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Review Article

EndoCompass project: research roadmap for adrenal and cardiovascular endocrinology

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Abstract

Background: Endocrine science remains underrepresented in European Union research programmes despite the fundamental role of hormone health in human well-being. Analysis of the CORDIS database reveals a persistent gap between the societal impact of endocrine disorders and their research prioritization. At national funding level, endocrine societies report limited or little attention of national research funding towards

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endocrinology. The EndoCompass project—a joint initiative between the European Society of Endocrinology and the European Society of Paediatric Endocrinology, aimed to identify and promote strategic research priorities in endocrine science to address critical hormone-related health challenges.

Methods: Research priorities were established through comprehensive analysis of the EU CORDIS database covering the Horizon 2020 framework period (2014-2020). Expert consultation in adrenal endocrinology was conducted to identify key research priorities, followed by broader stakeholder engagement including society members and patient advocacy groups.

Results: For adrenal disorders, research priorities span primary and secondary adrenal insufficiency, adrenal tumours, and endocrine hypertension. Key areas include development of biomarkers and replacement therapies, improved understanding of disease mechanisms, diagnostic procedure optimization, and establishment of pan-European registries. Special emphasis is placed on personalized treatment approaches.

Conclusions: The adrenal component of the EndoCompass project provides an evidence-based roadmap for strategic research investment. This framework identifies crucial investigation areas into adrenal disease pathophysiology, prevention, and treatment strategies, ultimately aimed at reducing the burden of adrenal disorders on individuals and society. The findings support the broader EndoCompass objective of aligning research funding with areas of highest potential impact in endocrine health.

Keywords: EndoCompass, adrenal, cardiovascular, funding, roadmap, adrenal insufficiency adrenal tumors endocrine hypertension

Introduction

The adrenal glands are a pair of remarkably dynamic endocrine organs. Their intricate structure and multifaceted functions make them a vital player in the orchestration of physiological responses to stress, salt and water balance, and metabolism.

The mesenchyme-derived adrenal cortex consists of 3 zones, each producing a specific class of steroid hormones:

- mineralocorticoids (aldosterone), regulating blood pressure, water, and electrolyte balance,
- glucocorticoids (cortisol), regulating stress, immune responses, and intermediary metabolism, and
- androgen precursors and adrenal-specific androgens.

The main regulator of cortisol secretion is adrenocorticotrophic hormone (ACTH), secreted from the pituitary, creating a pulsatile feedback loop. Aldosterone is largely regulated by the renin-angiotensin system and potassium levels.

The neural crest-derived adrenal medulla consists of chromaffin cells, modified secondary sympathetic neurones that produce catecholamines, noradrenaline, and (mainly) adrenaline.

Endocrine disorders of the adrenal cortex can be broadly divided into deficient hormone production (adrenal insufficiency), overproduction of hormones, and combinations of these, such as in congenital adrenal hyperplasia (CAH). Many of these conditions are rare, but overproduction of aldosterone (primary aldosteronism) and cortisol (mild autonomous cortisol secretion, MACS) affects millions of individuals living in Europe and they are major causes of hypertension, type 2 diabetes, obesity, and osteoporosis. Adrenal tumour types are highly diverse in terms of prevalence, malignancy, secretion level, and molecular mechanisms.

There are still major knowledge gaps in our understanding of the basic mechanisms underlying these diseases. Diagnostic procedures are often laborious and unspecific and lack standardization. Current treatment is unable to restore normal hormonal function, and patients often suffer from reduced quality of life and ability to work. Efficient diagnostic and therapeutic strategies for adrenal disorders are fundamental to public health in Europe, and in many areas, there is a high unmet medical need that requires increased research efforts.

Primary adrenal insufficiency, including CAH

Adrenal insufficiency is defined by the failure to produce cortisol and/or aldosterone from the adrenal cortex. This may be caused by a condition affecting the function of the adrenal cortex (primary adrenal insufficiency, PAI) or by a condition affecting the regulatory system (secondary/tertiary adrenal insufficiency, see below) (Figure 1).

Acquired PAI is most commonly caused by destruction of the adrenal by an autoimmune attack, infection, tumour, or haemorrhage. Inherited enzyme defects of steroidogenesis, CAH, are another common cause. Similar to PAI, there is a deficiency of cortisol; however, depending on the specific enzyme deficiency, this is accompanied by either deficiency or excess of mineralocorticoids and sex steroids, respectively.

The symptoms of adrenal insufficiency depend on the cause, but most patients experience fatigue, nausea, reduced stress tolerance, and weight loss. Skin pigmentation depends on ACTH concentrations; typically, patients with PAI show hyperpigmentation, while those with secondary and tertiary causes do not.

