipidus occurs in pregnant women due to the degradation of endogenous AVP by a placenta-derived enzyme called vasopressinase. The clinical and biochemical characteristics are similar to those of CDI [169].
- Primary polydipsia (chronic) results in decreased renal concentrating ability due to excessive fluid ingestion. In effect, an abundance of free water promotes the downregulation of aquaporins ("wash-out effect") [170].

1.5.2 Water

1.5.2.1 Physiology

Osmotic Center and the Regulation of Sodium Balance

The previously described osmotic center (also known as the osmostat, see Section 1.5.1) is composed of two discrete structures known as the *organum vasculosum of the lamina terminalis* (OVLT) and the *subfornical organ* (SFO). These structures have projecting from them neurons that supply parts of the forebrain involved in the executive response to thirst, the hypothalamus (SON and PVN), and the sympathetic nervous system [171]. OVLT and SFO are activated by elevated serum osmolarity and angiotensin II levels. The response to the activation of OVLT and SFO includes increased thirst sensation, AVP release, and a sympathoadrenergic increase in blood pressure [172, 173].

1.5.2.2 Mechanism of Action

The role of free water in maintaining hydration status has been discussed. See Figure 1.12.

1.5.2.3 Practice Guide

- Access to free water is essential in the management of CDI. Indeed, in mild diabetes insipidus, optimal water ingestion (as monotherapy) could be enough to maintain sodium and water balance [174].
- Patients with adipsic CDI have all the features of CDI but are unable to sense thirst. It is a complex disease to manage due to marked variability in serum sodium and apparent challenges in maintaining oral hydration [175]

Clinical Trial Evidence

In a long-term retrospective study of 137 CDI-positive subjects at maintenance doses of DDAVP, the risk of sodium imbalance was compared between those with adipsia (impaired thirst sensation) and those with an intact thirst sensation. The risk of hypernatremia between the adipsic and non-adipic groups was 20% and 1.4%, respectively (*P*-value = 0.02). The risk of hyponatremia between the adipsic and non-adipic groups was 50% and 11.1%, respectively (*p*-value = 0.02%) [176].

Key Message

Adipsia increases the risk of a significant sodium imbalance in patients with CDI. Since these patients do not have the ability to respond to increased serum osmolarity, they are prone to profound dehydration in the setting of polyuria [176].

1.5.3 Natriuretic Agents

1.5.3.1 Physiology

Physiology of Diuresis in the Distal Convoluted Tubule (DCT)

The sodium-chloride symporter (secondary active transport system) and the electrochemical gradient created by the sodium-potassium adenosine triphosphatase (Na-K ATPase) (primary active transport system) are both essential for sodium reabsorption in the DCT. However, the DCT is impermeable to water, making urine in this segment hypotonic [177].

1.5.3.2 Mechanism of Action

Thiazide diuretics exert their natriuretic effects by inhibiting thiazide-sensitive Na^+-Cl^- symporters in the distal convoluted tubules of the nephron. The net effect will be the wasting of both sodium and water at the distal nephron (see Figure 1.13). Mechanistically this seems counterintuitive since patients with CDI are polyuric at baseline [178, 180]. See Figure 1.14 for a proposed mechanistic pathway that explains the role of natriuretic agents in the management of CDI.

1.5.3.3 Practice Guide

- Thiazide diuretics, either as monotherapy or dual therapy with amiloride (potassium-sparing diuretic) or indomethacin, are reasonable therapeutic approaches in diabetes insipidus [181].
- A low-salt diet potentiates the paradoxical "antidiuretic effect" of thiazide diuretics [167].

Clinical Pearl

Gitelman syndrome is an inherited form of hypokalemic alkalosis that occurs as a result of a mutation in the gene encoding the sodium chloride symporter. This syndrome simulates exposure to a thiazide diuretic agent [182].

Clinical Trial Evidence

There are no published RCTs on the use of thiazide diuretics in CDI. Some pediatric case reports and retrospective studies exploring the use of thiazide diuretics in CDI gave promising results in terms of treatment efficacy (achievement of eunatremia and control of polyuria) [178, 183, 184]. Most importantly, the use of diuretics is not recommended in the management of CDI. However, diuretic therapy is indicated in treating nephrogenic diabetes insipidus.

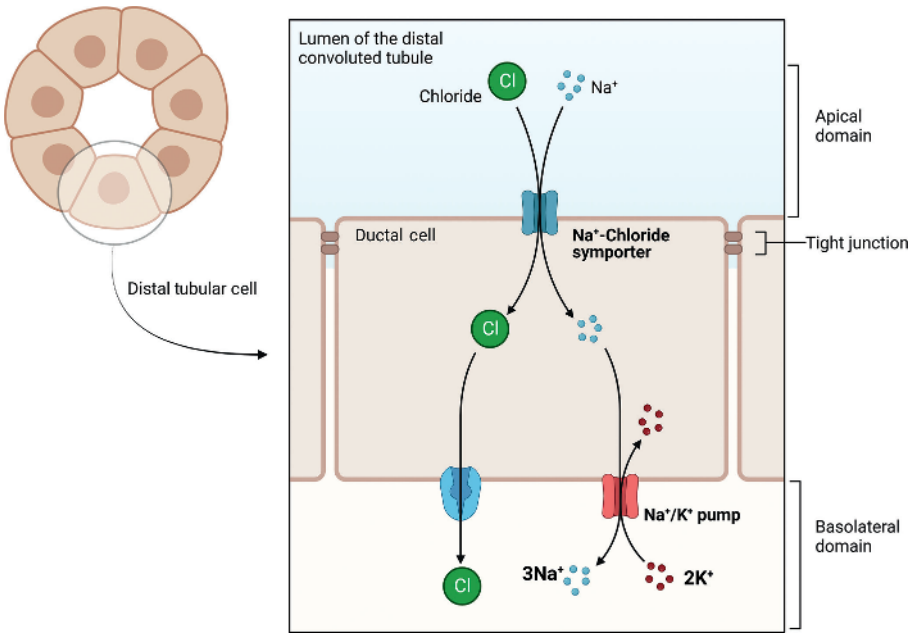

FIGURE 1.13 Mechanism of action of thiazide diuretics in the DCT. The sodium-potassium pump (Na-K ATPase) present on the basolateral membrane of the DCT creates an electrochemical gradient that facilitates the transport of sodium and chloride ions (Cl^-) by the sodium-chloride symporter (luminal or apical membrane) [161]. Chloride ions move from the lumen into the ductal cell against an electrochemical gradient. Cl^- is then ferried from the ductal cell into the peritubular capillaries by chloride channels in the basolateral membrane. Potassium ions (K^+) are also transported from the ductal cell to peritubular capillaries via dedicated K^+ channels. Aldosterone, produced as a consequence of activation of the renin-angiotensin-aldosterone system (RAAS), increases the transcription and translation of the sodium-chloride symporter [162]. *Source*: Adapted from ref. [161].

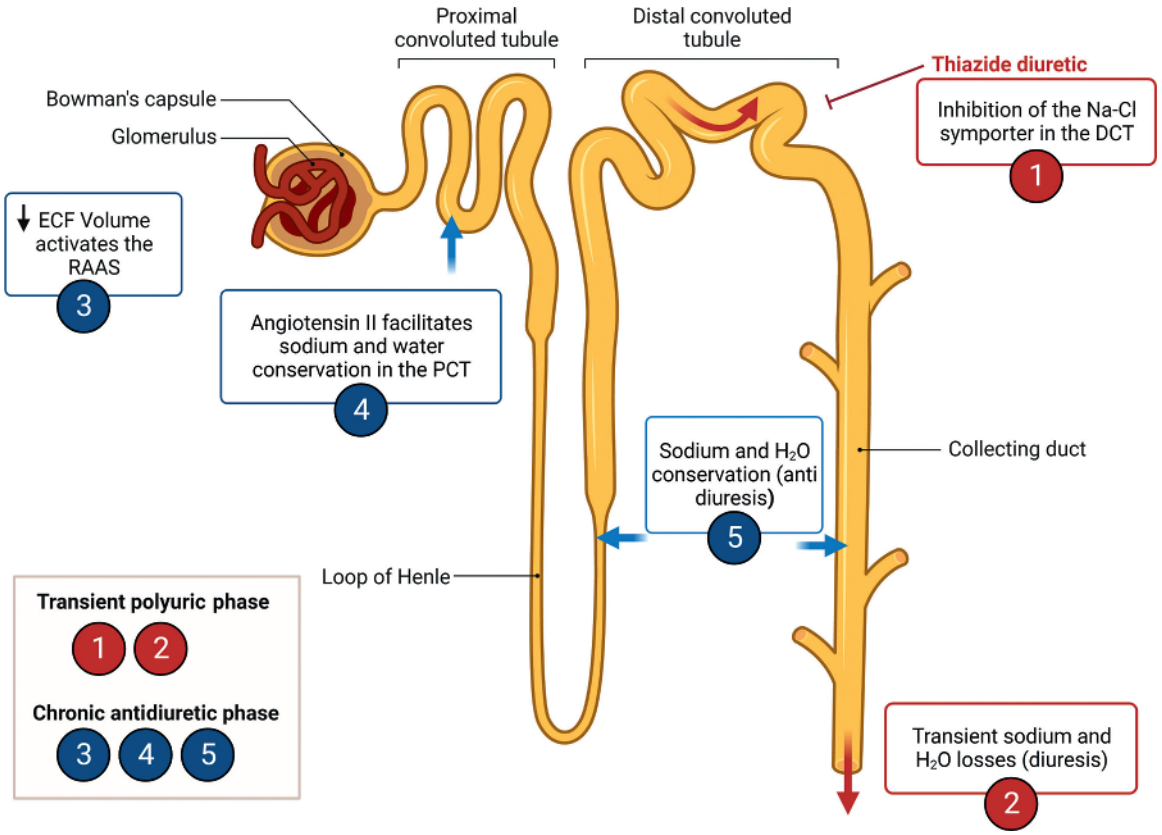

FIGURE 1.14 Schematic representation of the role of thiazide diuretics in central diabetes insipidus. Thiazide diuretics promote sodium wasting in the distal renal tubule. The high sodium load in the renal tubular fluid also increases water loss (osmotic effect). A reduction in extracellular fluid volume causes a decrease in the estimated glomerular filtration rate, ultimately activating the RAAS. Increased levels of Angiotensin II promote a compensatory increase in sodium and water conservation at the proximal tubule (see Section 3.1.2). Consequently, less sodium and water are delivered to collecting tubules, leading to less renal water loss [178, 179].

