Review

Signal transduction systems and atrial fibrillation

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Abstract

Cell communication, an essential component of integrated physiological function in multicellular organisms, is mediated largely through informational molecules, such as hormones and neurotransmitters. After binding to specific receptors, these first messengers activate intracellular signaling cascades and, thereby, translate extracellular messenger levels into intracellular events. Atrial fibrillation is associated with significant electrophysiological and structural alterations of atrial tissue. Most of these changes seem to be related to activation of signal transduction systems at the molecular atrial level. This review will describe the role and regulation of different signal transduction systems in fibrillating atria.

Keywords: Angiotensin; Protein kinases; Receptors; Signal transduction; Supraventr. arrhythmia

1. Introduction

Atrial fibrillation (AF) is known to cause significant changes in atrial tissue architecture and atrial electrophysiology [1–6]. In addition, preexisting alterations (autonomic dysbalance, degenerative tissue changes, fibrosis, etc.) can provide a morphologic substrate which increases the likelihood of AF occurring in response to triggering events [7–11]. At the molecular level, several AF-related alterations of atrial tissue are due to activation of different signal transduction systems [12–17]. Signal transduction systems provide a dynamic interaction between extracellular cues and intracellular events and, thereby, these molecular pathways are involved in regulation of gene expression, cell proliferation, hypertrophy, differentiation, migration, and cell death. More knowledge about these fundamental mechanisms may help to identify entirely novel targets for pharmacological interventions. This review will focus on the effects of different extracellular messengers (Table 1) and their intracellular signaling pathways in fibrillating atrial tissue (Table 2). The effect of ion channels and ion channel receptors on atrial electrophysiology will be discussed elsewhere in this journal.

Abbreviations: AC, adenylyl cyclase; ACE, angiotensin-converting enzyme; ADAM, a disintegrin and metalloprotease; AF, atrial fibrillation; APA, aminopeptidase A; APB, aminopeptidase B; APN, alanine-aminopeptidase; bFGF, basic fibroblast growth factor; BK, bradykinin; CPM, carboxypeptidase M; DAG, diacylglycerol; DPP IV, dipeptidyl peptidase IV (CD26); ERK-1,-2, extracellular-signal regulated kinase-1,-2; FAK, focal adhesion kinase; GDP, guanosine diphosphate; GTP, guanosine triphosphate; IL, interleukin; IP3, inositol trisphosphate; JAK2, janus kinase 2; JNK, c-jun terminal kinase; MAPK, mitogen-activated protein kinase; MEK-1,-2, Erk-activating kinase-1,-2; MKK, MAP kinase kinase; MKKK, MAP kinase kinase kinase; MMP, matrix metalloproteinase; NC, ADP-ribosyl cyclase; NEP, neutral endopeptidase; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; Shc, sequence homology of collagen; SOD, superoxide dismutase; SOS, 'son of sevenless'; STAT, signal transducer and activators of transcription; TGF-\(\beta\), transforming growth factor \(\beta\)

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Table 1: Extracellular cardiac messengers

**Peptides**
- G-protein-coupled (heptahelical) receptor agonists
  - Angiotensin II
  - Bradykinin
  - Endothelin
- Tyrosine kinase receptor agonists
- Fibroblast growth factor (FGF)
- Insulin-like growth factor (IGF)
- Platelet-derived growth factor (PDGF)
- Epidermal growth factor (EGF)
- Vascular endothelial growth factor (VEGF)
- Serine/threonine kinase receptor agonist
  - Transforming growth factor (TGF)
- Cytokine receptor agonists
  - Tumor necrosis factor alpha (TNF-α)
  - Interleukins

**Catecholamines**
- Epinephrine
- Norepinephrine

**Steroids**
- Aldosterone

**Others**
- Thyroxin
- Growth hormone
- Nitric oxide (NO)

2. Heptahelical receptor agonists

Heptahelical receptors contain seven membrane-spanning α-helices. Because these receptors interact with guanyl nucleotide-binding proteins (G proteins), they are called G protein-coupled receptors. This receptor family is the largest in biology and includes ~1000 different proteins [18]. The ligand-binding site of these receptors is on the extracellular surface of the plasma membrane, while the G protein binding site faces the cytosol. Heterotrimeric G proteins consist of three subunits (α, β, and γ), of which α has guanosine triphosphate (GTP) binding and GTPase activity [19]. The activated α-subunits regulate effector molecules such as adenyl cyclase, and phospholipase C (Table 3). Signaling is terminated after hydrolysis of GTP to guanosine diphosphate (GDP). Desensitization of G protein-coupled receptor leads to uncoupling from the G protein, which is associated with receptor phosphorylation, internalization and recycling. Receptor phosphorylation is mediated by G protein receptor kinases (serine/threonine kinases) [20]. In the cardiovascular system, G protein-coupled receptors transmit signals from various neurohormones and peptides.

