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Signal transduction and regulation: Are all α_1-adrenergic receptor subtypes created equal?

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ABSTRACT

The current manuscript reviews the evidence whether and how subtypes of α_1-adrenergic receptors, i.e. α_{1A}-, α_{1B}- and α_{1D}-adrenergic receptors, differentially couple to signal transduction pathways and exhibit differential susceptibility to regulation. In both regards studies in tissues or cells natively expressing the subtypes are hampered because the relative expression of the subtypes is poorly controlled and the observed effects may be cell-type specific. An alternative approach, i.e. transfection of multiple subtypes into the same host cell line overcomes this limitation, but it often remains unclear whether results in such artificial systems are representative for the physiological situation. The overall evidence suggests that indeed subtype-intrinsic and cell type-specific factors interact to direct α_1-adrenergic receptor signaling and regulation. This may explain why so many apparently controversial findings have been reported from various tissues and cells. One of the few consistent themes is that α_{1D}-adrenergic receptors signal less effectively upon agonist stimulation than the other subtypes, most likely because they exhibit spontaneous internalization.

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1. Introduction

α_1-Adrenergic receptors (AR) mediate many of the physiological functions of the endogenous catecholamines noradrenaline and adrenaline such as smooth muscle contraction or cellular hypertrophy. Moreover, they are the molecular target for clinically used drugs for the treatment of e.g. arterial hypertension or benign prostatic hyperplasia. During the last 20 years it became clear that α_1-ARs are not a homogeneous entity but rather a subfamily of the ARs comprising three subtypes, which are designated α_{1A}, α_{1B} and α_{1D} [1,2]. Each of these subtypes is encoded by a distinct gene located on a distinct chromosome. Moreover, α_1-ARs with surprisingly low affinity for prazosin have been reported [3] but more recent evidence suggests that they are a phenotypic state of the α_{1A}-AR rather than a distinct entity [4–6]. Some α_1-AR subtypes can also have splice variants [4,6–8] or exhibit single nucleotide polymorphisms (SNPs) [9].

The present manuscript will review two aspects of heterogeneity between α_1-AR subtypes, i.e. possible differences in their signal transduction and in their susceptibility to regulation. For both aspects a similar general problem applies: The interpretation of studies in tissues and cells natively expressing the subtypes under investigation is hampered by the fact that it is in principle unknown whether observed differences between subtypes are related to intrinsic properties of those subtypes and/or reflect specific properties of the cells expressing them. Experiments in which the three subtypes are expressed in the same cell type, mostly based upon heterologous transfection, allow exploring intrinsic differences between subtypes; on the other

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hand, this approach is limited by the fact that these intrinsic differences may manifest differentially depending on the cellular background in which the subtype is being expressed. The specific advantages and disadvantages of both approaches need to be considered when interpreting the data reviewed hereafter.

2. Signal transduction

2.1. Overview of signal transduction pathways

The prototypical signaling pathway of α_1-ARs involves coupling to G proteins of the $G_{q/11}$-family [10,11] followed by activation of a phospholipase Cβ (PLCβ) [12,13] to yield cleavage of phosphatidylinositol-4,5-bisphosphate into inositol-1,4,5-trisphosphate and diacylglycerol [14,15]. The former promotes release of Ca^{2+} from intracellular stores, while the latter activates protein kinase C (PKC).

However, α_1-ARs may also activate a variety of other signaling molecules. At the G protein level this includes pertussis-sensitive G proteins (G_i and G_o) [16–18], and G_s-family [19] and also $G_{12/13}$-family G proteins [20]. Moreover, α_1-ARs may activate a non-heterotrimeric guanine nucleotide-binding protein termed G_h [21,22], which represents an alternative link to PLC activation, albeit different PLC isoforms seem to be involved [23]. Other proximal signaling includes activation of the phospholipases A_2 (PLA_2) via PKC [24] as well as activation of phospholipase D (PLD) [25–27] and elevation of intracellular cAMP concentrations [28].

