Phosphodiesterases in endocrine physiology and disease

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Abstract

The cAMP–protein kinase A pathway plays a central role in the development and physiology of endocrine tissues. cAMP mediates the intracellular effects of numerous peptide hormones. Various cellular and molecular alterations of the cAMP-signaling pathway have been observed in endocrine diseases.

Phosphodiesterases (PDEs) are key regulatory enzymes of intracellular cAMP levels. Indeed, PDEs are the only known mechanism for inactivation of cAMP by catalysis to 5′-AMP. It has been suggested that disruption of PDEs could also have a role in the pathogenesis of many endocrine diseases. This review summarizes the most recent advances concerning the role of the PDEs in the physiopathology of endocrine diseases. The potential significance of this knowledge can be easily envisaged by the development of drugs targeting specific PDEs.

Introduction

The cAMP pathway plays an important role in the development and function of endocrine tissues. It is also altered in various endocrine disorders. Indeed, numerous genetic alterations of the cAMP-signaling pathway have been observed (1). First, abnormalities of the hormone receptor of a given endocrine pathway have been reported, for example, activating mutations of the gene encoding for the TSH receptor (TSHR) in thyroid toxic adenomas (2), for the LH receptor in Leydig cell tumors (3), for the calcium sensing receptor in familial hypocalcaemia (4), and aberrant expression of G-protein-coupled receptors in bilateral macronodular adrenal hyperplasia (5–7). Secondly, somatic activating mutations of the stimulatory subunit z of the Gs protein have been found in McCune–Albright syndrome or in sporadic pituitary GH adenomas (8, 9). Finally, germ line inactivating mutations of the protein kinase A regulatory subunit type 1 (PRKAR1A) have been demonstrated in primary pigmented nodular adrenocortical diseases (PPNAD) and Carney complex (CNC) (10–12).

Phosphodiesterases (PDEs) have a key regulatory role in the cAMP pathway, as they are the only known mechanism for inactivating cAMP by its catalysis to 5′-AMP (Fig. 1). During the last several years, various attempts have been made to identify diseases associated with disruption of PDEs. Gene knockout, gene inactivation, and genetic association studies have implicated PDEs in numerous diseases such as asthma (13), depression (14), schizophrenia (15), and stroke (16). Moreover, in daily clinical practice, PDE inhibitors are able to effectively and safely treat diseases such as erectile dysfunction (17), heart failure (18), severe forms of Raynaud’s phenomenon (19), pulmonary arterial hypertension (20), and chronic obstructive pulmonary disease or asthma (21, 22).

In this review, a brief overview of the PDE family will be presented, followed by a description of their role in endocrine physiology. Finally, the known and potential roles of PDEs in endocrine diseases will be discussed.

The PDE superfamily

Adenylyl and guanylyl cyclases are the effector enzymes accounting for cyclic nucleotide production by converting ATP to cAMP or GTP to cGMP respectively. By contrast, PDEs cause the cyclic nucleotide degradation by hydrolyzing cAMP into 5′-AMP or, depending on the type of PDE, cGMP into 5′-GMP. Thus, PDEs play a critical role in the intracellular cAMP and cGMP homeostasis. Moreover, in combination with A-kinase anchoring proteins (AKAPs), PDEs contribute to compartmentalizing the cyclic nucleotides. It has been shown that cAMP does not have a uniform intracellular distribution but accumulates at specific sites within a cell. AKAPs, PDEs, and protein kinase A (PKA) form
complexes that act to create these simultaneous, multiple cAMP gradients. A cell without these complexes and PDEs would be swamped with cAMP after activation of adenylyl cyclase. Thus, PDEs have a major role in ensuring the proper intensity and spatio-temporal distribution of cyclic nucleotides (14, 23).

