Published in final edited form as:
J Recept Signal Transduct Res. 2011 April ; 31(2): 98–110. doi:10.3109/10799893.2010.550008.

Cardiac and neuroprotection regulated by α_1-adrenergic receptor subtypes

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Abstract

Sympathetic nervous system regulation by the α_1-adrenergic receptor (AR) subtypes (α_{1A}, α_{1B}, α_{1D}) is complex, whereby chronic activity can be either detrimental or protective for both heart and brain function. This review will summarize the evidence that this dual regulation can be mediated through the different α_1-AR subtypes in the context of cardiac hypertrophy, heart failure, apoptosis, ischemic preconditioning, neurogenesis, locomotion, neurodegeneration, cognition, neuroplasticity, depression, anxiety, epilepsy, and mental illness.

Keywords

Adrenergic; cardiac; cognition; epilepsy; heart failure; ischemia; receptor; neurodegeneration; neurogenesis; neurological; norepinephrine; preconditioning; protection; stem Cells

Nomenclature, initial tissue characterization, and cloning

α_1-Adrenergic receptor (AR) subtypes (α_{1A}, α_{1B}, and α_{1D}) are G-protein-coupled receptors (GPCRs) that mediate the sympathetic nervous system by binding the endogenous catecholamines, epinephrine, and norepinephrine (NE) (1). Raymond Ahlquist (2) introduced the initial concept of different subtypes of ARs (α and β), and all nine of the adrenergic subtypes (α_{1A}, α_{1B}, α_{1D}, α_{2A}, α_{2B}, α_{2C}, β_1, β_2, and β_3,) are activated by the same catecholamines.

After further characterization in tissue, α_1-ARs were subdivided into the α_{1A}- and α_{1B}-AR subtypes in the late 1980s based upon experimental data of two-site competition binding curves in rat brain to the antagonists WB4101 and phentolamine. The α_{1A}-AR subtype was characterized as having a 10–100-fold higher affinity for these ligands than the α_{1B}-AR subtype (3). During this same time period, the α_{1B}-AR was cloned utilizing oligonucleotide probes made by peptide fragments of purified receptor (4). This receptor was correctly classified as the α_{1B}-AR because of the cloned receptor's lower affinity for WB4101 and phentolamine. The next α_1-AR cloned was designated the α_{1C}-AR, considered a newly discovered α_1-AR subtype, because it did not neatly fit into previous pharmacological

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Declaration of interest
The authors report no declarations of interest.

criteria for the α_{1A}-AR subtype (5). This expressed receptor did have high affinity for typical α_{1A}-AR ligands. However, because it was isolated from a bovine cDNA library, which had high sequence variation to the rat gene, its expression could not be detected in rat tissues. In addition, the receptor was insensitive to chloroethyl clonidine (an α_{1A}-AR criteria). Thus, not having α_{1A}-AR-like tissue distribution and having sensitivity to chloroethyl clonidine, an alkylating agent mistakenly thought at the time to be selective for the α_{1B}-AR, led to this receptor being misclassified. A few years later, two groups recloned the same receptor from a rat cDNA library, whose tissues were previously characterized for α_{1A}-AR pharmacology and thus allowing for a more accurate comparison. Both groups demonstrated that the misclassified α_{1C}-AR really represented the tissue-defined α_{1A}-AR (6,7). Before the publication of this corrective work for the α_{1C}-AR misclassification, another receptor was cloned and was designated the α_{1A}-AR because this receptor had high affinity for WB4101 (8). In reality, this clone was the real novel receptor subtype, not being previously pharmacologically described in tissues, and was independently cloned and more extensively characterized to reveal its novel pharmacology and was named the α_{1D}-AR (9). This classification was accepted by the IUPHAR Adrenergic Receptor Subcommittee (10). Therefore, the α_{1C}-AR subtype designation does not exist anymore and three α_1-AR subtypes have now been fully characterized in both expressed systems and native tissues: the α_{1A}, α_{1B}, and α_{1D}-ARs (10). With the sequencing of mammalian genomes, there does not appear to be additional AR subtypes.