Epidemiology, societal impact, and research state of the art

The prevalence of PAI varies in different age groups. Genetic conditions commonly present during infancy and childhood; however, increasing evidence suggests delayed onset of milder forms.[1] The prevalence of acquired autoimmune PAI, also known as Addison's disease, is about 150/1 000 000 (about 100 000 cases in Europe), and the incidence is about 5/1 000 000 per year. This is a condition where the immune system attacks the adrenal cortex.[1] The most common cause of inherited PAI is CAH due to 21-hydroxylase deficiency, occurring in its severe classic form in about 1/15 000 live births (about 45 000-60 000 affected individuals in the whole of Europe).[2]

Autoimmune PAI commonly affects individuals between 30 and 50 years of age and is more common in females than males, with a female-to-male ratio of about 1.5.[3] The risk of developing autoimmune PAI is increased in patients with other autoimmune diseases, such as type 1 diabetes, autoimmune thyroid disease, pernicious anaemia, or vitiligo, and many develop several of these disorders, called autoimmune polyglandular syndromes.[4] The pathogenesis of autoimmune PAI is incompletely known. Almost all patients develop autoantibodies against 21-hydroxylase,[5] which can be used as a diagnostic biomarker,[6] but autoreactive T cells are thought to be the main mediators of the adrenocortical destruction.[7] The key associated genes were recently mapped in a genome-wide association study (GWAS), explaining 40% of the heritability across 9 loci,[8] and a polygenic risk score has been developed.[9]

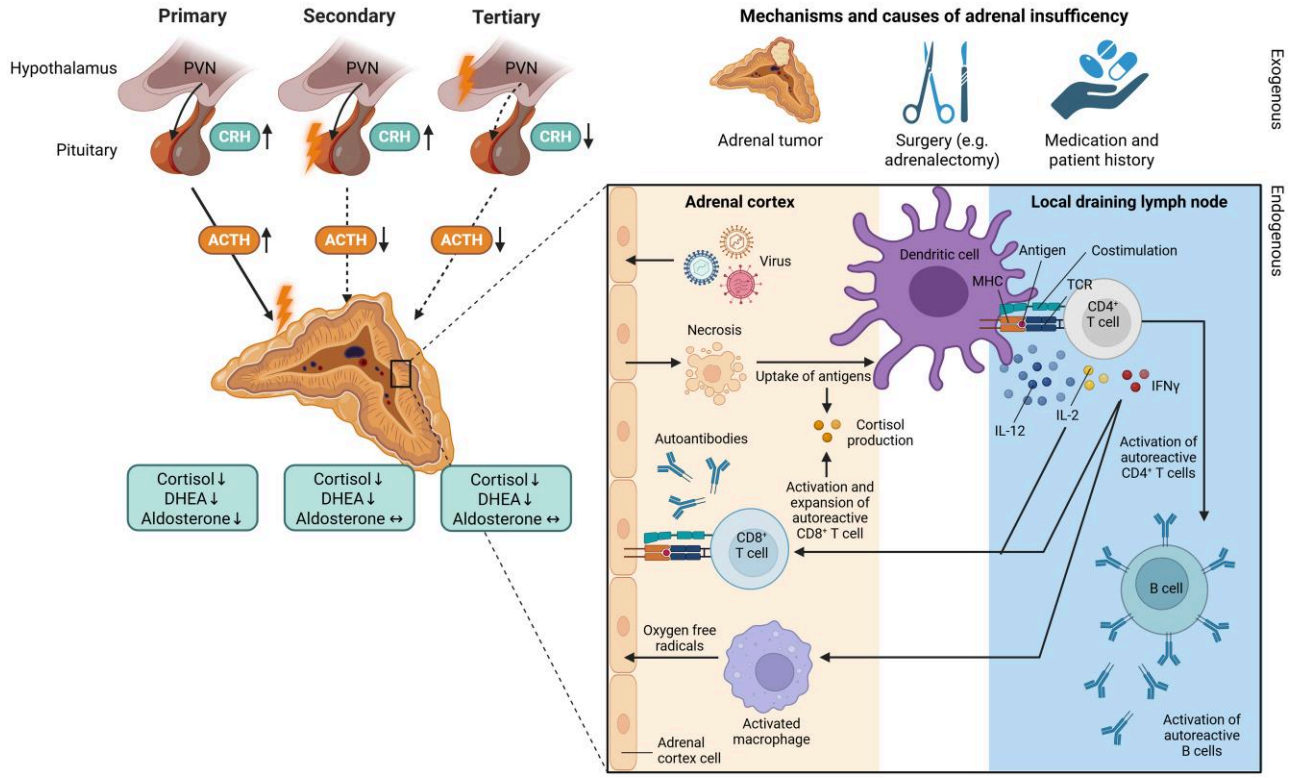

Figure 1. The left panel illustrates the hypothalmic-pituitary-adrenal axis in primary, secondary, and tertiary adrenal insufficiency. The upper right panel illustrates etiologies of adrenal insufficiency, with a detailed illustration of how a virus infection could break immunological tolerance and activate autoreactive T and B cells. ACTH, adrenocorticotropic hormone; CRH, corticotropin releasing hormone; DHEA, dehydroepiandrosterone; IL2, interleukin 2; IL-12, interleukin 12; MHC, major histocompatibility complex; TCR, T cell receptor.

The aetiology of PAI in the elderly population is quite different, dominated by infections, haemorrhage, and malignant diseases affecting the adrenals (for example, metastasis or primary tumours).

