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INVITED SPOTLIGHT REVIEW

New aspects of endocrine control of atrial fibrillation and possibilities for clinical translation

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Abstract

Hormones are potent endo-, para-, and autocrine endogenous regulators of the function of multiple organs, including the heart. Endocrine dysfunction promotes a number of cardiovascular diseases, including atrial fibrillation (AF). While the heart is a target for endocrine regulation, it is also an active endocrine organ itself, secreting a number of important bioactive hormones that convey significant endocrine effects, but also through para-/autocrine actions, actively participate in cardiac self-regulation. The hormones regulating heart-function work in concert to support myocardial performance. AF is a serious clinical problem associated with increased morbidity and mortality, mainly due to stroke and heart failure. Current therapies for AF remain inadequate. AF is characterized by altered atrial function and structure, including electrical and profibrotic remodelling in the atria and ventricles, which facilitates AF progression and hampers its treatment. Although features of this remodelling are well-established and its mechanisms are partly understood, important pathways pertinent to AF arrhythmogenesis are still unidentified. The discovery of these missing pathways has the potential to lead to therapeutic breakthroughs. Endocrine dysfunction is well-recognized to lead to AF. In this review, we discuss endocrine and cardiocrine signalling systems that directly, or as a consequence of an underlying cardiac pathology, contribute to AF pathogenesis. More specifically, we consider the roles of products from the hypothalamic-pituitary axis, the adrenal glands, adipose tissue, the renin–angiotensin system, atrial cardiomyocytes, and the thyroid gland in controlling atrial electrical and structural properties. The influence of endocrine/paracrine dysfunction on AF risk and mechanisms is evaluated and discussed. We focus on the most recent findings and reflect on the potential of translating them into clinical application.

Keywords Atrial fibrillation • Arrhythmia • Endocrine system • Heart

This article is part of the Spotlight Issue on Atrial Fibrillation.

1. The hypothalamus-pituitary axis and AF

The hypothalamus-pituitary axis is a key component of the endocrine system. The pituitary gland is located in the sella turcica, a pouch of the sphenoid bone, and connected to the hypothalamus via the hypophyseal stalk. It is composed of the anterior (adenohypophysis) and posterior (neurohypophysis) pituitary, embryologically separate, and functionally independent units. The posterior pituitary secretes oxytocin and vasopressin synthesized in the hypothalamus; they do not have any known direct electrophysiological effects or associations with atrial fibrillation (AF). The anterior pituitary secretes the six tropic hormones, thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), growth hormone (GH), follicle-stimulating hormone (FSH), luteinizing

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hormone (LH), and prolactin, in response to stimulation from the hypothalamus. Over or underproduction of pituitary hormones lead to characteristic disease-conditions (*Figure 1*).

ACTH stimulates cortisol production by the adrenal cortex. Cushing's disease is caused by pituitary ACTH-dependent hypercortisolism.[1] Cushing's syndrome can be caused by ectopic ACTH-secreting extra-pituitary tumours and iatrogenic glucocorticoid administration. AF is more prevalent in patients taking high-dose exogenous corticosteroids[2] and in those with cortisol-secreting adrenal adenomas vs. age-matched controls[3]; the association between Cushing's disease *per se* and AF is not well-characterized and the underlying mechanisms are incompletely understood. Cushing's syndrome/disease causes important AF-associated risk factors, like hypertension, diabetes, dyslipidaemia, and obesity.[4,5] Adrenal insufficiency results in hypocortisolism and can be primary (adrenal), secondary (pituitary), or tertiary (hypothalamus). Association between adrenal dysfunction and AF has not been described.

Glucocorticoid receptors (GRs) are expressed in cardiomyocytes and mediate a wide range of genomic and non-genomic anabolic and metabolic effects. The electrophysiological effects of GR activation, particularly with respect to AF,[6] are understudied; however, cortisol affects intracellular calcium (Ca^{2+}) homeostasis. Hydrocortisone administration led to a protein kinase C (PKC)-dependent shortening of the ventricular action potential duration (APD) and changes in Ca^{2+}-transients[7], while adrenalectomized rats showed abnormal sarcoplasmic Ca^{2+}-uptake correctable with exogenous dexamethasone.[8] These effects may be due to serum- and glucocorticoid-inducible kinase 1 (SGK1)-mediated upregulation of cardiac potassium (K^+) currents, including I_{to}, I_{Ks}, I_{Kr}, and I_{Kur}.[9,10] Adrenal insufficiency is associated with QT-prolongation and polymorphic ventricular tachycardia responsive to exogenous corticosteroids.[11,12] While excess cortisol increases the risk of AF, likely mediated by a combination of direct electrophysiological effects and indirectly through AF-associated risk factors, the effects of cortisol deficiency on atrial electrophysiology and AF are unknown. Recent studies have identified the importance of GR-transcriptionally induced glucocorticoid-induced leucine zipper (GILZ or tsc22d3) protein. GILZ mediates multiple effects of glucocorticoids that has not been linked to AF potentially due to more selective, as opposed to glucocorticoids, effects.[13]

GH is secreted by the anterior pituitary and has direct as well as indirect anabolic and positive inotropic effects mediated via the GH-directed hepatic secretion of insulin-like growth factor (IGF)-1.[14] Both GH excess and deficiency have been associated with increased cardiac arrhythmias, including AF, cardiovascular morbidity, and mortality.[15] Chronic GH excess, most often caused by a pituitary GH-secreting adenoma, leads to acromegaly, with typical morphological and clinical features. Elevated GH is associated with left ventricular (LV) hypertrophy, left-sided valvular heart disease, and other cardiovascular risk factors for AF, including diabetes, coronary artery disease, hypertension, and dyslipidaemia.[16] The mechanism underlying acromegaly-associated AF has not been fully elucidated but likely involves left atrial (LA) enlargement with pro-fibrillatory structural remodelling (*Figure 2*).

GH deficiency, a common manifestation of hypopituitarism, presents with growth retardation in children and as a cardiometabolic syndrome in adults.[15] Patients with GH deficiency GH develop hypertension, reduced LV mass (*Figure 2*),[17] and LA structural remodelling that may mediate increased AF risk in patients with GH deficiency. Cardiomyocytes express GH and IGF-1 receptors but there are no reported direct effects of GH/IGF-1 on atrial electrophysiology.[18]

FSH and LH stimulate oestrogen production in women (ovaries) and testosterone in men (testis), among other functions. Changes in cardiac electrophysiology across the menstrual cycle have been described, with

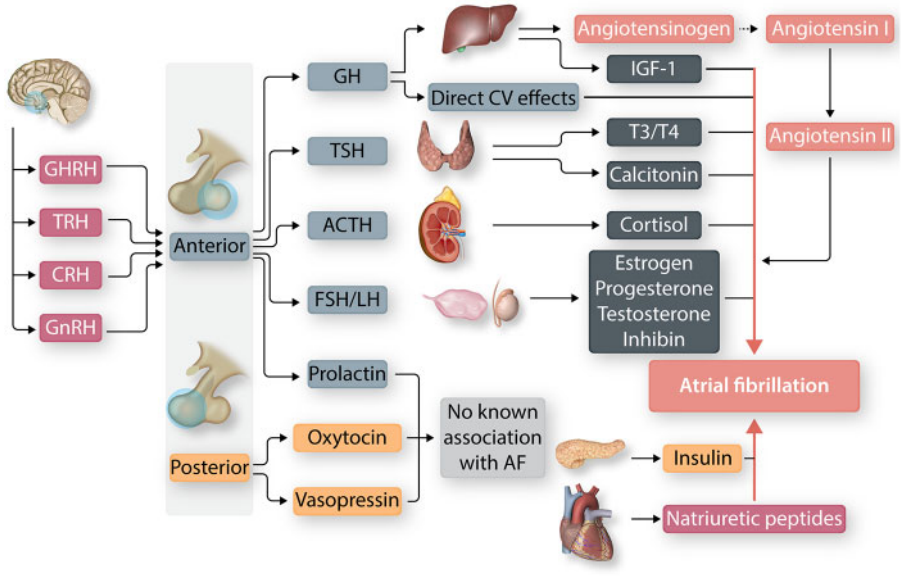

Figure 1 Summary of the endocrine glands and hormones associated with atrial fibrillation (AF). The anterior pituitary secretes tropic hormones in response to hypothalamic stimulation. Tropic hormones stimulate the release of physiologically active hormones from their target organ(s). The posterior pituitary hormones do not have known direct electrophysiological effects. ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; CV, cardiovascular; FSH, follicle-stimulating hormone; GH, growth hormone; GHRH, GH releasing-hormone; GnRH, gonadotropin-releasing hormone; IGF-1, insulin-like growth factor-I; LH, luteinizing hormone; T3, triiodothyronine; T4, tetraiodothyronine; TRH, thyrotropin-releasing hormone.