Numerous additional mediators have been shown or implicated in α_1-AR signaling, but in most cases it remains to be determined how these, mostly distal, response specifically relate to the more proximal signaling events mentioned above. These include various ion channels, transporters, protein kinases and transcription factors and proteins related to cell cycle control. α_1-AR stimulation can modulate the activity of various types of potassium channels including transient outward currents [29,30], outward rectifying channels [31], inward rectifying channels [30,32], delayed rectifying channels [33] and HERK channels [34]. Moreover, α_1-AR stimulation can also modulate the activity of L-type Ca^{2+} channels [35], sodium channels [36] and of cation channels from the TRP family [37]. Examples of transporter proteins under functional control of α_1-ARs include the Na/H exchanger [38], the Na/K-ATPase [39] and magnesium efflux transporters [40]. Moreover, α_1-ARs have been reported to activate or inhibit various protein kinases including ERK, JNK and p38 members of the mitogen-activated protein (MAP) kinase family [18,41], various receptor and non-receptor tyrosine kinases including Src or the epidermal growth factor receptor [42–46], and a variety of other protein kinases including calmodulin-dependent protein kinase [30], myosin light chain kinase [47], glycogen synthase kinase 3β [48], p70 S6 kinase [49], phosphatidylinositol 3-kinase and Akt [49], rho kinase [20,50] and $p90^{rsk}$ [18]. Another group of targets of α_1-AR stimulation are various transcription factors, response elements and cell cycle-related proteins including the cyclin-dependent kinase inhibitor $p27^{Kip1}$ [51], serum response element (SRE) [41,52], NF-κB [41,53], activator protein 1 (AP1) [41], Zfp260, a member of the Krüppel family [54], cyclic AMP response element (CRE) binding protein [41,55], nuclear factor of activated T-cells (NFAT) [41], RTEF-1 [56] and eukaryotic initiation factor 4E-binding protein 1 [57]. Finally, miscellaneous other signaling pathways can be targets of α_1-AR stimulation including NO and cGMP formation [58], Ras activation [59], metalloproteinases to activate EGF receptors [60], and Jak/STAT [46,61].

Some of these pathways can be activated, inhibited or remain unaffected depending upon the cell type and/or α_1-AR subtype under investigation. The reported splice variants of α_1-ARs differ in their C-terminus, and apparently have no major influence on signal transduction [6,7,9]. A detailed discussion of the specific signaling networks regulated by α_1-ARs is beyond the scope of this manuscript. Rather we will focus in the following on possible differences among subtypes in their effects on cellular signaling.

2.2. Subtype-specific signaling

The idea of a subtype-selective signaling of α_1-ARs was introduced by observations that α_{1A}-AR-mediated contraction of rat vas deferens involved Ca^{2+} influx through voltage-operated channels, whereas α_{1B}-AR-mediated contraction of rat spleen did not and was rather accompanied by PLC activation [62]. Subsequently, several studies have demonstrated differential signal transduction of α_1-AR subtypes natively expressed in various tissues such as heart [30,31,52,63–67], kidney [68,69] and brain [39,70].

Based upon the original proposal that α_{1B}-ARs act via PLC whereas α_{1A}-ARs do not [62], several groups of investigators have transfected multiple α_1-AR subtypes into the same cell line to compare their signaling properties. Such experiments have been done in rat-1 fibroblasts, CHO, HEK, SK-N-MC and PC12 cells and in cardiomyocytes. With few exceptions [15,71], all studies have reported the α_{1D}-AR to cause weaker PLC stimulation than the other subtypes [41,51,72–75]. Studies on the relative efficacy of PLC coupling of the other two subtypes are inconclusive as some investigators found the α_{1A}-AR to be more effective [72–74], including one using constitutively active receptors [52], one found the α_{1B}-AR to be more effective [51], and two others reported roughly similar efficacy for both subtypes [41,75].

Several studies assessed the ability of α_1-ARs to mediate increases in cytosolic Ca^{2+} concentrations. Here, a similar picture was observed as with PLC activation: in a number of cell lines stably expressing a single subtype, including SK-N-MC cells [15], rat-1 fibroblasts [73,75] (Fig. 1) and PC12 cells [76], a rank order of $\alpha_{1A} > \alpha_{1B} > \alpha_{1D}$ was observed. However, in rat pineal cells, Ca^{2+} signals haven been shown to follow α_{1B}-AR stimulation rather than stimulation of the other subtypes [77]. Results from experiments in HEK293 cells suggest that Ca^{2+} release and entry are regulated differentially: Ca^{2+} release from intracellular stores was largest in cells expressing the α_{1B} subtype, while Ca^{2+} entry into the cell was similar with all subtypes [78]. Another second messenger, cAMP, was decreased in CHO cells after stimulation of α_{1A}- and α_{1B}-, but not α_{1D}-ARs, with the α_{1B}-AR having a greater propensity to do so compared to the α_{1A}-AR [51]. These data were also confirmed on the level of the adenylyl cyclase [51].