1.5.4 Clofibrate, Chlorpropamide, and Carbamazepine

1.5.4.1 Physiology

The physiology of central ADH regulation and its peripheral effects is reviewed in Section 1.5.1.

1.5.4.2 Mechanism of Action

Clofibrate: Clofibrate, an antilipidemic agent, has antidiuretic properties. It exerts its antidiuretic effects by increasing ADH release from the neurohypophysis [185]. This drug was withdrawn from the market in 2002 and is mentioned here due to its historical significance [167].

Chlorpropamide: Chlorpropamide, a first-generation sulfonylurea, increases release of ADH and also promotes the antidiuretic effects of ADH at the renal collecting duct [185]. Alternative mechanisms of action include an increase in the circulating half-life of AVP and a lower osmotic threshold for the release of endogenous AVP [186].

Carbamazepine: Carbamazepine, an antiepileptic agent, potentiates ADH effects at the renal collecting duct [187].

1.5.4.3 Practice Guide

None of these agents are recommended as an alternative to DDAVP in the management of CDI.

Clinical Trial Evidence

There are no RCTs comparing any of these agents with guideline-recommended DDAVP. In a recent case report of a patient with CDI, oxcarbazepine (structurally homologous to carbamazepine) was proposed as an alternative to DDAVP [186].

Concepts to Ponder Over

What is the triphasic response of diabetes insipidus?

The triphasic response of central diabetes insipidus represents a unique state of sodium imbalance characterized by rapid changes in serum sodium and, consequently, intravascular volume among patients with pituitary stalk injury [188]. Disruption of the stalk occurs commonly in the setting of neurosurgery [189] but has also been described in traumatic brain injury [190].

An initial phase of overt CDI occurs due to axonal shock, and it presents with an impaired neuronal transfer of AVP from the hypothalamus to the posterior pituitary gland. The second phase is characterized by axonal death and the release of preformed AVP from their neuronal stores. This is similar to the syndrome of inappropriate ADH (SIADH) secretion. After an 80–90% depletion of AVP stores, the final phase of permanent CDI occurs (see Figure 1.15) [191].

What are the causes of adipsic central diabetes insipidus?

Adipsic CDI manifests itself as an inability to perceive thirst in the setting of AVP deficiency that results in hypotonic polyuria and hypernatremia [192]. It occurs due to the disruption of vascular supply to the osmostat center (OVLT or SFO), infiltrative tumors(craniopharyngioma), autoimmune disease, or congenital malformations of the corpus callosum [193].

Phase I: neuronal shock, which leads to transient diabetes insipidus [191]. This phase lasts for about 72 hours. The timely use of DDAVP or hypotonic fluids is reasonable [189].

Phase II: Neuronal death (distal to the site of stalk transection) and release of preformed AVP (from the neurohypophysis) leads to an SIADH-like picture [191]. This phase may last up to 2 weeks. Careful fluid restriction is key [189].

Phase III: The depletion of neuronal stores of AVP in the paraventricular nucleus (PVN) and supraoptic nucleus (SON) leads to a recurrence of diabetes insipidus. This tends to be permanent, especially in the setting of complete pituitary stalk transection [191].

Source: Adapted from Redrawn and modified from Hoorn and Zietse [189].

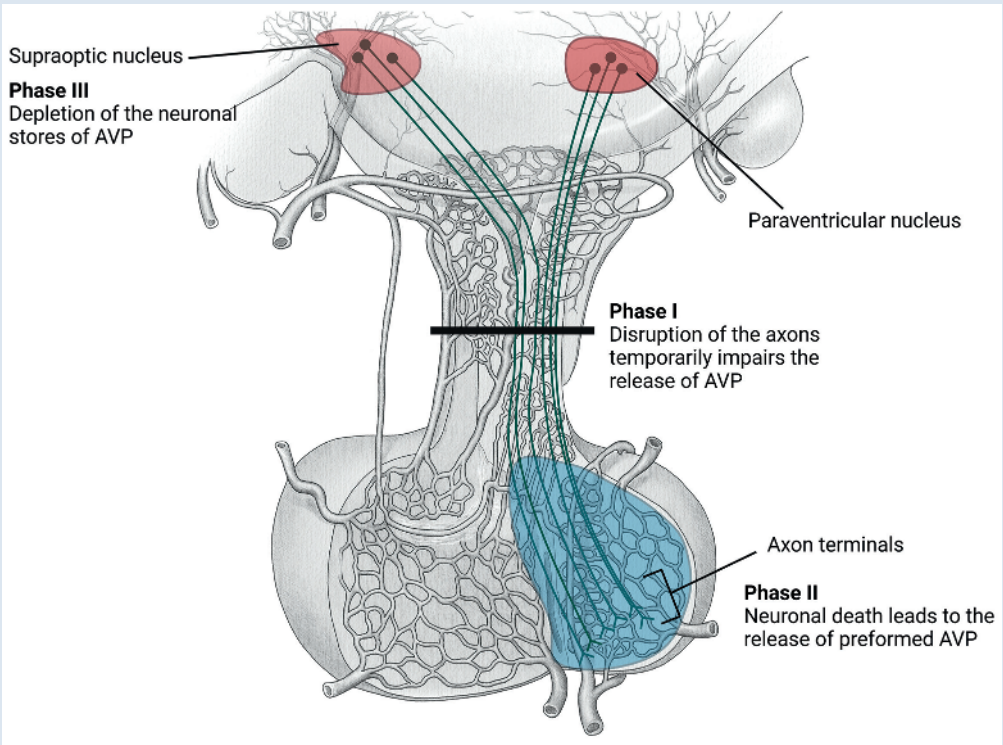

FIGURE 1.15 The triphasic response of central diabetes insipidus. *Source*: Adapter from [181].

1.6 SYNDROME OF INAPPROPRIATE ADH SECRETION

1.6.1 Vaptans

1.6.1.1 Physiology

The *hypothalamic–pituitary-renal* axis with regards to the role of AVP in the conservation of renal water was reviewed in Section 1.5.1. AVP has various effects in different tissues, depending on the AVP receptor subtype expressed in the target tissue (Table 1.8) [194, 195].

Clinical Pearl

The syndrome of inappropriate antidiuretic hormone (SIADH) secretion is the leading cause of hyponatremia in outpatient and inpatient settings. It is particularly relevant due to morbidity and mortality associated with untreated or poorly managed hyponatremia [194]. Although eponyms are increasingly being replaced by labels that clarify the pathophysiological basis of diseases, the contributions of pioneering physicians should be appreciated. SIADH was previously called the Schwartz–Bartter syndrome. Bartter syndrome, a rare condition of electrolyte imbalance, is also named after Frederic Bartter [196].

TABLE 1.8 Subtypes of AVP receptors and their physiologic effects.

AVP receptor	Tissue	Effect(s)
V1a	Vascular smooth muscle Myocardium	Vasoconstriction and platelet function Cardiac inotropic function
V1b	Pituitary	Pituitary ACTH secretion (see Figure 1.1)
V2	Renal collecting duct Vascular endothelium	Water conservation (see Figure 1.13) Release of vWF and factor VIII

vWF, von Willebrand factor.
Source: Adapted from Verbalis et al. [194].

1.6.1.2 Mechanism of Action

Vaptans are V2 receptor antagonists that impair the binding of endogenous AVP to its cognate V2 receptors. It is essential to appreciate that vaptans cause an *"aquaresis"* (i.e. loss of free water with the conservation of electrolytes) as opposed to the effects of diuretics, which promote both fluid and electrolyte losses. In SIADH, there is an excessive amount of free water (relative to sodium) conservation due to the effects of ADH in the renal collecting tubule. This makes vaptans a more reasonable therapeutic option in SIADH, than monotherapy with conventional diuretic agents [194].

1.6.1.3 Practice Guide

Patients taking vaptans are at risk of dehydration due to polyuria and polydipsia [196].

Although this class of medications has an acceptable safety profile, they should be started in the inpatient setting to avoid significant increases in serum sodium and the risk of osmotic demyelination syndrome [197].

Clinical Trial Evidence

Clinical trials evaluating the safety and efficacy of vaptans in the treatment of euvolemic hyponatremia (SIADH) include SALT-1, SALT-2, and SALTWATER.

In the *Study of Ascending Levels of Tolvaptan in Hyponatremia* (SALT-1 and SALT-2), serum sodium increased significantly in the tolvaptan group compared to the placebo group (p-value of < 0.001) across a heterogeneous population of hyponatremic patients (euvolemic or hypervolemic hyponatremia) [198]. The *Safety and sodium assessment of Long-term Tolvaptan With hyponatremia: A year-long, open-label Trial to gain Experience under Real-world conditions* (SALTWATER), an extension study of SALT-1 and SALT-2 demonstrated the long-term safety and efficacy of tolvaptan in hyponatremia [196].

1.6.2 Fluid Restriction

1.6.2.1 Physiology

The role of free water in the determination of serum osmolarity was discussed earlier (see Figure 1.13).

1.6.2.2 Mechanism of Action

The mechanistic pathways for the sensation of thirst (see Section 1.5.2) and AVP-mediated regulation of serum osmolarity (see Section 1.5.1) have been discussed.

1.6.2.3 Practice Guide

- Fluid restriction performs abysmally in routine clinical practice, most likely due to the poor selection of patients for this therapeutic option among patients with SIADH [199].

Poor Predictors of Response to Fluid Restriction

Urine osmolarity >500 mOsm/kg/H_2O
Urine output of less than 1500 mL per 24 hours
An estimated "Fürst equation" ratio of >1

Fürst equation

([Urine sodium] + [Urine Potassium]) / [Serum sodium]
[] = concentration.

There are various adjunctive therapies utilized in the management of diabetes insipidus. Their mechanisms of action are shown in Table 1.9.

TABLE 1.9 Mechanism of action of adjunctive therapies in SIADH.