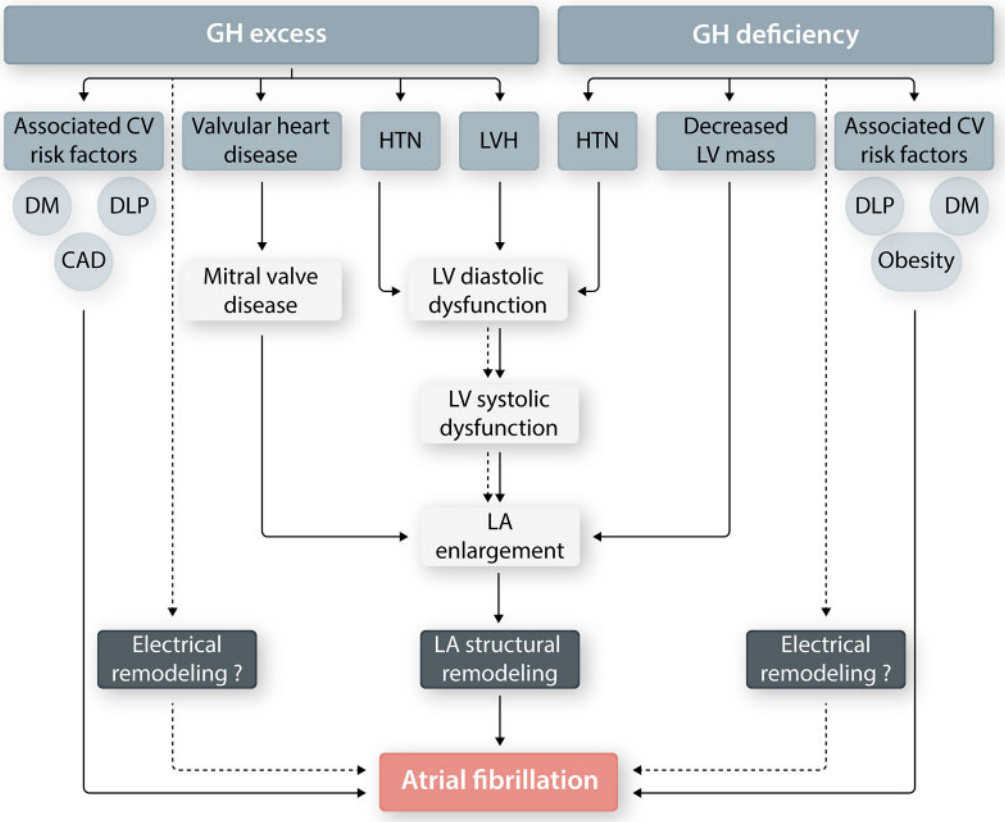

Figure 2 Growth hormone (GH) and AF. GH excess and deficiency have both been associated with an increased risk of AF. Chronic GH excess leads to left-ventricular (LV) diastolic dysfunction and left-atrial (LA) enlargement, contributing to pro-arrhythmic LA structural remodelling. In addition, GH deficiency has been associated with decreased LV mass and LV systolic dysfunction. GH dysregulation also often co-exists with pro-AF cardiovascular (CV) risk factors [i.e. hypertension (HTN), diabetes (DM), dyslipidaemia (DLP), coronary artery disease (CAD)]. The effect of GH excess and/or deficiency, if any, on LA electrophysiology (electrical remodelling) is not known.

oestrogen having APD-prolonging effects (follicular phase) while progesterone tends to shorten APD (luteal phase) by decreasing and increasing K^+ repolarizing currents, respectively[19]; however, oestrogen abnormalities have not been formally linked to a higher risk of AF.

Low testosterone levels can result from primary (testis), secondary (pituitary), or tertiary (hypothalamus) male hypogonadism in young individuals, or as the result of normal ageing in older men.[20] Males with lower testosterone levels have worse cardiovascular outcomes in general, including higher rates of AF.[21] Low testosterone levels are associated with several AF-related cardiovascular risk factors such as diabetes, premature coronary artery disease, dyslipidaemia, and obesity. Accordingly, recent work suggests that transgender women on hormonal therapy might be at increased risk of AF[22]; however, the available data are scarce, and a larger database is needed to confirm this association.

Furthermore, proinflammatory markers like C-reactive protein (CRP) and interleukin-6 (IL-6) have an inverse correlation with testosterone levels,[23] suggesting that inflammation may contribute to pro-fibrillatory atrial structural remodelling. Testosterone affects cardiac electrophysiology, as castrated rats showed increased expression of the ryanodine receptor type-2 (RyR2), sodium (Na^+)/Ca^{2+} exchanger (NCX), late Na^+ current (I_{NaL}), APD prolongation, and higher AF susceptibility vs. control animals.[24,25] Androgen receptor knock-out (KO) rats have reduced resting membrane potential, increased APD, and enhanced sensitivity to isoproterenol-induced delayed afterdepolarizations,[26] that are partly reversed by testosterone replacement therapy.[20]

A TSH-producing adenoma is the most common cause of central hyperthyroidism, a rare cause of thyrotoxicosis. Similarly, central hypothyroidism is much less common than its primary counterpart. Although poorly characterized, the cardiovascular consequences of central hypo-/hyperthyroidism are expected to parallel those observed with primary hypo-/hyperthyroidism, as described below.

Prolactin stimulates milk production in the gravid woman and has not been association with AF.

2. The adrenals and AF

The adrenal, or suprarenal, glands are composed of two embryologically distinct and functionally independent cortical and medullary units. The adrenal cortex contains three layers secreting aldosterone (zona glomerulosa), cortisol (zona fasciculata), and androgens (zona reticularis).

The adrenal medulla is part of the sympathetic nervous system and releases epinephrine and norepinephrine.

Aldosterone is normally secreted in response to hypovolemia and hyperkalaemia and binds mineralocorticoid receptors (MRs) to regulate $Na^+/K^+/H^+$ homeostasis by activating the epithelial Na^+ channel (ENaC) in the nephron distal tubule and collecting duct.[27] MRs are also expressed on other cell types, including atrial and ventricular cardiomyocytes. The association between aldosterone and AF has most clearly been demonstrated in patients with primary hyperaldosteronism (PA; renin-independent aldosterone production), the most common cause of secondary hypertension.[28] AF is more prevalent in patients with PA (7.3%) vs. matched patients with essential hypertension (0.6%)[29], adrenalectomy lowers the PA-associated risk of AF[30] and the MR-specific antagonist eplerenone is associated with a 42% relative risk reduction of AF,[31] all suggesting a potential role of aldosterone in the pathogenesis of AF independent of upstream regulatory hormones (i.e. renin/angiotensin-II).

The mechanisms linking hyperaldosteronism and AF are complex and incompletely understood (*Figure 3*). However, chronic excess aldosterone leads to LA enlargement and remodelling, indirectly via hypertension and diastolic dysfunction and/or directly via blood pressure-independent effects.[32–34] Aldosterone-binding to cardiac macrophage MRs increases expression of the profibrotic markers transforming growth factor-beta 1 (TGF-β1), matrix metalloproteinase-12, tumour necrosis factor-alpha (TNFα), and plasminogen activator inhibitor-1 (PAI-1)[35,36], promotes macrophage-mediated oxidative stress[37] and stimulates the Keep1/Nrf2-dependent cardiac fibroblast to myofibroblast transformation[38] contributing to pro-fibrillatory LA structural remodelling. Conduction time and P-wave duration are increased in a rat model of hyperaldosteronism, compatible with increased atrial fibrosis and slowed conduction.[39]

Aldosterone also has direct electrophysiological effects, the clinical significance of which remains to be fully elucidated. Aldosterone administration to rats caused APD shortening, mediated by an increase in Kir2.1 (inward rectifier K^+ current, I_{K1}) and Kv1.5 (ultrarapid delayed rectifier K^+ current, I_{Kur}) expression; these changes were reversed by the MR antagonist spironolactone.[40] Conversely, ventricular APD was prolonged in a MR-overexpression model because of the downregulation of transient outward K^+ current (I_{to}) and upregulation of L-type Ca^{2+} current (I_{CaL}).[41] It has been shown that ventricular I_{CaL} magnitude correlates with aldosterone levels[42,43] and MR-activation increases sarcoplasmic-reticulum (SR) Ca^{2+}-sparks and delayed afterdepolarizations,[44]

