Available online at www.sciencedirect.com

SCIENCE DIRECT®

European Journal of Pharmacology 500 (2004) 167–176

www.elsevier.com/locate/ejphar

Review

Autonomic receptor systems in the failing and aging human heart: similarities and differences

Otto-Erich Brodde*, Kirsten Leineweber

Departments of Pathophysiology and Nephrology, University of Essen School of Medicine, IG I., 9.OG, Hufelandstr. 55, D-45147 Essen, Germany

Accepted 1 July 2004
Available online 17 August 2004

Abstract

Changes in autonomic receptor systems (α- and β-adrenoceptors and muscarinic receptors) were compared in the aging and failing human heart. In both settings responsiveness of β-adrenoceptors and all other receptor systems that evoke their effects via cyclic AMP accumulation was diminished. Muscarinic receptor function, on the other hand, was decreased in the aging, but unchanged in the failing heart; in contrast, G protein-coupled receptor kinase activity was increased in the failing, but unchanged in the aging heart. α-Adrenoceptor function was unchanged or slightly decreased in the failing heart. However, nothing is known on α-adrenoceptor changes in the aging heart. These results indicate that in the failing human heart all autonomic receptor systems appear to be altered in the direction to attenuate β-adrenoceptor responses to sympathetic (over)stimulation while in the aging human heart autonomic receptor systems appear to be altered in a direction that protects the heart against too pronounced reduction in β-adrenoceptor responsiveness.

Keywords: Failing human heart; Aging human heart; α-Adrenoceptor; β-Adrenoceptor; Muscarinic receptor; Sympathetic activity

Contents

* Corresponding author. Tel.: +49 201 723 4467; fax: +49 201 723 5963.
E-mail address: otto-erich.brodde@uni-essen.de (O.-E. Brodde).

0014-2999/$ - see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejphar.2004.07.022

1. Introduction

In the human heart there are several receptor systems that are involved in regulation of contractility and/or heart rate. Among these there are receptors coupled to the G_s-protein (β-adrenoceptors, histamine (H)- and serotonin (5-HT) receptors) that mediate their effects by increases in the intracellular level of cyclic AMP; receptors coupled to the G_i protein (muscarinic (M)-receptors, adenosine (A) receptors) that lead upon stimulation to decreases in the intracellular level of cyclic AMP and receptors that mediate their effects independent of cyclic AMP via the $G_{q/11}$/phospholipase C/diacylglycerol/inositoltrisphosphate/protein kinase C pathway (α_1-adrenoceptors, endothelin (ET)- and angiotensin (AT)-receptors) (Fig. 1). The aim of this overview was to compare changes in autonomic receptors in the aging and failing human heart.

2. Autonomic receptors in the human heart

2.1. β-Adrenoceptors

At present, three β-adrenoceptor subtypes have been identified in mammals, β_1-, β_2- and β_3-adrenoceptors (for recent reviews, see Brodde and Michel, 1999; Lohse et al., 2004; Leineweber et al., 2004). In the human heart both β_1- and β_2-adrenoceptors coexist, whereby β_1-adrenoceptors predominate (β_1:β_2-adrenoceptors ratio, about 70:30%). Both β-adrenoceptor subtypes couple to G_s, thereby elevating the intracellular level of cyclic AMP and cause positive inotropic and chronotropic effects, in vitro as well as in vivo. However, in contrast to the β_1-adrenoceptor β_2-adrenoceptors can also couple to G_i protein, at least in murine and rat cardiomyocytes (Xiao et al., 1999; Steinberg, 1999). Whether this holds true also for the human heart has to be elucidated.

Similarly, it is still an open question whether or not β_3-adrenoceptors might exist in the human heart. Several groups did not find any evidence for β_3-adrenoceptor mediated effects whereas Gauthier and associates recently found in ventricular endomyocardial biopsy samples of heart transplant recipients β_3-adrenoceptors that obviously couple to a G_i/nitric oxide (NO) pathway and mediate negative inotropic effects (for reviews, see Brodde and Michel, 1999; Gauthier et al., 2000; Lohse et al., 2004).

2.2. α_1-Adrenoceptors

At present three α_1-adrenoceptor subtypes have been identified: α_{1A}-, α_{1B}- and α_{1D}-adrenoceptors (Hieble et al., 1995; Michel et al., 1995; Calzada and De Artinano, 2001). α_1-Adrenoceptors in the human heart have been identified at the mRNA level, at the protein level and in functional studies (for recent reviews, see Brodde and Michel, 1999; Benfey, 1993); the density of α_1-adrenoceptors, however, is only 10–15% of that of β-adrenoceptors. In addition, the subtype(s) of α_1-adrenoceptors present in the human heart is not well characterized. At the mRNA level all studies agree that the α_{1A}-adrenoceptor is the most abundant α_1-adrenoceptor subtype, but mRNA for α_{1B}-adrenoceptors and α_{1D}-adrenoceptors has been also demonstrated in some but not all studies. Moreover, on a protein level and in functional studies

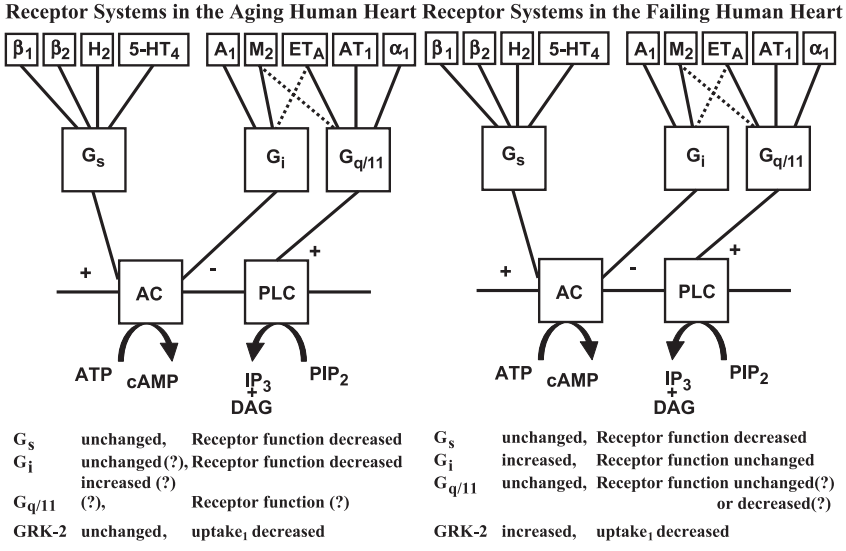

Fig. 1. Receptor systems and their signal-transduction mechanisms in the aging (left) and failing (right) human heart. For details, see text. β_1, β_2, α_1=β_1-, β_2-, and α_1-adrenoceptors; H_2=histamine H_2-receptors; 5-HT_4=serotonin 5-HT_4-receptors; M_2=muscarinic M_2-receptors; A_1=adenosine A_1-receptors; ET_A=endothelin ET_A-receptors; AT_1=angiotensin II AT_1-receptors; G_s=stimulatory G-protein; G_i=inhibitory G-protein; $G_{q/11}$=the G-protein that couples ET-, AT-receptors and α_1-adrenoceptors to phospholipase C (PLC); AC=adenylyl cyclase: PIP_2=phosphatidylinositol 4,5-bisphosphate; DAG=diacylglycerol; IP_3=inositol trisphosphate; GRK=G-protein-coupled receptor kinase; $uptake_1$=noradrenaline re-uptake transporter. +=activation; −=inhibition.

nothing is known on the subtype of α_1-adrenoceptors in the human heart.