2.1. Angiotensin II

The presence of all components of the highly complex renin angiotensin system has been demonstrated in the heart (Fig. 1) [21–25]. Although we have gained much knowledge about the physiological and pathophysiological roles of angiotensin II, the role of other angiotensin peptides has yet to be elucidated. Angiotensin II, a vasoactive peptide, is generated from angiotensin I by either the angiotensin-converting enzyme (ACE), tissue chymase, cathepsin G, or CAGE (chymostatin-sensitive angiotensin generating enzyme). However, angiotensin I can also be cleaved by neutral endopeptidases (NEP) to angiotensin peptide 1–7 which antagonizes some of the effects of angiotensin II [26,27]. Besides the known gene polymorphism of ACE, a second converting enzyme called ACE 2 has recently been described that cleaves angiotensin I to angiotensin peptide 1–9 [28].

Two major classes of angiotensin II receptors have been described. Qualitatively, they induce different responses that oppose one another (Fig. 2). Activation of the angiotensin II type 1 receptors (AT-1) induces a cascade of phosphorylations that activate so-called mitogen-activated protein kinases (MAP kinases), which stimulate proliferation of fibroblasts, cellular hypertrophy, and apoptosis [29–31]. Signaling pathways mediated by AT-1 receptors are linked predominantly to Go_q/11, Go_12/13, and Go_i classes of G proteins (Fig. 3) [32]. Binding of angiotensin II to AT-1 receptors activates kinases of the Src family (c-Src) via G proteins [33]. This leads to tyrosine phosphorylation of receptor tyrosine kinases in the absence of the receptor tyrosine kinase ligands. Thereafter, a Shc/Grb_2/SOS complex is formed that leads to activation of a monomeric G protein called Ras. Ras-GTP interacts with Raf-1 (MAP kinase kinase kinase, MKKK) and activated Raf-1 then phosphorylates Erk-activating kinase-1 and -2.
Table 3
Heterotrimeric GTP-binding coupling proteins (G proteins)

<table>
<thead>
<tr>
<th>α-Subunit</th>
<th>Effector</th>
<th>Effect on second messenger</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gα family</td>
<td>Adenylyl cyclase</td>
<td>Increase cyclic AMP</td>
</tr>
<tr>
<td>(stimulatory)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gβ family</td>
<td>Adenylyl cyclase</td>
<td>Decrease cyclic AMP</td>
</tr>
<tr>
<td>(inhibitory)</td>
<td>L-type calcium channel</td>
<td>Decrease Ca²⁺ current</td>
</tr>
<tr>
<td>Gγ family</td>
<td>Phospholipase C-β</td>
<td>Increase IP3 and diacylglycerol</td>
</tr>
<tr>
<td>G12 family</td>
<td>Rho GTP exchange factor</td>
<td>Activate Rho targets</td>
</tr>
</tbody>
</table>

Fig. 1. The renin-angiotensin system. Abbreviations are explained in the abbreviation list.

Fig. 2. Angiotensin II-dependent signal transduction. Opposing effects of angiotensin II type 1 receptor (AT-1) and angiotensin II type 2 receptor (AT-2) activation. For details see text.