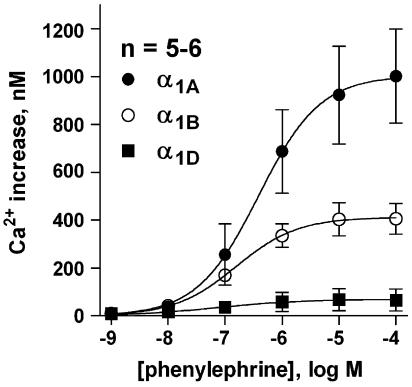

Fig. 1 – Elevations of intracellular Ca^{2+} concentrations by α_1-adrenergic receptor subtypes. Data are taken from Ref. [75].

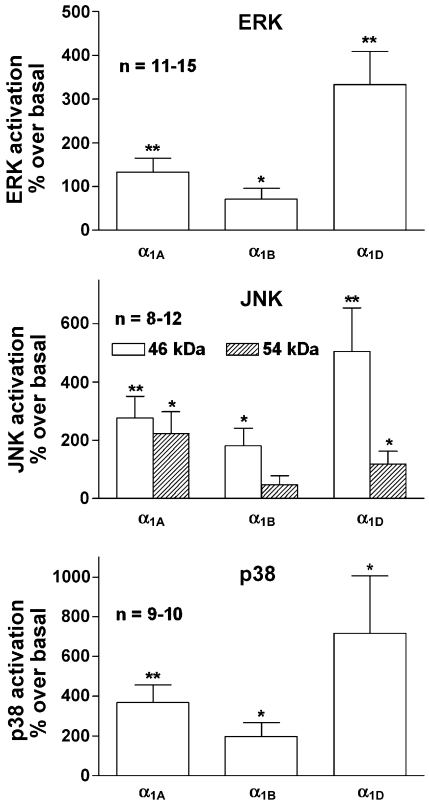

Fig. 2 – Activation of mitogen-activated protein kinases by α_1-adrenergic receptor subtypes. * and ** $p < 0.05$ and <0.01, respectively, relative to basal. Data are taken from Ref. [83].

PLD activation in isolated perfused rat hearts is mediated by α_{1A}-, and not by α_{1D}-ARs [63], which is in line with results from experiments in rat-1 fibroblasts [75]. PLA_2 activation was not observed via α_{1D}-ARs but via the other two subtypes [74], as was PKC activation [75]. Moreover, the α_{1A}- and α_{1B}-, but not α_{1D}-ARs could activate PI3 kinase in NIH 3T3 cells [59]. Since co-expression of the α subunit of transducin, which scavenges $G_{\beta\gamma}$ subunits, blocked PI3 kinase activity mediated by the α_{1B}- but not the α_{1A}-AR, PI3 kinase activation via stimulation of the latter involved the α subunit of G_q, while stimulation of the former was followed by $G_{\beta\gamma}$-mediated PI3 kinase activation [59].

Some of the above differences could relate to differential G protein coupling of the α_1-AR subtypes. Thus, in murine hearts, β-adrenergic inotropy was down-regulated by both α_{1A}- and α_{1B}-ARs, with only the former being mediated via PTX-sensitive G proteins [64], and in rat de-endothelialized tail artery the α_{1A}-AR but not the other two subtypes couples to G_i [17]. Coupling to G_o has first been described in rat aortas for α_{1B}-ARs [16]; here, contraction was sensitive to pertussis toxin treatment and antisera to G_o, but not to G_i. Concerning stimulatory G proteins, the α_{1B}-AR directly interacts with and activates G_s proteins [19]; this has later been confirmed for the α_{1A}- but not the α_{1D}-subtype [79]. α_{1A}- and α_{1B}-AR both can couple to G_{14}, but only α_{1B} to G_{16} in COS-7 cells [13]. Only the α_{1B}- and α_{1D}-subtype couple to G_h assessed as ability to stimulate G_h-mediated inositoltrisphosphate synthesis in transfected COS-1 cells [80]. Moreover, α_1-AR coupling to G proteins may also be modulated in a subtype-selective manner. For example, RGS2 selectively inhibited G_q coupling for the α_{1A}-, but not the α_{1B}- or α_{1D}-AR due to subtype specific interaction of the receptor with RGS2 [81].