Human cardiac α_1-adrenoceptors couple presumably via $G_{q/11}$-protein to inositol phosphate formation (Bristow et al., 1988) and mediate positive inotropic effects (for review, see Terzic et al., 1993; Benfey, 1993; Li et al., 1997; Brodde and Michel, 1999). The maximum positive inotropic effect following α_1-adrenoceptor stimulation, however, is by far less than that evoked by β-adrenoceptor stimulation in the human heart.

In addition, it should be mentioned, that stimulation of cardiac α_1-adrenoceptors can cause the development of a hypertrophic phenotype, at least in neonatal and adult rat cardiomyocytes (Simpson, 1983; Schlüter and Piper, 1999). We have recently convincingly demonstrated that, in adult rat cardiomyocytes, the α_1-adrenoceptor subtype involved in this hypertrophic response is the α_{1A}-adrenoceptor (Pönicke et al., 2001). Whether or not activation of α_1-adrenoceptors in the human heart might also induce a hypertrophic response is not known at present.

2.3. Muscarinic receptors

At present five different muscarinic receptor subtypes exists: M_1-, M_2-, M_3-, M_4- and M_5-receptors (for reviews, see Caulfield and Birdsall, 1998; Brodde and Michel, 1999; Dhein et al., 2001). These muscarinic receptor subtypes are subclassified into two large groups according to their differential signal transduction mechanisms: “odd”-numbered muscarinic receptors (M_1-, M_3-, and M_5-receptors) couple via a $G_{q/11}$ protein to the phospholipase C/diacylglycerol/inositoltrisphosphate/protein kinase C pathway; “even”-numbered muscarinic receptors (M_2- and M_4-receptors) couple via a $G_{i/o}$ protein to the adenylyl cyclase in an inhibitory fashion.

In the human heart, the predominant muscarinic receptor subtype is the M_2-receptor (Dhein et al., 2001). Stimulation of these muscarinic M_2-receptors evokes negative inotropic and chronotropic effects, in atria directly, in ventricles indirectly (i.e., only after force of contraction is enhanced by cyclic AMP elevating agents). Thus, in isolated electrically driven human right atria carbachol decreased basal force of contraction as well as force of contraction that had been previously elevated by stimulation of β_1-adrenoceptors, β_2-adrenoceptors, histamine H_2-receptors and serotonin 5-HT_4-receptors (Wangemann et al., 2003), while in ventricular preparations carbachol did not decrease basal force of contraction, but did decrease only force of contraction that had been activated by isoprenaline or forskolin (Caulfield, 1993; Brodde and Michel, 1999; Dhein et al., 2001).

Evidence had accumulated that, in the human heart, there might exist another muscarinic receptor subtype. Thus, expression of muscarinic M_2- and M_3-receptors in the human heart has been demonstrated (Hellgren et al., 2000; Oberhauser et al., 2001). In addition, in vivo studies had shown that low doses of atropine and the selective muscarinic M_1-receptor antagonist pirenzepine could evoke negative chronotropic effects (Pitschner and Wellstein, 1988; Poller et al., 1997; Jakubetz et al., 2000) and it had been speculated (see Brodde and Michel, 1999) that this effect might be caused by inhibition of presynaptic muscarinic autoreceptors thereby leading to enhanced acetylcholine release; since these effects were achieved by rather low pirenzepine doses (i.e., M_1-selective) this autoreceptor could be of the M_1-subtype. However, Oberhauser et al. (2001) recently demonstrated that, in human right atria, the presynaptic muscarinic autoreceptor regulating the release of acetylcholine is of the M_2-subtype.

Moreover, it had been shown that, in the human heart, carbachol can increase inositol phosphate formation (Bristow, 1993). We very recently could demonstrate that this effect of carbachol is mediated by activation of a muscarinic M_3-receptor (Willmy-Matthes et al., 2003): thus, in human right atrial slices carbachol-induced increase in inositol phosphate formation was antagonized by atropine (indicating that it is mediated by muscarinic receptors) and by the selective muscarinic M_3-receptor antagonist darifenacin, but was not affected by the muscarinic M_1-receptor antagonist pirenzepine or the muscarinic M_2-receptor antagonist himbacine. The functional role of these muscarinic M_3-receptors in the human heart remains, however, to be investigated.

3. Changes of autonomic receptors with aging

Human aging is associated with an increase in the activity of the sympathetic nervous system. This has been first proposed from the fact that plasma noradrenaline levels (that are often taken as an indirect index for sympathetic activity; Esler et al., 1979; Folkow et al., 1983; Goldstein, 1988) are higher in old vs. young people (Ziegler et al., 1976; for reviews, see Esler et al., 1990; Folkow and Svanborg, 1993; Lakatta, 1993), and has been subsequently confirmed directly by microneurographic recordings of post-ganglionic sympathetic nerve activity to skeletal muscle (Sundlof and Wallin, 1978; Ng et al., 1993; for further references, see Seals and Esler, 2000). Thus, there can be no doubt that sympathetic nervous activity increases with age; this is, however, a mild increase in sympathetic activity that develops slowly (plasma noradrenaline levels increase only 10–15% per decade, Seals and Esler, 2000). Nevertheless, in this setting cardiac adrenoceptors are exposed to chronic stimulation; hence, a desensitization of cardiac β-adrenoceptors with age could be expected.

3.1. β-Adrenoceptors

Numerous studies in animals have shown that with increasing age cardiac β-adrenoceptor responses decrease. While assessment of β-adrenoceptor density in aging myocardium did not result in consistent results (decrease,

increase, no change with aging) a general finding was that coupling of the β-adrenoceptor to the G_s protein and to the catalytic unit of the adenylyl cyclase is impaired with aging (for references, see Docherty, 1990; Lakatta, 1993; Ferrara et al., 1997).

Only a few studies on age-dependent changes of β-adrenoceptors in the human myocardium ex vivo exist. Davies et al. (1996) could show that, in isolated ventricular myocytes from nonfailing hearts, the maximal contractile response to isoprenaline was significantly reduced in the elder patients, whereas the EC_{50} values for isoprenaline were in the elder patients nearly twice as high as in young patients. White et al. (1994) studied ventricular β-adrenoceptors in explanted nonfailing human hearts. They found a decrease in β_1-adrenoceptors, a reduction in agonist-evoked induction of the high affinity state of the β-adrenoceptor (i.e., impaired coupling to the G_s protein), and a diminished activation of the adenylyl cyclase by the β-adrenoceptor agonist isoprenaline as well as by the β_2-adrenoceptor agonist zinterol. Moreover, activation of adenylyl cyclase by Gpp(NH)p, NaF and forskolin was attenuated with age, as was the maximal positive inotropic effect of isoprenaline on isolated electrically driven right ventricular trabeculae decreased and the EC_{50} value for isoprenaline significantly increased. In this study, G_i protein was unchanged, while G_s protein was decreased (when assessed by cholera toxin induced ADP ribosylation) or unchanged (when assessed by Western blotting).

Rather comparable data have been found by our group (Brodde et al., 1995b). We have investigated right atria from patients of different ages who were undergoing coronary artery bypass grafting. We found only the tendency of a decrease of β-adrenoceptors with age, but activation of adenylyl cyclase by isoprenaline, terbutaline (a β_2-adrenoceptor agonist), GTP, NaF, and forskolin was significantly diminished with age; moreover, there was a significant negative correlation for each parameter with age. However, in contrast to the White et al. (1994) paper we found a decreased Mn^{2+}-induced adenylyl cyclase activation, indicating that with age the activity of the catalytic unit of the adenylyl cyclase declines. G_s protein (as assessed by Western blotting) was unchanged, while G_i protein showed a slight but significant increase with age. Interestingly, in our study activation of adenylyl cyclase by serotonin (via serotonin 5-HT_4 receptors) and histamine (via histamine H_2 receptors) was also diminished in aging. Taken together, in the aging human heart responses to all receptors that involve increases in the intracellular level of cyclic AMP appear to be diminished.