Fig. 3. Signal transduction via AT-1 receptors involving receptor tyrosine kinases. Activation of the JAK/STAT pathway by Gβγ proteins may possibly contribute to regulation of angiotensinogen gene transcription. Activation of different MAP kinases accounts for proliferation of cardiac fibroblasts (ERK-1/2) and proapoptotic effects (p38 MAP kinase). Activation of p38 MAP kinase also regulates the Na⁺/H⁺ exchanger. For details see text.
Attral expression of ACE, MEK-1 and -2, and ERK-1 and -2 are increased at the protein and mRNA-levels in patients with AF [15]. Immunohistological staining has shown that fibroblasts are the source for increased amounts of ERK-1 and -2 in atrial tissue [15]. Thus, as with the described impact of angiotensin II on the development of severe degenerative changes in ventricular failure, the atrial angiotensin system contributes to the development of atrial myopathy in patients with chronic AF and concomitant cardiovascular diseases [14]. The observed pattern of atrial angiotensin II receptor in patients with permanent AF (downregulation of AT-1, upregulation of AT-2) further supports this concept, because, as with ventricular receptor expression in terminal heart failure, the altered expression of angiotensin II receptors seems to beadaptive in preventing further collagen accumulation. The angiotensin II-dependent effects in fibrillating atria, however, suggest that there may be potentially beneficial effects from using ACE inhibitor or AT-1 receptor antagonist therapy in patients with AF [15,47,48]. Experiments have shown that inhibition of the generation or action of angiotensin II in atrial tissue reduces the amount of ERK-1/2, and the...
degree of fibrosis [13]. Furthermore, Pedersen et al. [48] have shown in a subanalysis of the TRACE study that prophylactic ACE inhibitor therapy reduces the incidence of AF in patients following myocardial infarction.

Due to PKC-dependent interaction with potassium and calcium channels, angiotensin II also has some electrophysiological effects. Nakshima et al. [49] have shown that candesartan and captopril have a beneficial effect on electrical remodeling. They found that these two substances significantly reduce the shortening of the atrial effective refractory period during 2 h of rapid atrial pacing. Angiotensin II activates protein kinase C and thereby phosphorylation of L-type calcium channels which increases calcium influx through the channels (Fig. 2) [50]. Therefore, inhibition of the angiotensin II activity may reduce calcium overload during AF. In addition, inhibition of potassium currents (e.g. transient outward current, delayed rectifier) may influence the voltage of the plateau of the action potential, and thereby, effect repolarization [51]. Angiotensin II causes a decrease in junctional conduction which increases the likelihood for re-entrant ventricular arrhythmia [52]. Alterations in gap junction expression have also been described during AF, however, the impact of angiotensin II on this phenomenon is unclear [53]. Further prospective studies are required to determine whether inhibition of the atrial angiotensin system offers therapeutic benefit in patients with AF.

2.2. Bradykinin

Bradykinin is a nonapeptide that is released from inactive precursors (high molecular weight kininogens) by serine proteases (kininogenases) [54,55]. The main kininogenases are plasma and tissue kallikreins. Bradykinin breakdown is mediated by the angiotensin converting enzyme (kininase II), neutral endopeptidases, aminopeptidases, and carboxypeptidases (kininase I) [55,56]. The half-life of kinins in vivo is short (<30 s). The effects of bradykinin are mediated by bradykinin (B) receptors. The B1 receptor is expressed mainly under pathological conditions and is thought to mediate inflammation [54,56]. It is activated by des-Arg9 bradykinin which is generated from bradykinin by carboxypeptidase M (CPM). The B2 receptor is responsible for most cardiovascular effects [16,56]. Stimulation of this receptor causes production of nitric oxide, prostaglandins, cAMP, and tissue plasminogen activator. Besides its potent effect as a vasodilator, antagonism of the B2 receptor by HOE 140 attenuates the antifibrictic and antiarrhythmic effects of ACE inhibitors and AT-1 receptor antagonists [57,58].

Initial results have shown that atrial bradykinin metabolism is significantly altered during AF [16]. Chronic AF is associated with reduced amounts of CPM-mRNA and protein levels in the atria. Although amounts of dipeptidyl peptidase IV (DPIV) and alanyl-aminopeptidase (APN) mRNA are unaltered during AF, DPIV activity, which catalyzes bradykinin degradation, is significantly increased during AF. The increase in atrial ACE expression acts synergistically with increased DPIV activity to lower bradykinin levels [15]. Thus, increased bradykinin degradation induced by altered ectopeptidase expression/activity may contribute to degenerative changes in fibrillating atrial tissue (Fig. 4).