Human PDEs comprise a complex superfamily of enzymes derived from 21 genes separated into 11 PDE gene families (PDE 1-11; Fig. 2). Transcription from different initiation sites in these genes and differential splicing of their mRNAs results in the generation of about 100 isoforms of PDE proteins found in all cells and in almost all subcellular compartments. These isoforms can have different substrate selectivity (cAMP versus cGMP), kinetics, allosteric regulation, tissue distribution, and susceptibility to pharmacological inhibition. Although PDEs are structurally, biochemically, and pharmacologically different, they share some common structural features. They contain a conserved catalytic domain with ~300 amino acids located near the C-terminal regions and a variable regulatory domain located in the N-terminal regions. In mammals, three of the 11 PDE families selectively hydrolyze cAMP (PDEs 4, 7, and 8), three families are selective for cGMP (PDEs 5, 6, and 9), and five families present a dual specificity for both cyclic nucleotides but with variable efficiency (PDEs 1, 2, 3, 10, and 11).

Figure 1 Phosphodiesterases in the cAMP pathway. The cAMP pathway mediates key cellular processes. When the G-protein-coupled receptor is activated by an extracellular ligand, a conformational change occurs. The Gsα subunit is released from the complex and binds to adenylyl cyclase, which then catalyzes the conversion of ATP into cAMP. Elevation in intra-cellular cAMP levels leads to dissociation of the catalytic subunit from the regulatory subunit of the protein kinase A. The activated protein kinase A can then phosphorylate a series of targets that regulate downstream effector enzymes, ion channels, and activates the transcription of specific genes mediating cell growth and differentiation. Phosphodiesterases are key regulators of the cAMP pathway, as they are able to hydrolyze the cAMP to inactive 5′-AMP leading to inactivation of the cAMP pathway. Abbreviations used: CREB, cAMP response element-binding protein; cAMP, cyclic adenosine monophosphate; 5′-AMP, 5′-adenosine monophosphate.

Figure 2 Schematic representation of the human phosphodiesterases. Adapted from (76, 77). Phosphodiesterases are isoenzymes encoded by at least 21 different genes and organized into 11 families. Transcription from different initiation sites in these genes and differential splicing of their mRNAs results in the generation of about 100 isoforms of PDE proteins. The catalytic properties of many PDEs overlap, so that assignment of a specific role to a particular PDE family or to variants within a family is typically challenging.

Nowadays, it has been demonstrated that six PDE families could have a role in endocrine physiology and endocrine diseases: PDE1, PDE2 (PDE2A), PDE3 (PDE3A), PDE4 (PDE4B and PDE4D), PDE8 (PDE8A and PDE8B), and PDE11 (PDE11A). The major properties and localization of PDEs are summarized in Table 1. However, it is important to underline that understanding PDE functions can be difficult due to the lack of selective pharmacological inhibitors and to the fact that the catalytic properties of many PDEs overlap, so that assignment of a specific role to a particular PDE family or to variants within a family is typically challenging.

Moreover, expression pattern of PDEs isoforms frequently varies with the developmental, proliferative status and with the hormonal stimuli of the cell. In addition, these PDE isoforms are subjected to different regulations or are targeted to different subcellular compartments that account at least in part for creation of microdomains that spatially restrict cyclic nucleotides diffusion. This phenomenon could take part in a tissue specificity of the consequences of PDE mutations.

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PDEs in endocrine physiology

Adrenals

PDE2A, PDE8A, PDE8B, and PDE11A are the major PDEs that are expressed in the adrenal cortex (24–26). Recently, it has been demonstrated that PDE2A, PDE8B, and PDE11A have a role in the adrenal physiology.

PDE2A

PDE2A is the predominant PDE in the adrenal cortex and may be implicated in adrenal physiology (25, 27, 28). To date, the regulation of intracellular cAMP accumulation after ACTH stimulation is not fully elucidated. PDE2A may be implicated in the regulation of the ACTH-induced increase in intracellular cAMP. In rat and human cell models, three sequential phases of the effect of ACTH leading to cAMP stimulation have
been described. First, a rapid and sustained activation of adenylyl cyclase was shown followed with a biphasic effect of ACTH on PDE2 activity with an initial and rapid inhibition of PDE2 activity followed with a delayed activation of PDE2A (29). Thus, PDE2A seems to be strongly involved in the regulation of cAMP levels as its activity controls the production of cAMP induced by ACTH.