In addition, we have recently found that in right atria from patients of different ages undergoing coronary artery bypass grafting without apparent heart failure, density and activity of the neuronal noradrenaline re-uptake transporter ($uptake_1$) significantly decreased with increasing age (Leineweber et al., 2002); in contrast, in right atria of a very similar group of patients the activity of the G-protein coupled receptor kinase (GRK), a kinase that is involved in desensitization of β-adrenoceptors, is not changed with aging (Leineweber et al., 2003). That is in good agreement with a recent study in aged myocardium of rats where GRK was also found to be unaltered (Xiao et al., 1998).

3.2. α_1-adrenoceptors

To the best of our knowledge, nothing is known on possible age-dependent changes of α_1-adrenoceptors in the human heart.

3.3. Muscarinic receptors

In aging parasympathetic activity appears to be reduced (Pfeifer et al., 1983; Fouad et al., 1984; O'Brien et al., 1986). However, animal data on changes in number and functional reponsiveness of cardiac muscarinic receptors are controversial: some studies indicate an increase while others show a decrease (for references see Docherty, 1990; Brodde and Michel, 1999; Dhein et al., 2001).

In the human heart, only a very few studies have been performed to assess changes of muscarinic receptors with aging. We (Brodde et al., 1998a) have recently shown that, in right atria from patients undergoing coronary artery bypass grafting, the density of muscarinic receptors decreased with age; this decrease was accompanied by a diminished ability of carbachol to inhibit forskolin-activated adenylyl cyclase and forskolin-stimulated force of contraction in isolated electrically driven right atrial trabeculae (Giessler et al., 1998).

This decrease in muscarinic receptor function is consistent with recently published data by Oberhauser et al. (2001) who demonstrated that the electrically stimulated release of acetylcholine from atrial tissue decreased with increasing age of the patients. Furthermore, the bradycardic effect of low dose pirenzepine on basal as well as on isoprenaline-stimulated heart rate is significantly attenuated in elder people (Poller et al., 1997; Brodde et al., 1998a).

And finally, in about 400 healthy subjects of different ages Liu et al. (1999) found antibodies against the muscarinic M_2-receptor; interestingly the frequency of occurrence of these antibodies increased with increasing age in these volunteers. Thus, taken together in the aging human heart number and functional responsiveness of muscarinic M_2-receptors appears to be reduced. Whether cardiac muscarinic M_3-receptors, that have been recently demonstrated in the human heart (see above), may be affected by age is not known at present.

4. Changes of autonomic receptors in heart failure

In heart failure sympathetic activity is increased. This has been directly demonstrated by studies with peroneal nerve recordings of sympathetic nerve traffic in patients

with chronic heart failure (Leimbach et al., 1986). In addition, numerous studies have shown that plasma noradrenaline levels are elevated in patients with chronic heart failure (Francis and Cohn, 1986; Cohn, 1990). The increase in plasma noradrenaline levels, that has been taken as a guide to prognosis for these patients (Cohn et al., 1984; Rector et al., 1987), is by higher and more rapid than that observed in aging (see above), and is caused by an enhanced cardiac noradrenaline spillover due to the increased sympathetic drive to the heart (for review, see Esler et al., 1997) and a decreased activity and density of the neuronal noradrenaline re-uptake transporter (uptake$_1$) (Petch and Nayler, 1979; Böhm et al., 1995; Eisenhofer et al., 1996). Accordingly, myocardial catecholamine stores are depleted in patients with chronic heart failure (Chidsey and Braunwald, 1966). Thus, in chronic heart failure cardiac β-adrenoceptors are chronically activated by the increased sympathetic activity (i.e., increased catecholamine concentrations) thus leading to a decrease in cardiac β-adrenoceptors, the most powerful physiologic mechanism to acutely augment contractility (and heart rate) in the human heart (Brodde et al., 1995a).

4.1. β-Adrenoceptors

Since the original findings of Bristow et al. (1982) that in the severely failing human heart β-adrenoceptors are decreased, numerous studies on alterations of the β-adrenoceptor system in the failing human heart have been performed. It is now generally accepted that, in the failing human heart, β_1-adrenoceptors are decreased, β_2-adrenoceptors may or may be not decreased but are uncoupled form the effector system adenylyl cyclase, the amount and activity of G_s protein is unchanged, the amount and activity of G_i protein is increased as is the amount and activity of the GRK, while activities of adenylyl cyclase and protein kinase A are unchanged (for reviews, see Brodde, 1993; Brodde and Michel, 1999; Port and Bristow, 2001; Lohse et al., 2004). The consequence of these changes is a reduction in cardiac β-adrenoceptor functional responsiveness. However, in heart failure not only functional responsiveness of β-adrenoceptors but also that of all receptors coupled to the G_s protein (histamine H_2-receptors, serotonin 5-HT_4-receptors) is diminished (Näbauer et al., 1988; Brodde et al., 1998b) presumably by the increase in the inhibitory G protein G_i, that might impair cyclic AMP formation. In fact, it has recently been shown that increases in G_i protein can suppress receptor-mediated activation of adenylyl cyclase (for references, see El-Armouche et al., 2003). Taken together, in the failing human heart responses to all receptors that involve increases in the intracellular level of cyclic AMP appear to be diminished.

Finally, it should be noted that evidence has accumulated that cardiac β-adrenoceptor stimulation can evoke programmed cell death (apoptosis) with β_1-adrenoceptors (via the G_s protein) inducing proapoptotic effects and β_2-adrenoceptors (via the G_i protein) inducing antiapoptotic effects, at least in rat cardiomyocytes (Communal et al., 1999; Chesley et al., 2000; Pönicke et al., 2003). Whether this holds also true for the human heart remains to be elucidated. However, it should be mentioned that in the failing human heart G_i is increased. One can speculate, therefore, that this increase in G_i would be protective to the human heart because it would enhance the antiapoptotic effects of β_2-adrenoceptor stimulation.

4.2. α_1-Adrenoceptors

Several studies on changes of α_1-adrenoceptors in the failing human heart have been published. From the data it appears that, in the failing heart, the density of α_1-adrenoceptors is somewhat increased (Vago et al., 1989; Steinfath et al., 1992; Hwang et al., 1996; Yoshikawa et al., 1996) although unchanged α_1-adrenoceptor density has also been found (Böhm et al., 1988; Bristow et al., 1988; Hwang et al., 1996). The changes in α_1-adrenoceptor density were, however, accompanied by an unchanged amount of immunodetectable $G_{q/11}$, the G protein that couples α_1-adrenoceptors to the phospholipase C (Pönicke et al., 1998) and by an unaltered inositol phosphate formation (Bristow, 1993). Moreover, α_1-adrenoceptor mediated positive inotropic effects in isolated ventricular preparations from failing hearts were either unaltered (Böhm et al., 1988) or even decreased (Steinfath et al., 1992).

Interestingly, this pattern of α_1-adrenoceptor changes in the failing human heart very closely resembles that of alterations of another cardiac $G_{q/11}$-coupled receptor in the failing human heart, the endothelin (ET)-receptor: density of ET-receptors is increased (Pönicke et al., 1998; Pieske et al., 1999; Zolk et al., 1999; Serneri et al., 2000; Walker et al., 2001; Asano et al., 2002), ET-1 induced inositol phosphate formation is unchanged (Pönicke et al., 1998) and the positive inotropic effect of ET-1 on isolated human ventricular preparations is rather decreased (Pieske et al., 1999).