Diagnosis of monogenic forms of PAI is more common in children and adolescents but may also manifest in adults. Congenital adrenal hyperplasia is a group of monogenic disorders, leading to cortisol deficiency due to a lack of steroidogenic enzymes. The most common is 21-hydroxylase deficiency (>95% of cases), causing cortisol deficiency and androgen excess and, in two-thirds of cases, clinical apparent aldosterone deficiency.[2] Adrenal insufficiency develops in severe forms in the neonatal period. Females display different degrees of hyperandrogenism, but males have no distinct phenotype. Individuals with CAH have increased long-term comorbidities affecting most organ systems, and an increased early mortality has been suggested. Other monogenic forms are X-linked, including adrenoleukodystrophy caused by mutations in the *ABCD1* gene, affecting peroxisomal β-oxidation and leading to accumulation of very long-chain fatty acids. Adrenal hypoplasia congenita is caused by mutations in DAX1/NR0B1, a nuclear receptor protein involved in the regulation of steroidogenesis. Several other rare genetic causes are known.[1]

Current treatment relies on replacement of lacking hormones. In addition, forms of CAH associated with androgen excess require normalization of adrenal androgen concentrations. Standard replacement treatment is with hydrocortisone tablets 2 or 3 times daily in adults and 3 or 4 times daily in children and young people, combined with fludrocortisone once per day. Children, young people, and physically active adults frequently require additional oral sodium replacement. The role of adrenal androgen replacement is poorly defined, although women with autoimmune PAI are generally deficient. Congenital adrenal hyperplasia associated with hyperandrogenism often requires higher glucocorticoid doses than in PAI and secondary adrenal insufficiency to normalize adrenal androgen production.[2]

Recently, extended-release and modified-release glucocorticoid formulations have become available.[10,11] Experimental pump treatment, with both circadian and ultradian (pulsed) replacement therapy, is now also feasible. Several novel additional therapy modalities are currently under development to treat hyperandrogenism in CAH, including corticotrophin-releasing hormone antagonists;[12,13] however, their usefulness in wider clinical practice needs to be established.

Despite best practice replacement therapy, many patients experience reduced quality of life and capacity to work.[14] There is an association between corticosteroid replacement and cardiovascular disease, especially in women.[15] Thus, treatment mimicking the physiological situation is required, but not yet feasible in clinical practice.

Future research priorities

Pathogenesis of adrenal insufficiency

The development of more targeted interventions requires a better understanding of the pathogenesis of autoimmune PAI, and the genetic and the environmental factors that drive autoimmunity. Therefore, we advocate the development of mouse and other in vivo models to explore genotype–

phenotype associations and disease modulators/compensators. Furthermore, this will support the development of novel immune modulatory treatment aimed at stopping, reversing, or, ideally, preventing autoimmune PAI. Such treatment modalities include gene therapy, stem cells, and chimeric antigen receptor T-cell therapy.

Application of rapid clinical genetic testing to diagnose rare forms of adrenal insufficiency is in demand, and its health benefit needs to be defined (health economic models).

Natural course of adrenal insufficiency

The natural history of adrenal insufficiency and CAH is not fully understood. Therefore, it will be vital to establish patient registries and biobanks to map the natural course and long-term outcome, including growth, sexual function, fertility, pregnancy, quality of life, cardiovascular risk, bone health, and adrenal crisis.

Treatment of adrenal insufficiency

We need to develop novel replacement modalities to normalize cortisol and mineralocorticoid rhythms and to normalize adrenal androgen production in CAH. In addition, better tools to tackle adrenal crises, including strategies for prevention and early treatment of adrenal crisis (eg, a hydrocortisone penject device), will be needed to decrease hospitalization, comorbidities, and mortality.

A better understanding of adrenal stem cell physiology would provide the foundation to develop new treatment modalities to replace missing adrenocortical cells (PAI). In addition, other approaches to correct altered gene function (eg, by viral vectors in CAH and other monogenic diseases) or transplantation of tissue/cells would revolutionize treatment of adrenal insufficiency.

Biomarkers of corticosteroid action

The current lack of biomarkers of corticosteroid action complicates the design of clinical outcome studies. Thus, defining biomarkers for cortisol and mineralocorticoid effects and their use could support the individualization and optimization of corticosteroid replacement across the lifespan, including during puberty, pregnancy, and stress. Furthermore, biomarkers would be useful to identify and prevent systemic consequences of corticosteroid excess and deficiency. They could also be used as hard endpoints in future clinical studies.

Clinical management

There is a need to develop education and information programmes and assess their ability to promote health in patients.

Anticipated impact of future research

The aims would be improved quality of life and ability of patients with adrenal insufficiency to work, reduction of complications (fertility, mortality and overtreatment, with its metabolic side effects), and adrenal crisis reduction (decreased mortality).

Novel diagnostic, treatment, and monitoring tools will improve early diagnosis, outcomes of adrenal insufficiency, quality of life, and ability to work, reduce mortality and complications, and enable more participation by patients in their own disease.

Secondary and tertiary adrenal insufficiency

Individuals with secondary and tertiary adrenal insufficiency lack ACTH, which causes deficiency of cortisol and androgen production, leaving aldosterone production intact.

Epidemiology, societal impact, and research state of the art

Secondary adrenal insufficiency is due to deficient stimulation of the adrenal cortex by ACTH (see chapter on Pituitary diseases). When the suppression of ACTH production is caused by exogenous glucocorticoid treatment, it is called tertiary adrenal insufficiency. Glucocorticoids are a cornerstone in treating a wide range of medical conditions, such as autoimmune diseases, inflammatory disorders, severe allergic reactions, prevention of transplant rejection, and cancer. Their use is very common. Continuous (>3 months) oral glucocorticoids were found to be prescribed for 0.5% of the total population and 1.4% of patients aged 55 years or older.[16] In a population-based study from Denmark, the annual prevalence of systemic glucocorticoid prescription in primary care was 3% of the population and up to 10% among the elderly.[17] Even glucocorticoids applied locally such in the lungs and nose by inhalation or on the skin, can cause adrenal insufficiency but systematic studies of side effects are few, after both short- and long-term use. The prevalence of adrenal insufficiency and adrenal crises requires systematic studies. There is also little evidence on how to taper and stop glucocorticoid treatment.