Other experiments focused on modulation of MAP kinase pathways and gene transcription responses following signaling by distinct subtypes. At least in NIH 3T3 cells the principal pathway leading to ERK activation seems to be different: for α_{1A}-ARs, this seems to involve PI3 kinase and $p21^{ras}$ activation, while ERK activation via α_{1B}-ARs is independent of PI3 kinase activation [59]. Subtype-specific activation of p38, ERK and JNK was reported in PC12 cells, where the α_{1A}-subtype could stimulate all three responses, α_{1B} only ERK and p38 but not JNK, and the α_{1D}-AR only activated ERK [76]. Due to the constitutive activity of the α_{1D}-AR, basal ERK levels have been reported to be elevated in α_{1D}-AR expressing cells [71,82]. In CHO cells, the subtypes' efficacy of activating ERK, JNK and p38 was D > A > B [83] (Fig. 2). A different study, however, linked the α_{1A}-subtype to ERK activation in the bovine inferior alveolar artery, but also demonstrated that blocking of all subtypes was necessary to completely suppress ERK activation [84]. In rat-1 cells, α_{1A}-AR stimulation was found to inhibit ERK, apparently due to coupling to p38 and subsequent cross-talk between the two MAP kinases [85].

As suggested by their ability to activate MAP kinases, α_1-AR stimulation also influences cell growth in several tissues in a subtype-selective manner. α_{1A}-AR stimulation inhibited [^{3}H]thymidine incorporation as a measure of cell growth by activation of p38, while α_{1D}-AR stimulation stimulated cell growth via ERK [83]. This is supported by findings that the α_{1A}- and α_{1B}- but not the α_{1D}-AR inhibited serum-stimulated growth in CHO cells [51]. In rat cardiomyocytes, which endogenously co-express α_{1A}- and α_{1B}-ARs, agonist-induced hypertrophy is mediated exclusively via the α_{1A}-subtype [66].

Some studies looked at effects on reporter gene transcription. For example, PC12 cells were differentiated by activation of α_{1A}- but not α_{1B}- and α_{1D}-ARs [41,76], indirectly indicating that the subtypes differentially modulate gene transcription. Other studies have shown that while all subtypes were linked to IL-6 transcription, only α_{1A}- and α_{1D}-AR stimulation led to expression of STAT3 and GP-130 [86,87]. As for transcription factor activity, AP1, CRE, NFAT, SRE and NFκB were all

activated by stimulation of α_{1A}-ARs, while only the first three were activated by α_{1B}-, and none of them by α_{1D}-ARs [41].

Ion channel activities can also be influenced differently by the three subtypes. The α_{1A}-subtype has been shown to mediate a transient (via PKC) [30] or a steady-state (via pertussis-toxin insensitive G proteins) [31] K^+ outward current in canine or rat ventricular myocytes, respectively, despite presence of at least one other subtype. In canine ventricular myocytes the α_{1D} subtype was able to promote inwardly rectifying K^+ currents via CAM kinase II [30]. Lastly, in Locus coeruleus neurons of juvenile rats, α_{1B}-adrenergic signaling modulated the activity of G protein regulated, inwardly rectifying K^+ channels activated by α_2-ARs despite presence of other α_1-AR subtypes [32].

3. Regulation

3.1. *Overview of regulation*

The responsiveness of a cell or tissue to α_1-AR stimulation is dynamically regulated in time [88–90]. This can involve alterations of the expression of the receptors at the plasma membrane, of the abundance of the signaling and effector molecules they are coupling to Ref. [91] and/or their ability to interact with each other. In this manuscript we will focus on alterations of receptor expression in the plasma membrane. They can involve internalization to intracellular compartments, mostly a rapid process induced by high agonist concentrations, and also a permanent reduction in receptor number, i.e. receptor down-regulation, a process which can require longer agonist exposure but may already be detectable with lower agonist concentrations. The two processes often co-exist but can involve different mechanisms and distinct structural features of the receptor [92]. Many studies have not specifically discriminated between the two processes and referred to any loss of receptors from the plasma membrane compartment, particularly as seen with extended agonist exposure, as ''down-regulation''. The opposite phenomena, i.e. receptor externalization and up-regulation can also occur. Moreover, the regulation of receptor expression can also be induced by molecules which do not directly act on the receptor, i.e. heterologous regulation. As the regulation of α_1-AR expression in general has been reviewed previously [90,93,94], we will focus on studies comparing the regulation of two or more α_1-AR subtypes.