4.3. Muscarinic receptors

In chronic heart failure patients activity of the parasympathetic nervous system appears to be attenuated (Eckberg et al., 1971; Porter et al., 1990; La Rovere et al., 1994). However, most studies have shown that the number of cardiac muscarinic receptors in patients with chronic heart failure is not altered (Böhm et al., 1990a,b; Fu et al., 1992; Giessler et al., 1999); only an in vivo positron emission tomography (PET) study has found a slight, but significant increase in cardiac muscarinic receptors in patients with chronic heart failure (Le Guludec et al., 1997). Interestingly, also functional responsiveness of cardiac muscarinic receptors (i.e., inhibition of adenylyl cyclase and negative inotropic effects) were not altered in atrial and ventricular preparations from patients with chronic heart failure (Böhm et al., 1990a,b; Bristow, 1993;

Pönicke et al., 1998; Giessler et al., 1999) although activity of G_i protein, the G protein coupling cardiac muscarinic M_2-receptors in an inhibitory fashion to adenylyl cyclase is increased (see above). Thus, the role of the increase in G_i in heart failure is still a matter of debate. On the one side it might be detrimental to the heart because it attenuates (via inhibition of adenylyl cyclase) positive inotropic effects brought about by stimulation of all receptors that involve formation of cyclic AMP. On the other hand, it might be protective to the heart because it could augment antiapoptotic effects of β_2-adrenoceptor stimulation (see above). Moreover, studies in rats had shown that chronic treatment with carbachol causes a decrease in muscarinic receptor density and in G_i protein, and this was accompanied by a marked increase in isoprenaline- or forskolin-evoked arrhythmias (Eschenhagen et al., 1996). Similarly, inactivation of G_i protein by pertussis toxin treatment in rats led to a marked increase in the arrhythmogenic effect of isoprenaline (Grimm et al., 1998). On the other hand, chronic treatment of rats with isoprenaline caused decreases in β-adrenoceptors and increases in G_i protein, and this was accompanied by a marked decrease in isoprenaline- or forskolin-induced arrhythmias (Eschenhagen et al., 1996). Taken together, these data are in favor of the idea that the increase in cardiac G_i protein in patients with chronic heart failure might protect the heart against catecholamine-induced arrhythmias.

5. Conclusion

From the data presented in the two previous chapters, it is clear that changes in autonomic receptors in the failing and the aging human heart have some similarities (see also Fig. 1). In both settings, the function of all G_s-coupled receptors is diminished; this holds true not only for β_1- and β_2-adrenoceptors, but also for other G_s-coupled receptors such as histamine H_2-receptors and serotonin 5-HT_4-receptors. In the failing heart the reduction in β-adrenoceptor function is due to a decrease in receptor number [which automatically leads—because the human heart has no spare receptors for β-adrenoceptors (Brown et al., 1992; Schwinger et al., 1990)—to a reduction in functional responsiveness) and is sustained (and possibly enhanced) by the increase in the inhibitory G_i protein (that inhibits cyclic AMP formation) and the increase in GRKs (that phosphorylate agonist-occupied receptors and, by this, uncouple them from the effector system, adenylyl cyclase). Morever, in the failing human heart neuronal uptake ($uptake_1$) of catecholamines is diminished. Since in chronic heart failure sympathetic drive to the heart is increased this leads to increases of catecholamines in the synaptic cleft to concentrations that easily can down-regulate β-adrenoceptors.

In the aging human heart, the reason for the reduction in β-adrenoceptor function is, however, not completely understood: in ventricular myocardium a decrease in β_1-adrenoceptor density and in G_s protein appears to be responsible (White et al., 1994) while in right atrial tissue the activity of the catalytic unit of the adenylyl cyclase is reduced in aging that leads to an attenuated cyclic AMP formation; this might be accompanied by a slight increase in G_i protein (that also inhibits cyclic AMP formation; Brodde et al., 1995b). However, independent from the underlying mechanism the aging human heart exhibits diminished responses not only to β-adrenoceptor stimulation but also to stimulation by all receptors that evoke their effects via accumulation of cyclic AMP. In addition, also in aging sympathetic activity is increased and cardiac neuronal uptake ($uptake_1$) of catecholamines is decreased. Thus, alterations in G_s-coupled receptors in the failing and aging human heart are quite comparable; however, one important exception is the fact, that in the aging human heart activity of GRKs is *not* altered—in contrast to the failing heart where it is increased (see above).

The reason for the different behaviors of GRK in the failing vs. the aging heart is not completely understood. However, it should be considered that stimulation of β-adrenoceptors is a strong stimulus to activate GRK (Iaccarino et al., 1999; Penn et al., 2000). In both settings, heart failure and aging, sympathetic activity is increased thus leading to chronic activation of β-adrenoceptors. However, in aging the increase in sympathetic activity develops slowly [plasma noradrenaline levels (an index for sympathetic activity, see above) increase only 10–15% per decade; Seals and Esler, 2000]. In heart failure, on the other hand, sympathetic activity increases much more rapidly (Francis and Cohn, 1986); in addition, increases in plasma noradrenaline levels are by far higher and reach within short time levels between 600 and 1300 pg/ml (Cohn et al., 1984). Thus, the time course and intensity of increases in sympathetic activity (as assessed by plasma noradrenaline levels) differ markedly between aging patients and heart failure patients, and these differences in time course and/or intensity may be one explanation for the different changes in GRK activity in the aging vs. failing human heart.

Striking differences, on the other hand, exist for alterations of muscarinic receptors in the failing vs. aging human heart (see also Fig. 1). In the failing human heart, the density of muscarinic receptors is not different from that in normal hearts; moreover, in the failing heart—despite the increase in G_i protein—carbachol-induced inhibition of adenylyl cyclase and the indirect negative inotropic effect of carbachol was nearly identical between failing and normal hearts. In contrast, in the aging human heart density of muscarinic receptors decreased with increasing age, and there was a significant inverse correlation between muscarinic receptor density and age of the subjects. This decrease in receptor density was accompanied by a diminished carbachol-induced inhibition of adenylyl cyclase and an attenuation of the indirect negative inotropic effect of carbachol with aging. Thus, alterations of G_i-coupled (muscarinic M_2) receptors appear to be quite different in

the aging vs. the failing human heart: in the aging human heart muscarinic receptor number and function declines, while in the failing human heart it is unaltered.

Unfortunately, alterations in α_1-adrenoceptors in the aging human heart have not been investigated so far; thus, no comparison with alterations in the failing human heart can be made.