Future research priorities

Define biomarkers for pharmacological glucocorticoid treatment

We need to develop biomarkers enabling us to individualize glucocorticoid treatment, to optimize treatment outcome, and minimize side effects. The sensitivity to glucocorticoids shows wide inter-individual variation, but usually patients are given a standard dose, putting many at risk of inferior treatment outcome, side effects, and complications.

Standardized tapering regimens

Evidence-based tapering regimes are lacking, and clinical trials are needed to define optimal and safe tapering of glucocorticoids, including reliable and efficient ways to screen for adrenal insufficiency.

Drug development

In order to reduce the side effects and complications of pharmacological glucocorticoid treatment, we need to develop novel glucocorticoids with fewer side effects.

Research into hypothalamus–pituitary–adrenal axis regulation

A number of patients experience permanent adrenal insufficiency after glucocorticoid treatment. We need research to understand why the hypothalamus–pituitary–adrenal axis "shuts down" in certain individuals and to develop ways to "reawaken" the axis, including cures for genetic disorders.

Patient education

We have to improve patient education to facilitate tapering and understand the difference between disease flare, glucocorticoid withdrawal, and adrenal insufficiency.

Anticipated impact of future research

Future research should allow improved diagnosis and outcome of secondary and tertiary adrenal insufficiency. This includes ways to individualize treatment and tapering of glucocorticoids and to reduce the risk of short-term (adrenal crisis) and long-term complications (eg, cardiovascular disease and osteoporosis).

Translational research questions are as follows:

- What is the differential impact of adrenal insufficiency on females and males as a consequence of altered steroid hormone levels, and how does this link into different health problems (eg, fertility issues)?
- What model systems, including animal models and organoids, are required to understand pathophysiology and systemic dysregulation due to hormone deficiency and excess?
- What is the effect of adrenocortical dysfunction on adrenal medullary function and catecholamine physiology?
- How can sex differences in adrenal diseases be explained?

Malignant adrenal tumours

These include adrenocortical carcinoma (ACC) and phaeochromocytoma and paraganglioma (PPGL).

Epidemiology, societal impact, and research state of the art

Adrenocortical carcinomas are rare tumours (between 0.5 and 2/1 000 000). Their clinical outcome is heterogeneous, with a 5-year survival ranging from 15% to 90%, mainly depending on initial tumour grade.[18] First-line treatment for patients with localized disease is surgical removal of the tumour. However, after a complete tumour resection, using current standard clinical and pathological features, it is not possible to properly predict whether the patient is going to remain free of disease or whether the disease will recur. Studies have identified different molecular subtypes with different outcomes, but proposed prognostic biomarkers have not been implemented in clinical practice so far.[19,20] For patients with localized ACC, adjuvant treatment by mitotane may be proposed.[21,22]

For patients with advanced ACC (either recurring or metastatic), effective treatments are dearly missed. Responses to routinely used mitotane and platin-based chemotherapies do not exceed 20%.[18] New therapies, including immunotherapy, insulin-like growth factor-1 receptor antagonists, or other tyrosine kinase inhibitors, have been tested with limited and unpredictable efficiency.[23] The lack of infiltration by cytotoxic T cells has spurred studies to investigate the importance of the tumour immune microenvironment.[24] Specifically, the immunosuppressive role of intra-tumour cortisol secretion in a subset of ACC might negatively impact the efficacy of immunotherapies and other targeted treatments. To what extent prior treatment with mitotane and/or cytotoxic chemotherapy further impairs responsiveness to immunotherapy is currently unknown.

Phaeochromocytomas and paragangliomas are tumours derived from the adrenal medulla or other sympathetic ganglia. The estimated prevalence of PPGLs is between 1/6500 and 1/2500. Approximately 15% of PPGLs are metastatic, with a heterogeneous 5-year survival rate varying from 40% to 80%.[25]

The majority of PPGLs are driven by a single inherited or acquired genetic variant. It is estimated that about 40% of patients carry a germline mutation in 1 of the 20 susceptibility genes, and a further 30%-40% of tumours are driven by somatic driver variants.[26] Genotype–phenotype correlations have facilitated personalized surveillance strategies, but management remains challenging due to the heterogeneous clinical behaviour of PPGLs, limited predictive markers of metastatic risk, and inefficient therapeutic strategies for metastatic disease. After complete resection of PPGLs, the risk of recurrence is difficult to predict. Germline *SDHB* variant status and tumour size >5 cm have been identified as the most sensitive predictors of local or metastatic recurrence.[27] International guidelines also define a category of high-risk patients (young patients and those with a hereditary predisposition, a large tumour, and/or an extra-adrenal paraganglioma), for whom lifelong annual follow-up is required. Recently, specific molecular alterations have been identified as sensitive predictors of metastatic potential, namely somatic *ATRX* variants, microsatellite instability, high cyclin-dependent kinase-1 expression, and *MAML3* fusions.[28] In this regard, metastatic PPGLs could benefit from precision medicine based on mutation status.