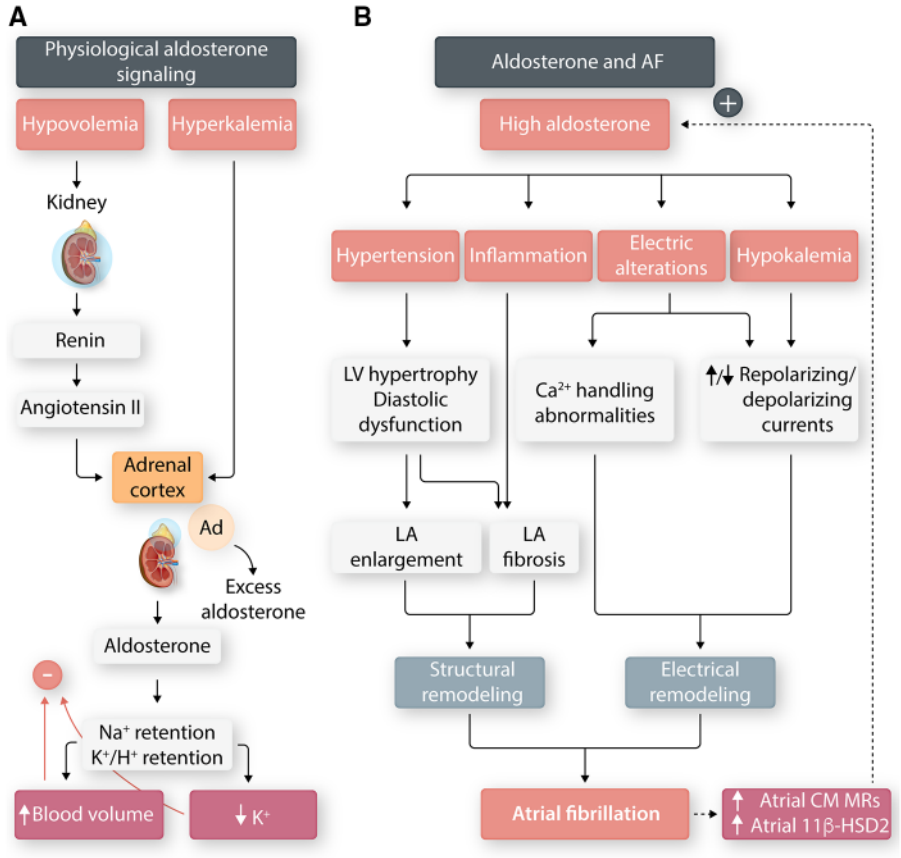

Figure 3 Hyperaldosteronism and AF. (*A*) Hypovolemia and hyperkalaemia are the primary physiological stimuli for adrenal aldosterone secretion, which acts on the nephron distal tubule and collecting duct to retain Na^+ and excrete K^+. (*B*) Mechanism of aldosterone-related AF. Hyperaldosteronism causes angiotensin-independent hypertension and left atrial (LA) inflammation, leading to pro-fibrillatory LA remodelling. It also produces pro-AF electrical remodelling in the form of LA action potential-shortening, increased sarcoplasmic reticulum Ca^{2+} sparks, and delayed afterdepolarizations. Sustained AF may potentiate the effects of hyperaldosteronism by upregulating of the mineralocorticoid receptor (MR) on AF atrial cardiomyocytes (CMs). Furthermore, AF increases 11b-hydroxysteroid dehydrogenase type 2 (11b-HSD2), which metabolizes cortisol, thereby increasing MR occupancy by aldosterone.

implicated in AF pathophysiology. A mouse model of spontaneous AF was associated with increased 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which inactivates cortisol, thereby allowing for increased MR occupancy by aldosterone.[45] Patients with AF have upregulated expression of MRs vs. sinus-rhythm controls[46] and MR antagonists reduce the risk of AF in heart failure patients.[31] Hence, AF may itself potentiate aldosterone's proarrhythmic effects.

Pheochromocytomas are epinephrine and norepinephrine-secreting adrenal tumours. The excess catecholaminergic state leads to hypertension, myocardial ischaemia/or, and cardiomyopathy.[47] Cardiac arrhythmias are common in pheochromocytoma and AF was documented in 11.3% of patients with this condition, all of which responded to tumour resection.[48]

3. Obesity and AF

Obesity and AF are both reaching epidemic levels. Obesity can result from endocrine abnormalities, and adipose tissue secretes a number of bioactive hormones.[49] Obesity is a well-established AF risk factor.[45] Weight loss reduces the risk of AF in obese patients improves outcomes after AF catheter ablation and reverses obesity-related electrical remodelling.[50] The relationship between obesity and AF has been framed into a two-component model: the *corporal load model* and the *lipotoxicity model* (*Figure 4*).[51]

The corporal load model stipulates that the increase in hemodynamic load imposed by excess weight leads to left ventricular (LV) hypertrophy, diastolic dysfunction with secondary LA enlargement, and pro-fibrillating remodelling. Interestingly, excess lean body mass, not merely adipose mass, is an important mediator of obesity-associated AF risk.[52]

The lipotoxicity model refers to the direct proinflammatory and profibrotic states associated with obesity. Obesity induces pro-inflammatory signalling in the atria[53] that can promote both ectopic firing and an AF-maintaining electrical and structural substrate, ultimately leading to AF.[54] Visceral adiposity is associated with increased blood leukocyte count, CRP, IL-6, and TNF-α.[55,56] Accelerated fibrogenesis mediated by the TGF-β1, connective tissue growth factor (CTGF), and endothelin-1 systems,[57] among others, contributes to the proarrhythmic lipotoxic effect. Epicardial adipose tissue (EpAT) is in direct contact with the epicardium and shares its blood supply, positioning it to affect atrial electrophysiology through paracrine and vasocrine interactions. EpAT volume correlates with areas of atrial fibrosis, slow conduction, electrogram fractionation, and lateralization of connexin (Cx)-40,[58] suggesting a direct effect on atrial electrophysiology. Similar to visceral fat, EpAT secretes metabolically active (e.g. free fatty acids), angiogenic (e.g. vascular endothelial growth factor), growth (e.g. activin A), and remodelling (TGF-β1/2 and MMPs) factors, as well as inflammatory cyto- and chemokines (e.g. IL-6 and PAI-1), and adipokines (e.g. leptin).[59] While leptin is implicated in angiotensin-II-mediated pro-fibrillatory atrial remodelling,[60,61] another adipokine, resistin, correlates with clinical AF risk.[62] Adipocytes also secrete neprilysin, a neutral endopeptidase that degrades cardioprotective endogenous natriuretic peptides (NPs),[63] that positively correlates with body mass index (BMI)[64] and regulates angiotensin-II concentrations in human adipose tissue.[65] An overproduction of aldosterone,[66] linked to AF pathogenesis, shorter atrial, and pulmonary vein refractory periods, conduction slowing, and heterogeneity[57,67] are also found obesity and may be involved in obesity-associated AF.

4. Renin–angiotensin system and AF

Hypertension, an important risk factor for AF,[68–71] is often associated with activation of the renin–angiotensin system (RAS).[72] The RAS system is a neuroendocrine axis involving kidney production of renin that converts liver-produced angiotensin into angiotensin-I, which is subsequently converted into active circulating angiotensin-II in the lungs. Hypertension leads to atrial remodelling as indicated by LA enlargement and prolongation of P-wave duration.[73,74]

Angiotensin-II infusion produces a rapid increase in systolic blood pressure (exceeding 140–150 mmHg)[75–77] and a substantial increase in susceptibility to AF in mice.[75–79] Enhanced AF-susceptibility in angiotensin-II infused mice occurs in association with atrial enlargement, atrial fibrosis, and prolonged P-wave duration.[75,80,81] Consistent with P-wave prolongation *in vivo*, optical mapping demonstrates conduction slowing in the right atrium (RA) and LA of angiotensin-II infused mice.[75] RA and LA APD are prolonged and sinoatrial node function is impaired in angiotensin-II infused mice (*Figure 5A*).[75] Notably, atrial tachyarrhythmia itself induces angiotensin-II type 1 receptor-mediated oxidative stress (mainly due to increased nicotinamide adenine dinucleotide phosphate oxidase activity, LOX-1 upregulation, and F_2-isoprostane generation) in the ventricular myocardium, negatively impacting on its function.[82] Ion-channel remodelling may explain the electrophysiological changes associated with AF promotion by angiotensin-II. LA I_{Na} is reduced by approximately 50% in angiotensin-II infused mice, apparently via enhanced PKCα activity as dialysis with BIM1 (a PKC inhibitor) normalized I_{Na} density and activation kinetics.[69,71] APD-prolongation occurred in conjunction with decreased outward K^+-current (I_K), attributed to reductions in I_{to} and I_{Kur} independently of a change in $K_v4.2$, $K_V4.3$, KChIP2, and $K_v1.5$ protein levels.