Therapy	Mechanism of action
Loop diuretics[a]	Diuresis (free water and electrolyte losses). Sodium chloride supplementation is mandatory [200, 201]
Sodium chloride[a]	Sodium chloride is best administered with fluid restriction or a diuretic agent ("aquaretic effect") [201]
Lithium	Anti-natriuresis (renal sodium conservation) [202] and limitation of AQP-2 expression in the renal collecting ducts (nephrogenic diabetes insipidus-like presentation) [203].
Demeclocycline	Nephrogenic diabetes insipidus [204]
Urea	Osmotic diuresis and compensatory passive sodium conservation at the level of the ascending limb of the loop of Henle [205].

[a] In the EFFUSE-FLUID clinical trial, a combination of loop diuretics and sodium chloride with fluid restriction did not fare any better than fluid restriction alone.
Source: Adapted from refs. [200–205].

Clinical Trial Evidence

In this retrospective study of 29 patients with SIADH, the efficacy of fluid restriction (1.5–2 L), with or without adjunctive urea supplementation, in the management of SIADH was explored. Changes in serum sodium and urine osmolarity were compared at one year with baseline. The mean serum sodium concentration and urine osmolarity were 129 mEq/L and 274 mOsm/kgH_2O, respectively, at baseline. At the end of 12 months of fluid restriction, serum sodium concentration and urine osmolarity improved to 138.5 mEq/L and 505 mOsm/kgH_2O, respectively. This occurred in 30% of subjects. For patients who had a suboptimal response to fluid restriction alone, most attained eunatremia after the institution of urea supplementation (15–30 g daily) [206].

Key Message

Moderate fluid restriction (1.5–2 L) per day led to eunatremia in 30% of patients with chronic SIADH, according to the results of this retrospective study.

There are other therapies reported for the management of SIADH. These include loop diuretics, urea, hypertonic saline, lithium, demeclocycline, and hemodialysis [207].

Concepts to Ponder On

What are the diagnostic criteria for SIADH?

The diagnosis of SIADH is based on the criteria proposed by Bartter and Schwartz in 1967 [208].

The classic Bartter and Schwartz criteria

1. Plasma osmolarity <275 mOsm/kg of H_2O
2. Inappropriately concentrated urine >100 mOsm/kg
3. Euvolemia
4. Urine sodium >20 mEq/L
5. Normal thyroid function, normal adrenal function, and no recent exposure to diuretic agents (effects on urine sodium).

Patients who meet ALL of the above criteria are more likely to have SIADH [194].

What conditions can mask the presence of partial central diabetes insipidus?

The coexistence of a paraneoplastic condition manifesting as SIADH may mask the presence of central diabetes insipidus [209].

Partial central diabetes insipidus can also be masked in the presence of glucocorticoid deficiency. It should be noted that glucocorticoids inhibit V2R-mediated water conservation in the collecting duct by impairing the translocation of V2R to the apical membrane of the collecting duct cell. Glucocorticoid deficiency, in part, promotes water reabsorption, thus masking the presence of *partial central diabetes insipidus*. Primary glucocorticoid deficiency leads to increased CRH production (AVP secretagogue) due to loss of negative feedback inhibition of hypothalamic centers by cortisol [209].

PRACTICE-BASED QUESTIONS

1. A 50-year-old woman with a six-month history of easy bruisability, hyperglycemia, and resistant hypertension is admitted to the medicine service. The endocrinologist on call recommends initiating pasireotide. Which of the following receptors is the primary target of Pasireotide in Cushing's disease?

   a. Somatostatin receptor subtype 2 (SSR2)
   b. Somatostatin receptor subtype 5 (SSR5)
   c. Melanocortin-2 receptor (MCR-2)
   d. Dopamine D2 receptor (D2R)

   Correct answer: b) Somatostatin receptor subtype 5 (SSR5). Pasireotide is a "near pan-somatostatin" receptor analog that binds to four of the five somatostatin receptor isoforms (SSR1, SSR2, SSR3, and SSR5). Due to its affinity for SSR5 receptors, pasireotide is an ideal therapeutic option in Cushing's disease. Corticotroph tumors in the anterior pituitary gland express more SSR5 receptors than the other somatostatin receptor subtypes making pasireotide an ideal agent for this tumor.

2. Which of the following transcription factors is inhibited by Retinoic Acid (RA)?

   a. Activator protein 1 (AP-1)
   b. Nuclear receptor 77 (Nur77)
   c. Chicken ovoalbumin upstream promoter transcription factor 1 (COUP-TF1)
   d. Both a and b

   Correct answer: d) Both a and b. In normal physiology, there are retinoid-sensitive intermediary mediators (transcription factors) of POMC promoter gene activation, namely, AP-1 and Nur77. Retinoic acid (RA), by binding to its nuclear retinoic acid receptors inhibits AP-1, and Nur77 expression, thus preventing POMC promoter gene activation.

3. What percentage of corticotroph adenomas express D2 receptors?

   a. 10%
   b. 40%
   c. 60%
   d. 80%

   Correct answer: d) 80%. Approximately 80% of corticotroph adenomas express D2 receptors, but they have a relatively low D2 receptor density making, dopaminergic agonists (DAs) a less favorable therapeutic option in Cushings disease, compared to other medical therapies.

4. Which of the following hormones is inhibited by Pasireotide through yet-to-be-characterized intestinal somatostatin receptors?

   a. Insulin
   b. Glucagon-like peptide 1
   c. Glucose-dependent insulinotropic peptide (GIP)
   d. Both b and c

   Correct answer: d) Both b and c. Pasireotide through yet-to-be-characterized intestinal somatostatin receptors inhibits the release of glucagon-like peptide 1(GLP-1) and glucose-dependent insulinotropic peptide (GIP) from K and L cells, respectively. Pasireotide causes hyperglycemia, gastrointestinal discomfort, and cholelithiasis.

5. A 50-year-old man with newly diagnosed Cushing's syndrome is started on medical therapy. What is the typical dose range for Pasireotide immediate-release as a subcutaneous injection?

   a. 0.1 to 0.5 mg
   b. 0.3 to 0.9 mg
   c. 1 to 3 mg
   d. 5–10 mg

   Correct answer: b) 0.3–0.9 mg. The typical dose range for pasireotide immediate-release is 0.3–0.9 mg (300–900 mcg) as a subcutaneous injection (thigh, upper arm, or abdomen) twice

a day. A long-acting release (LAR) formulation is administered once a month (10–30 mg) intramuscularly as a depot injection.

6. Which of the following steroidogenesis inhibitors has been recently approved for persistent and recurrent Cushing's disease?

   a. Metyrapone
   b. Mitotane
   c. Ketoconazole
   d. Osilodrostat

   Correct Answer: d) Osilodrostat. Osilodrostat inhibits 11-beta hydroxylase activity in the adrenal cortex, and it has been recently approved for persistent and recurrent Cushing's disease.

7. Which of the following steroidogenesis inhibitors used in the treatment of Cushings syndrome has been suggested to have both adrenolytic and adrenostatic properties?

   a. Metyrapone
   b. Mitotane
   c. Ketoconazole
   d. Osilodrostat

   Correct answer: b) Mitotane. Mitotane is suggested to have both adrenolytic and adrenostatic properties. Mitotane is a chemotherapeutic agent with a diphenylmethane moiety that causes mitochondrial dysfunction, lysis, and necrosis.

8. A 28-year-old woman presents with oligomenorrhea and is diagnosed with Cushing's syndrome. Her urine pregnancy test returned negative. Which of the following steroidogenesis inhibitors is the recommended first-line medical therapy for nonpregnant adults with confirmed endogenous hypercortisolemia?

   a. Metyrapone
   b. Mitotane
   c. Ketoconazole
   d. Osilodrostat

   Correct answer: c) Ketoconazole. Ketoconazole is the recommended first-line medical therapy for nonpregnant adults with confirmed endogenous hypercortisolemia.

9. You are considering various treatment options for Cushing's syndrome in a newly diagnosed patient. You are concerned about the risk of medical therapy on a fetus. Which of the following agents has both anti-glucocorticoid and anti-progesterone effects?

   a. Metyrapone
   b. Mitotane
   c. Ketoconazole
   d. Mifepristone

   Correct answer: d) Mifepristone. Mifepristone has both anti-glucocorticoid and anti-progesterone effects. It actually exerts its effects by binding to the ligand-binding domain of the cytosolic glucocorticoid receptor without directly promoting its downstream effects.

10. An endocrinologist on call evaluates a newly diagnosed patient with a small 4 mm pituitary adenoma. He makes a diagnosis of Cushing's disease. What is the recommended first-line treatment for Cushing's disease?

    a. Ketoconazole
    b. Metyrapone
    c. Mitotane
    d. Transsphenoidal surgery

    Correct answer: d) Transsphenoidal surgery. Transsphenoidal surgery is the recommended first-line treatment for Cushing's disease. However, a high recurrence rate of about 20% makes medical therapies an essential adjunctive approach.

11. A 54-year-old man with poor libido, excessive diaphoresis, and wide spaced teeth is noted to have elevated growth hormone levels after an oral glucose tolerance test. His IGF-1 level remains elevated on two occasions. You are considering the use of somatostatin analogs in his treatment. What is the role of somatostatin in growth hormone regulation?

    a. Promotes the release of growth hormone from somatotrophs
    b. Blocks the release of growth hormone from somatotrophs
    c. Enhances the sensitivity of the liver to growth hormone
    d. Enhances the synthesis of insulin-like growth factor 1 in the liver

    Correct answer: b. Blocks the release of growth hormone from somatotrophs. Somatostatin inhibits the release of GH by somatotrophs by acting on somatostatin receptors (primarily the SSR2 receptor subtype).

12. Which of the following organs does not produce insulin-like growth factor 1 (IGF-1)?

    a. Liver
    b. Skeletal muscle
    c. Adipose tissue
    d. Brain

    Correct answer: d. Brain. IGF-1 is produced in various tissues, including the liver, skeletal muscle, and adipose tissue, but not by the brain.

13. A 63-year-old woman is diagnosed with acromegaly. What is the mechanism of action of pegvisomant?

    a. It activates the growth hormone receptor and induces IGF-1 production
    b. It inhibits the growth hormone receptor and blocks IGF-1 production
    c. It activates the somatostatin receptor and inhibits growth hormone production
    d. It inhibits the somatostatin receptor and enhances growth hormone production

    Correct answer: b. It inhibits the growth hormone receptor and blocks IGF-1 production. Pegvisomant occupies the GH receptor pocket, depriving the receptor of direct activation by GH. This subsequently induces defective dimerization of the receptor, thus preventing key signal transduction pathways (JAK–STAT signaling) and the eventual production of IGF-1.