Future research priorities

1. To better stratify patients with malignant adrenal tumours at diagnosis, after surgery and during follow-up, combining clinical, morphological, and molecular markers.
   - For ACC after complete surgery, additional markers are needed to predict the risk of recurrence in order to personalize surveillance modalities and potential adjuvant treatments. In the case of advanced ACC, markers predicting response to existing treatments (mitotane, chemotherapy, immunotherapy, and tyrosine kinase inhibitors) are needed to identify, for each treatment, the small subset of patients for whom a response is expected—thus sparing precious time when the disease is growing rapidly, and heavy side effects for a majority of unresponsive treatments.
   - For PPGL, the known relevance of genetic status should be further exploited and combined with clinical, morphological, biochemical, and molecular imaging features to personalize treatment options, stratify long-term surveillance, and better identify those patients at highest risk of metastatic or aggressive disease. The penetrance of susceptibility genes should be investigated, as well as the potential modifying factors (environmental factors, family history and polygenic risk scores), to identify the factors, leading to recurrence or to the development of new tumours, for the patients and their relatives carrying the mutation.
2. To develop efficient treatments for advanced adrenal malignant tumours.

- Screening for targetable molecular alterations should be generalized for all advanced ACC and PPGL, in a time frame compatible with the potentially rapid evolution of the disease. Any targetable molecular alteration should direct the role for new treatments, with a systematic collection of the effect, whether positive or negative.
- The elucidation of mechanisms of resistance to immunotherapy is a priority. The identification of targetable factors that impair responsiveness to immunotherapy is urgently required. One prime example that requires further mechanistic understanding is the specific immunosuppressive action of secreted hormones and metabolites in metastatic adrenal tumours: cortisol for ACC and catecholamines and oncometabolites in PPGL. The impact on the tumour immune microenvironment should be explored in humans and in preclinical models, with the perspective of developing specific anti-tumour strategies, targeting intra-tumour blockade of hormone and metabolite secretions. In PPGL, the influence of genotype on tumour immune environment should also be specifically explored.

3. To pursue the research effort at the European level, owing to the rarity of these cancers.
   - Convenient clinical data-sharing solutions should be sought, targeting the inclusion of all patients with malignant adrenal tumours, and aiming at extensively reporting the drugs tested and their efficiency. These shared data should incorporate translational research arms, addressing the need for novel biomarkers of treatment response (eg, tumour/serum/urine metabolomics, genomics, and radiomics).
   - A European infrastructure promoting multicentric clinical trials should be created, testing the efficacy of innovative pharmacological and local treatments, aiming to reach sufficient statistical power to conclude whether the treatment is efficient or not.

Anticipated impact of future research

Patients with advanced ACC or PPGL are left with limited therapeutic options, so their therapeutic need is major.

Discoveries related to the specificity of hormones and immune-modulating metabolites secreted by adrenal tumours may impact cancer management in general, beyond the rare and specific adrenal tumours.[26-28]

Benign adrenocortical tumours

Epidemiology, societal impact, and research state of the art

Benign adrenal tumours are common, most often being observed incidentally, with a prevalence of 1%-8% on imaging and autopsy series. Among these common tumours, up to 40% demonstrate hormone hypersecretion, most frequently MACS.[29,30] Despite the absence of obvious clinical signs of Cushing's syndrome, MACS is associated with an increased prevalence of type 2 diabetes, obesity, hypertension, and dyslipidaemia, as well as osteoporosis and psychiatric symptoms (15%-40% higher), with a significant impact on morbidity and mortality.[29] Adrenal surgery may improve this outcome.[30,31] However, it is currently not possible to establish the precise impact of MACS at an individual scale, nor the benefit of correcting MACS on blood pressure, weight, and metabolism at the individual level. Finally, a subset of incidentally discovered tumours display intermediate morphological features.[30] For these patients, the evaluation of the malignancy risk is challenging (Figure 2).

Less common are benign tumours and benign adrenal cortex alterations (eg, bilateral adrenal nodular hyperplasia), responsible for overt Cushing's syndrome, associated with severe comorbidities and increased mortality.[32] In most cases, these diseases are sporadic, but occasionally they can be associated with familiar syndromes, especially in patients with bilateral macronodular and micronodular adrenal hyperplasia. Patients with adrenal Cushing's syndrome require specific treatments targeting cortisol excess and may benefit from genetic counselling to exclude germline genetic alterations occurring in one of the few causative genes that have recently been discovered.[33]

Future research priorities

1. To improve the management of patients with MACS.
   - Patients should be better stratified, addressing the following questions. Which are the best diagnostic criteria and best laboratory assays to recognize MACS in patients with adrenal tumours? Is autonomous cortisol secretion variable over the time? In the general population, what is the prevalence of MACS in common diseases such as hypertension, diabetes, overweight, and osteoporosis?
   - Treatments (steroidogenesis inhibitors, adrenolytic compounds, glucocorticoid receptor antagonists, and adrenal surgery) should be better evaluated. What are the benefits regarding blood pressure, metabolism, weight, bone density, and mortality)?
2. To differentially diagnose benign tumours, focusing on masses with borderline features. For these tumours, large collections of clinical, morphologic (radiomic, nuclear medicine), and molecular (metabolomic, genomic) data are required to better predict the risk of malignancy, using multimodal machine learning approaches.
3. To understand the biology and disease burden (cardiovascular and metabolic) of primary adrenal hyperplasia/dysplasia. There is a need to find the genes that predispose to these rare diseases as well as the potentially associated diseases, to understand their role, and to explore the penetrance in relatives, in order to improve the management of these patients and their relatives.

Anticipated impact of future research

Identifying the glucocorticoid contribution to common health disorders such as hypertension, overweight, diabetes, osteoporosis, and dyslipidaemia could greatly improve the individual management of patients presenting with these disorders.