A subtype-selective regulation of α_1-ARs has been demonstrated in many tissues, e.g. related to physiological factors such as sex [95], ageing [96] or β-AR stimulation [97]. It has also been observed under various pathophysiological conditions such as hypothyroidism [98–101], hyperthyroidism [102], cardiac hypoxia [103], heart failure [104], cardiac hypertrophy [105], after induction of bladder outlet obstruction [106] or nerve ligation [107], and in an animal model of spreading cortical depression [108]. While these in vivo studies have provided clear evidence for the existence of subtype-selective regulation of α_1-ARs, the underlying molecular mechanisms have mostly remained unclear due to the complexity of the primary intervention and, in some cases, conflicting results. Moreover, in most cases it did not become clear whether differences between the subtypes indeed relate to intrinsic differences among them or rather to differences between the cell types that express them.

The exposure to high agonist concentrations can induce a rapid internalization of α_1-ARs, a phenomenon shown even before it became clear that multiple subtypes exist [109]. Most studies into the mechanisms involved in α_1-AR internalization have been done with the α_{1B} subtype. Internalization involves the cytoskeleton [110] and requires an intact C-terminus of the receptor [111], possibly to provide acceptor sites for phosphorylation. The overall process of α_1-AR internalization apparently involves two steps, an initial loss from the cell surface followed by endocytosis into the light vesicle fraction, and the structural requirements within the C-terminus for the two steps may differ [112]. While direct stimulation of PKC can induce α_1-AR internalization [113,114], it has remained somewhat controversial whether agonist-induced internalization involves PKC [113,114]. The agonist-induced internalization is arrestin-dependent [82,115].

3.2. *Subtype-selective internalization*

Some data indicate that the above mechanisms may, at least quantitatively, differ between α_1-AR subtypes. Thus, a comparison of α_{1B}- and α_{1D}-ARs expressed in rat-1 fibroblasts showed that under resting conditions α_{1B}-ARs are located predominantly at the cell surface whereas α_{1D}-ARs reside mainly intracellularly [71]. These observations were confirmed in HEK cells and extended by demonstrating that α_{1A}-ARs are found both on the surface and intracellularly [82]. The intracellular localization of the α_{1D}-ARs was attributed to constitutive activity [71], which is in line with the observation that constitutively active α_{1B}-ARs are more susceptible to agonist-induced internalization [116]. Moreover, specific proteins such as gC1q-R may selectively associate with some α_1-ARs subtypes to promote receptor internalization [117]. The agonist-independent internalization of α_{1A}-ARs has also been linked to constitutive activity as exposure to the inverse agonist prazosin increased cell surface expression but did not prevent de novo internalization in the absence of agonist [118].

3.3. *Subtype-selective down-regulation*

A more extended agonist exposure of α_1-ARs typically leads to receptor down-regulation, and the underlying mechanisms have also mainly been studied for the α_{1B}-AR. Thus, agonist-induced down-regulation apparently does not involve a reduced stability of the receptor protein [119] but rather destabilization of the corresponding mRNA [120]; hence, receptor density declines over time because the natural turnover is no longer counteracted by de novo synthesis. PKC activation can down-regulate α_1-ARs in some [73,121] but not all cell types [122], and accordingly PKC may play a role in agonist-induced α_1-AR down-regulation in some [121] but not other cell types [123].

A differential regulation of natively expressed α_1-AR subtypes upon agonist exposure has been shown in cardiomyocytes [124], vascular smooth muscle [125] and brown adipose tissue [126] and also upon treatment with indirect

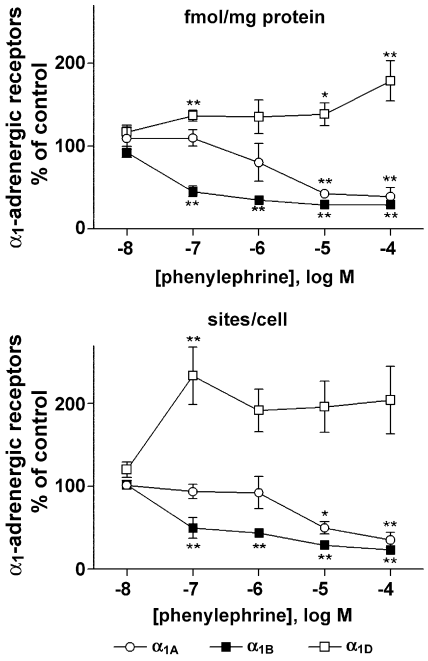

Fig. 3 – Agonist-induced regulation of α_1-adrenergic receptor subtypes. $^{*}p < 0.05$ and $^{**}p < 0.01$, respectively, relative to control. Data are taken from Ref. [122].

sympathomimetics, i.e. the noradrenaline uptake inhibitor desipramine, in the brain [98].