AF following angiotensin-II infusion in mice is also associated with oxidative stress, leading to oxidation of Ca^{2+}-calmodulin-dependent protein kinase II (CaMKII).[78] CaMKII-oxidation leads to pathological, constitutively active CaMKII-signalling.[83] Oxidized CaMKII expression is increased in both AF patients and mice infused with angiotensin-II.[78] CaMKII oxidation causes arrhythmogenic alterations in SR Ca^{2+}-handling, with increased Ca^{2+}-sparks leading to delayed afterdepolarizations. Knock-in mice resistant to CaMKIIδ oxidation are protected from Ca^{2+}-mishandling and show less AF inducibility.[78]

Angiotensin-II infusion also causes atrial interstitial fibrosis[75,77] (*Figure 5A*), resulting from altered extracellular matrix (ECM) remodelling by MMPs and TIMPs under the influence of oxidative stress and inflammation.[78,79]

5. Natriuretic peptides in AF

Natriuretic peptides (NPs) are cardioprotective hormones that play important roles in regulating cardiac electrophysiology and arrhythmogenesis.[84,85] NPs modulate atrial AP morphology and alter atrial conduction patterns by regulating ion-channel function.[84–88] NPs elicit their effects by binding to NP receptors (NPRs), including NPR-A, NPR-B, and NPR-C.[89] NPR-A and NPR-B are guanylyl cyclase-linked receptors that modulate cGMP signalling, while NPR-C is coupled to the inhibitory G protein (Gi) and phospholipase C signalling.[84,90,91]

NPR-C is highly expressed in the atria,[86,92] and recent studies have identified an essential role for NPR-C in regulating atrial conduction and AF inducibility.[77,92] NPR-C knockout (NPR-$C^{-/-}$) mice display increased susceptibility to burst pacing-induced AF in association with impaired

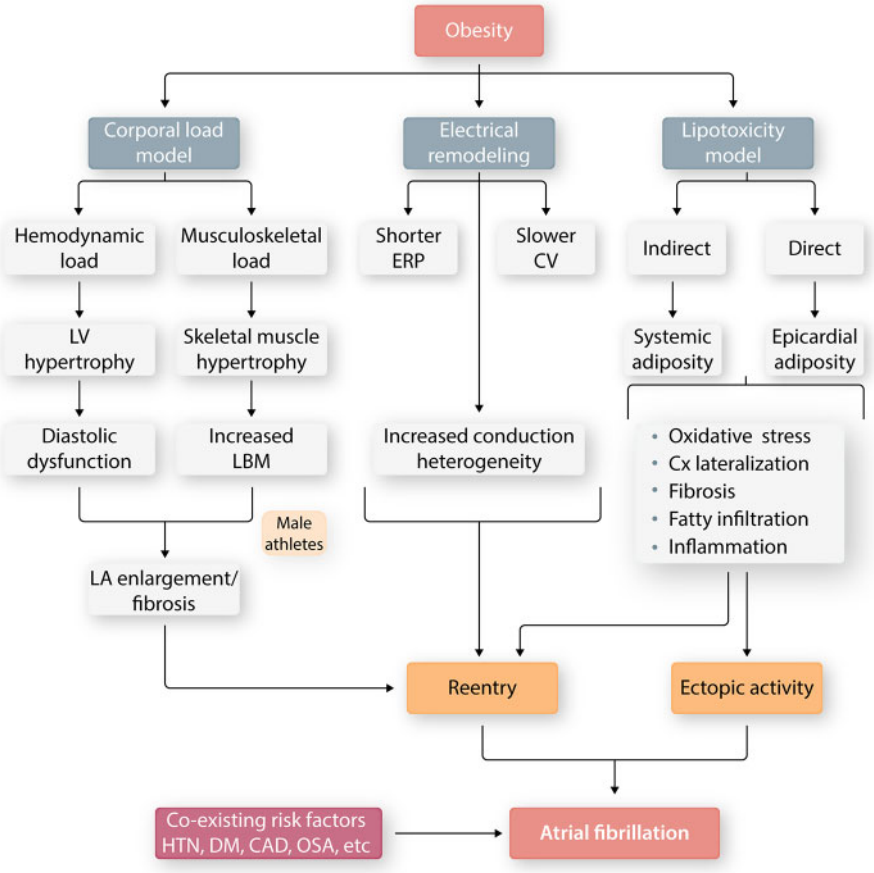

Figure 4 Current understanding of the mechanistic links between obesity and AF. The corporal load model states that excess body mass (adipose and/or lean) poses a haemodynamic load culminating in pro-AF left-atrial (LA) remodelling. Obesity has also been associated with pro-fibrillatory electrical remodelling in the form of shorter effective refractory period (ERP), slower conduction velocity (CV) and increased conduction heterogeneity. Adipocytes have a pro-inflammatory secretome which can affect LA electrophysiology indirectly (systemic adiposity) or directly (epicardial adiposity). Finally, obesity often co-exists with a number of pro-AF cardiovascular risk factors.

atrial conduction. Atrial interstitial fibrous-tissue content is increased in NPR-C$^{-/-}$ mice, whereas no differences in atrial AP morphology occur.[92] In contrast, no ventricular arrhythmias or ventricular fibrosis were observed in NPR-C$^{-/-}$ mice,[92] further indicating that NPR-C is particularly important for regulation of atrial structure and function.

NPR-C plays a modulating role in angiotensin-II mediated AF.[77] Angiotensin-II infusion in NPR-C$^{-/-}$ mice produces enhanced effects on AF vulnerability and duration, P-wave duration, and atrial conduction. Reductions in AP upstroke velocity (V_{max}) and I_{Na}, as well as APD prolongation, are seen, particularly in LA cardiomyocytes. Angiotensin-II infusion also produced larger increases in PKCα protein expression in NPR-C$^{-/-}$ mice, as well as enhanced RA and LA fibrosis.[77] Co-treatment of wild-type mice with angiotensin-II and cANF (a synthetic, selective NPR-C agonist[90]) reduces AF burden, while improving atrial conduction, attenuating atrial fibrosis, and improving AP properties.[77] These findings are consistent with other work showing that NPR-C plays protective roles in the cardiovascular system.[76,93–95] On the other hand, one study using transverse aortic constriction and TGF-β-overexpression found that the absence of NPR-C was protective against AF and atrial fibrosis.[96] The basis for these contradictory observations is unclear and further studies are warranted.

Studies showed that mutations in the atrial natriuretic peptide (ANP) gene are linked to AF.[97,98] A family with familial AF was shown to have a frameshift mutation in the *NPPA* gene (encoding ANP) that results in a mutated ANP (mANP) circulating at concentrations 5–10 times greater than wild-type ANP because of increased resistance to proteolytic degradation.[98,99] While ANP has been shown to increase funny current (I_f) in human atrial cardiomyocytes and predispose to AF,[100] ANP and mANP have also been found to demonstrate opposite effects on mouse and human atrial cardiomyocytes.[101] Specifically, ANP increased V_{max}, APD, and $I_{Ca,L}$ in isolated atrial cardiomyocytes via the NPR-A receptor. In intact mouse atrial preparations, ANP speeded atrial conduction and increased atrial effective refractory period (AERP). In contrast, mANP decreased atrial V_{max}, shortened atrial APD, decreased atrial $I_{Ca,L}$, slowed atrial conduction, and shortened AERP. These effects were mediated by the NPR-C receptor, as the effects of mANP were absent in NPR-C$^{-/-}$ mice. ANP and mANP also had opposing effects on $I_{Ca,L}$ in human RA cardiomyocytes. Finally, mANP administration caused re-entrant conduction patterns, ectopic firing, and disorganized conduction in mouse atria exposed to programmed stimulation, an effect not seen with ANP. These studies suggest that mANP is proarrhythmic in