**PDE8B** Recently, it was demonstrated that PDE8B is a major regulator of adrenal steroidogenesis by both acute and chronic mechanisms (28). Indeed, PDE8B knockout mouse have elevated levels of corticosterone due to adrenal hypersensitivity to ACTH. In cell culture models, pharmacological inhibition of PDE8 has the same effects. This suggests that in normal adrenal cortex, PDE8B acts as a negative regulator of adrenal steroidogenesis.

**PDE11A4** The role of PDE11A4 in adrenal physiology has been poorly investigated. Mice deficient in PDE11A4 have been generated but no effects on the adrenal have been reported (30). Even if selective PDE11 inhibitors have not yet been discovered, inhibitors that can partially inhibit PDE11 have been used in murine models and in humans. Tadalafil, a PDE5 inhibitor that can partially inhibit PDE11, is widely used without reports of adrenal dysfunction. Tadalafil was used to study glucocorticoid secretion after a maximal exercise-related stress in healthy humans (31). Conversely, it was shown that tadalafil administration is able, compared to placebo, to amplify mean salivary cortisol. The sites of action and the mechanisms involved in the observed effect of tadalafil on the hypothalamus–pituitary–adrenal axis response to physical stress are not known. However, these results suggest that PDE5 and/or PDE11A4 could have a role in the regulation of the hypothalamus–pituitary–adrenal axis.

**Thyroid**

PDE1A, PDE7A, and PDE8B are the PDEs most highly expressed in the thyroid (25, 26).

TSH regulates thyroid function through stimulation of the cAMP pathway. Its serum level is a sensitive indicator of thyroid function even within the normal range. It has been suggested that up to 65% of baseline TSH levels are genetically determined and could vary within the limit of the normal range in healthy people (32, 33).

Recently, a genome-wide association study was performed to identify genes associated with TSH levels in normal subjects (34). The strongest association was shown at the PDE8B locus. Indeed, an association between a single nucleotide polymorphism rs4704397 in the PDE8B gene and circulating TSH levels was observed. This suggests that PDE8B is one of the major genetic determinants of TSH levels. Each additional copy of the minor PDE8B A allele was associated with a TSH increase of 0.13 mIU/l (thyroxine (T 4) and triiodothyronine (T 3) levels were not assessed in this study). This finding in the Sardinian population was confirmed by a meta-analysis that included multiple populations (34). The proposed mechanism by which PDE8B may influence TSH levels is through control of cAMP signaling. PDE8B acts in the thyroid to catalyze the hydrolysis and inactivation of cAMP after TSH signaling. Thus, PDE8B polymorphisms may reduce cAMP in the thyroid, leading to a decreased thyroid stimulatory response to TSH and hence lower subsequent thyroid hormone production. This is likely to result via feedback in a higher TSH levels required to maintain T4 and T3 in the normal range. However, the consequence of this PDE8B polymorphism has not yet been shown in vitro.

Thus, it is possible that PDE8B genetic variants might be involved in regulation of TSH levels.

**Pituitary**

PDE1, PDE2, PDE4, and PDE11A are the PDEs most highly expressed in the pituitary (35–40). The physiological role of these PDEs in human pituitary has not been extensively investigated. Nonetheless, few studies conducted in rodents’ adenohypophysis demonstrated that PDEs have a role in the release of prolactin and ACTH.