Cardiac physiology

Myocardial α_1-ARs

Of the ARs, myocardium contains β- and α_1-ARs. Of the α_1-ARs, the myocyte contains both the α_{1A}- and α_{1B}-AR subtypes. There are no α_2-ARs present in the myocyte as well as little if any expression of the α_{1D}-AR, despite the present of its mRNA in PCR studies (11,12). There is evidence to suggest that α_1-ARs are also present in the cardiac fibroblast (13,14) and may regulate protein synthesis and secretion that are also needed for cardiac function. The ARs regulate both the contractility as well as the growth of the myocardium. While the β-ARs predominate in the regulation of heart function under normal physiological conditions, the α_1-ARs are thought to become more important during pathological conditions and disease, such as hypertrophy, heart failure, and ischemic disease. For example, α_1-ARs are generally thought to be more important in preserving or increasing myocardial contractility in the setting of heart failure and β-AR downregulation (15–17). Since α_1-ARs are GPCRs, the major signaling pathways utilize G_q, coupling to phospholipase Cβ and resulting in the membrane release of inositol 1,4,5- trisphosphate (IP3) and diacylglycerol. These second messengers activate the release of intracellular calcium and activation of PKC, respectively. However, there is evidence that α_{1A}- and α_{1B}-AR subtypes are differentially coupled to different G-proteins and signaling pathways in myocytes that may mediate the potential differences in cardiac physiology (18,19) as reviewed here.

α_1-AR-mediated cardiac hypertrophy

Early studies (20,21) indicated that incubation of myocytes with catecholamines causes cellular hypertrophy by activation of α_1-ARs. Subsequent reports established that the α_1-AR-stimulated hypertrophy in myocytes progresses through a series of genetic events with induction of immediate–early genes followed by expression of embryonic genes, and increased contractile proteins (22). The end result of these changes in gene expression is an increased size of the myocyte. Cardiac hypertrophy initially has beneficial effects in terms of muscular economy by normalizing wall stress (i.e. adaptive hypertrophy). However, several studies have demonstrated that chronic hypertrophy is associated with a significant

increase in the risk of heart failure, ischemic heart disease, and apoptosis (i.e. maladaptive hypertrophy; reviewed in ref. 23). We believed that the differential outcomes of hypertrophy can depend upon the α_1-AR subtype, with the α_{1A}-AR mediating adaptive and compensatory hypertrophy, whereas the α_{1B}-AR mediates hypertrophy that is maladaptive and cardiac damaging.

Most cellular studies indicated that the α_{1A}-AR subtype is the mediator of hypertrophy in neonatal myocytes (24,25). Knowlton et al. (25) showed that stimulation of the α_{1A}-AR subtype in neonatal myocytes caused phosphoinositide hydrolysis and was responsible for cardiac hypertrophy, whereas stimulation of the α_{1B}-AR subtype did not mediate hypertrophy. Similar results were obtained by Autelitano and Woodcock (24) using subtype-selective agonists. *In vivo*, an α_{1A}-AR transgenic mouse model with constitutively active mutations (CAM) in the receptor and under the control of the native promoter to achieve systemic expression demonstrated cardiac hypertrophy independent of changes in blood pressure (manuscript in preparation), corroborating earlier cellular studies. This hypertrophy appears to be adaptive as these mice are protected against ischemia (26). In contrast, myocyte-targeted wild type (WT) α_{1A}-AR do not display hypertrophy (27), even with vast amounts of receptor over expression. This same mouse model limits postinfarct ventricular remodeling and dysfunction and improves survival due to heart failure after myocardial infarction and thus appears to be cardiac adaptive (28). However, long-term effects of this heightened contractility eventually become pathological (29). Discrepancies between the mouse models could be due to the CAM receptor coupling promiscuously to signaling pathways not associated with a WT receptor. On the other hand, the CAM α_{1A}-AR mouse also expresses the CAM receptor in cells other than the myocyte, and displays high secreted serum levels of interleukin (IL)-6 (manuscript in preparation), which may promote adaptive cardiac hypertrophy through the gp130 and STAT3 pathways (30–33).