What are the consequences of the similar changes in β-adrenoceptors and different changes in muscarinic receptors in the aging vs. failing human heart? In the human heart the β-adrenoceptor–G_s–adenylyl cyclase system is the most powerful physiologic mechanism to acutely augment cardiac contractility (and heart rate; Brodde et al., 1995a). One possibility to test the functional responsiveness of human cardiac β-adrenoceptors is to measure the heart rate response to isoprenaline infusion (McDevitt, 1989). Arnold and McDevitt (1984) had shown that, in healthy volunteers, the isoprenaline infusion-induced increase in heart rate is markedly enhanced in the presence of the anticholinergic drug atropine. This holds true not only for isoprenaline (acting at β_1- and β_2-adrenoceptors), but also for terbutaline infusion (acting at β_2-adrenoceptors) and bicycle exercise-induced increase in heart rate (acting at β_1-adrenoceptors; Bruck et al., 2003). This indicates that (1) in the human heart β_1-adrenoceptor and β_2-adrenoceptor stimulation evoked increases in heart rate are composed of two components: increases in heart rate due to β-adrenoceptor stimulation and simultaneously decreases in heart rate by (reflective) increases in vagal tone; and (2) the pure β-adrenoceptor mediated increase in heart rate can be only obtained if vagal tone is blocked. Recently, several studies have shown that, in healthy volunteers of different ages, infusion of isoprenaline resulted in increases in heart rate that were not different between young and elder volunteers (for references, see Brodde and Michel, 1999; see also Fig. 2). However, when these studies were repeated in the presence of trimetaphan thus blocking compensatory reflexes (White and Leenen, 1994; White et al., 1998) or in the presence of atropine (thus blocking vagal tone, Brodde et al., 1998a) heart rate responses to isoprenaline were significantly larger in young vs. elder volunteers (see Fig. 2). Thus, in the aging human heart the attenuated response to β-adrenoceptor stimulation in vivo is masked by the fact, that the counteracting effect of vagal tone (i.e., muscarinic receptor stimulation) is also diminished resulting in an unchanged response when compared with that in young subjects. This is in sharp contrast to the situation in the failing human heart, where cardiac β-adrenoceptor responses are reduced while cardiac muscarinic receptor responses are unchanged. Under these conditions isoprenaline infusion-induced increase in heart rate is markedly attenuated because of the reduced β-adrenoceptor function that is further enhanced by the maintained function of the muscarinic receptors (Fig. 2).

Taken together, in the failing human heart autonomic receptor systems are all altered in the direction to attenuate β-adrenoceptor responses to sympathetic stimulation: β-adrenoceptors are down-regulated and/or uncoupled from the effector system adenylyl cyclase, muscarinic receptors are unchanged and can, therefore, further contribute to the attenuated β-adrenoceptor response, GRK activity is increased thus inducing further desensitization of the β-adrenoceptors, and neuronal uptake ($uptake_1$) of catecholamines is decreased thus leading to enhanced noradrenaline levels in the synaptic cleft that induce β-adrenoceptor down-regulation. In the aging human heart, however, it appears that autonomic receptor systems are altered in a direction that protects the heart against too pronounced reduction in β-adrenoceptor responsiveness: β-adrenoceptors are desensitized but muscarinic receptors are also desensitized thus leading to an unaltered in vivo response of β-adrenoceptor stimulation. In addition, GRK activity is not changed and therefore does not contribute to (or exaggerate) β-adrenoceptor desensitization. On the other hand, neuronal uptake ($uptake_1$) of catecholamines is reduced in the aging human heart; this leads to an impaired inactivation of sympatheti-

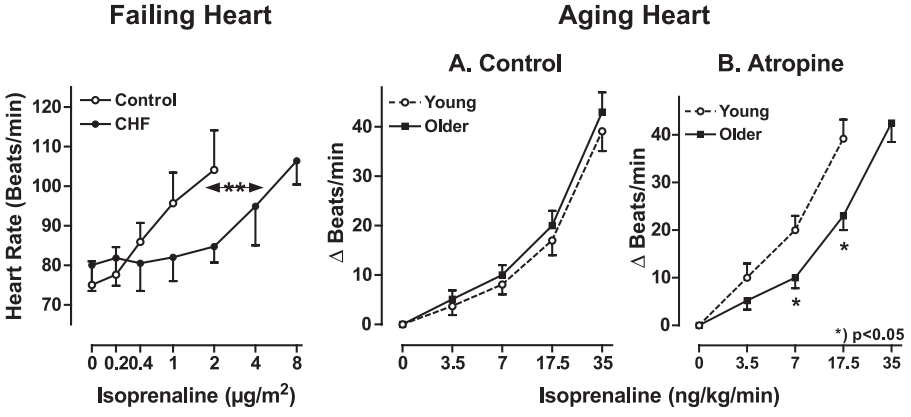

Fig. 2. Heart rate response to intravenously applied isoprenaline (left) in 6–8 healthy volunteers (control) and 6–7 patients with congestive heart failure (CHF, NYHA class III–IV). **P<0.001 vs. control. Data from Erne et al. (1988) with slight modifications, and (middle and right) in 6 young (age: 26 years) and 6 older volunteers (age: 61 years) in the absence ((A) Control) and presence ((B) Atropine) of atropine (15 μg/kg/body weight as bolus followed by i.v. infusion of 0.15 μg/kg/min throughout the experiments).*P<0.05 vs. the corresponding values in young volunteers. Data from Brodde et al. (1998a) with modifications.

cally released noradrenaline resulting in higher synaptic cleft noradrenaline levels. Because in aging sympathetic activity is by far less enhanced than in chronic heart failure, the increase in synaptic cleft noradrenaline might be less than in chronic heart failure. Under these conditions there might be an increased noradrenaline concentration at the cardiac β-adrenoceptor thus (at least partly) masking reduced β-adrenoceptor response seen in the elderly. Whether these increased synaptic cleft noradrenaline levels might contribute to β-adrenoceptor desensitization is difficult to estimate; however, it should be less than in the failing human heart because GRK activity (that markedly increases β-adrenoceptor desensitization) is not changed in the aging human heart (see above).

Acknowledgements

Part of the authors work cited in this review was supported by grants from the Deutsche Forschungsgemeinschaft (Bonn/Germany: BR 526/3-3, BR 526/7-1, SFB/TR2-01, SFB 598-02 to O.-E.B.).

References

Arnold, J.M.O., McDevitt, D.G., 1984. Vagal activity is increased during intravenous isoprenaline infusion in man. Br. J. Clin. Pharmacol. 18, 311–316.

Asano, K., Bohlmeyer, T.J., Westcott, J.Y., Zisman, L.S., Kinugawa, K., Good, M., Minobe, W.A., Roden, R.L., Wolfel, E.E., Lindenfeld, J., Port, J.D., Perryman, M.B., Cleveland, J., Lowes, B.D., Bristow, M.R., 2002. Altered expression of endothelin receptors in failing human left ventricles. J. Mol. Cell. Cardiol. 34, 833–846.

Benfey, D.G., 1993. Functions of myocardial α-adrenoceptors. J. Auton. Pharmacol. 13, 351–372.

Böhm, M., Diet, F., Feiler, G., Kemkes, B., Erdmann, E., 1988. α-Adrenoceptors and α-adrenoceptor-mediated positive inotropic effects in the failing human myocardium. J. Cardiovasc. Pharmacol. 12, 357–364.

Böhm, M., Gierschik, P., Jakobs, K.-H., Pieske, B., Schnabel, P., Ungerer, M., Erdmann, E., 1990a. Increase of $G_{i\alpha}$ in human hearts with dilated but not ischemic cardiomyopathy. Circulation 82, 1249–1265.

Böhm, M., Ungerer, M., Erdmann, E., 1990b. Beta adrenoceptors and m-cholinoceptors in myocardium of hearts with coronary artery disease or idiopathic dilated cardiomyopathy removed at cardiac transplantation. Am. J. Cardiol. 66, 880–882.

Böhm, M., LaRosee, K., Schwinger, R.H.G., Erdmann, E., 1995. Evidence for reduction of noradrenaline uptake sites in the failing human heart. J. Am. Coll. Cardiol. 25, 146–153.

Bristow, M.R., 1993. Changes in myocardial and vascular receptors in heart failure. J. Am. Coll. Cardiol. 22 (Suppl. A), 61A–71A.

Bristow, M.R., Ginsburg, R., Minobe, W., Cubicciotti, R.S., Sageman, W.S., Lurie, K., Billingham, M.E., Harrison, D.C., Stinson, E.B., 1982. Decreased catecholamine sensitivity and β-adrenergic-receptor density in failing human hearts. N. Engl. J. Med. 307, 205–211.