First, it was shown that the addition of 3-isobutyl-1-methylxanthine (IBMX), a common inhibitor of PDE subtypes, increased cyclic nucleotides in primary culture of rats anterior pituitary cells (41). Moreover, application of IBMX caused a dose-dependent increase in basal prolactin release. In addition, PDE4 inhibitors are known to activate the hypothalamic–pituitary–adrenocortical system at the pituitary level, implicating PDE4 in the control of corticotroph cell function (42, 43). Recently, it was demonstrated that PDE1 and PDE4 are key cAMP metabolizing enzymes in rat corticotrophs cells (38). In the normal human pituitary gland and similarly to that reported in rodent pituitary, PDE activity was almost completely inhibited by IBMX treatment with major and similar contributions of the PDE1 and the PDE4 (37).

**Gonads**

**Testis** PDEs 1A, 1C, 3B, 5A, 8A, 10A, 11A are those most highly expressed in the testis (26, 44, 45).

The role of two of these PDEs has been investigated and demonstrated in the testis: PDE11A in spermatozoa physiology and PDE8A in the regulation of hormone production.

PDE11A. PDE11A plays a role in spermatozoa physiology. However, data are conflicting. PDE11A-deficient
mice present with alterations of spermatogenesis and sperm function. A significant reduction in sperm progression rate, sperm concentration, and percentage of alive ejaculated sperm compared with wild-type mice were shown in Pde11a−/− mice (30). However, despite these alterations, the fertility of PDE11-null mice and the viability, histological features, and anatomical abnormalities of offspring were comparable to that of wild-type mice.

Another way to demonstrate the role of PDE11A in spermatozoa physiology is to use PDE11A inhibitors. Tadalafil, a PDE5 inhibitor, has been tested, as it is the most effective available PDE11A inhibitor. There are conflicting reports about the inhibition of PDE11A using this medication. In a clinical trial, daily intake of tadalafil at doses of 10 and 20 mg for 6 months produced no change in spermatogenesis or reproductive hormones in men (46). Another study demonstrated that tadalafil causes a statistically significant decrease in sperm motility (47). In mice, it was shown that chronic overexposure to tadalafil causes testicular tissue alterations with decreased testis weight, degeneration, and atrophy of the seminiferous epithelium and decrease in sperm production.

As tadalafil inhibits PDE11 activity with a 40-fold weaker potency than for PDE5 activity, these effects should be carefully assessed before concluding that they are simply attributable to PDE11A inhibition in the testis (48).

These findings could be consistent with the involvement of the cAMP signaling pathway, and particularly PDE11A, in testis functions. However, studies with a potent and selective PDE11A inhibitor and more extensive clinical studies should be pursued to investigate the effects of PDE11A inhibition in testicular and sperm function.

PDE8A. Leydig cells are interstitial cells located adjacent to the seminiferous tubules in the testis and produce testosterone under the control of LH. cAMP is the major intracellular messenger for LH action on steroidogenesis, as stimulation of testosterone production by LH in Leydig cells is known to be mediated by an increase in the levels of cAMP (49).

PDE8A plays a key role in the control of LH signaling and steroidogenesis in Leydig cells. Using PDE8A-deficient mice, it was shown that LH-induced testosterone basal release was increased compared with controls (50). Leydig cells from deficient mice are sensitized to the effects of LH on testosterone synthesis. Thus, pharmacological manipulation of PDE8A could be used to modulate testosterone synthesis and represents a potential pharmacological target for modulation of testosterone synthesis.

Ovary. The PDEs, PDE3A and PDE4D are highly expressed in human ovary (26, 51, 52).

PDE3A. PDE3 is the predominant functional PDE family expressed in human oocytes (52). In addition, it has been demonstrated that inhibition of PDE3A blocks oocyte maturation in vitro and in vivo (53). Similarly, PDE3A-deficient mice are viable and ovulate a normal number of oocytes but are completely infertile as their oocytes contain higher levels of cAMP and fail to undergo spontaneous maturation (54).