14. A 38-year-old obese patient is diagnosed with a pituitary adenoma. You are considering the use of pasireotide. What is the hallmark side effect of pasireotide?

    a. Hypoglycemia
    b. Hyperglycemia
    c. Diarrhea
    d. Cholelithiasis

    Correct answer: b. Hyperglycemia. Pasireotide is associated with a disproportionate risk of hyperglycemia, particularly in patients with diabetes or prediabetes, and should be screened for before and during treatment.

15. You are considering the use of dopaminergic modulators in the management of acromegaly. What is the differential effect of dopamine on growth hormone secretion in normal physiology?

    a. It increases growth hormone secretion at the level of the anterior pituitary gland
    b. It increases growth hormone secretion at the level of the hypothalamus
    c. Growth hormone decreases growth hormone secretion at the level of the anterior pituitary gland
    d. Growth hormone decreases growth hormone secretion at the level of the hypothalamus

    Correct answer: c. It decreases growth hormone secretion at the level of the anterior pituitary gland. The effects of dopamine on GH secretion are more profound at the level of the anterior pituitary gland than at the level of the hypothalamus. The net effect is a reduction in GH secretion.

16. A 56-year-old woman presents with polyuria. You have scheduled a formal water deprivation test. What is the relationship between plasma osmolarity and plasma AVP levels?

    a. Plasma AVP levels are independent of plasma osmolarity
    b. Significant decreases in plasma osmolarity cause a corresponding increase in plasma AVP levels
    c. Significant increases in plasma osmolarity cause a corresponding decrease in plasma AVP levels
    d. Plasma AVP levels are not affected by changes in plasma osmolarity

    Correct answer: b. Significant increases in plasma osmolarity cause a corresponding increase in plasma AVP levels. This linear relationship between plasma osmolarity and plasma AVP levels ensures the proper regulation of water balance in the body, allowing for the conservation of water when necessary.

17. A patient with central diabetes insipidus reports a significant improvement in polyuria after starting desmopressin therapy. Which receptors are involved in the water-conserving properties of desmopressin?

    a. V1 receptors
    b. V2 receptors
    c. Beta-1 receptors
    d. Alpha-2 receptors

Correct answer: b. Desmopressin binds to V2 receptors on the basolateral membrane of the principal cell in the renal collecting duct. This initiates a cascade of intracellular processes that ultimately lead to the promotion of water conservation at the level of the collecting duct, resulting in the restoration of normal plasma osmolarity.

18. What is adipsic CDI?

    a. A form of CDI in which patients are unable to sense thirst
    b. A form of CDI in which the kidneys are unresponsive to vasopressin
    c. A form of CDI caused by a pituitary adenoma
    d. A form of CDI caused by a genetic mutation

    Correct answer: a. Adipsic CDI is a condition in which patients with CDI are unable to sense thirst. This makes management of the condition challenging, as patients may have difficulty maintaining oral hydration, leading to significant sodium imbalances.

19. What is the recommended timing of administration for oral desmopressin?

    a. With food
    b. On an empty stomach
    c. With a high-fat meal
    d. With a glass of water

    Correct answer: b. Gastrointestinal peptidases denature oral Desmopressin, which can lead to reduced efficacy of the medication. Patients should be advised to take this medication either on an empty stomach or at least 90 minutes after a meal to ensure optimal absorption.

20. A 26-year-old woman presents with seizures after starting an antidepressant medication. What is the likely explanation for her presentations

    a. Hypernatremia
    b. Polyuria
    c. Hyperkalemia
    d. Hyponatremia

    Correct answer: d. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is characterized by excessive release of ADH, which results in increased water reabsorption in the kidneys. A state of dilutional hyponatremia therefore results, a condition where there is a low concentration of sodium in the blood due to an excessive amount of water. The other options, hypernatremia, polyuria, and hyperkalemia, are not typically associated with SIADH.

REFERENCES

1. Martin-Grace, J., Dineen, R., Sherlock, M., and Thompson, C.J. (2020). Adrenal insufficiency: Physiology, clinical presentation and diagnostic challenges. *Clin. Chim. Acta Int. J. Clin. Chem.* 505: 78–91.
2. Rotondo, F., Butz, H., Syro, L.V. et al. (2016). Arginine vasopressin (AVP): a review of its historical perspectives, current research and multifunctional role in the hypothalamo-hypophysial system. *Pituitary* 19 (4): 345–355.
3. Spencer, R.L. and Deak, T. (2017). A users guide to HPA axis research. *Physiol. Behav.* 178: 43–65.
4. Osterlund, C.D., Rodriguez-Santiago, M., Woodruff, E.R. et al. (2016). Glucocorticoid fast feedback inhibition of stress-induced ACTH secretion in the male rat: rate independence and stress-state resistance. *Endocrinology* 157 (7): 2785–2798.
5. Myers, B., McKlveen, J.M., and Herman, J.P. (2012). Neural regulation of the stress response: The many faces of feedback. *Cell. Mol. Neurobiol.* 32 (5): 683–694.
6. Hofland, L.J., Lamberts, S.W.J., and Feelders, R.A. (2010). Role of somatostatin receptors in normal and tumoral pituitary corticotropic cells. *Neuroendocrinology* 92 (Suppl 1): 11–16.
7. Herman, J.P., McKlveen, J.M., Ghosal, S. et al. (2016). Regulation of the hypothalamic-pituitary-adrenocortical stress response. *Compr. Physiol.* 6 (2): 603–621.
8. Giordano, R., Pellegrino, M., Picu, A. et al. (2006). Neuroregulation of the hypothalamus-pituitary-adrenal (HPA) axis in humans: effects of GABA-, mineralocorticoid-, and GH-Secretagogue-receptor modulation. *Sci. World J.* 6: 1–11.
9. Tateno, T., Kato, M., Tani, Y. et al. (2009). Differential expression of somatostatin and dopamine receptor subtype genes in adrenocorticotropin (ACTH)-secreting pituitary tumors and silent corticotroph adenomas. *Endocr. J.* 56 (4): 579–584.
10. Lacroix, A., Gu, F., Schopohl, J. et al. (2020). Pasireotide treatment significantly reduces tumor volume in patients with Cushing's disease: results from a Phase 3 study. *Pituitary* 23 (3): 203–211.

11. Silverstein, J.M. (2016). Hyperglycemia induced by pasireotide in patients with Cushing's disease or acromegaly. *Pituitary* 19 (5): 536–543.
12. Novartis Pharmaceuticals. (2016). A randomized, double-blind study to assess the safety and efficacy of different dose levels of pasireotide (SOM230) subcutaneous (sc) over a 6 month treatment period in patients with de Novo, persistent or recurrent Cushing's disease.
13. Tritos, N.A. and Biller, B.M.K. (2020). Advances in the medical treatment of Cushing disease. *Endocrinol. Metab. Clin. N. Am.* 49 (3): 401–412.
14. Henry, R.R., Ciaraldi, T.P., Armstrong, D. et al. (2013). Hyperglycemia associated with pasireotide: results from a mechanistic study in healthy volunteers. *J. Clin. Endocrinol. Metab.* 98 (8): 3446–3453.
15. Colao, A., De Block, C., Gaztambide, M.S. et al. (2014). Managing hyperglycemia in patients with Cushing's disease treated with pasireotide: medical expert recommendations. *Pituitary* 17 (2): 180–186.
16. Ahrendt, S.A., McGuire, G.E., Pitt, H.A., and Lillemoe, K.D. (1991). Why does somatostatin cause gallstones? *Am. J. Surg.* 161 (1): 177–182. discussion 182–183.
17. Colao, A., Petersenn, S., Newell-Price, J. et al. (2012). A 12-month phase 3 study of pasireotide in Cushing's disease. *N. Engl. J. Med.* 366 (10): 914–924.
18. Sano, T. (2010). The 11th meeting of the international pituitary pathology society October 16–20, 2009 Awaji Island, Japan. *Endocr. Pathol.* 21 (1): 48–68.
19. Mason, D., Hassan, A., Chacko, S., and Thompson, P. (2002). Acute and chronic regulation of pituitary receptors for vasopressin and corticotropin releasing hormone. *Arch. Physiol. Biochem.* 110 (1–2): 74–89.
20. Pecori Giraldi, F., Ambrogio, A.G., Andrioli, M. et al. (2012). Potential role for retinoic acid in patients with Cushing's disease. *J. Clin. Endocrinol. Metab.* 97 (10): 3577–3583.
21. Sesta, A., Cassarino, M.F., Tapella, L. et al. (2016). Effect of retinoic acid on human adrenal corticosteroid synthesis. *Life Sci.* 151: 277–280.
22. Theodoropoulou, M. and Reincke, M. (2019). Tumor-directed therapeutic targets in Cushing disease. *J. Clin. Endocrinol. Metab.* 104 (3): 925–933.
23. Occhi, G., Regazzo, D., Albiger, N.M. et al. (2014). Activation of the dopamine receptor type-2 (DRD2) promoter by 9-cis retinoic acid in a cellular model of Cushing's disease mediates the inhibition of cell proliferation and ACTH secretion without a complete corticotroph-to-melanotroph transdifferentiation. *Endocrinology* 155 (9): 3538–3549.
24. Vilar, L., Albuquerque, J.L., Lyra, R. et al. (2016). The role of isotretinoin therapy for Cushing's disease: results of a prospective study. *Int. J. Endocrinol.* 2016: 8173182.
25. Cuevas-Ramos, D., Lim, D.S.T., and Fleseriu, M. (2016). Update on medical treatment for Cushing's disease. *Clin. Diabetes Endocrinol.* 2 (1): 16.
26. Auriemma, R.S., Pivonello, R., Ferreri, L. et al. (2015). Cabergoline use for pituitary tumors and valvular disorders. *Endocrinol. Metab. Clin. N. Am.* 44 (1): 89–97.
27. Stiles, C.E., Tetteh-Wayoe, E.T., Bestwick, J.P. et al. (2019). A meta-analysis of the prevalence of cardiac valvulopathy in patients with hyperprolactinemia treated with cabergoline. *J. Clin. Endocrinol. Metab.* 104 (2): 523–538.
28. Verhelst, J., Abs, R., Maiter, D. et al. (1999). Cabergoline in the treatment of hyperprolactinemia: a study in 455 patients. *J. Clin. Endocrinol. Metab.* 84 (7): 2518–2522.
29. Vroonen, L., Jaffrain-Rea, M.-L., Petrossians, P. et al. (2012). Prolactinomas resistant to standard doses of cabergoline: a multicenter study of 92 patients. *Eur. J. Endocrinol.* 167 (5): 651–662.
30. Burman, P., Edén-Engström, B., Ekman, B. et al. (2016). Limited value of cabergoline in Cushing's disease: a prospective study of a 6-week treatment in 20 patients. *Eur. J. Endocrinol.* 174 (1): 17–24.
31. Ferriere, A., Cortet, C., Chanson, P. et al. (2017). Cabergoline for Cushing's disease: a large retrospective multicenter study. *Eur. J. Endocrinol.* 176 (3): 305–314.
32. Godbout, A., Manavela, M., Danilowicz, K. et al. (2010). Cabergoline monotherapy in the long-term treatment of Cushing's disease. *Eur. J. Endocrinol.* 163 (5): 709–716.
33. Liddle, G.W., Estep, H.L., Kendall, J.W. et al. (1959). Clinical application of a new test of pituitary reserve. *J. Clin. Endocrinol. Metab.* 19: 875–894.
34. Kamenický, P., Droumaguet, C., Salenave, S. et al. (2011). Mitotane, metyrapone, and ketoconazole combination therapy as an alternative to rescue adrenalectomy for severe ACTH-dependent Cushing's syndrome. *J. Clin. Endocrinol. Metab.* 96 (9): 2796–2804.
35. Daniel, E., Aylwin, S., Mustafa, O. et al. (2015). Effectiveness of metyrapone in treating Cushing's