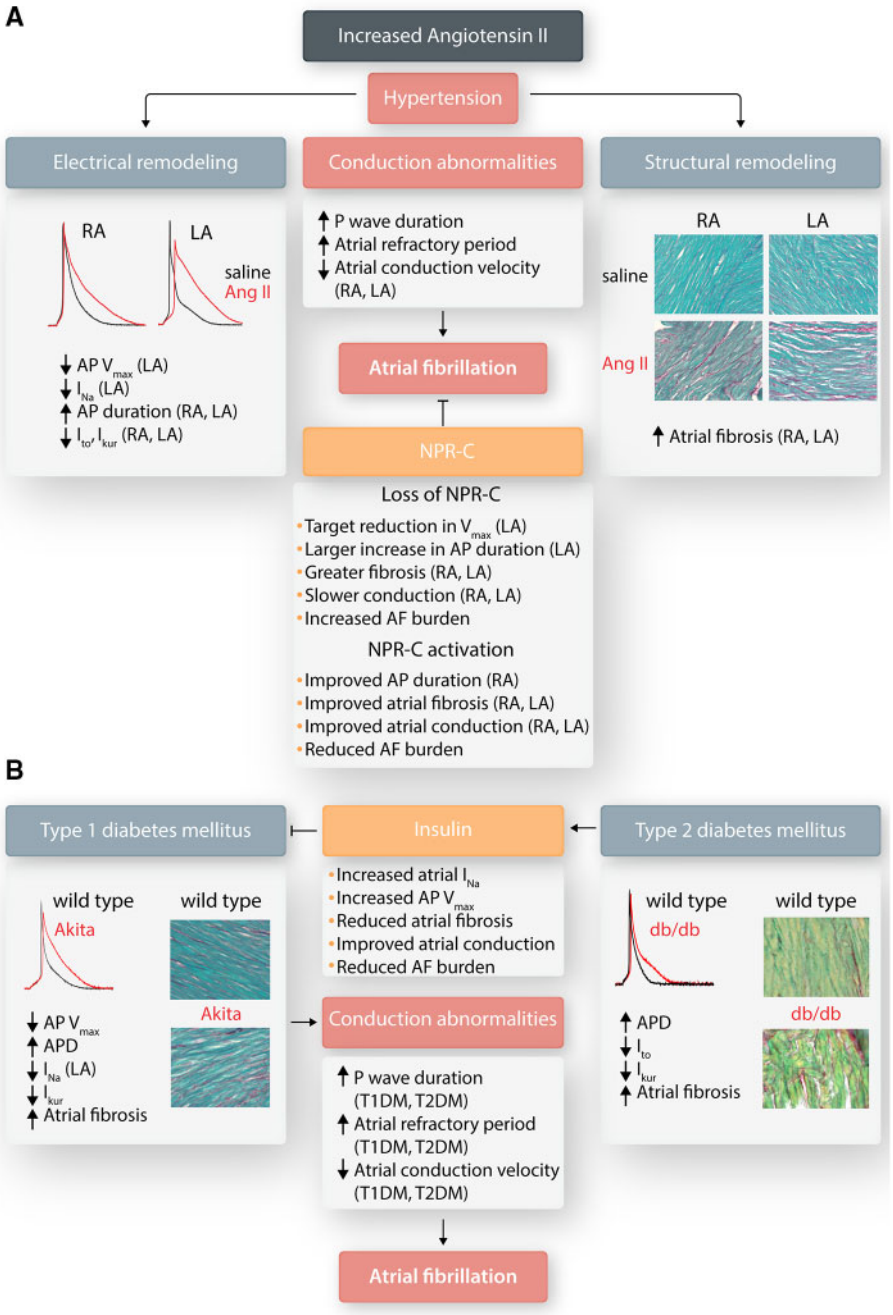

Figure 5 Atrial electrical and structural remodelling in angiotensin-II mediated hypertension and in mouse models of type-1 (T1DM) and type-2 (T2DM) diabetes mellitus. (*A*) Angiotensin-II infusion in mice causes distinct patterns of ion channel remodelling and changes in action potential morphology in left and right atrial myocytes. Angiotensin-II also causes right and LA fibrosis. These alterations lead to conduction abnormalities and increased susceptibility to AF. Loss of NPR-C leads to worsened ion channel remodelling and atrial fibrosis, as well as enhanced AF susceptibility, while NPR-C activation prevents some ion channel remodelling, reduces right and LA fibrosis, and decreases AF burden. (*B*) T1DM (Akita mice) is associated with reductions in AP V_{max} due to reduction in atrial I_{Na} as well as increases in AP duration due to reduction in I_{Kur}. T2DM (db/db mice) show increases in AP duration due to reduction in both I_{to} and I_{Kur} while I_{Na} amplitude and AP V_{max} are not altered. Both T1DM and T2DM are associated with increased atrial fibrosis. These alterations lead to conduction abnormalities and increased susceptibility to AF. Insulin treatment in T1DM prevents reductions in atrial I_{Na} and reduces atrial fibrosis leading to improved conduction and reduced AF susceptibility.

association with a shift in the balance between NPR-A and NPR-C mediated NP-signalling. Mice expressing the same *nppa* frameshift mutation show increased AF burden in association with APD shortening, in association with ion-channel remodelling, including changes in amplitude and expression of Na^+, Ca^{2+}, and K^+ channels.[94] Collectively, the available data indicate that this frameshift *nppa* mutation increases

susceptibility to AF in association with increased circulating mANP levels and shortening of the atrial AP, which could decrease the wavelength for re-entry (*Figure 5A*).

6. AF in diabetes mellitus

Type-1 (T1DM) and type-2 (T2DM) diabetes mellitus (DM) are metabolic disorders associated with hyperglycaemia and changes in insulin production and signalling.102-104 T1DM is characterized by the loss of insulin-producing β-islet cells in the pancreas and deficient insulin generation. T2DM, which often occurs in association with obesity, is characterized by insulin resistance in peripheral tissues while insulin can still be produced in the pancreas.[102] T2DM can ultimately lead to insulin insufficiency requiring insulin therapy.

AF is prevalent in both T1DM and T2DM.[69,71,105] T1DM is associated with atrial electrical and structural remodelling.[69] Experimental studies have evaluated atrial effects in genetic (Akita mice) or chemically induced [streptozotocin (STZ) or alloxan] animal models, of T1DM[106] that are characterized by substantial increases in AF susceptibility and duration.[107,108] Akita and STZ mice had increased P-wave duration; Akita mice also had impaired RA and LA conduction,[107] reduced atrial V_{max}, and prolonged APD. These AP morphology changes occurred in association with reductions in I_{Kur} and I_{Na}, associated with decreased *SCN5a* gene and $Na_V1.5$ protein expression, as well as a loss of phosphoinositide 3-kinase (PI3K) signalling via the second messenger PIP_3. Strikingly, insulin treatment protected against changes in I_{Na}, but not the changes in I_{Kur}, in Akita mice. Chronic insulin treatment increased $Na_V1.5$ protein levels, atrial I_{Na} density, and AP upstroke velocity. Insulin could also increase atrial I_{Na} and AP upstroke velocity acutely via the rapid activation of PIP_3 signalling. These effects of insulin on atrial I_{Na} were associated with increases in atrial conduction velocity and were sufficient to reduce the AF burden. Consistent with previous work on the PI3K- and PIP_3-mediated effects on Na^+-channel function,[109] these studies revealed a critical role for insulin in regulating atrial electrophysiology and AF susceptibility via effects on atrial Na^+ channels in T1DM, though the basis for I_{Na} dysregulation in T1DM remains unclear. Structural profibrotic remodelling in T1DM[110-112] is increased in the atria of Akita mice,[110] STZ-treated rodents,[111-113] and alloxan-treated rabbits,[114] that in STZ-treated rats was prevented by inhibition of the type-1 angiotensin-II receptors,[112] suggesting a critical role of angiotensin-II in T1DM-related atrial fibrosis (*Figure 5B*). STZ-treated rats showed reduced velocity and increased heterogeneity of the LA conduction associated with a reduced LA Cx40 expression, leading to increased arrhythmogenesis,[113] while atrial Cx40 or Cx43 mRNA expression were unaltered in Akita mice.[107]

T2DM, which accounts for up to 90% of DM-patients, continues to increase at epidemic proportions in association with rising rates of obesity and metabolic syndrome.[115] AF is prevalent in T2DM.[105,116] Clinical studies in T2DM patients have shown that alterations in Ca^{2+}-handling may contribute to atrial remodelling.[117] T2DM patients have atrial interstitial fibrosis and increased EpAT, potentially infiltrating atrial myocardium,118-123 that could lead to impaired electrical conduction and AF (*Figure 5B*). While mechanistic studies in animal models are limited, recent work in T1DM and T2DM mouse models demonstrated that AF promotion is related to pro-arrhythmic activation of CaMKII (due to oxidative stress-mediated oxidation and O-GlcNAcylation of CaMKII)[124] that would potentially affect multiple ion currents.[83]

AF in T2DM was recently investigated in db/db mice, which carry a mutation in the leptin receptor leading to obesity, insulin resistance, and hyperglycaemia.[125] The db/db mice have increased susceptibility to burst-pacing induced AF, associated with increased P-wave duration and AERP, reduced RA and LA conduction velocity, and prolonged heterogeneous APD. These changes were accompanied by a decrease in I_{to} (associated with reduced expression of *Kcnd2* mRNA and $K_V4.2$ protein) and suppressed $I_{Kur,}$ occurring in the presence of unchanged $K_V1.5$ expression. Zucker diabetic fatty (ZDF) rats also showed increased AF susceptibility and APD,[126] associated with reduced atrial I_{to}, I_{Kur}, and $I_{Ca,L}$ currents, and respective channel protein subunits Kv4.3, Kv1.5, and Cav1.2, indicating some model-specific differences. In contrast to Akita (T1DM) mice,[107] atrial I_{Na} was not reduced in db/db atrial myocytes.[125] The only alteration observed in atrial I_{Na} in db/db mice was a shift in steady-state inactivation that resulted in a larger I_{Na} window current, which could contribute to the prolongation of APD. This observation identifies potentially important differences in electrical remodelling between T1DM and T2DM that may have important implications for AF therapy in these related, but distinct conditions.