PDE4D. PDE4D also plays a critical role in the ovarian follicle. It was shown in follicle culture that PDE4 inhibitors cause oocyte maturation in the absence of gonadotropin stimulation (55). In addition, s.c. injection of PDE4 inhibitors alone or in combination with low doses of human chorionic gonadotropin could induce ovulation in rats (56). Moreover, mice deficient in Pde4d exhibit impaired ovulation with reduced female fertility (57). This decrease in fertility is caused by impaired follicular function and development. Although inactivation of Pde4d does not cause a complete arrest of follicular development, the reduced viability of the oocytes in Pde4d−/− mice resulted in a consequent reduced number of ovulated oocytes. Furthermore, a diminished sensitivity of the granulosa cells to gonadotropins at the level of receptor-G-protein coupling might also take part in the decreased fertility of these mice. Gonadotropin responses at the level of cAMP accumulation in granulosa cells, estrogen production, and ovulation rate were decreased, suggesting that granulosa cell differentiation is disrupted after the inactivation of Pde4d.

PDEs and endocrine diseases

Table 2 summarizes the major implications of PDEs in endocrine diseases.

Adrenals

Primary PPNAD is a bilateral form of micronodular adrenal hyperplasia causing ACTH-independent Cushing syndrome. Most patients with PPNAD suffer from CNC. This is an autosomal dominant multiple neoplasia syndrome responsible for skin pigmented lesions, cardiac myxomas, and other endocrine and non-endocrine tumors. The CNC gene 1 encodes the PRKAR1A (58). However, over the last several years, it has become apparent that PPNAD, when isolated without other clinical signs of CNC, was less frequently explained by PRKAR1A mutations. Germ-line mutations in two PDEs, PDE11A and PDE8B, have been identified in such patients. Figure 3 summarizes the implications of these PDEs in adrenal Cushing syndrome.

PDE11A. A genome-wide scan associated with the study of allelic losses in the adrenal tumors of PPNAD patients using DNA chips have identified a region in 2q31–2q35 that encompasses the PDE11A gene (24). Further sequencing of the PDE11A gene in 16 patients.
with PPNAD but with no PRKAR1A mutation has uncovered five germ-line sequence variations, two producing a frameshift mutation disrupting the PDE11A4 adrenal-specific isoform protein, two missense substitutions, and one substitution that led to a premature stop codon. A decreased expression of PDE11A4 within the adrenal tumors of these patients was observed, together with increased cAMP and cGMP levels (24, 59). Subsequently, missense variants of PDE11A that are rare in the general population were found with increased frequency among patients with macronodular adrenocortical hyperplasia, adrenocortical adenomas, and adrenal cancer (60). This association of PDE11A4 variants and adrenocortical tumors suggests a role in the susceptibility to develop these tumors. Moreover, consistent with the hypothesis that PDE11A may play a role as a tumor suppressor gene, it has been reported that adrenal tumors expressing PDE11A variants present a loss of the wild-type allele, thus resulting in a significant reduction of enzyme levels in the affected tissue.

In addition, in patients with CNC and PRKAR1A inactivating mutations, an association of these PDE11A variants with the development of PPNAD and testicular tumors has been demonstrated. This suggests that PDE11A could be a modifier gene of the phenotype in patients with CNC due to PRKAR1A mutation (61). In vitro studies have shown that the simultaneous inactivation of PRKAR1A and PDE11A by siRNA leads to a stimulation of the PKA-dependent transcription (61). These observations are compatible with the hypothesis of a synergistic effect of PRKAR1A mutations and PDE11A4 variants in the tissues expressing PDE11A4 and in which tumorigenesis is sensitive to the dysregulation of the cAMP/PKA pathway.