Given the prevalence of adrenal incidentaloma on abdominal imaging, a standardized strategy for properly identifying tumours requiring extra work-up is needed.

Novel genes and mechanisms can lead to unpredictable development in other diseases, either rare or common.

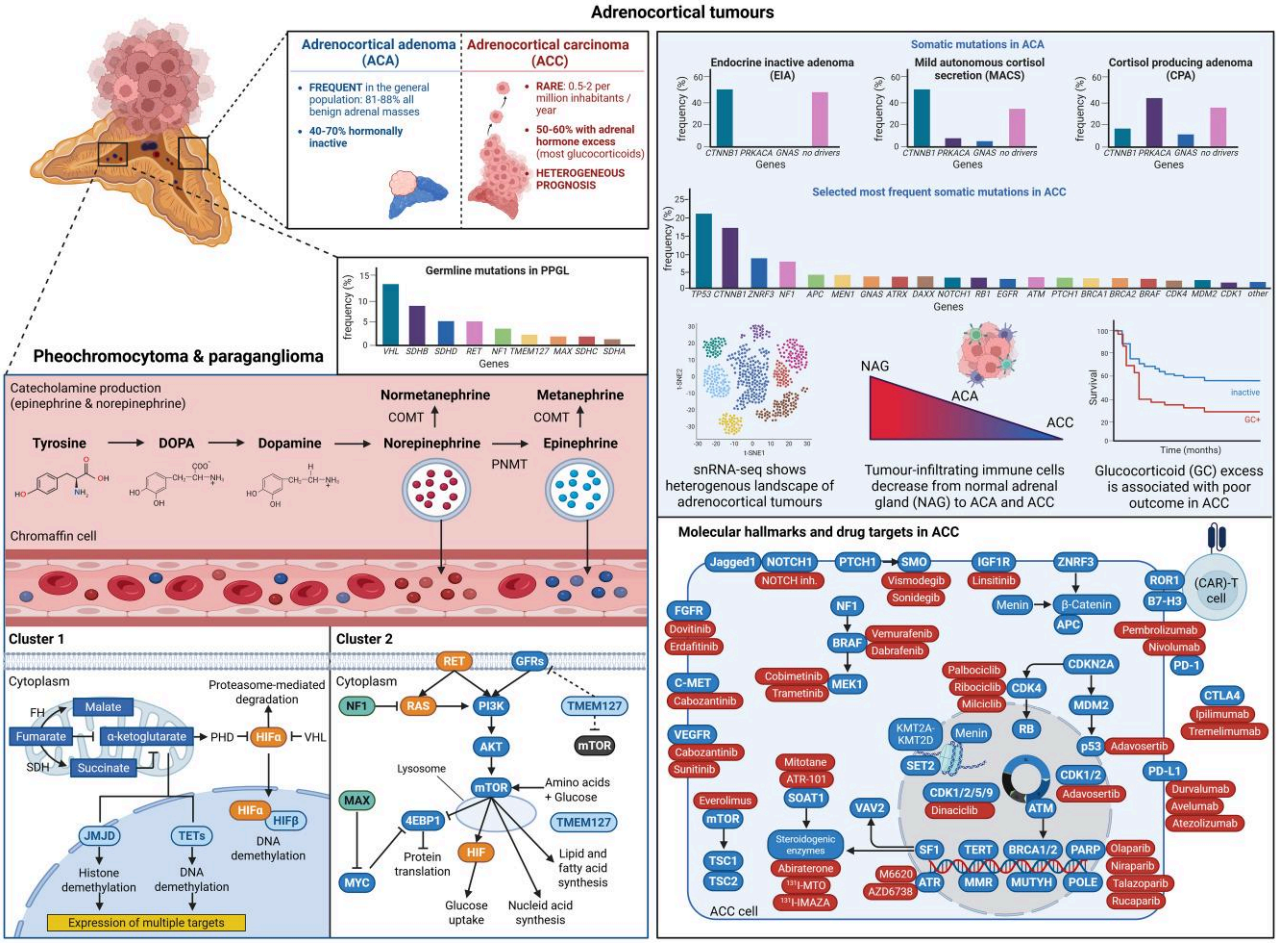

Figure 2. The upper left panel demonstrates the main types of adrenal tumors; adrenal adenoma, adrenal carcinoma, and pheochromocytoma/paraganglioma. The middle left panel depicts the synthetic pathway of catecholamines, the main hormone produced in the adrenal medulla. The lower left panel shows the molecular mechanisms and pathogenic pathways of the different mutations leading to pheochromocytoma/paraganglioma divided into cluster 1 (pseudohypoxia) and cluster 2. The upper right panel shows genes involved in the pathogenesis of adrenal adenomas and carcinomas. The lower right panel shows the molecular hallmarks and drugs involved in adrenocortical carcinoma.

Endocrine hypertension

Epidemiology, societal impact, and research state of the art

Arterial hypertension is the most important cardiovascular risk factor, accounting for more than 10 million deaths per year due to myocardial infarction, heart failure, stroke, cognitive disorders, end-stage renal disease, and premature death.[34] Within Europe, hypertension places increased strain on healthcare systems by negatively affecting economic development and impairing the health of many Europeans, particularly the elderly population.

A significant proportion (5%-20%) of patients with hypertension suffer from so-called secondary hypertension, due to a specific, identifiable, and curable underlying disease. Among them, endocrine hypertension constitutes most cases and is a major target for stratified intervention. The main endocrine causes of hypertension are a group of adrenal disorders resulting in increased production of hormones that affect blood pressure, mainly aldosterone (primary aldosteronism, PA), catecholamines (PPGL), and cortisol (Cushing's syndrome) (Figure 3).