In contrast, myocyte-targeted CAM α_{1B}-AR mice were shown to have hypertrophy *ex vivo*, although mild (34), and displayed a hastened time to heart failure with pressure overload (35). However, cardiac overexpression of the WT α_{1B}-AR, while displaying ventricular dysfunction, did not display hypertrophy (36). However, this same mouse displayed elevated activation of signaling pathways associated with cardiac hypertrophy, such as calcineurin activity (37). A similar but different myocytetargeted WT α_{1B}-AR mouse model (38) did not have basal hypertrophy, but developed a severe maladaptive hypertrophy with cardiac abnormalities when subjected to a 14-day treatment of phenylephrine (39). Both CAM and WT α_{1B}-AR mice under the control of the endogenous promoter demonstrated both cardiac hypertrophy and cardiac dysfunction (40). Therefore, both overexpressed α_{1B}-AR mouse models suggest a maladaptive response to cardiac hypertrophy. Consistent with the observation that the α_{1B}-AR mediates cardiac hypertrophy is that the α_{1B}-AR knockout (KO) mouse do not display NE-mediated hypertrophy (41).

α_1-ARs in heart failure

Chronic heart failure is associated with prolonged stimulation of the adrenergic and sympathetic nervous system and increased plasma levels of catecholamines, resulting in β_1-AR down-regulation and myocardial apoptosis (42–44). This increased sympathetic activity is first initiated as an adaptive process and the heart hypertrophies to compensate for the decreased cardiac contractility. However, sustained cardiac contractility cannot be maintained indefinitely and this compensatory process becomes maladaptive, contributing significantly to disease progression by wall thinning, dilation, and finally heart failure.

Previous studies during the 1980–1990s on the roles of α_1-ARs in human heart failure is controversial. Some studies indicated they were protective, whereas other studies indicated that α_1-AR activation was detrimental that progressed heart failure (45). However many of

these studies were performed before we knew the existence of the α_1-AR subtypes and had the tools to define them, so these disparate reports or findings could be due to subtype-specific signaling. α_1-AR antagonists were initially thought to be useful in treating heart failure due to decreasing sympathetic overload. However, in the *Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial*, the use of a nonselective α_1-AR antagonist increased the risk of heart failure and mortality (46). In contrast, carvedilol, an antagonist of α_1- and β-ARs but with higher affinity for the α_{1B}-AR subtype (47) (and thus promoting α_{1A}-AR signaling and inotropism), provided an effective treatment for chronic heart failure, suggesting that α_1-AR subtypes may contribute to these differential effects on heart failure.

α_1-ARs can direct either positive or negative inotropism depending upon the species or tissue preparation studied (48,49). One study indicated that in mouse trabecular tissue, the inotropism changes from positive to negative when analyzing right versus left trabeculae (50). However, this effect may also be dependent upon the α_1-AR subtype. In rats, the right ventricular (RV) inotropic response to α_1-ARs was switched from negative to positive in heart failure, through a pathway involving increased myofilament calcium sensitivity. This study suggested that increased α_1-AR inotropic responses in the RV myocardium may be adaptive in heart failure by helping the failing RV respond to increased pulmonary pressures (51). In corroboration with this study, α_{1A}-AR density increased compared with non-failing hearts when specifically analyzed in the failing human RV although overall α_1-AR density did not change (52). In addition, mechanical unloading of the failing human heart with a left ventricular-assisted device significantly increased α_1-AR density than before explantation (53). α_{1AB} double KO mice had increased morbidity due to heart failure and a maladaptive cardiac phenotype from pressure overload (54), opposite from α_{1A}-AR-mediated cardiac protection. The hypercontractile myocyte-targeted WT α_{1A}-AR transgenic mouse also protected against pressure overload (55). Therefore, all of these studies suggest that α_{1A}-AR supplementation or stimulation may be cardioprotective.

In Langendorff *ex vivo* heart studies, CAM α_{1B}-AR mice under the control of the endogenous promoter were found to have an impaired cardiac inotropy when stimulated with phenylephrine (56). Similar results were obtained when adult myocytes were isolated from this mouse model. This mouse also displayed impaired cardiac relaxation times and decreased cardiac output (40). Myocyte-targeted CAM α_{1B}-AR mice displayed hastened time to heart failure with pressure overload (35). In addition, myocyte-targeted WT α_{1B}-AR mice also showed development of dilated cardiomyopathy (57). These mice had systolic dysfunction and progressed to heart failure and died prematurely. Recent evidence also suggests that these mice regulate pathological cardiac arrhythmias due to the down-regulation of potassium channels (58) and may also contribute to their premature death. The α_{1B}-AR KO mice did not display any difference from controls when subjected to pressure overload (59). These results suggest that the α_{1B}-AR may hasten cardiac pathological and maladaptive conditions such as cardiac arrhythmias and heart failure due to pressure overload.