2.3. Endothelin

Endothelins (ET-1, ET-2, and ET-3) are 21 amino-acid peptides that are derived from proendothelin by the action of endothelin converting enzyme, a metalloproteinase [59,60]. Endothelin receptors (ET-A and ET-B) bind different endothelin isoforms. ET-1 is the main ligand of the ET-A receptor, while ET-3 is the main ligand of the ET-B receptor. Stimulation of the ET-A receptor induces fibroblast growth and proliferation via Giq proteins and MAP kinases. In addition, activation of phospholipase C affects intracellular calcium handling and protein kinase C activity. Coupled to Giq proteins, ET-B receptors have counterregulatory effects. ET-B receptor activation reduces inotropy, causes vasodilatation, and induces apoptosis [59,60].

In right atrial tissue samples from patients with and without AF, Brundel et al. [61] have demonstrated that ET-1 mRNA levels are significantly increased in patients with AF in the presence of valve diseases. Interestingly, patients with AF but without concomitant valve disease had unaltered ET-1 mRNA levels. The protein expression of ET-A and ET-B receptors was reduced by up to 47% in patients with paroxysmal and persistent AF, regardless of the underlying heart disease. These observed changes in ET-1 may trigger elevation of intracellular calcium via phospholipase C-dependent mechanisms, and thereby contribute to electrical remodeling, contractile dysfunction, and interstitial fibrosis in fibrillating atria. Even in the presence of heart failure, patients with AF have higher endothelin levels compared to those in sinus rhythm [17,62]. Interestingly, the proarrhythmogenic action of ET-1 is reduced by administration of verapamil, which demonstrates that an interaction between ET-1 signaling and L-type calcium channels is involved [63]. In contrast, l-NAME (NO synthase inhibitor) enhances the ET-1 dependent increase in intracellular calcium and proarrhythmic effects whereas SNAP (S-nitrosoacetylpenicillamine), which is a donor of nitric oxide, attenuates the effects of endothelin. In a similar fashion to SNAP, 8-bromo-cyclic GMP has been shown to protect against ET-1-induced fibrillation [64], thus, NO-cGMP signaling may also have beneficial effects in ET-1-dependent atrial arrhythmias. As with angiotensin II, atrial stretch is a potent factor in the production and release of ET-1 [65]. Thus, in addition to possible ET-1-dependent effects on intracellular calcium during AF, pre-existing cardiac diseases (valve diseases, etc.) may induce morphological alterations in the tissue
architecture via ET-1-dependent signaling which increase the likelihood of the occurrence of AF.

2.4. Catecholamines

Endogenous catecholamines, norepinephrine and epinephrine, are released by postganglionic nerve terminals. After interaction with membrane bound (heptahelial) receptors, they activate several intracellular signaling cascades [66,67]. Classically, adrenergic receptors are divided into five subfamilies: α1, α2, β1, β2, and β3, and each type couples to a different G protein (Table 3). Typically, α1-receptors are linked by Gqα to phospholipases, L-type calcium channels, Na+/H+ and Na+/Ca2+ exchangers, and potassium channels [18,67]. The α2-receptors are linked by Goα to inhibition of adenylyl cyclase. Classically, β-adrenoreceptors activate adenylyl cyclase via Goα to increase intracellular cAMP levels (Fig. 5). Activation by G1 proteins links β-adrenoreceptors to other signaling cascades, such as MAP kinases [68]. Through various interactions with ion channels and second messengers, different adrenergic receptors enable catecholamines to have a broad range of actions [66–68]. Adrenergic receptors are regulated by desensitization, which occurs by a three-step process: uncoupling, internalization, and digestion. Uncoupling occurs, for example, after a ligand-bound β-adrenergic receptor is phosphorylated by so-called β-adrenergic receptor kinases (βARK). The effect of βARK requires the cofactor β-arrestin, which binds to the phosphorylated intracellular C-terminal of the receptor [20]. Thereafter, the phosphorylated receptor cannot activate its G proteins. However, this desensitization step is reversible via dephosphorylation by G protein receptor phosphatases. After uncoupling of phosphorylated receptors from their G protein, β-arrestin-bound receptors are transferred to clathrin-coated pits within the cell (internalization) [69] to be digested by proteolytic enzymes.