Due to the diagnostic complexity of the work-up of these diseases, patients remain exposed to increased cardiovascular and metabolic risks and diminished quality of life, because of delayed diagnosis and treatment and the specific cardiovascular effects of hormone excess, which increase their risk beyond that of blood pressure-matched hypertensive patients. Phaeochromocytoma and paraganglioma and Cushing's syndrome are detailed above; here, we will focus on research priorities and future perspectives relating to primary aldosteronism.

Primary aldosteronism is the most common form of secondary and curable hypertension, affecting 6% of the hypertensive population in primary care, and up to 20% of patients with treatment-resistant hypertension.[35,36] Given the diagnostic complexity, including invasive adrenal vein sampling, <2% of high-risk patients with treatment-resistant hypertension are tested for primary aldosteronism over their lifetime, and much fewer than 1% are ever diagnosed or appropriately treated with a targeted therapy.[37,38] In addition, recent clinical evidence suggests a continuum between dysregulated aldosterone production and primary aldosteronism in patients with hypertension, which parallels the severity of hypertension and may play a role in the development of high blood pressure in the general population.[39]

Primary aldosteronism is caused by autonomous aldosterone production from the adrenal cortex, due in most cases

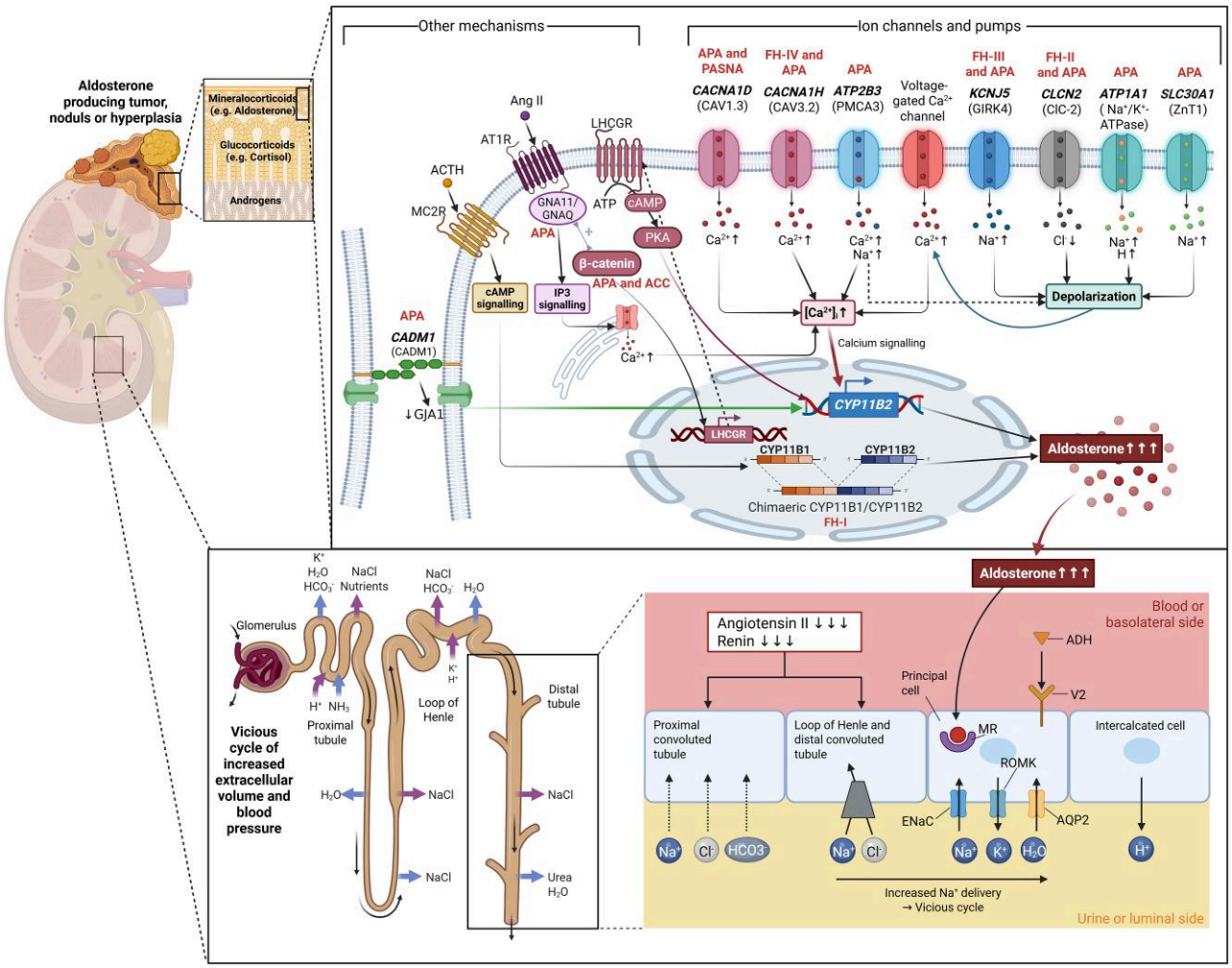

Figure 3. The left panel illustrates an adrenal gland with different types of aldosterone producing lesions. The upper right panel shows the various genetic causes and molecular mechanisms by which aldosterone is overproduced. Mutations in genes coding for different ion channels and pumps lead to cell membrane depolarisation and/or increase in intercellular calcium, which activates the biosynthetic pathway leading to increased aldosterone production. The lower right panel illustrates how binding of aldosterone to the mineralocorticoid receptor leads to retention of NaCl and water leading to arterial hypertension. High levels of aldosterone, suppresses renin, and angiotensin II levels. ACC, adrenocortical carcinoma; ACTH, adrenocorticotropic hormone; Ang II, angiotensin II; APA, aldosterone-producing adenoma; AT1R, angiotensin II receptor type 1; cAMP, cyclic adenosine mono phosphate; CYP11B1, cytochrome P450 family 11 subfamily B member 1 (encoding 11-beta-hydroxylase; CYP11B2, cytochrome P450 family 11 subfamily B member 2 (encoding aldosterone synthase); IP3, inositol 3-phosphate; LHCGR, luteinizing hormone/choriogonadotropin receptor; PKA, protein kinase A.

to a unilateral aldosterone-producing adenoma (APA), which is amenable to surgical cure, or bilateral adrenal hyperplasia (BAH), which can be treated by mineralocorticoid receptor antagonists (MRA) and possibly aldosterone synthase inhibitors (ASI) currently under development.[40,41]

Four familial forms (familial hyperaldosteronism types I-IV) and 1 rare disease (primary aldosteronism, seizures, and neurological abnormalities, known as PASNA) have been described. Familial forms account for ~6% of cases of primary aldosteronism, are transmitted as an autosomal dominant trait, and are due to heterozygous germline mutations in different genes. Age of onset is variable, with most cases being diagnosed before 20 years of age. Somatic mutations in the same genes, as well as in additional ones, are found in more than 90% of cases of APA. Mutations affect genes coding for ion channels (*KCNJ5*, *CLCN2*, *CACNA1D*, *CACNA1H*, *SLC30A1*) or ATPases (*ATP1A1*, *ATP2B3*) involved in the regulation of aldosterone biosynthesis, and genes regulating other cellular functions (*CTNNB1* and *GNA11/GNAQ*, *CADM1*).[41,42] Somatic mutations have also been identified in so-called aldosterone-producing micronodules (also called aldosterone-producing cell clusters) in adrenals with an APA, in BAH, and in normal adrenals.