Bristow, M.R., Minobe, W., Rasmussen, R., Hershberger, W.E., Hoffman, B.B., 1988. Alpha-1 adrenergic receptors in the nonfailing and failing human heart. J. Pharmacol. Exp. Ther. 247, 1039–1045.

Brodde, O.-E., 1993. β-Adrenoceptors in cardiac disease. Pharmacol. Ther. 60, 405–430.

Brodde, O.-E., Michel, M.C., 1999. Adrenergic and muscarinic receptors in the human heart. Pharmacol. Rev. 51, 651–689.

Brodde, O.-E., Michel, M.C., Zerkowski, H.-R., 1995a. Signal transduction mechanisms controlling cardiac contractility and their alterations in chronic heart failure. Cardiovasc. Res. 30, 570–584.

Brodde, O.-E., Zerkowski, H.-R., Schranz, D., Broede-Sitz, A., Michel-Reher, M., Schäfer-Beisenbusch, E., Piotrowski, J.A., Oelert, H., 1995b. Age dependent changes in the β-adrenoceptor–G-protein(s)–adenylyl cyclase system in human right atrium. J. Cardiovasc. Pharmacol. 26, 20–26.

Brodde, O.-E., Konschak, U., Becker, K., Rüter, F., Poller, U., Jakubetz, J., Radke, J., Zerkowski, H.-R., 1998a. Cardiac muscarinic receptors decrease with age: in vitro and in vivo studies. J. Clin. Invest. 101, 471–478.

Brodde, O.-E., Vogelsang, M., Broede, A., Michel-Reher, M., Beisenbusch-Schäfer, E., Hakim, K., Zerkowski, H.-R., 1998b. Diminished responsiveness of G_s-coupled receptors in severely failing human hearts: no difference in dilated versus ischemic cardiomyopathy. J. Cardiovasc. Pharmacol. 31, 585–594.

Brown, L., Deighton, N.M., Bals, S., Söhlmann, W., Zerkowski, H.-R., Michel, M.C., Brodde, O.-E., 1992. Spare receptors for β-adrenoceptor-mediated positive inotropic effects of catecholamines in the human heart. J. Cardiovasc. Pharmacol. 19, 222–232.

Bruck, H., Ulrich, A., Gerlach, S., Radke, J., Brodde, O.-E., 2003. Effects of atropine on human cardiac β_1- and/or β_2-adrenoceptor stimulation. Naunyn-Schmiedeberg's Arch. Pharmacol. 367, 572–577.

Calzada, B.C., De Artinano, A.A., 2001. Alpha-adrenoceptor subtypes. Pharmacol. Res. 44, 195–208.

Caulfield, M.P., 1993. Muscarinic receptors: characterization, coupling and function. Pharmacol. Ther. 58, 319–379.

Caulfield, M.P., Birdsall, N.J.M., 1998. International Union of Pharmacology XVII. Classification of muscarinic acetylcholine receptors. Pharmacol. Rev. 50, 279–290.

Chesley, A., Lundberg, M.S., Asai, T., Xiao, R.P., Ohtani, S., Lakatta, E.G., Crow, M.T., 2000. The β_2-adrenergic receptor delivers an antiapoptotic signal to cardiac myocytes through G(i)-dependent coupling to phosphatidylinositol 3′ -kinase. Circ. Res. 87, 1172–1179.

Chidsey, C.A., Braunwald, E., 1966. Sympathetic activity and neurotransmitter depletion in congestive heart failure. Pharmacol. Rev. 18, 685–700.

Cohn, J.N., 1990. Abnormalities of peripheral sympathetic nervous system control in congestive heart failure. Circulation 82 (Suppl. I), I-59–I-67.

Cohn, J.N., Levine, T.B., Olivari, M., Garberg, V., Lura, D., Francis, G.S., Simon, A.B., Rector, T., 1984. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N. Engl. J. Med. 305, 185–190.

Communal, C., Singh, K., Sawyer, D.B., Colucci, W.S., 1999. Opposing effects of beta(1)- and beta(2)-adrenergic receptors on cardiac myocyte apoptosis: role of a pertussis toxin-sensitive G protein. Circulation 100, 2210–2212.

Davies, C.H., Ferrara, N., Harding, S.E., 1996. β-Adrenoceptor function changes with age of subject in myocytes from non-failing human ventricle. Cardiovasc. Res. 31, 152–156.

Dhein, S., Van Koppen, C.J., Brodde, O.-E., 2001. Muscarinic receptors in the mammalian heart. Pharmacol. Res. 44, 161–182.

Docherty, J.R., 1990. Cardiovascular responses in ageing: a review. Pharmacol. Rev. 42, 104–124.

Eckberg, D.L., Drabinsky, M., Braunwald, E., 1971. Defective parasympathetic control in patients with heart disease. N. Engl. J. Med. 285, 877–883.

Eisenhofer, G., Friberg, P., Rundqvist, B., Quyyumi, A.A., Lambert, G., Kaye, D.M., Kopin, I.J., Goldstein, D.S., Esler, M.D., 1996. Cardiac sympathetic nerve function in congestive heart failure. Circulation 93, 1667–1676.

El-Armouche, A., Zolk, O., Rau, T., Eschenhagen, T., 2003. Inhibitory G-proteins and their role in desensitization of the adenylyl cyclase pathway in heart failure. Cardiovasc. Res. 60, 478–487.

Erne, P., Lipkin, D., Maseri, A., 1988. Impaired beta-adrenergic receptor and normal postreceptor responsiveness in congestive heart failure. Am. J. Cardiol. 61, 1132–1134.

Eschenhagen, T., Mende, U., Diederich, M., Hertle, B., Memmesheimer, C., Pohl, A., Schmitz, W., Scholz, H., Steinfath, M., Böhm, M., Michel, M.C., Brodde, O.-E., Raap, A., 1996. Chronic treatment with carbachol sensitizes the myocardium to cAMP-induced arrhythmia. Circulation 93, 763–771.

Esler, M., Jackman, G., Bobik, A., 1979. Determination of norepinephrine apparent release rate and clearance in humans. Life Sci. 25, 1461–1470.

Esler, M., Jennings, G., Lambert, G., Meredith, I., Horne, M., Eisenhofer, G., 1990. Overflow of catecholamine neurotransmitters to the circulation: source, fate, and functions. Physiol. Rev. 70, 963–985.

Esler, M., Kaye, D., Lambert, G., Esler, D., Jennings, G., 1997. Adrenergic nervous system in heart failure. Am. J. Cardiol. 80, 7L–14L.

Ferrara, N., Davia, K., Abete, P., Rengo, F., Harding, S.E., 1997. Alterations in β-adrenoceptor mechanisms in the aging heart. Relationship with heart failure. Aging Clin. Exp. Res. 9, 391–403.

Folkow, B., Svanborg, A., 1993. Physiology of cardiovascular ageing. Physiol. Rev. 73, 725–764.

Folkow, B., DiBona, G.F., Hjemdahl, P., Toren, P.H., Wallin, B.G., 1983. Measurements of plasma norepinephrine concentrations in human primary hypertension. Hypertension 5, 399–403.

Fouad, F.M., Tarazi, R.C., Ferrario, C.M., Fighaly, S., Alicandri, C., 1984. Assessment of parasympathetic control of heart rate by a noninvasive method. Am. J. Physiol. 246, H838–H842.

Francis, G.S., Cohn, J.N., 1986. The autonomic nervous system in congestive heart failure. Annu. Rev. Med. 37, 235–247.