**PDE8B** During the genome-wide search for genes conferring a predisposition to PPNAD, a second chromosomal locus located at 5q13 was identified (62, 63). This locus contains the gene encoding PDE8B. The PDE8B coding region was then sequenced in 22 patients with isolated micronodular adrenal disease and Cushing syndrome and a single base substitution

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<td>Could have a role in the pathogenesis of GH-secreting adenomas because of protein interaction between AIP and PDE2A</td>
<td>(72)</td>
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<td><strong>PDE4</strong></td>
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<td>Could have a role in the autonomous thyroid adenomas bearing a TSHR or Gsα mutation</td>
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<td><strong>PDEBB</strong></td>
<td>Adrenals</td>
<td>Predisposition gene to PPNAD (inactivating point mutations)</td>
<td>(37, 67, 69–71)</td>
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<tr>
<td><strong>PDE11A</strong></td>
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<td>Predisposition gene to PPNAD (inactivating point mutations, leading mainly to premature stop codon). Missense variants of PDE11A were found with increased frequency among patients with macronodular adrenocortical hyperplasia, adrenocortical adenomas, and adrenal cancer compared with control patients. PDE11A is a modifier of the phenotype in patients with CNC due to PRKAR1A mutations</td>
<td>(24, 59–61)</td>
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<td>Testis</td>
<td>Association between non-synonymous substitutions of PDE11A and familial testicular germ cell tumors</td>
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**Figure 3** Phosphodiesterases in adrenal Cushing syndrome. (A) The left part of the figure shows the control of the cAMP pathway in the normal adrenal cortex. The pituitary hormone ACTH (adrenocorticotropic) stimulates its specific seven-transmembrane receptor, leading to activation of adenylyl cyclase (AC) and cAMP synthesis. cAMP activate the protein kinase A made of two regulatory subunits (R) and two catalytic subunits (C). Activation of the phosphodiesterases (PDEs) stimulates degradation of cAMP to 5′-AMP leading to cAMP levels decrease. ACTH stimulates steroid synthesis and secretion and is required for adrenocortical cells survival. (B) The right part of the figure illustrates the dysregulation caused by PDEBB or PDE11A inactivating mutations. The reduced PDE activity leads to increased cAMP levels and PKA stimulation. This potentiates or mimics the effects of ACTH and takes part in the steroid oversecretion and/or adrenal nodular hyperplasia observed in animal models and/or human diseases. In adrenal Cushing syndrome, the negative feedback of cortisol on the hypothalamic and pituitary adrenal axis lead to reduced ACTH circulating levels.
(c.914A→C, p.His305Pro) was found in one patient. This substitution was not found in any of the 1030 unrelated control subjects studied (62).

In vitro studies performed in HEK 293 cells significantly showed higher cAMP levels after transfection with the mutant PDE8B, indicating an impaired ability of the protein to degrade cAMP (62, 63).

**Thyroid**

**PDE8B** As previously described, PDE8B genetic variants may be involved in regulation of TSH levels and could be responsible for the increased serum TSH occasionally observed in individuals with no evidence of thyroid autoimmunity or loss of function mutations in the thyroid hormone or TSHR genes (34).

PDE8B could also have a role in the regulation of thyroid function during pregnancy (64). Serum TSH, Free T4, and Free T3 were measured in 970 pregnant women at 28 weeks of gestation. The single nucleotide polymorphism rs4704397 genotype was available in 877 subjects. It was shown that TSH varied with genotype and was highest in patients with the AA genotype. These results suggested that a single nucleotide polymorphism in PDE8B leads to serum TSH concentration in the upper limit of the reference range and could even be associated with subclinical hypothyroidism during pregnancy.

**PDE4** In autonomous thyroid adenomas, cAMP signaling can be constitutively activated by mutations affecting two elements, the TSHR and the Gsα protein. Although somatic mutations in the TSHR gene are frequent finding in autonomous thyroid adenomas, somatic mutations of the Gsα gene are rare. It was also shown that some PDEs could have a role in the pathogenesis of these adenomas. A study demonstrated a PDE4 induction in the autonomous thyroid adenomas bearing a TSHR or Gsα mutation (65). In these tumors, a two to threefold increase in total PDE activity was observed. The authors demonstrated that this increase was due to the increase of PDE4 activity, with a tenfold higher activity than measured in the surrounding normal tissue. These results indicate that the constitutive activation of the cAMP pathway in autonomous thyroid adenomas is associated with the upregulation of PDE4. This suggests that in these adenomas, the induction of specific PDE expression constitutes a mechanism opposing the chronic cAMP increase.