Cardiac apoptosis

Long-term exposure to catecholamines is toxic to cardiac myocytes (60), a process mediated primarily through β-AR stimulation (61). In contrast, while stimulation of α_1-ARs does not appear to mediate cardiac myocyte apoptosis, it may promote protection against cell death. In neonatal rat myocytes, α_1-AR stimulation inhibited apoptosis caused by cAMP (44), and was abolished by a MEK inhibitor suggesting a role for ERK1/2. Inhibition of protein phosphatase 1 by okadaic acid, which induces apoptosis in rat neonatal myocytes, was blocked by α_1-AR stimulation (62). Ischemic preconditioning, which we demonstrated to be regulated through the α_{1A}-AR subtype (26), limited apoptotic cell death through an

increased bclx/bax ratio in the rabbit heart when stimulated by phenylephrine (63). In more recent studies, the α_{1A}-AR subtype was shown to protect myocytes from apoptosis also through an ERK-mediated mechanism (64). These results suggest that α_{1A}-ARs may mediate survival antiapoptotic signaling in cardiac myocytes.

As it appears that the α_{1A}-AR promotes anti-apoptotic signaling, the α_{1B}-AR may promote apoptosis. However, myocyte-targeted WT α_{1B}-AR mice do not show increased apoptosis, whereas overexpression of G_q results in hypertrophy and/or apoptosis depending on the level of expression (65). Since α_1-ARs in adult mouse myocytes may not activate the G_q-phospholipase C pathway (66), this may explain why α_{1B}-AR mice do not promote apoptosis. There is also evidence that the α_{1B}-AR may be coupled to G_i in the heart (67,68).

α_1-AR ischemic preconditioning

Ischemic preconditioning is an endogenous protective mechanism in which brief episodes of cardiac ischemia protect the heart from damage caused by a subsequent episode of prolonged ischemia. Ischemia and hypoxia have been shown to increase the number of myocardial α_1-ARs in both acute and chronic conditions (69). Ischemic preconditioning is mimicked by the α_1-AR agonist phenylephrine and blocked by α_1-AR antagonists (70,71). However, studies to determine which α_1-AR subtype mediates this effect have produced conflicting results which were likely due to the use of nonselective ligands. Several studies looking at the early phase of preconditioning using 5-methylurapidil and chloroethyl clonidine have concluded that ischemic preconditioning is mediated by the α_{1B}-AR, but not the α_{1A}-AR (72–74). However, subsequently, it was shown that chloroethyl clonidine was not differentially selective for α_1-AR subtypes (75).

In mouse models, the CAM α_{1A}-AR mice under the control of the endogenous promoter demonstrated inherent preconditioning (26). However, CAM α_{1B}-AR mice, which utilize the endogenous promoter, did not display not only protection but also any worsening of the ischemic damage (26). In agreement, the myocyte-targeted WT α_{1A}-AR limited postinfarct ventricular remodeling and dysfunction (28) and suppressed ischemia-induced IP3 generation (76). These studies are consistent with the study of Gao et al. (77), who found that heart-targeted CAM α_{1B}-AR mice were not protected from ischemic injury. Therefore, data using transgenic mice provide clear evidence that ischemic preconditioning is mediated by α_{1A}-ARs but not α_{1B}-ARs.