Fu, L.-X., Liang, Q.-M., Waagstein, F., Hoebeke, J., Sylven, C., Jansson, E., Sotonyi, P., Hjalmarson, A., 1992. Increase in functional activity rather than in amount of Gi-α in failing human heart with dilated cardiomyopathy. Cardiovasc. Res. 26, 950–955.

Gauthier, C., Langin, D., Balligand, J.L., 2000. β_3-Adrenoceptors in the cardiovascular system. Trends Pharmacol. Sci. 21, 426–431.

Giessler, C., Wangemann, T., Zerkowski, H.-R., Brodde, O.-E., 1998. Age-dependent decrease in the negative inotropic effect of carbachol on isolated human right atrium. Eur. J. Pharmacol. 357, 199–202.

Giessler, C., Dhein, S., Pönicke, K., Brodde, O.-E., 1999. Muscarinic receptors in the failing human heart. Eur. J. Pharmacol. 375, 197–202.

Goldstein, D.S., 1988. Plasma catecholamines and essential hypertension: an analytical review. Hypertension 5, 86–99.

Grimm, M., Gsell, S., Mittmann, C., Nose, M., Scholz, H., Weil, J., Eschenhagen, T., 1998. Inactivation of $G_{i\alpha}$ proteins increases arrhythmogenic effects of β-adrenergic stimulation in the heart. J. Mol. Cell. Cardiol. 30, 1917–1928.

Hellgren, I., Mustafa, A., Riazi, M., Suliman, I., Sylven, C., Adem, A., 2000. Muscarinic M_3 receptor subtype gene expression in the human heart. Cell. Mol. Life Sci. 57, 175–180.

Hieble, J.P., Bylund, D.B., Clarke, D.E., Eikenburg, D.C., Langer, S.Z., Lefkowitz, R.J., Minneman, K.P., Ruffolo Jr., R.R., 1995. International Union of Pharmacology X. Recommendation for nomenclature of α_1-adrenoceptors: consensus update. Pharmacol. Rev. 47, 267–270.

Hwang, K.-C., Gray, C.D., Sweet, W.E., Moravec, C.S., Im, M.-J., 1996. α_1-Adrenergic receptor coupling with G_h in the failing human heart. Circulation 94, 718–726.

Iaccarino, G., Dolber, P.C., Lefkowitz, R.J., Koch, W.J., 1999. Beta-adrenergic receptor kinase-1 levels in catecholamine-induced myocardial hypertrophy: regulation by beta- and not alpha$_1$-adrenergic stimulation. Hypertension 33, 396–401.

Jakubetz, J., Schmuck, S., Wochatz, G., Ruhland, B., Poller, U., Radke, J., Brodde, O.-E., 2000. Human cardiac β_1- or β_2-adrenergic receptor stimulation and the negative chronotropic effect of low-dose pirenzepine. Clin. Pharmacol. Ther. 67, 549–557.

Lakatta, E.G., 1993. Cardiovascular regulatory mechanisms in advanced age. Physiol. Rev. 73, 413–467.

La Rovere, M.T., Mortara, A., Pantaleo, P., Maestri, R., Cobelli, F., Tavazzi, L., 1994. Scopolamine improves autonomic balance in advanced congestive heart failure. Circulation 90, 838–843.

Le Guludec, D., Cohen-Solal, A., Delforge, J., Delahaye, N., Syrota, A., Merlet, P., 1997. Increased myocardial muscarinic receptor density in idiopathic dilated cardiomyopathy. An in vivo PET study. Circulation 96, 3416–3422.

Leimbach, W.N., Wallin, G., Victor, R., Aylward, P.E., Sundlof, G., Mark, L., 1986. Direct evidence from intraneuronal recordings for increased central sympathetic outflow in patients with heart failure. Circulation 73, 913–919.

Leineweber, K., Wangemann, T., Giessler, C., Bruck, H., Dhein, S., Kostelka, M., Mohr, F.-W., Silber, R.-E., Brodde, O.-E., 2002. Age-dependent changes of cardiac neuronal noradrenaline reuptake transporter (uptake$_1$) in the human heart. J. Am. Coll. Cardiol. 40, 1459–1465.

Leineweber, K., Klapproth, S., Beilfuß, A., Silber, R.-E., Heusch, G., Philipp, T., Brodde, O.-E., 2003. Unchanged G-protein-coupled receptor kinase activity in the aging human heart. J. Am. Coll. Cardiol. 42, 1487–1492.

Leineweber, K., Büscher, R., Bruck, H., Brodde, O.-E., 2004. β-Adrenoceptor polymorphisms. Naunyn-Schmiedeberg's Arch. Pharmacol. 369, 1–22.

Li, K., He, H., Li, C., Sirois, P., Rouleau, J.L., 1997. Myocardial α_1-adrenoceptor: inotropic effect and physiologic and pathologic implications. Life Sci. 60, 1305–1318.

Liu, H.R., Zhao, R.R., Zhi, J.M., Wu, B.W., Fu, M.L., 1999. Screening of serum autoantibodies to cardiac beta1-adrenoceptors and M2-muscarinic acetylcholine receptors in 408 subjects of varying ages. Autoimmunity 29, 43–51.

Lohse, M.J., Engelhardt, S., Eschenhagen, T., 2004. What is the role of β-adrenergic signaling in heart failure? Circ. Res. 93, 896–906.

McDevitt, D.G., 1989. In vivo studies on the function of cardiac β-adrenoceptors in man. Eur. Heart J. 10 (Suppl. B), 22–28.

Michel, M.C., Kenny, B., Schwinn, D.A., 1995. Classification of α_1-adrenoceptor subtypes. Naunyn-Schmiedeberg's Arch. Pharmacol. 352, 1–10.

Näbauer, M., Böhm, M., Brown, L., Diet, F., Eichhorn, M., Kemkes, B., Pieske, B., Erdmann, E., 1988. Positive inotropic effects in isolated ventricular myocardium from non-failing and terminally failing human hearts. Eur. J. Clin. Investig. 18, 600–606.

Ng, A.V., Callister, R., Johnson, D.G., Seals, D.R., 1993. Age and gender influence muscle sympathetic nerve activity at rest in healthy humans. Hypertension 21, 498–503.

Oberhauser, V., Schwertfeger, E., Rutz, T., Beyersdorf, F., Rump, L.C., 2001. Acetylcholine release in human heart atrium: influence of muscarinic autoreceptors, diabetes and age. Circulation 103, 1638–1643.

O'Brien, J.A.D., O'Hare, P., Corrall, R.J.M., 1986. Heart rate variability in healthy subjects: effect of age and derivation of normal ranges for tests of autonomic function. Br. Heart J. 55, 348–354.

Penn, R.B., Pronin, A.N., Benovic, J.L., 2000. Regulation of G-protein coupled receptor kinases. Trends Cardiovasc. Med. 10, 81–89.

Petch, M.C., Nayler, W.G., 1979. Uptake of catecholamines by human cardiac muscle in vitro. Br. Heart J. 41, 336–339.

Pfeifer, M.A., Weinberg, C.R., Cook, D., Best, J.D., Reenan, A., Halter, J.B., 1983. Differential changes of autonomic nervous system function with age in man. Am. J. Med. 75, 249–258.

Pieske, B., Beyermann, B., Breu, V., Löffler, B.M., Schlot-Thauer, K., Maier, L.S., Schmidt-Scheda, S., Just, H., Hasenfuss, G., 1999. Functional effects of endothelin and regulation of endothelin receptors in isolated human nonfailing and failing myocardium. Circulation 99, 1802–1809.