Animal models of T2DM also consistently display atrial structural remodelling, including fibrosis, lipidosis, and inflammation (*Figure 5B*),[125,127–130] which has been shown to promote AF.[54] Adipokines (cytokines with pro-inflammatory properties) like leptin are also implicated in the atrial fibrosis of diabetic mice,[131] while cathepsin-A (a proteolytic enzyme active in the extracellular space) contributes to atrial fibrosis in ZDF rats.[127] Gene expression of Cx40 and Cx43 remained unchanged in both db/db mice and ZDF rats,[125,127] yet lateralization of Cx43 was observed in ZDF rats[127] that could underlie higher conduction heterogeneity.

7. Thyroid dysfunction in AF

Thyroid disease has a large number of well-characterized cardiac manifestations and both hypo- and hyperthyroidism have been associated with worse cardiovascular outcomes.[132] Although clinical (low TSH, elevated T_4) and subclinical (normal TSH, elevated T_4) hyperthyroidism, even with marginally increased T_4 levels, have been linked to a higher risk of AF,[133–135] overt hyperthyroidism is present in less than 1% of patients with new-onset AF.[136] Conversely, antiarrhythmic treatment with amiodarone is itself an important potential cause of hyperthyroidism in cardiac patients, so-called amiodarone-induced thyrotoxicosis.[137] Elevated thyroid hormone (TH) levels have also been associated with increased atrial premature depolarizations and supraventricular tachyarrhythmias.[138,139] Hypothyroidism appears to have relatively protective effects, especially against malignant ventricular arrhythmias, and a much less robust association with AF.[140]

Thyrotropin-releasing hormone (TRH) release from the hypothalamus stimulates secretion of TSH by the anterior-pituitary and subsequent release of tetraiodothyronine (thyroxine; T_4) and in lesser amounts (~1:9 ratio), triiodothyronine (T_3) by the epithelial cells of the thyroid gland (*Figure 6*). The enzyme 5′-iodinase converts T_4 into T_3, the more metabolically active TH. T_3 and T_4 inhibit TRH and TSH release, forming a negative-feedback loop. TH actions can be genomic or non-genomic (*Figure 6*). Genomic effects are mediated as T_3 enters the nucleus and interacts with the nuclear thyroid α receptor-1 (TRα1), which binds the thyroid release elements (TREs), promoting/repressing transcription of TH-regulated genes like sarcoplasmic reticulum Ca^{2+} adenosine triphosphate (SERCA2), phospholamban, Na^+/K^+ ATPase, NCX, selected voltage-gated K^+ currents, I_{CaL}, and β_1-adrenergic receptor.[141] Non-genomic effects (reviewed elsewhere[142]) have a rapid onset of

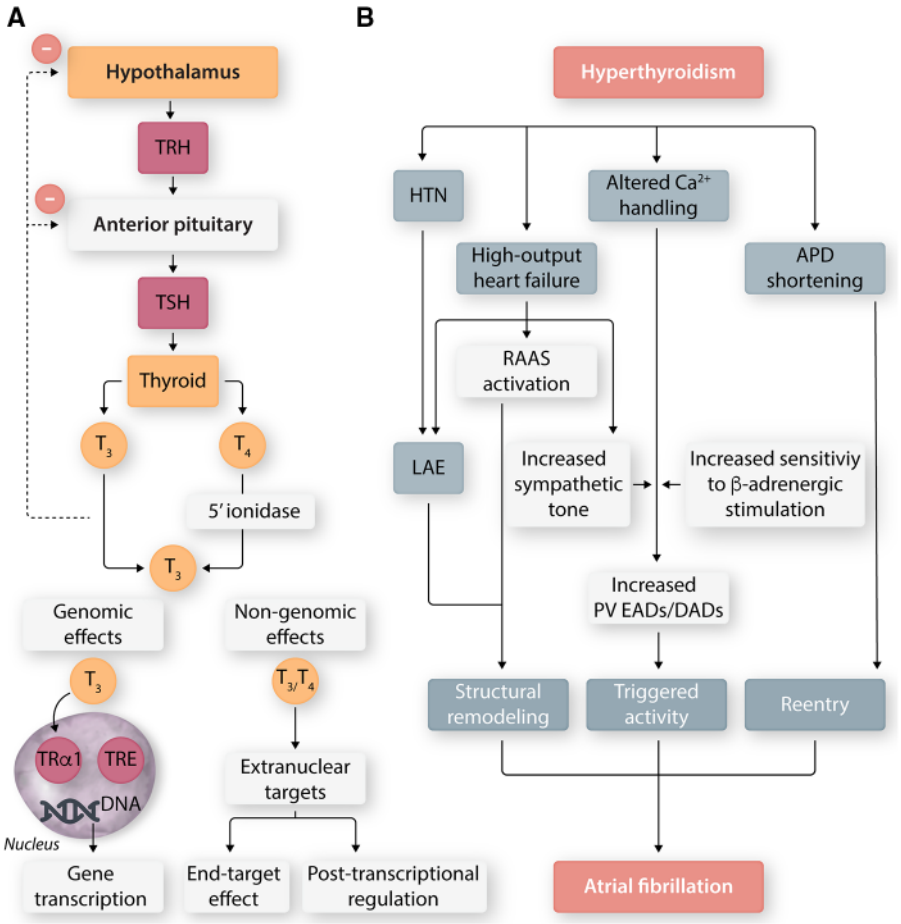

Figure 6 Thyroid dysfunction and AF. (*A*) The hypothalamic-pituitary-thyroid axis forms a closed negative-feedback system. The thyroid secretes primarily T4, which is converted to T_3, the more metabolically active thyroid hormone, by the enzyme 5′-ionidase. Thyroid hormone effects can be genomic or non-genomic. Genomic effects are mediated by binding of T_3 to the nuclear thyroid α-receptor-1 (TRα1), which interacts with the thyroid release elements (TREs) to promote/suppress thyroid hormone-regulated genes. Non-genomic effects are mediated by T_3 and T_4 as they interact with extra-nuclear receptors, which may or may not be structurally related to the thyroid receptor. (*B*) Hyperthyroidism leads to high-output heart failure (HF), causing left atrial enlargement (LAE), activation of the renin–angiotensin–aldosterone system (RAAS), and increased adrenergic stimulation. Altered intracellular Ca^{2+} promotes the formation of early (EADs) and delayed afterdepolarizations (DADs) from the pulmonary veins (PVs). Action potential duration (APD) shortening promotes re-entry. Finally, hypertension (HTN) also contributes to pro-fibrillatory left-atrial structural remodelling. TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; DNA, deoxyribonucleic acid.

actions that are transcription/translation-independent and are mediated by extra-nuclear receptors, structurally related to the thyroid receptor-like integrin αvβ3, cytoskeleton, mitogen-activated protein kinase ½ and PI3K.

Hyperthyroidism leads to so-called high-output heart failure characterized by hyperdynamic congestive failure in patients with normal baseline LV-function.[143] Left untreated, heart failure leads to LA-enlargement, activation of the RAAS, and increased sympathetic tone (*Figure 6*)[142] and hypertension.[142]

THs also have important electrophysiological effects. Hyperthyroidism leads to sinus tachycardia from increased rates of diastolic depolarization in sinoatrial cells; hypothyroidism has the opposite effect.[144,145] Similarly, APD is consistently prolonged in animal models of hypothyroidism,[146–150] whereas hyperthyroidism shortens APD.[147,148,151] There are no documented effects of thyroid disease on the resting membrane potential. Beyond these well-characterized macroscopic electrophysiological changes, there is substantial heterogeneity in the reported TH-induced ion-channel remodelling.

7.1 Depolarizing currents

There are no documented effects of hypo-/hyperthyroidism on I_{Na}, although one study reported increased/decreased conduction velocity in hyper-/hypothyroid rabbit atria, respectively.[146] I_{CaL} has been found to be increased,[148,152,153] unchanged[154] or decreased[155,156] in hyperthyroid models. Interestingly, one study found hyperthyroidism to increase I_{CaL} sensitivity to β-adrenergic stimulation, which may favour the occurrence of the triggered activity.[153] Hence, the effects of hyperthyroidism on depolarizing currents are incompletely defined.