**Pituitary**

It is well established that somatotroph cells represent a cell type in which the activation of the cAMP-dependant pathway leads to cell proliferation and differentiation. As a consequence, alterations of the cAMP pathway appear to be molecular hallmarks of most GH-secreting adenomas (9, 66). As PDEs catalyze cAMP, some authors hypothesize the role of these enzymes in the pathogenesis of GH-secreting adenoma.

**PDE4** It was initially shown that PDE activity was dramatically increased in human GH-secreting adenomas with activating Gsα mutations compared with wild-type Gsα adenomas and normal pituitary (37, 67). This high PDE activity was caused largely by PDE4. Indeed, a selective PDE4 inhibitor, rolipram, is nearly as effective as IBMX, a non-selective PDE inhibitor, in stimulating cAMP accumulation in intact cells and blocking the enzyme activity in membrane preparations.

The aryl hydrocarbon receptor-interacting protein (AIP) is a co-chaperon protein involved in the functional maturation of aryl hydrocarbon receptor. It has previously been shown that germ-line mutations in the gene encoding AIP cause pituitary adenomas predisposition (68). Close interactions were demonstrated between AIP and PDE4A5 (69). Indeed, AIP mutations disrupt protein interaction between AIP and PDE4A5 (70, 71). Another PDE, PDE2A, is also a known partner of AIP (72).

**PDE8B** The induction of PDE isoforms by gsp mutations was not limited to PDE4, but also involved PDE8B. Indeed, it was shown that expression of PDE8B was absent in the normal pituitary but was detectable in almost all GH-secreting adenomas and higher in adenomas with activating mutations of the Gsα gene (37).

**PDE11A** Recently, one study screened 78 acromegalic patients and 110 controls for the presence of variants of the PDE11A gene (73). The frequency of PDE11A missense variants in acromegalic patients was found to be only slightly increased compared with controls. In addition, the presence of the wild-type allele resulting in the normal expression of the enzyme in the majority of tumor tissues together with the lack of significant clinical phenotype suggests that these variants might only marginally contribute to the development of GH-secreting adenomas.

**Gonads**

**Testis** PDE11A. The PDE11A gene coding region was sequenced in 95 patients with testicular germ cell tumors from 64 unrelated multiple-case kindreds (74). Non-synonymous substitutions of PDE11A have been detected with a frequency significantly higher in patients with familial and bilateral testicular germ cell tumors compared with controls. Moreover, functional studies showed that these mutations reduce PDE activity and increase cAMP levels. Thus, PDE11A-inactivating sequence variants may contribute to inherited testicular germ line tumor susceptibility.
**Ovary** As it was shown that PDE8A is a key regulator of LH signaling and testosterone production in Leydig cells, one study evaluated the human PDE8A gene as a polycystic ovary syndrome (PCOS) candidate gene (75). This was based on the hypothesis that reduced PDE8 activity or expression would contribute to excessive ovarian androgen production. However, these authors showed that the more common of these PDE8A variants were not associated with PCOS, excluding a significant role of PDE8A as PCOS candidate gene.

**Conclusion**

Significant progress has been made toward the elucidation of the role of PDE in endocrine physiology. This is not surprising, considering the important role of the cAMP signaling pathway in endocrine glands. However, as is often seen in the progress of cell biology, the mechanisms that inactivate a cellular function are studied later than the activating mechanisms. Over the last decade, several observations have shown a dysregulation of PDEs in endocrine diseases. As the development of specific drugs to target PDEs have been successful in non-endocrine diseases, and the development of new drugs is conceivable, this could lead to new therapeutic approaches in endocrine disorders. However, despite the recent progress summarized in this review, it is clear that the field needs to be investigated more deeply. There is no doubt that future studies of PDEs will reveal new aspects of the endocrine physiology and pathophysiology helping to progress toward new treatments.

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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