To get a more direct understanding how intrinsic properties of the α_1-AR subtypes affect their susceptibility to agonist-induced regulation, direct comparative studies where performed where a given cell line was transfected with all three subtypes. One such study with transfected rat-1 cells found a concentration- and time-dependent down-regulation of α_{1A}- and α_{1B}-ARs, whereas the α_{1D}-AR density paradoxically increased [122] (Fig. 3). The down-regulation of α_{1A}- and α_{1B}-ARs differed as the latter required lower agonist concentrations and was accompanied by reductions of mRNA expression, whereas mRNA for the former remained unchanged. Another study with expression in HEK 293 cells found agonist-induced down-regulation of α_{1A}- and α_{1D}-ARs, whereas the α_{1B}-AR density paradoxically increased [121]. In that study subtype down-regulation was attributed to PKC, whereas up-regulation was attributed to elevations of intracellular Ca^{2+} concentrations. While both studies show that the agonist-induced regulation of α_1-AR subtypes can differ quantitatively, qualitatively and with regard to the mechanisms being involved within a single cell line, they have associated the paradoxical agonist-induced up-regulation with different subtypes. Paradoxical up-regulation of α_{1B}-ARs has also been found in CHO cells where it was found in some but not other cell clones [127].

While the agonist-induced up-regulation of some α_1-AR subtypes in transfected cell lines remains difficult to understand, it has also been observed for α_{1A}-ARs in rat cardiomyocytes [124] and brown adipose tissue [126], indicating that it cannot solely be viewed as an experimental artifact of transfected cells. An up-regulation of α_{1A}-AR expression in brown adipose tissue upon sympathomimetic stimulation was confirmed by other investigators, but they found that this in vivo effect was due to β_3-AR stimulation [97]. While this could be explained by the presence of a CRE in the promoter of the α_{1A}-AR gene [128], it remains unclear why the α_{1B}-AR did not up-regulate in heart or brown adipose tissue [97,124,126] despite the presence of a similar CRE in its promoter [129]. Therefore, it remains to be determined whether the agonist-induced up-regulation indeed always represents a homologous regulation or rather involves stimulation of other receptors. Differences in heterologous down-regulation among α_1-AR subtypes upon PKC stimulation were suggested by some but not other studies [73,121].

Receptor up-regulation is more typically seen upon antagonist treatment. Interestingly, even antagonists with similar affinity for all α_1-AR subtypes such as doxazosin [130] have been reported to induce subtype-selective regulation in vivo [131,132]. While antagonist-induced up-regulation of α_1-ARs has classically been interpreted as reversal of tonic agonist-induced down-regulation, more recent data demonstrate that it may rather reflect the inverse agonist properties of several α_1-AR antagonists [71,133,134], which is particularly strong in antagonists with a quinazoline structure such as prazosin or doxazosin [135]. This may explain why the quinazoline prazosin induced more up-regulation in vivo than the non-quinazoline silodosin or agonist removal by reserpine treatment [136].

4. Conclusions

Taken together the available data demonstrate that subtype-intrinsic factors exist which regulate the strength of coupling to signaling pathways and, in some cases, may also lead to preferences for certain pathways; moreover, intrinsic factors appear to affect the susceptibility to regulation. The molecular identity of these factors has remained elusive in many cases. Moreover, a given molecular feature of a subtype may lead to distinct phenotypic consequences upon expression in one as compared to other cell types. Thus, the overall signaling and regulatory properties depend on the interaction between subtype-intrinsic factors and its cellular background. This may also explain why the observed in vivo regulation of α_1-AR subtypes in tissues is so complex. Such complexity offers exciting possibilities to target drugs to specific tissues and responses in an attempt for a more efficacious and/or better tolerated treatment of various diseases in which α_1-AR subtypes play a role.

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