syndrome: a retrospective multicenter study in 195 patients. *J. Clin. Endocrinol. Metab.* 100 (11): 4146–4154.

36. Pivonello, R., De Leo, M., Cozzolino, A., and Colao, A. (2015). The treatment of Cushing's disease. *Endocr. Rev.* 36 (4): 385–486.
37. Daniel, E. and Newell-Price, J.D.C. (2015). Therapy of endocrine disease: steroidogenesis enzyme inhibitors in Cushing's syndrome. *Eur. J. Endocrinol.* 172 (6): R263–R280.
38. Fleseriu, M., Pivonello, R., Young, J. et al. (2016). Osilodrostat, a potent oral 11β-hydroxylase inhibitor: 22-week, prospective, Phase II study in Cushing's disease. *Pituitary* 19 (2): 138–148.
39. Bronstein, M., Machado, M., and Fragoso, M. (2015). Management of pregnant patients with Cushing's syndrome. *Eur. J. Endocrinol.* 173 (2): R85–R91.
40. Baudry, C., Coste, J., Khalil, R.B. et al. (2012). Efficiency and tolerance of mitotane in Cushing's disease in 76 patients from a single center. *Eur. J. Endocrinol.* 167 (4): 473–481.
41. Lindsay, J.R., Jonklaas, J., Oldfield, E.H., and Nieman, L.K. (2005). Cushing's syndrome during pregnancy: personal experience and review of the literature. *J. Clin. Endocrinol. Metab.* 90 (5): 3077–3083.
42. Luque-Ramírez, M., Ortiz-Flóres, A.E., Nattero-Chávez, L., and Escobar-Morreale, H.F. (2020). Apparent mineralocorticoid excess as a side effect of ketoconazole therapy in a patient with Cushing's disease. *Clin. Endocrinol.* 92 (1): 80–83.
43. Pivonello, R., Fleseriu, M., Newell-Price, J. et al. (2020). Efficacy and safety of osilodrostat in patients with Cushing's disease (LINC 3): a multicentre phase III study with a double-blind, randomised withdrawal phase. *Lancet Diabetes Endocrinol.* 8 (9): 748–761.
44. Manni, A. and Quarde, A. (2020). *Endocrine Pathophysiology: A Concise Guide to the Physical Exam*. Springer International Publishing.
45. Edwards, C.R. and Stewart, P.M. (1991). The cortisol-cortisone shuttle and the apparent specificity of glucocorticoid and mineralocorticoid receptors. *J. Steroid Biochem. Mol. Biol.* 39 (5B): 859–865.
46. Oakley, R.H. and Cidlowski, J.A. (2013). The biology of the glucocorticoid receptor: new signaling mechanisms in health and disease. *J. Allergy Clin. Immunol.* 132 (5): 1033–1044.
47. Weikum, E.R., Knuesel, M.T., Ortlund, E.A., and Yamamoto, K.R. (2017). Glucocorticoid receptor control of transcription: precision and plasticity via allostery. *Nat. Rev. Mol. Cell Biol.* 18 (3): 159–174.
48. Panettieri, R.A., Schaafsma, D., Amrani, Y. et al. (2019). Non-genomic effects of glucocorticoids: an updated view. *Trends Pharmacol. Sci.* 40 (1): 38–49.
49. Cadepond, F., Ulmann, A., and Baulieu, E.E. (1997). RU486 (mifepristone): mechanisms of action and clinical uses. *Annu. Rev. Med.* 48: 129–156.
50. Cohan, P. (2013). Pasireotide and mifepristone: new options in the medical management of cushing's disease. *Endocr. Pract.* 20 (1): 84–93.
51. Yuen, K.C.J., Moraitis, A., and Nguyen, D. (2017). Evaluation of evidence of adrenal insufficiency in trials of normocortisolemic patients treated with mifepristone. *J. Endocr. Soc.* 1 (4): 237–246.
52. Carmichael, J.D. and Fleseriu, M. (2013). Mifepristone: is there a place in the treatment of Cushing's disease? *Endocrine* 44 (1): 20–32.
53. Fleseriu, M., Biller, B.M.K., Findling, J.W. et al. (2012). Mifepristone, a glucocorticoid receptor antagonist, produces clinical and metabolic benefits in patients with Cushing's syndrome. *J. Clin. Endocrinol. Metab.* 97 (6): 2039–2049.
54. Hinojosa-Amaya, J.M., Cuevas-Ramos, D., and Fleseriu, M. (2019). Medical management of cushing's syndrome: current and emerging treatments. *Drugs* 79 (9): 935–956.
55. Fleseriu, M., Findling, J.W., Koch, C.A. et al. (2014). Changes in plasma ACTH levels and corticotroph tumor size in patients with Cushing's disease during long-term treatment with the glucocorticoid receptor antagonist mifepristone. *J. Clin. Endocrinol. Metab.* 99 (10): 3718–3727.
56. Fountas, A. and Karavitaki, N. (2020). Nelson's syndrome: an update. *Endocrinol. Metab. Clin. N. Am.* 49 (3): 413–432.
57. Shraga-Slutzky, I., Shimon, I., and Weinshtein, R. (2006). Clinical and biochemical stabilization of Nelson's syndrome with long-term low-dose cabergoline treatment. *Pituitary* 9 (2): 151–154.
58. van der Hoek, J., Lamberts, S.W.J., and Hofland, L.J. (2004). The role of somatostatin analogs in Cushing's disease. *Pituitary* 7 (4): 257–264.
59. Budayr, A., Tan, T.C., Lo, J.C. et al. (2020). Cardiac valvular abnormalities associated with use and cumulative exposure of cabergoline for hyperprolactinemia: the CATCH study. *BMC Endocr. Disord.* 20 (1): 25.
60. Blum, W.F., Alherbish, A., Alsagheir, A. et al. (2018). The growth hormone–insulin-like growth factor-I

axis in the diagnosis and treatment of growth disorders. *Endocr. Connect.* 7 (6): R212–R222.