In addition, genetic loci that increase the susceptibility of developing primary aldosteronism have recently been identified by GWAS, suggesting a continuum between APA and BAH.[43,44] These risk loci are partially shared with genetic loci identified for blood pressure, providing a mechanistic basis to the continuum between dysregulated aldosterone production and primary aldosteronism observed in hypertension.

Future research priorities

Early detection of primary aldosteronism and initiation of targeted treatment have a major impact on clinical outcome and survival, given the important contribution of aldosterone excess to target organ damage. Since primary aldosteronism is one of the most underdiagnosed, prevalent diseases worldwide,

effective screening strategies constitute a top priority and a major unmet need. Future research priorities include implementation of new stratification biomarkers directed at primary aldosteronism, new approaches for subtyping unilateral versus bilateral primary aldosteronism, identification of patients who would most benefit from surgery, stratification of patients for optimal treatment strategies, establishment of surrogate biomarkers for the underlying genetic causes, and development of new targeted treatments. The following are specific research priorities.

1. To implement new biomarkers and artificial intelligence (eg, omics biomarkers, clinical scoring system, B-type natriuretic peptide) for improved diagnosis, subtype identification, treatment, and prediction of outcome following specific surgical or medical therapy (MRA, ASI).
2. To investigate and optimize new imaging techniques, including ASI-based positron emission tomography ligands, for:
   - diagnosis and subtype identification,
   - prediction of outcome after surgery, to identify patients who will benefit from unilateral adrenalectomy (identification of patients with asymmetric primary aldosteronism, or latent foci of autonomous aldosterone production in the contralateral adrenal, which might become activated after removal of the dominant adrenal), and
   - understanding the natural history of development of aldosterone-producing micronodules and to discover whether they are a maladaptive response to excess salt intake, and are preventable/reversible by reduction of salt intake.
3. To implement new clinical trials:
   - to assess new diagnostic and therapeutic procedures,
   - to assess whether screening for primary aldosteronism in all hypertensive patients improves morbidity, mortality, and quality of life,
   - to establish whether targeted treatment with ASI and MRA reduces the cardiovascular and metabolic risk for patients along the continuum of dysregulated aldosterone biosynthesis from low-renin hypertension to florid primary aldosteronism,
   - to assess therapeutic options in women with primary aldosteronism during pregnancy, and
   - to assess the value of lifestyle interventions (ie, reduced salt intake) to improve cardiovascular outcome and quality of life in patients with bilateral PA.
4. To investigate the genetic contribution to primary aldosteronism development and outcome, including:
   - the relationship between dysregulated aldosterone production, primary aldosteronism susceptibility alleles, and resistant hypertension
   - whether different genotypes in APA reflect a different pathogenesis and are associated with a different prognosis, and to validate surrogate biomarkers for somatic mutations to select patients who will benefit from diagnostic/therapeutic interventions.

Anticipated impact of future research

Future research should allow improved diagnosis and outcome for patients with primary aldosteronism, reducing cardiovascular risk and improving quality of life through earlier and better targeted treatment. This may extend to patients along the continuum of dysregulated aldosterone biosynthesis from low-renin hypertension to florid primary aldosteronism.

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Authors' contributions

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