Studies have shown that AF produces a heterogeneous increase in atrial sympathetic stimulation [11,70]. Sympathetic hyperinnervation and nerve sprouting have been demonstrated in a canine model of AF [11]. In addition, administration of verapamil in the absence of autonomic blockade seems to prolong the duration of AF episodes by an intense sympathetic neurohumoral effect [71,72]. These findings underline the well-known proarrhythmic effect resulting from a local excess of catecholamines [11,70,73]. However, plasma catecholamines levels are not elevated ini patients with AF [74,75]. The inotropic response to catecholamines in fibrillating atria is modest [76]. Schotten et al. [77] showed that, compared to sinus rhythm, a tenfold higher concentration of isoproterenol was required in fibrillating atrial tissue to elicit a half-maximal positive inotropic response. This reduced response to isoproterenol, however, was not due to downregulation of β-adrenergic receptors or to alteration in G protein expression [78]. Also, the ratio of atrial β1/β2-adrenoceptors expressed is not altered during AF and the function of the sarcoplasmic reticulum is preserved [77,79]. Thus, the impaired β-adrenergic modulation in fibrillating atrial tissue does not appear to be due to alterations in β-adrenergic signal transduction, but rather to downregulation of L-type calcium channels [77]. However, prolonged activation of β-adrenoceptors causes internalization of the receptor and formation of a β-receptor–β-arrestin complex, which can activate MAP kinases via Ras-independent mechanisms. This may result in harmful proliferative responses and cell death [69]. There is increasing evidence of ‘cross talk’ between the adrenergic system and the renin-angiotensin-aldosterone system. Musgrave Foucart and Majewski [80] have shown that angiotensin II increases norepinephrine release from atrial sympathetic nerves via activation of prejunctional AT-1 receptors. Continuous angiotensin II stimulation can cause a progressive decrease in β-adrenergic receptor density [81]. Further studies are warranted to determine the specific impact of prejunctional modulation of norepinephrine release during AF (Fig. 5).

3. Enzyme-linked receptors

After binding of an extracellular messenger, enzyme linked receptors activate an intracellular enzyme (usually a protein kinase) and, thereby, regulate gene transcription, cell growth, and proliferation.
3.1. Tyrosine kinase receptor agonists

These receptors have latent tyrosine kinase activity [82,83]. Peptide growth factors that bind to this receptor family include PDGF, EGF, FGF, IG, and VEGF (Table 1). Receptor tyrosine kinases autophosphorylate the receptor after binding of an agonist protein (Fig. 2 and Fig. 6). Phosphorylation of the receptor allows binding and phosphorylation of an adaptor protein (Shc). Thereafter, a Shc/Grb₂/SOS complex is formed that leads to activation of MAP kinases via Ras (Fig. 2).

Seko et al. [83] have recently shown that VEGF serum levels are elevated in patients with AF. Pulsatile mechanical stretch is known to be a very potent stimulus for increasing the release of growth factors [84]. Thus, irregular intravascular blood flow during AF (e.g. impulsive flow) may induce pulsatile vascular stretch and, thereby, increase VEGF secretion.

3.2. Serine/threonine kinase receptor agonists

Transforming growth factor β (TGF-β) can induce fibrous tissue formation, cell differentiation, and programmed cell death [85]. Like other growth peptides, TGF-β operates predominantly by autocrine and paracrine mechanisms. Binding of a TGF-β homodimer to two TGF-β type II receptors causes formation of a tetrameric ligand–receptor complex. This complex aggregates with two TGF-β type I receptors to form a heterohexamer. The serine/threonine kinase of the type II receptor phosphorlates and thereby activates the type I receptors. Thereafter, activated type I receptors mediate signal transduction by phosphorylation of different cytosolic proteins [86,87]. Intracellular substrates for TGF-β-dependent phosphorylation include the cyclin-dependent kinase inhibitors (CDKI), which inhibit the cell cycle [87]. In addition, signaling molecules belonging to the family known as SMAD are major substrates for phosphorylation by activated type I receptors; when phosphorylated, SMADs aggregate and enter the nucleus to induce myocardial fibrosis [86]. In addition, TGF-β can redirect protein synthesis to favor expression of fetal genes as described in fibrillating atria [5,88].Ausma et al. have shown reexpression of embryonic alpha smooth muscle actin during AF (e.g. impulsive synthesis to favor expression of fetal genes as described in atrial fibrillation [86]. In addition, TGF-β can redirect protein synthesis to favor expression of fetal genes as described in fibrillating atria [5,88].}

3.3. Cytokine/TNF-α receptor agonists

Besides their actions on immune cells, cytokines have a potent effect on other cells and tissues, including the heart (Fig. 6) [90,91]. Members of the heterologous group of cytokines bind to different types of specific receptors, including receptor kinases (e.g. TGF-β receptor) and tyrosine-kinase linked receptors that lack intrinsic kinase activity; the latter are also referred to as cytokine receptors (e.g. IL-1β and TNF-α receptor). Activation of these receptors by a wide variety of cytokines or growth factors generally provokes di- or trimerisation of monomeric subunits. This, in turn, induces rapid activation of the JAK/STAT pathway (Fig. 6).