61. Anderson, L.L. and Scanes, C.G. (2012). Nanobiology and physiology of growth hormone secretion. *Exp. Biol. Med.* 237 (2): 126–142.
62. Ranke, M.B. and Wit, J.M. (2018). Growth hormone - past, present and future. *Nat. Rev. Endocrinol.* 14 (5): 285–300.
63. de Fátima Borges, M., Teixeira, F.C.C., Feltrin, A.K. et al. (2016). Clonidine-stimulated growth hormone concentrations (cut-off values) measured by immunochemiluminescent assay (ICMA) in children and adolescents with short stature. *Clinics* 71 (4): 226–231.
64. Fazeli, P.K. and Klibanski, A. (2014). Determinants of growth hormone resistance in malnutrition. *J. Endocrinol.* 220 (3): R57–R65.
65. Mazziotti, G. and Giustina, A. (2013). Glucocorticoids and the regulation of growth hormone secretion. *Nat. Rev. Endocrinol.* 9 (5): 265–276.
66. Leung, K.-C., Johannsson, G., Leong, G.M., and Ho, K.K.Y. (2004). Estrogen regulation of growth hormone action. *Endocr. Rev.* 25 (5): 693–721.
67. Hawkes, C.P., Grimberg, A., Dzata, V.E., and De Leon, D.D. (2016). Adding glucagon-stimulated GH testing to the diagnostic fast increases the detection of GH-sufficient children. *Horm. Res. Paediatr.* 85 (4): 265–272.
68. Donaghy, A.J., Delhanty, P.J.D., Ho, K.K. et al. (2002). Regulation of the growth hormone receptor/binding protein, insulin-like growth factor ternary complex system in human cirrhosis. *J. Hepatol.* 36 (6): 751–758.
69. Domené, H.M., Hwa, V., Jasper, H.G., and Rosenfeld, R.G. (2011). Acid-labile subunit (ALS) deficiency. *Best Pract. Res. Clin. Endocrinol. Metab.* 25 (1): 101–113.
70. Poyrazoğlu, Ş., Hwa, V., Baş, F. et al. (2019). A novel homozygous mutation of the acid-labile subunit (IGFALS) gene in a male adolescent. *J. Clin. Res. Pediatr. Endocrinol.* 11 (4): 432–438.
71. Devesa, J., Almengló, C., and Devesa, P. (2016). Multiple effects of growth hormone in the body: is it really the hormone for growth? *Clin. Med. Insights Endocrinol. Diabetes* 9: 47–71.
72. Carmichael, J.D., Bonert, V.S., Nuño, M. et al. (2014). Acromegaly clinical trial methodology impact on reported biochemical efficacy rates of somatostatin receptor ligand treatments: a meta-analysis. *J. Clin. Endocrinol. Metab.* 99 (5): 1825–1833.
73. Gariani, K., Meyer, P., and Philippe, J. (2013). Implications of Somatostatin Analogues in the Treatment of Acromegaly. *Eur. Endocrinol.* 9 (2): 132–135.
74. McKeage, K. (2015). Pasireotide in acromegaly: a review. *Drugs* 75 (9): 1039–1048.
75. Dineen, R., Stewart, P.M., and Sherlock, M. (2017). Acromegaly. *QJM Int. J. Med.* 110 (7): 411–420.
76. Iacovazzo, D., Carlsen, E., Lugli, F. et al. (2016). Factors predicting pasireotide responsiveness in somatotroph pituitary adenomas resistant to first-generation somatostatin analogues: an immunohistochemical study. *Eur. J. Endocrinol.* 174 (2): 241–250.
77. Mayr, B., Buslei, R., Theodoropoulou, M. et al. (2013). Molecular and functional properties of densely and sparsely granulated GH-producing pituitary adenomas. *Eur. J. Endocrinol.* 169 (4): 391–400.
78. Amarawardena, W.K.M.G., Liyanarachchi, K.D., Newell-Price, J.D.C. et al. (2017). Pasireotide: successful treatment of a sparsely granulated tumour in a resistant case of acromegaly. *Endocrinol. Diabetes Metab. Case Rep.* 2017: 17-0067.
79. Gomes-Porras, M., Cárdenas-Salas, J., and Álvarez-Escolá, C. (2020). Somatostatin analogs in clinical practice: a review. *Int. J. Mol. Sci.* 21 (5): 1682. https://doi.org/10.3390/ijms21051682.
80. Gadelha, M.R., Bronstein, M.D., Brue, T. et al. (2014). Pasireotide versus continued treatment with octreotide or lanreotide in patients with inadequately controlled acromegaly (PAOLA): a randomised, phase 3 trial. *Lancet Diabetes Endocrinol.* 2 (11): 875–884.
81. Gadelha, M., Bex, M., Colao, A. et al. (2020). Evaluation of the efficacy and safety of switching to pasireotide in patients with acromegaly inadequately controlled with first-generation somatostatin analogs. *Front. Endocrinol.* 10: 931.
82. Waters, M.J., Shang, C.A., Behncken, S.N. et al. (1999). Growth hormone as a cytokine. *Clin. Exp. Pharmacol. Physiol.* 26 (10): 760–764.
83. Brooks, A.J., Wooh, J.W., Tunny, K.A., and Waters, M.J. (2008). Growth hormone receptor; mechanism of action. *Int. J. Biochem. Cell Biol.* 40 (10): 1984–1989.
84. Waters, M.J. and Brooks, A.J. (2015). JAK2 activation by growth hormone and other cytokines. *Biochem. J.* 466 (1): 1–11.
85. Dehkhoda, F., Lee, C.M.M., Medina, J., and Brooks, A.J. (2018). The growth hormone receptor: mechanism of receptor activation, cell signaling, and physiological aspects. *Front. Endocrinol.* 9: 35.

86. Chia, D.J. (2014). Minireview: mechanisms of growth hormone-mediated gene regulation. *Mol. Endocrinol.* 28 (7): 1012–1025.
87. Veldhuis, J.D., Bidlingmaier, M., Bailey, J. et al. (2010). A pegylated growth hormone receptor antagonist, pegvisomant, does not enter the brain in humans. *J. Clin. Endocrinol. Metab.* 95 (8): 3844–3847.
88. Trainer, P.J., Drake, W.M., Katznelson, L. et al. (2000). Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant. *N. Engl. J. Med.* 342 (16): 1171–1177.
89. Tritos, N.A. and Biller, B.M.K. (2017). Pegvisomant: a growth hormone receptor antagonist used in the treatment of acromegaly. *Pituitary* 20 (1): 129–135.
90. Giustina, A., Arnaldi, G., Bogazzi, F. et al. (2017). Pegvisomant in acromegaly: an update. *J. Endocrinol. Investig.* 40 (6): 577–589.
91. Hodish, I. and Barkan, A. (2008). Long-term effects of pegvisomant in patients with acromegaly. *Nat. Clin. Pract. Endocrinol. Metab.* 4 (6): 324–332.
92. Grottoli, S., Maffei, P., Bogazzi, F. et al. (2015). ACROSTUDY: the Italian experience. *Endocrine* 48 (1): 334–341.
93. Tritos, N.A., Mattsson, A.F., Vila, G. et al. (2020). All-cause mortality in patients with acromegaly treated with pegvisomant: an ACROSTUDY analysis. *Eur. J. Endocrinol.* 182 (3): 285–292.
94. Lu, M., Flanagan, J.U., Langley, R.J. et al. (2019). Targeting growth hormone function: strategies and therapeutic applications. *Signal Transduct. Target. Ther.* 4 (1): 3.
95. Vance, M.L., Kaiser, D.L., Frohman, L.A. et al. (1987). Role of dopamine in the regulation of growth hormone secretion: dopamine and bromocriptine augment growth hormone (GH)-releasing hormone-stimulated GH secretion in normal man. *J. Clin. Endocrinol. Metab.* 64 (6): 1136–1141.
96. Cooper, O. and Greenman, Y. (2018). Dopamine agonists for pituitary adenomas. *Front. Endocrinol.* 9: 469.
97. Lawton, N.F., Evans, A.J., and Weller, R.O. (1981). Dopaminergic inhibition of growth hormone and prolactin release during continuous in vitro perifusion of normal and adenomatous human pituitary. *J. Neurol. Sci.* 49 (2): 229–239.
98. Chanson, P. (2016). Medical treatment of acromegaly with dopamine agonists or somatostatin analogs. *Neuroendocrinology* 103 (1): 50–58.
99. Sandret, L., Maison, P., and Chanson, P. (2011). Place of cabergoline in acromegaly: a meta-analysis. *J. Clin. Endocrinol. Metab.* 96 (5): 1327–1335.
100. Cook, D.M., Ludlam, W.H., and Cook, M.B. (1999). Route of estrogen administration helps to determine growth hormone (GH) replacement dose in GH-deficient adults. *J. Clin. Endocrinol. Metab.* 84 (11): 3956–3960.
101. Janssen, Y.J., Helmerhorst, F., Frölich, M., and Roelfsema, F. (2000). A switch from oral (2 mg/day) to transdermal (50 microg/day) 17beta-estradiol therapy increases serum insulin-like growth factor-I levels in recombinant human growth hormone (GH)-substituted women with GH deficiency. *J. Clin. Endocrinol. Metab.* 85 (1): 464–467.
102. Molitch, M.E., Clemmons, D.R., Malozowski, S. et al. (2011). Evaluation and treatment of adult growth hormone deficiency: an endocrine society clinical practice guideline. *J. Clin. Endocrinol. Metab.* 96 (6): 1587–1609.
103. Lindberg-Larsen, R., Møller, N., Schmitz, O. et al. (2007). The impact of pegvisomant treatment on substrate metabolism and insulin sensitivity in patients with acromegaly. *J. Clin. Endocrinol. Metab.* 92 (5): 1724–1728.
104. Higham, C.E., Rowles, S., Russell-Jones, D. et al. (2009). Pegvisomant improves insulin sensitivity and reduces overnight free fatty acid concentrations in patients with acromegaly. *J. Clin. Endocrinol. Metab.* 94 (7): 2459–2463.
105. Freeman, M.E., Kanyicska, B., Lerant, A., and Nagy, G. (2000). Prolactin: structure, function, and regulation of secretion. *Physiol. Rev.* 80 (4): 1523–1631.
106. Saleem, M., Martin, H., and Coates, P. (2018). Prolactin biology and laboratory measurement: an update on physiology and current analytical issues. *Clin. Biochem. Rev.* 39 (1): 3–16.
107. Gorvin, C.M. (2015). The prolactin receptor: diverse and emerging roles in pathophysiology. *J. Clin. Transl. Endocrinol.* 2 (3): 85–91.
108. Brooks, C.L. (2012). Molecular mechanisms of prolactin and its receptor. *Endocr. Rev.* 33 (4): 504–525.
109. Liu, X., Tang, C., Wen, G. et al. (2019). The mechanism and pathways of dopamine and dopamine agonists in prolactinomas. *Front. Endocrinol.* 9: 768–768.
110. Shimazu, S., Shimatsu, A., Yamada, S. et al. (2012). Resistance to dopamine agonists in prolactinoma is

correlated with reduction of dopamine D2 receptor long isoform mRNA levels. *Eur. J. Endocrinol.* 166 (3): 383–390.