7.2 Repolarizing currents

THs were shown to increase I_{K1} by activating channel open probability, while the resting membrane potential remained unchanged.[146,148] It was

proposed that the rapid time course of action of T_3 on I_{K1} is suggestive of a non-genomic mechanisms.[157] THs have been reported to differentially increase ventricular I_{to} without affecting its atrial counterpart.[148,150,152,158] Conversely, Kv1.4 was found to be reduced[159–161] and Kv4.2 was unaffected[156,159–161] by THs, while Kv1.5, the I_{Kur} α-subunit, was increased in hyperthyroid animals.[151,156,159–161] APD prolongation due to decreased I_{Ks} was reported in thyroidectomized guinea pigs.[149] Finally, Kv1.2 has been reported to be reduced[159,160] and Kv2.1 unchanged[159,161] or increased[151,160] in hyperthyroid models. Hence, the mechanisms of hyperthyroidism-induced APD shortening are likely multifactorial.

THs also modulate intracellular Ca^{2+} homeostasis characterized by decreased phospholamban and increased SERCA2, potentially promoting the occurrence of proarrhythmic afterdepolarizations in hyperthyroid rats.[162] Similarly, pulmonary vein cardiomyocytes from a hyperthyroid rabbits have higher automaticity, more frequent early and delayed afterdepolarizations and shorter APD.[163] The pro-AF changes encountered in hyperthyroidism are summarized in *Figure 6*.

7.3 Thyroid dysfunction and cardiac remodelling

Dysregulated THs mediate multiple cardiac remodelling processes, e.g., necrosis, apoptosis, inflammation, and regression to the foetal heart phenotype. However, cardiac fibrosis remains the hallmark of AF-associated remodelling. THs were shown to downregulate interstitial collagen content[164] and collagen I gene expression in the rat myocardium and cardiofibroblast culture[165] and increased degradation of LV collagen-I/III protein, associated with an activation of MMPs and inhibition of TIMPs, in hyperthyroid rats.[166,167] T3 supplementation in a rat model of ischemia/reperfusion inhibited TGF-β1, reduced scar size, and improved cardiac performance[168]; T3 was also shown to inhibit activator-protein-1 (AP-1),[169] involved in the stimulation of MMPs and collagen mRNA.[170] RAS appears to play a role in T4-induced cardiac hypertrophy,[171] which was prevented by treatment with angiotensin-converting enzyme-inhibitor or angiotensin-1 receptor blocker.[172] While hyperthyroidism in rats decreased LV levels of TGF-β1, SMAD2/3, total and phospho-serin368-Cx43 without enhanced interstitial collagen deposition, the TGF-β1 and SMAD2/3 were increased in hypothyroid rats.[173] Although, the majority of studies argue for the anti-fibrotic effects of THs, longstanding hyperthyroidism has been demonstrated to impair LV function and increase interstitial fibrosis in hamsters.[174] Thus, the TH-induced cardiac remodelling may continue to develop over time.

Hypothyroidism is primarily thought to exert profibrotic phenotype associated with increases in the LV TGF-β1 and procollagen-I mRNAs and protein,[164] induced LV hypertrophy with fibrotic lesions, and upregulated α-SMA expression; all these changes were reversed by euthyroid state. Collagen-I/III gene expression was unaltered, while TGF-β1, CTGF, IL-1, and MCP1 gene expression were increased in hypothyroid rats.[175] Interestingly, the TGF-β1 gene promoter has binding sites for Sp1, a critical transcription factor that interacts with TRH-binding protein associated factors,[176–178] while pro-α1(I) collagen gene contains a binding site for the receptor, which functions as a TRE.[179] Hypothyroidism was also shown to increase LV collagen-based diastolic wall stiffness[180] and content of collagen and glycosaminoglycans in rat LV.[181] Experiments in cultured rat cardiofibroblasts found increased biosynthesis of fibrillar collagen under TH-depleted conditions[179] and increased proliferation in both TH-depleted[179] and TH-treated cells.[165]

Atrial remodelling mediated by thyroid dysfunction is not fully understood; however, a recent study in rats showed that both hypo- and hyperthyroidism increased AF vulnerability, that, as well as the decreased LV and LA dimensions, AERP prolongation, and atrial fibrosis, were decreased by T4 administration.[182] The cross-sectional area and diameter of LA myocytes were reduced in hypothyroid and increased in hyperthyroid rats.[182] While some studies reported an association of hypothyroidism with LA remodelling (marked by increased LA diameter) and increased preoperative AF incidence in patients with heart valvular disease[183] or dilated cardiomyopathy,[184] others did not confirm this.[185,186] The impaired ejection fraction, presence of multiple valvular lesions, and a lower recovery rate of LA enlargement after valve surgery were also observed in hypothyroidism.[183] Overt and subclinical hypothyroidism also increased the risk of post-operative-AF in the patients after cardiac surgery[187–189] At the molecular level, hypothyroidism was associated with increased serum levels of CRP, TNF-1α, IL-6, and TGF-β1 in rats, induced secretion of the cardiac stress markers ANP, brain natriuretic peptide (BNP) (regulated by TH) and cardiac troponin-T.[175] Hyperthyroidism also caused increase in cardiac TGF-β1 in cardiac hypertrophy mediated by angiotensin-II receptors[190] and was associated with increased protein and ribosome synthesis.[191,192] These observations suggest that TH are important regulators of cardiac remodelling (*Figure 6*).

8. Calcitonin and AF

Calcitonin (CT) is canonically secreted by parafollicular cells (C cells) of the thyroid gland and is a 32 amino acid single-chain peptide that is cleaved from a precursor pro-CT by protein convertases.[193] Human CT originates from the CT-related polypeptide-alpha (*CALCA*) gene on chromosome-11 (ID: ENSG00000110680) that also encodes alpha-calcitonin gene-related peptide (αCGRP, a potent vasodilator with functions in the nervous and vascular systems).[194]

CT plays a well-known role in bone metabolism[195] and plasma Ca^{2+}-homeostasis.[196] Extra-thyroidal CT expression is present in organs, such as the brain, uterus, prostate, and central nervous system.[197,198] We recently discovered that atrial cardiomyocytes actively produce CT.[199] Regardless of where CT is produced, it exerts its effects via binding to the CT receptor (CTR),[200] the seven-transmembrane domain class II (family B) G protein-coupled receptor that can couple to Gs, Gi, or Gq proteins.[201,202] The CTRs are expressed in tissues such as kidneys,[203], osteoclasts,[204] skeletal muscle,[205] and recently identified in human atrial fibroblasts.[199] A wide distribution of the CT and CTR indicates that CT-CTR signalling may be involved in the (patho)physiology of multiple systems, including the heart.

The role of the CT-CTR cascade in AF is unclear, however, key risk factors for AF, age[206] and BMI,[207] are associated with decreased circulating CT-levels and CTR single-nucleotide polymorphisms respectively.[208,209] Early work in dog and rabbit models of Ca^{2+}-induced arrhythmias observed antiarrhythmic effects of CT on Ca^{2+}-induced ventricular arrhythmias[210] and the inhibition of atrial chrono-/inotropic function.[211] The mechanisms of these effects are unknown, though studies in non-cardiac cells showed that CT affected ion fluxes (e.g. neuronal Ca^{2+}-currents,[212] kidney Ca^{2+}-channels and NCX[213] and, intracellular Ca^{2+}[214,215] and implicated in AF pathogenesis[216] mitochondrial Ca^{2+} influx,[217] in CT-secreting cells) and channel expression (e.g. neuronal $Na_V1.3$, $Na_V1.8$, and $Na_V1.9$[218]). RA cardiomyocytes from patients with persistent AF secrete six-fold less CT compared to sinus-rhythm controls.[199] Knockdown (KD)