Cardiac cytokines are not necessarily expressed by endothelial or infiltrating immune cells; for example, various pathophysiological conditions induce TNF-α expression in cardiomyocytes [90,91], which normally lack detectable amounts of TNF-α mRNA or protein. One important signaling pathway induced by cytokines (e.g. TNF-α) is apoptotic cell death. Loss of myocytes (apoptosis) has been demonstrated during AF [12,42]. Oxidative or mechanical stresses lead to activation of p38 MAP kinase and the transcription factor NFκB. Both are key factors in cellular signaling pathways that drive the expression of, for example, cytokines, receptors, or adhesion molecules [92–94] (Fig. 6). The NFκB family of transcription factors plays a crucial role in inflammatory and apoptotic responses. They are retained in the cytoplasm by interaction with the inhibitory molecule IκB. In response to various signals IκB becomes phosphorylated by serine

protein kinases (IKK) and degraded, which allows translocation of NFκB into the nucleus. NFκB activation is required to promote cellular growth and prevent apoptotic cell death.

The contribution of both pro-inflammatory and immunosuppressing cytokines in the structural remodeling of the fibrillating atria remains to be fully elucidated. Frustaci et al. [6] reported on atrial lymphomononuclear infiltrates with adjacent necrosis of myocytes in about two-thirds of patients with lone AF. It has also been speculated that lone AF is promoted by autoimmune processes [95]. Thus, cytokine-dependent signaling seems to be important for the development of structural and functional changes in this specific patient population with AF. In contrast to inflammatory alterations during lone AF, patients with AF in the presence of concomitant cardiovascular diseases do not show signs of atrial inflammation [12,14,89]. In these patients, structural atrial changes are not associated with an increased expression of pro-inflammatory (TNF-α, IL-1β and IL-6) or immunosuppressive (IL-10) cytokines [89]. Relatively small amounts of IL-2 and TGF-β1 have been found in atrial tissue in patients with and without AF; the expression of these cytokines appeared not to be related to the arrhythmia itself, but rather to the underlying ventricular disease [89]. Thus, the development of atrial apoptosis/fibrosis triggered by ventricular diseases seems to depend only partly on intracellular cytokine pathways. Primary inflammatory processes, however, are more likely to be involved in patients with lone AF.

4. Intracellular receptor agonists

Intracellular receptors are activated in the cytoplasm or nucleus after an receptor agonist has passed the cell membrane; a typical example of such an agonist is aldosterone. Aldosterone is the most important mineralcorticoid that is released after angiotensin II stimulation by the adrenal gland and extra-adrenal tissue. Mineralcorticoid receptors (steroid receptor type I) bind aldosterone and glucocorticoids with equal affinity. After binding of an agonist to the COOH-terminal of the receptor, a heat shock protein is released and the receptor undergoes a conformational change to allow dimerization. The dimer binds with high-affinity to regulatory sites of specific target genes [96,97]. Recently, Fiebeler et al. [97] have shown that mineralocorticoid receptors also affect NF-kappaB, transcription factor AP-1, and basic fibroblast growth factor (bFGF).

Besides the profibrotic effects of aldosterone, elevated plasma aldosterone enhances potassium and magnesium excretion, decreases myocardial reuptake of catecholamines, and induces baroreceptor dysfunction [98]. Through aldosterone antagonism, spironolactone is effective in reducing circulating levels of procollagen type III N-terminal amino peptide (a marker of collagen turnover) and influencing heart rate and heart rate variability [99]. Recent data suggest that aldosterone is produced in failing human ventricles [100]. Systemic aldosterone levels are increased in patients with AF [75,101]. In addition, successful electrical cardioversion has been shown to decrease aldosterone levels [101]. Thus, elevated levels of aldosterone during AF may contribute to the described fibrotic changes in the myocardium and they may disturb the autonomic balance. Interestingly, a study by Harada et al. [102] has recently shown that aldosterone increases cardiac ACE expression. Thus, it seems likely that increased levels of aldosterone interact with ACE levels/activity in fibrillating atria (Fig. 4).