111. Molitch, M.E. (2005). Pharmacologic resistance in prolactinoma patients. *Pituitary* 8 (1): 43–52.
112. Vermeulen, E., D'Haens, J., Stadnik, T. et al. (2020). Predictors of dopamine agonist resistance in prolactinoma patients. *BMC Endocr. Disord.* 20 (1): 68.
113. Almalki, M.H., Alzahrani, S., Alshahrani, F. et al. (2015). Managing prolactinomas during pregnancy. *Front. Endocrinol.* 6: 85.
114. Huang, H.Y., Lin, S.J., Zhao, W.G., and Wu, Z.B. (2018). Cabergoline versus bromocriptine for the treatment of giant prolactinomas: A quantitative and systematic review. *Metab. Brain Dis.* 33 (3): 969–976.
115. Sabuncu, T., Arikan, E., Tasan, E., and Hatemi, H. (2001). Comparison of the effects of cabergoline and bromocriptine on prolactin levels in hyperprolactinemic patients. *Intern. Med. Tokyo Jpn.* 40 (9): 857–861.
116. Brichta, C.M., Wurm, M., Krebs, A. et al. (2019). Start low, go slowly – Mental abnormalities in young prolactinoma patients under cabergoline therapy. *J. Pediatr. Endocrinol. Metab.* 32 (9): 969–977.
117. Miura, J., Kikuchi, A., Fujii, A. et al. (2009). Pathological gambling associated with cabergoline in a case of recurrent depression. *Drug Discov. Ther.* 3 (4): 190–192.
118. Zamanipoor Najafabadi, A.H., Zandbergen, I.M., de Vries, F. et al. (2020). Surgery as a viable alternative first-line treatment for prolactinoma patients. a systematic review and meta-analysis. *J. Clin. Endocrinol. Metab.* 105 (3): e32–e41.
119. Sharma, S., Salehi, F., Scheithauer, B.W. et al. (2009). Role of MGMT in tumor development, progression, diagnosis, treatment and prognosis. *Anticancer Res.* 29 (10): 3759–3768.
120. Zhang, J., Stevens, M.F.G., and Bradshaw, T.D. (2012). Temozolomide: mechanisms of action, repair and resistance. *Curr. Mol. Pharmacol.* 5 (1): 102–114.
121. Cankovic, M., Nikiforova, M.N., Snuderl, M. et al. (2013). The role of MGMT testing in clinical practice: a report of the association for molecular pathology. *J. Mol. Diagn.* 15 (5): 539–555.
122. Whitelaw, B.C., Dworakowska, D., Thomas, N.W. et al. (2012). Temozolomide in the management of dopamine agonist–resistant prolactinomas. *Clin. Endocrinol.* 76 (6): 877–886.
123. Raverot, G., Sturm, N., de Fraipont, F. et al. (2010). Temozolomide treatment in aggressive pituitary tumors and pituitary carcinomas: a french multicenter experience. *J. Clin. Endocrinol. Metab.* 95 (10): 4592–4599.
124. Almalki, M.H., Aljoaib, N.N., Alotaibi, M.J. et al. (2017). Temozolomide therapy for resistant prolactin-secreting pituitary adenomas and carcinomas: a systematic review. *Hormones (Athens)* 16 (2): 139–149.
125. Khasraw, M., Bell, D., and Wheeler, H. (2009). Long-term use of temozolomide: Could you use temozolomide safely for life in gliomas? *J. Clin. Neurosci.* 16 (6): 854–855.
126. Kocova, M., Netkov, S., and Sukarova-Angelovska, E. (2001). Pituitary pseudotumor with unusual presentation reversed shortly after the introduction of thyroxine replacement therapy. *J. Pediatr. Endocrinol. Metab. JPEM* 14 (9): 1665–1669.
127. Khawaja, N.M., Taher, B.M., Barham, M.E. et al. (2006). Pituitary enlargement in patients with primary hypothyroidism. *Endocr. Pract. Off. J. Am. Coll. Endocrinol. Am. Assoc. Clin. Endocrinol.* 12 (1): 29–34.
128. Kostoglou-Athanassiou, I. and Ntalles, K. (2010). Hypothyroidism - new aspects of an old disease. *Hippokratia* 14 (2): 82–87.
129. Coopmans, E.C., van Meyel, S.W.F., Pieterman, K.J. et al. (2019). Excellent response to pasireotide therapy in an aggressive and dopamine-resistant prolactinoma. *Eur. J. Endocrinol.* 181 (2): K21–K27.
130. Jaquet, P., Ouafik, L., Saveanu, A. et al. (1999). Quantitative and functional expression of somatostatin receptor subtypes in human prolactinomas. *J. Clin. Endocrinol. Metab.* 84 (9): 3268–3276.
131. Ceccato, F., Lombardi, G., Albiger, N. et al. (2019). Temozolomide cytoreductive treatment in a giant cabergoline-resistant prolactin-secreting pituitary neuroendocrine tumor. *Anti-Cancer Drugs* 30 (5): 533–536.
132. Felker, J., Patterson, B., Wrubel, D., and Janss, A. (2016). Successful treatment of a child with a prolactin secreting macroadenoma with temozolomide. *J. Pediatr. Endocrinol. Metab. JPEM* 29 (12): 1413–1415.
133. Root, A.W. and Root, M.J. (2002). Clinical pharmacology of human growth hormone and its secretagogues. *Curr. Drug Targets Immune Endocr. Metabol. Disord.* 2 (1): 27–52.

134. Frayn, K.N., Coppack, S.W., Fielding, B.A., and Humphreys, S.M. (1995). Coordinated regulation of hormone-sensitive lipase and lipoprotein lipase in human adipose tissue in vivo: Implications for the control of fat storage and fat mobilization. *Adv. Enzym. Regul.* 35: 163–178.

135. Hjelholt, A.J., Søndergaard, E., Pedersen, S.B. et al. (2020). Growth hormone upregulates ANGPTL4 mRNA and suppresses lipoprotein lipase via fatty acids: Randomized experiments in human individuals. *Metabolism* 105: 154188.

136. Song, Z., Xiaoli, A.M., and Yang, F. (2018) Regulation and metabolic significance of de novo lipogenesis in adipose tissues. *Nutrients*, 10 (10): 1383. https://doi.org/10.3390/nu10101383.

137. Kopchick, J.J., Berryman, D.E., Puri, V. et al. (2020). The effects of growth hormone on adipose tissue: old observations, new mechanisms. *Nat. Rev. Endocrinol.* 16 (3): 135–146.

138. Nilsson, O., Marino, R., De Luca, F. et al. (2005). Endocrine regulation of the growth plate. *Horm. Res.* 64 (4): 157–165.

139. Shim, K.S. (2015). Pubertal growth and epiphyseal fusion. *Ann. Pediatr. Endocrinol. Metab.* 20 (1): 8–12.

140. Wallace, J.D., Cuneo, R.C., Bidlingmaier, M. et al. (2001). Changes in non-22-kilodalton (kDa) isoforms of growth hormone (GH) after administration of 22-kDa recombinant human GH in trained adult males. *J. Clin. Endocrinol. Metab.* 86 (4): 1731–1737.

141. Saugy, M., Robinson, N., Saudan, C. et al. (2006). Human growth hormone doping in sport. *Br. J. Sports Med.* 40 (Suppl 1): i35–i39.

142. Rezaei, M. and Zarkesh-Esfahani, S.H. (2012). Optimization of production of recombinant human growth hormone in *Escherichia coli*. *J. Res. Med. Sci. Off. J. Isfahan Univ. Med. Sci.* 17 (7): 681–685.

143. Díez, J.J., Sangiao-Alvarellos, S., and Cordido, F. (2018). Treatment with growth hormone for adults with growth hormone deficiency syndrome: benefits and risks. *Int. J. Mol. Sci.* 19 (3).

144. Souza, F.M. and Collett-Solberg, P.F. (2011). Adverse effects of growth hormone replacement therapy in children. *Arq. Bras. Endocrinol. Metabol.* 55 (8): 559–565.

145. Maison, P., Griffin, S., Nicoue-Beglah, M. et al. (2004). Impact of growth hormone (GH) treatment on cardiovascular risk factors in GH-deficient adults: a metaanalysis of blinded, randomized, placebo-controlled trials. *J. Clin. Endocrinol. Metab.* 89 (5): 2192–2199.

146. Ramos-Leví, A.M. and Marazuela, M. (2018). Treatment of adult growth hormone deficiency with human recombinant growth hormone: an update on current evidence and critical review of advantages and pitfalls. *Endocrine* 60 (2): 203–218.

147. Beauregard, C., Utz, A.L., Schaub, A.E. et al. (2008). Growth hormone decreases visceral fat and improves cardiovascular risk markers in women with hypopituitarism: a randomized, placebo-controlled study. *J. Clin. Endocrinol. Metab.* 93 (6): 2063–2071.

148. Swerdlow, A.J., Cooke, R., Beckers, D. et al. (2017). Cancer risks in patients treated with growth hormone in childhood: the SAGhE European cohort study. *J. Clin. Endocrinol. Metab.* 102 (5): 1661–1672.

149. Kim, S.-H. and Park, M.-J. (2017). Effects of growth hormone on glucose metabolism and insulin resistance in human. *Ann. Pediatr. Endocrinol. Metab.* 22 (3): 145–152.

150. Luger, A., Mattsson, A.F., KoŁtowska-Häggström, M. et al. (2012). Incidence of diabetes mellitus and evolution of glucose parameters in growth hormone–deficient subjects during growth hormone replacement therapy: a long-term observational study. *Diabetes Care* 35 (1): 57–62.

151. Ishunina, T.A. and Swaab, D.F. (1999). Vasopressin and oxytocin neurons of the human supraoptic and paraventricular nucleus; size changes in relation to age and sex. *J. Clin. Endocrinol. Metab.* 84 (12): 4637–4644.

152. Miyata, S. (2015). New aspects in fenestrated capillary and tissue dynamics in the sensory circumventricular organs of adult brains. *Front. Neurosci.* 9: 390.

153. Verbalis, J.G. (2007). How does the brain sense osmolality? *J. Am. Soc. Nephrol.* 18 (12): 3056–3059.

154. Terwel, D. and Jolles, J. (1994). The relationship between plasma osmolality and plasma vasopressin concentration is altered in old male Lewis rats. *Eur. J. Endocrinol.* 131 (1): 86–90.

155. Kanbay, M., Yilmaz, S., Dincer, N. et al. (2019). Antidiuretic hormone and serum osmolarity physiology and related outcomes: what is old, what is new, and what is unknown? *J. Clin. Endocrinol. Metab.* 104 (11): 5406–5420.

156. Bankir, L., Bichet, D.G., and Morgenthaler, N.G. (2017). Vasopressin: physiology, assessment and osmosensation. *J. Intern. Med.* 282 (4): 284–297.

157. Boone, M. and Deen, P.M.T. (2008). Physiology and pathophysiology of the vasopressin-regulated renal water reabsorption. *Pflugers Arch.* 456 (6): 1005–1024.

158. Elder, C.J. and Dimitri, P.J. (2017). Diabetes insipidus and the use of desmopressin in hospitalised children. *Arch. Dis. Child. Educ. Pract. Ed.* 102 (2): 100–104.

159. Vilhardt, H. (1990). Basic pharmacology of desmopressin. *Drug Investig.* 2 (5): 2–8.

160. Sawyer, W.H., Acosta, M., Balaspiri, L. et al. (1974). Structural changes in the arginine vasopressin molecule that enhance antidiuretic activity and specificity. *Endocrinology* 94 (4): 1106–1115.

161. Subramanya, A.R. and Ellison, D.H. (2014). Distal Convoluted Tubule. *Clin. J. Am. Soc. Nephrol.* 9 (12): 2147–2163.