Pitschner, H.F., Wellstein, A., 1988. Dose–response curves of pirenzepine in man in relation to M_1- and M_2-cholinoceptor occupancy. Naunyn-Schmiedeberg's Arch. Pharmacol. 338, 207–210.

Poller, U., Nedelka, G., Radke, J., Pönicke, K., Brodde, O.-E., 1997. Age-dependent changes in cardiac muscarinic receptor function in healthy volunteers. J. Am. Coll. Cardiol. 29, 187–193.

Pönicke, K., Vogelsang, M., Heinroth, M., Becker, K., Zolk, O., Böhm, M., Zerkowski, H.-R., Brodde, O.-E., 1998. Endothelin receptors in the failing and nonfailing human heart. Circulation 97, 744–751.

Pönicke, K., Schlüter, K.-D., Heinroth-Hoffmann, I., Seyfarth, T., Goldberg, M., Osten, B., Piper, H.M., Brodde, O.-E., 2001. Noradrenaline-induced increase in protein synthesis in adult rat cardiomyocytes: involvement of α_{1A}-adrenoceptors. Naunyn-Schmiedeberg's Arch. Pharmacol. 364, 444–453.

Pönicke, K., Heinroth-Hoffmann, I., Brodde, O.-E., 2003. Role of β_1- and β_2-adrenoceptors in hypertrophic and apoptotic effects of noradrenaline and adrenaline in adult rat ventricular cardiomyocytes. Naunyn-Schmiedeberg's Arch. Pharmacol. 367, 592–599.

Port, J.D., Bristow, M.R., 2001. Altered beta-adrenergic receptor gene regulation and signaling in chronic heart failure. J. Mol. Cell. Cardiol. 33, 887–905.

Porter, T.R., Eckberg, D.L., Fritsch, J.M., Rea, R.F., Beightol, L.A., Schmedtje, F.R., Mohanty, P.K., 1990. Autonomic pathophysiology in heart failure patients. Sympathetic–cholinergic interrelations. J. Clin. Invest. 85, 1362–1371.

Rector, T.S., Olivari, M.T., Levine, T.B., Francis, G.S., Cohn, J.N., 1987. Predicting survival for an individual with congestive heart failure using the plasma norepinephrine concentration. Am. Heart J. 114, 148–152.

Schlüter, K.-D., Piper, H.M., 1999. Regulation of growth in the adult cardiomyocytes. FASEB J. 13 (Suppl.), S17–S22.

Schwinger, R.H.G., Böhm, M., Erdmann, E., 1990. Evidence against spare or uncoupled β-adrenoceptors in the human heart. Am. Heart J. 119, 899–904.

Seals, D.R., Esler, M.D., 2000. Human ageing and sympathoadrenal system. J. Physiol. 528, 407–417.

Serneri, G.G., Cecioni, I., Vanni, S., Pannicia, R., Bandinelli, B., Vetere, A., Janming, X., Bertolozzi, I., Boddi, M., Lisi, G.F., Sani, G., Modesti, P.A., 2000. Selective upregulation of cardiac endothelin system in patients with ischemic but not idiopathic dilated cardiomyopathy: endothelin-1 system in the human failing heart. Circ. Res. 86, 377–385.

Simpson, P., 1983. Noradrenaline-stimulated hypertrophy of cultured rat myocardial cells is an alpha 1-adrenergic response. J. Clin. Invest. 72, 732–738.

Steinberg, S.F., 1999. The molecular basis for distinct β-adrenergic receptor subtype action in cardiomyocytes. Circ. Res. 85, 1101–1111.

Steinfath, M., Danielsen, W., von der Leyen, H., Mende, U., Meyer, W., Neumann, J., Nose, M., Reich, T., Schmitz, W., Scholz, H., Starbatty, J., Stein, B., Döring, V., Kalmar, P., Haverich, A., 1992. Reduced α_1- and β_2-adrenoceptor-mediated positive inotropic effects in human end-stage heart failure. Br. J. Pharmacol. 105, 463–469.

Sundlof, G., Wallin, B.G., 1978. Human muscle nerve sympathetic activity at rest. Relationship to blood pressure and age. J. Physiol. 274, 621–637.

Terzic, A., Puceat, M., Vassort, G., Vogel, S.M., 1993. Cardiac α_1-adrenoceptors: an overview. Pharmacol. Rev. 45, 147–175.

Vago, T., Bevilacqua, M., Norbiato, G., Baldi, G., Chebat, E., Bertora, P., Baroldi, G., Accinni, R., 1989. Identification of α_1-adrenergic receptors on sarcolemma from normal subjects and patients with idiopathic dilated cardiomyopathy: characteristics and linkage to GTP-binding protein. Circ. Res. 64, 474–481.

Walker, C.A., Ergul, A., Grubbs, A., Zile, M.R., Zellner, J.L., Crumbley, A.J., Spinale, F.G., 2001. Beta-adrenergic and endothelin receptor interaction in dilated cardiomyopathic myocardium. J. Card. Fail. 7, 129–137.

Wangemann, T., Giessler, C., Willmy-Matthes, P., Silber, R.-E., Brodde, O.-E., 2003. The indirect negative inotropic effect of carbachol in β_1-adrenoceptor antagonist-treated human right atria. Eur. J. Pharmacol. 458, 163–170.

White, M., Leenen, F.H.H., 1994. Aging and cardiovascular responsiveness to β-agonist in humans: role of changes in β responses versus baroreflex activity. Clin. Pharmacol. Ther. 56, 543–553.

White, M., Roden, R., Minobe, W., Khan, M.F., Larrabee, P., Wollmering, M., Port, J.D., Anderson, F., Campbell, D., Feldman, A.M., Bristow, M.R., 1994. Age-related changes in β-adrenergic neuroeffector systems in the human heart. Circulation 90, 1225–1238.

White, M., Fourney, A., Leenen, F.H.H., 1998. Age, hypertension, and cardiac responses to β-agonist in humans. Clin. Pharmacol. Ther. 63, 663–671.

Willmy-Matthes, P., Leineweber, K., Wangemann, T., Silber, R.-E., Brodde, O.-E., 2003. Existence of functional M_3-muscarinic receptors in the human heart. Naunyn-Schmiedeberg's Arch. Pharmacol. 368, 316–319.

Xiao, R.-P., Tomhave, E.D., Wang, D.-J., Ji, X., Boluyt, M.O., Cheng, H., Lakatta, E.G., Koch, W.J., 1998. Age-associated reductions of cardiac β_1- and β_2-adrenergic responses without changes in inhibitory G proteins or receptor kinases. J. Clin. Invest. 101, 1273–1282.

Xiao, R.P., Cheng, H., Zhou, Y.Y., Kuschel, M., Lakatta, E.G., 1999. Recent advances in cardiac β_2-adrenergic signal transduction. Circ. Res. 85, 1092–1100.

Yoshikawa, T., Port, J.D., Asano, K., Chidiak, P., Bouvier, M., Dutcher, D., Roden, R.L., Minobe, W., Tremmel, K.D., Bristow, M.R., 1996. Cardiac adrenergic receptor effects of carvedilol. Eur. Heart J. 17 (Suppl. B), 8–16.

Ziegler, M.G., Lake, C.R., Kopin, I.J., 1976. Plasma noradrenaline increases with age. Nature 261, 333–335.

Zolk, O., Quattek, J., Sitzler, G., Schrader, T., Nickenig, G., Schnabel, P., Shimada, K., Takahashi, M., Böhm, M., 1999. Expression of endothelin-1, endothelin-converting enzyme, and endothelin receptors in chronic heart failure. Circulation 99, 2118–2123.