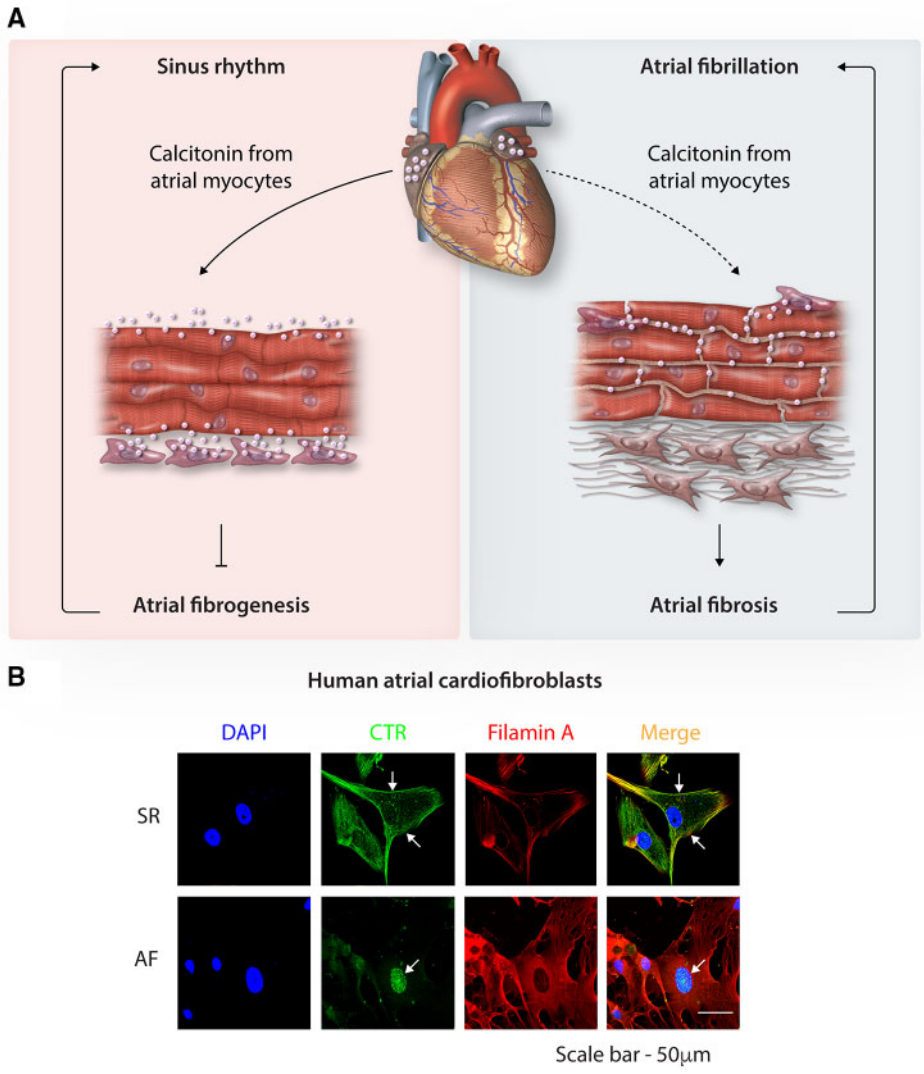

Figure 7 Calcitonin signalling and AF-induced remodelling. (*A*) In healthy hearts, atrial cardiomyocytes secrete calcitonin, which binds to the calcitonin-receptors (CTRs) on atrial fibroblasts, controlling extracellular matrix deposition and helping to maintain normal sinus rhythm. In AF, calcitonin signalling is disordered by reduced secretion of calcitonin by atrial cardiomyocytes and reduced calcitonin-receptor responsiveness; these changes impede the calcitonin-mediated brake on fibrogenesis causing atrial fibrosis and increased arrhythmogenesis (created with *Biorender.com*). (*B*) CTRs (green) in atrial fibroblasts co-stained with filamin A (red) and 4′,6-diamidino-2-phenylindole (DAPI) (blue). Relocalization of CTRs from the cell membrane to the nucleus explains CTR hyporesponsiveness. Scale bar = 50 μm; adapted from Moreira *et al.*[199]

of atrial cardiomyocyte-CT in an atrial-specific LKB1-KD model of spontaneous AF caused ∼three-fold higher incidence and ∼16-fold longer duration of spontaneous AF episodes, which commenced at a younger age vs. control LKB1-KD mice.[199] Overexpression of CT in atrial cardiomyocytes of the LKB1-KD mice prevented atrial arrhythmia.[199] Global deletion of the CTR in mice resulted in increased AF-inducibility.[199] These findings point to a potentially important relationship between the cardiac CT-CTR axis and AF arrhythmogenesis.

CT-CTR signalling is important for tissue fibrogenesis, as it regulates collagen homeostasis, e.g., CT inhibits collagen breakdown in bones[197] and in chondrocytes,[219] while CTR-cKO promotes fibrosis in murine skeletal muscle.[220] Binding of cardiac CT to the surface CTRs of neighbouring human atrial fibroblasts inhibits the production of ECM proteins like collagens-I/III, TIMP2, and SERPIN.[199] In patients with persistent AF, accompanied by significant fibrotic remodelling, fibroblast-CTR localization was altered and confined to the intracellular space, thus, precluding CT from binding CTR (*Figure 7A*). CTR-KO mice or atrial-specific cardiomyocyte-CT-KD in the LKB1-KD mice exacerbated atrial fibrosis, suppressed by overexpression of CT in atrial cardiomyocytes.[199] In the light of this work (*Figure 7B*), maintaining CT-CTR signalling in atrial myocardium may benefit patients with AF.

9. Towards ‘hormonal therapeutics’ in AF

The evidence discussed in this review unequivocally demonstrates a potent regulatory role of both endocrine and cardiac para-/autocrine

systems on myocardial function and structure in AF. Although currently not performed, screening of patients with AF for both systemic and cardiac (when possible) hormonal imbalance (in combination with other conventionally used diagnostic tests) may potentially advance treatment-stratification and existing treatment options with the new hormone-based therapies.

Such therapies would first of all aim to treat the prime underlying endocrine pathology (e.g. diabetes, pheochromocytoma, and obesity) with conventional therapies to reduce the risk of new-onset AF or prevent arrhythmia progression. In some cases, available therapies can fully cure the underlying endocrine disorder (e.g. resection of pheochromocytoma) and, hence, reduce risk of AF. Current treatment options for common endocrine conditions (e.g. diabetes and obesity) are often suboptimal; nevertheless, they help to reduce, while not completely eliminating, the risk of AF onset and progression. Furthermore, contemporary medications with improved safety profile may offer improved possibilities for control of AF, for example, with sodium-glucose co-transporter-2 inhibitors that may reduce risk of AF in T2DM,[221] or with glucagon-like peptide-1 receptor agonists (except albiglutide[222]) that advantageously do not increase risk of AF in obese patients with DM.[223] Looking into the future, control of metabolism with, for example, modified synthetic secreted factors or inhibitors may not only improve cardiometabolic conditions like DM and hypertension[224] but may also hold promise to control AF risks associated with these serious pathologies.

Some endocrine therapies targeting selective pathways, e.g., inflammation and fibrosis, are likely to aid treatment of specific type(s) of AF, e.g., corticosteroids, due to their potent anti-inflammatory properties, might reduce AF recurrence after ablation procedures[225] and incidence of post-operative AF.[226] Selective inhibition of inflammation, for instance with GILZ small molecules, may help to circumvent undesirable side-effects of broad-spectrum glucocorticoids and improve therapeutic options in AF.[13]

Availability of the RAAS antagonists [angiotensin-II-converting enzymes inhibitors and angiotensin II receptor blockers (ARB)], owing to their pronounced antifibrotic effects, may not only control blood pressure in hypertensive patients but to also reduce the occurrence, development, and duration of AF.[227] A recent meta-analysis of 7914 patients showed that aldosterone pathway blockade with MR antagonists limited AF recurrence and, to a lesser extent, prevented the new onset of AF.[228] Since NPs counter-balance RAAS, recombinant human NPs (e.g. nesiritide—recombinant BNP) combined with neprilysin inhibitors (e.g. sacubitril, enhancing NP signalling) and ARBs (e.g. valsartan), denoted ARNi (currently approved for the heart failure management)[228] or synthetic modified NPs designed to preferentially enhance signalling via specific NPRs, may also have potential benefits for AF management.

Sex hormone (testosterone and oestrogen) replacement therapies in patients with AF may also help to prevent AF.[229,230] However, altering sex hormone-dependent pathways may increase the risk of stroke, cardiac arrest, and life-threatening ventricular arrhythmias (due to altered ventricular repolarization and prolonged QT interval).[231,232] Thus, potential risks of such therapies should be carefully balanced against their benefits.

TH replacement therapy can also be beneficial.[233,234] Disrupted CT-CTR signalling in AF might be amenable to CT-based therapies used to treat conditions like osteoporosis and Paget's disease. However, their use is limited due to a release of anti-CT antibodies in some patients and CTR internalization during prolonged CT treatment.[235] Gene-therapy to overexpress CT in atrial cardiomyocytes might offer a tool to manipulate CT levels in a controlled manner. Patients with persistent AF do not maintain membrane CTR localization (*Figure 7A*)[199]; thus, strategies to normalize localization of the CTR is a necessary and challenging objective in attempts to exploit CT-CTR signalling to prevent atrial structural remodelling in AF-patients. In addition, off-target effects of CTR-activation need to be avoided.

10. Conclusions

It is clear that endocrine/paracrine/autocrine effects play an important role in AF pathogenesis and might present interesting, presently underdeveloped, therapeutic targets. AF management is still very challenging, with many obstacles to optimal management.[236] Recent discoveries, like those of cardiac CT-production and involvement in AF, novel molecular mediators (like GILZ) and the potential mechanistic role of inflammatory signalling, highlights how little we know about endocrine control of AF and how much more there is to learn in order to harness the full therapeutic potential of this critical system.

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