162. McCormick, J.A. and Ellison, D.H. (2015). The distal convoluted tubule. *Compr. Physiol.* 5 (1): 45–98.

163. Bichet, D.G. (2018). Vasopressin and the regulation of thirst. *Ann. Nutr. Metab.* 72 (Suppl 2): 3–7.

164. García, E.B.G., Ruitenberg, A., Madretsma, G.S., and Hintzen, R.Q. (2003). Hyponatraemic coma induced by desmopressin and ibuprofen in a woman with von Willebrand's disease. *Haemophilia* 9 (2): 232–234.

165. Verrua, E., Mantovani, G., Ferrante, E. et al. (2013). Severe water intoxication secondary to the concomitant intake of non-steroidal anti-inflammatory drugs and desmopressin: a case report and review of the literature. *Hormones (Athens)* 12 (1): 135–141.

166. Garrahy, A., Moran, C., and Thompson, C.J. (2019). Diagnosis and management of central diabetes insipidus in adults. *Clin. Endocrinol.* 90 (1): 23–30.

167. Oiso, Y., Robertson, G.L., Nørgaard, J.P., and Juul, K.V. (2013). Treatment of neurohypophyseal diabetes insipidus. *J. Clin. Endocrinol. Metab.* 98 (10): 3958–3967.

168. Kataoka, Y., Nishida, S., Hirakawa, A. et al. (2015). Comparison of incidence of hyponatremia between intranasal and oral desmopressin in patients with central diabetes insipidus. *Endocr. J.* 62 (2): 195–200.

169. Barron, W.M., Cohen, L.H., Ulland, L.A. et al. (1984). Transient vasopressin-resistant diabetes insipidus of pregnancy. *N. Engl. J. Med.* 310 (7): 442–444.

170. Cadnapaphornchai, M.A., Summer, S.N., Falk, S. et al. (2003). Effect of primary polydipsia on aquaporin and sodium transporter abundance. *Am. J. Physiol.-Ren. Physiol.* 285 (5): F965–F971.

171. Leib, D.E., Zimmerman, C.A., and Knight, Z.A. (2016). Thirst. *Curr. Biol.* 26 (24): R1260–R1265.

172. Zimmerman, C.A., Leib, D.E., and Knight, Z.A. (2017). Neural circuits underlying thirst and fluid homeostasis. *Nat. Rev. Neurosci.* 18 (8): 459–469.

173. Fitzsimons, J.T. (1998). Angiotensin, thirst, and sodium appetite. *Physiol. Rev.* 78 (3): 583–686.

174. Saifan, C., Nasr, R., Mehta, S., Sharma Acharya, P., Perrera, I., Faddoul, G., Nalluri, N., Kesavan, M., Azzi, Y., and El-Sayegh, S. (2013). Diabetes insipidus: a challenging diagnosis with new drug therapies. *ISRN Nephrol.*, 2013:797620. https://doi.org/10.5402/2013/797620.

175. Cuesta, M., Hannon, M.J., and Thompson, C.J. (2017). Adipsic diabetes insipidus in adult patients. *Pituitary* 20 (3): 372–380.

176. Behan, L.A., Sherlock, M., Moyles, P. et al. (2015). Abnormal plasma sodium concentrations in patients treated with desmopressin for cranial diabetes insipidus: results of a long-term retrospective study. *Eur. J. Endocrinol.* 172 (3): 243–250.

177. Mistry, A.C., Wynne, B.M., Yu, L. et al. (2016). The sodium chloride cotransporter (NCC) and epithelial sodium channel (ENaC) associate. *Biochem. J.* 473 (19): 3237–3252.

178. Raisingani, M., Palliyil Gopi, R., and Shah, B. (2017). Use of chlorothiazide in the management of central diabetes insipidus in early infancy. *Case Rep. Pediatr.* 2017: 2407028.

179. Magaldi, A.J. (2000). New insights into the paradoxical effect of thiazides in diabetes insipidus therapy. *Nephrol. Dial. Transplant.* 15 (12): 1903–1905.

180. Loffing, J. (2004). Paradoxical antidiuretic effect of thiazides in diabetes insipidus: another piece in the puzzle. *J. Am. Soc. Nephrol.* 15 (11): 2948–2950.

181. Rivkees, S.A., Dunbar, N., and Wilson, T.A. (2007). The management of central diabetes insipidus in infancy: desmopressin, low renal solute load formula, thiazide diuretics. *J. Pediatr. Endocrinol. Metab. JPEM* 20 (4): 459–469.

182. Graziani, G., Fedeli, C., Moroni, L. et al. (2010). Gitelman syndrome: pathophysiological and clinical aspects. *QJM Mon. J. Assoc. Physicians* 103 (10): 741–748.

183. Al Nofal, A. and Lteif, A. (2015). Thiazide diuretics in the management of young children with central diabetes insipidus. *J. Pediatr.* 167 (3): 658–661.

184. Abraham, M.B., Rao, S., Price, G., and Choong, C.S. (2014). Efficacy of hydrochlorothiazide and low renal solute feed in neonatal central diabetes insipidus with transition to oral desmopressin in early infancy. *Int. J. Pediatr. Endocrinol.* 2014 (1): 11.

185. Moses, A.M., Howanitz, J., Gemert, M.V., and Miller, M. (1973). Clofibrate-induced antidiuresis. *J. Clin. Invest.* 52 (3): 535–542.

186. Abdallah, B., Hodgins, S., Landry, D. et al. (2018). Oxcarbazepine therapy for complete central diabetes insipidus. *Case Rep. Nephrol. Dial.* 8 (1): 20–24.

187. Kamiyama, T., Iseki, K., Kawazoe, N. et al. (1993). Carbamazepine-induced hyponatremia in a patient with partial central diabetes insipidus. *Nephron* 64 (1): 142–145.

188. Goel, A., Farhat, F., Zik, C., and Jeffery, M. (2018). Triphasic response of pituitary stalk injury following TBI: a relevant yet uncommonly recognised endocrine phenomenon. *Case Rep. Dermatol.* 2018: bcr-2018-226725.

189. Hoorn, E.J. and Zietse, R. (2010). Water balance disorders after neurosurgery: the triphasic response revisited. *NDT Plus* 3 (1): 42–44.

190. Capatina, C., Paluzzi, A., Mitchell, R., and Karavitaki, N. (2015). Diabetes insipidus after traumatic brain injury. *J. Clin. Med.* 4 (7): 1448–1462.

191. Loh, J.A. and Verbalis, J.G. (2008). Disorders of water and salt metabolism associated with pituitary disease. *Endocrinol. Metab. Clin. N. Am.* 37 (1): 213–234.

192. Eisenberg, Y. and Frohman, L.A. (2015). Adipsic diabetes insipidus: a review. *Endocr. Pract.* 22 (1): 76–83.

193. Dalan, R., Chin, H., Hoe, J. et al. (2019). Adipsic diabetes insipidus—The challenging combination of polyuria and adipsia: a case report and review of literature. *Front. Endocrinol.* 10: 630.

194. Verbalis, J.G., Goldsmith, S.R., Greenberg, A. et al. (2013). Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. *Am. J. Med.* 126 (10): S1–S42.

195. Izumi, Y., Miura, K., and Iwao, H. (2014). Therapeutic potential of vasopressin-receptor antagonists in heart failure. *J. Pharmacol. Sci.* 124 (1): 1–6.

196. Berl, T., Quittnat-Pelletier, F., Verbalis, J.G. et al. (2010). Oral tolvaptan is safe and effective in chronic hyponatremia. *J. Am. Soc. Nephrol. JASN* 21 (4): 705–712.

197. Peri, A. (2013). The use of vaptans in clinical endocrinology. *J. Clin. Endocrinol. Metab.* 98 (4): 1321–1332.

198. Schrier, R.W., Gross, P., Gheorghiade, M. et al. (2006). Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. *N. Engl. J. Med.* 355 (20): 2099–2112.

199. Cuesta, M., Ortolá, A., Garrahy, A. et al. (2017). Predictors of failure to respond to fluid restriction in SIAD in clinical practice; time to re-evaluate clinical guidelines? *QJM Int. J. Med.* 110 (8): 489–492.

200. Decaux, G., Waterlot, Y., Genette, F., and Mockel, J. (1981). Treatment of the syndrome of inappropriate secretion of antidiuretic hormone with furosemide. *N. Engl. J. Med.* 304 (6): 329–330.

201. Krisanapan, P., Vongsanim, S., Pin-On, P. et al. (2020). Efficacy of furosemide, oral sodium chloride, and fluid restriction for treatment of syndrome of inappropriate antidiuresis (SIAD): An open-label randomized controlled study (the effuse-fluid trial). *Am. J. Kidney Dis.* 76 (2): 203–212.

202. Finsterer, U., Beyer, A., Jensen, U. et al. (1982). The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) – treatment with lithium. *Intensive Care Med.* 8 (5): 223–229.

203. Kazama, I., Arata, T., Michimata, M. et al. (2007). Lithium effectively complements vasopressin V2 receptor antagonist in the treatment of hyponatraemia of SIADH rats. *Nephrol. Dial. Transplant. Off. Publ. Eur. Dial. Transpl. Assoc. - Eur. Ren. Assoc.* 22 (1): 68–76.

204. Miell, J., Dhanjal, P., and Jamookeeah, C. (2015). Evidence for the use of demeclocycline in the treatment of hyponatraemia secondary to SIADH: a systematic review. *Int. J. Clin. Pract.* 69 (12): 1396–1417.

205. Pierrakos, C., Taccone, F.S., Decaux, G. et al. (2012). Urea for treatment of acute SIADH in patients with subarachnoid hemorrhage: a single-center experience. *Ann. Intensive Care* 2: 13.

206. Decaux, G., Gankam Kengne, F., Couturier, B. et al. (2018). Mild water restriction with or without urea for the longterm treatment of syndrome of inappropriate antidiuretic hormone secretion (SIADH): Can urine osmolality help the choice? *Eur. J. Intern. Med.* 48: 89–93.

207. Gross, P. (2012). Clinical management of SIADH. *Ther. Adv. Endocrinol. Metab.* 3 (2): 61–73.

208. Bartter, F.C. and Schwartz, W.B. (1967). The syndrome of inappropriate secretion of antidiuretic hormone. *Am. J. Med.* 42 (5): 790–806.

209. Chin, H.X., Quek, T.P., and Leow, M.K. (2017). Central diabetes insipidus unmasked by corticosteroid therapy for cerebral metastases: beware the case with pituitary involvement and hypopituitarism. *J. R. Coll. Physicians Edinb.* 47 (3): 247–249.