5. Adhesion molecules

Adhesion molecules allow cells to adhere to each other and to the extracellular matrix [103]. Cell adhesion is necessary for several cell functions including differentiation, growth, migration, and cell survival [103]. Adhesion molecules share similarities to enzyme-linked receptors. In addition to the formation of physical linkages to extracellular proteins, they also activate intracellular tyrosine kinases, and thereby, adhesion molecules mediate proliferative signaling [103,104]. Increased expression of adhesion molecules on blood cells (e.g. P-selectin) may further enhance cell aggregation and adhesion, which may contribute to intravascular thrombus formation [105–107].

5.1. Integrins

Integrins are a ubiquitous family of transmembrane receptors. They are heterodimers composed of α and β-subunits and at least 16 different α and eight different β-subunits have been described [103,104]. The extracellular portion of the protein binds to extracellular matrix proteins including collagen, vitronectin, fibronectin, fibrinogen, and thrombospondin. The short cytoplasmic β tail binds to adaptor proteins, which interact with enzyme-linked receptors, cytoplasmic kinases, and cytoskeletal proteins [104]. When integrin binds to the extracellular matrix, integrins cluster within the cell membrane and promote assembly of actin filaments into stress-fibers. Integrins are linked to α-actinin by the cytoskeletal proteins talin, paxillin, and vinculin. Stress fibers promote further integrin clustering and this results in formation of focal adhesions. Focal adhesions activate focal adhesion kinases (FAK), which in turn phosphorylate tyrosine kinases such as Src and Fyn, which are potent activators of ERKs [104]. In addition, due to interaction with cell cycle proteins, integrins regulate cell death as well as cell growth [102]. Interestingly, angiotensin II stimulation causes an up-regulation of integrin expression and FAK activation, which demonstrates an important ‘cross-talk’ between these signal transduction systems [108].
The interaction between cardiac myocytes and the surrounding extracellular matrix helps to adapt the shape and size of cardiac cells as well as the chamber architecture, especially under physical forces. Initial results imply that members of recently described families of membrane-bound metalloproteases called ADAMs (‘a disintegrin and metalloprotease’) interact with integrin β1 and β3 in atrial tissue [109,110]. Due to the disintegrin activity, increased atrial expression of ADAMs during AF may prevent integrin binding to the extracellular matrix. Thus, increased ADAM activity in the tissue may enhance sliding and slippage of cells which may contribute to the well-described dilation of fibrillating atria [110,111]. Interestingly, Coker et al. [112] have shown that neurohumoral stimuli (angiotensin II, isoproterenol, and endothelin-1) induce the synthesis and release of matrix metalloproteinase-2 (MMP-2) in isolated LV myocytes. Thus, it appears likely that elevated levels of angiotensin II and endothelin-1 may also affect MMP expression in patients with AF which may further influence the tissue architecture.

6. Conclusions

Atrial tissue from patients with AF shows significant abnormalities. Most of the described structural changes are related to altered signal transduction at the cellular level. Activation of intracellular MAP kinases by various stimuli (heptahelical receptor agonists, growth factors, etc.) seems to play an especially important role. Activated MAP kinases can contribute to hypertrophy of atrial myocytes, apoptosis and alterations of interstitial matrix composition in patients with AF. In addition to MAP kinase-dependent effects, loss of cell–matrix interactions by increased ADAM expression is associated with atrial dilation. Activation of PKC-dependent pathways can influence atrial potassium and calcium currents. Furthermore, stimulation of signaling pathways and their complex interactions may help to explain why electrophysiological and structural components of ‘atrial remodeling’ are at least partially dissociable. Paroxysmal episodes of AF, which do not induce long-lasting electrophysiological abnormalities, may cause prolonged alterations in atrial signal transduction and gene expression. Accumulation of such changes may contribute to the conversion of an ‘electrical abnormality’ into a ‘structural atrial disease’. In contrast, in the presence of cardiovascular diseases like hypertension or heart failure, AF appears as a consequence rather than a primary cause of altered signal transduction. However, more experimental evidence is needed to clarify these important issues. Further elucidation of atrial signal transduction systems and their regulation will contribute to a better understanding of the pathophysiology of AF and, in addition, may offer novel therapeutic and prophylactic approaches in the future.

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