α_1-AR cardiac protective signaling pathways

The low-molecular-weight GTPase RhoA has been shown to be involved in the α_1-AR growth pathways in myocytes (78,79). In addition, the AKAP-Lbc, an A-kinase-anchoring protein with an intrinsic Rho-specific guanine nucleotide exchange factor activity, was shown to be critical for activating RhoA and transducing hypertrophic signals downstream of α_1-ARs (80). However, these pathways have not been shown to be either adaptive or maladaptive. Other pathways associated with α_1-AR-mediated hypertrophy are Ras (81) and $G_{\alpha q}$ (78). While α_1-ARs couple to $G_{\alpha q}$, which can mediate hypertrophic signaling, G_q-mediated hypertrophy ultimately leads to its decompensation and apoptosis as evidenced by the G_q transgenic mouse model (65,82). G_q overexpressing hearts also had a lack of ERK activation (83). In contrast, Ras-mediated events convey characteristic features of hypertrophy but with normal contractile functions (84,85). α_{1A}-AR-mediated ERK anti-apoptotic effects will be downstream of Ras and ERK can also be pro-hypertrophic (86,87). Thus, Ras/ERK signaling appears to be adaptive. Therefore, we suggest that α_{1A}-AR-mediated adaptive hypertrophy may be mediated through Ras/ERK downstream signals, whereas the α_{1B}-AR-mediated maladaptive hypertrophy is mediated through $G_{\alpha q}$.

In addition to ERK signaling in α_1-AR mediation of cardiac apoptosis and protection (64), the transcriptional coactivator p300 or histone deacetylase activity was also shown to mediate hypertrophy and protection from cell death by α_1-ARs due to ischemia and reperfusion (88–90). Inhibition of apoptosis by α_1-ARs could also be part of the protective mechanism in delayed preconditioning (63). However, α_1-ARs were also found to activate the forkhead box family of proapoptotic transcription factors (FOXO1) in cardiomyocytes (91) via nuclear translocation. Therefore, this pathway is associated with potential role of α_1-ARs in mediating apoptosis in the heart and its maladaptive processes that we speculate are associated with α_{1B}-AR-mediated signaling.

In addition, the cardioprotective pathways of α_1-AR-mediated preconditioning have been linked to PKCε involvement (26,92,93). Preferential activation of PKCε, but not PKCα, has also been observed in phenylephrine-treated isolated neonatal and adult rat myocytes (94). PKC isoforms are also predicted to act as molecular switches that regulate the balance of signaling via proapoptotic JNK and anti-apoptotic PDK-1/AKT α_1-AR-mediated pathways in myocytes (95). α_1-AR-mediated late phase of ischemic protection has also been linked to heat shock protein (HSP) 70 (96) and α_1-AR signaling mediates induction of the heat shock 70 promoter (97). In addition, another HSP27 and PKCε were both associated with ischemic protection via α_1-AR signaling in myocytes (98). Interestingly, one study suggests that the PKC mediation of ischemic preconditioning is through factors secreted from the heart (99). Therefore, at least part of the cardioprotection mediated by the α_{1A}-AR may be through PKCε signaling pathways.

Cardiac summary

Heart failure and other pathological cardiac effects are increased by sympathetic overdrive and provided the rationale for the successful use of β-blockers to treat heart failure (100). However, the adverse effects observed for α_1-AR antagonists in heart failure (46) might be explained through cardioprotective pathways mediated by stimulation of the α_{1A}-AR subtype summarized here. Therapeutic strategies to only activate the α_{1A}-AR subtype during infarction or in the setting of heart failure may be a viable treatment option.

Neurophysiology

The noradrenergic (NA) system in the mammalian central nervous system (CNS) originates primarily in the locus coeruleus. From this nucleus in the brain stem, a highly divergent and diffuse projection of NE-containing axons radiate throughout the CNS innervating the spinal cord, cerebellum, thalamus, amygdala, hippocampus, and cortex (reviewed in ref. 101). The wide distribution of afferents is congruent with a global regulatory role in CNS function. Indeed, the central NE system has been shown to regulate a number of behavioral states including sleep and arousal, cognitive functions such as learning and memory, affective states such as anxiety and depression, changes in neuroplasticity, embryonic brain development, and adult neurogenesis (reviewed in ref. 102). The central NE system has also been implicated in a number of neurological disorders including Alzheimer’s disease, attention-deficit/hyperactivity (ADHD), depression, epilepsy, mania, Parkinson’s disease, posttraumatic stress disorder (PTSD), and schizophrenia (reviewed in ref. 103). Specificity in the central NE system arises from its diversity of nine AR subtypes with discrete expression patterns. Although all AR subtypes occur in the brain, the α_1-ARs may be the most abundant. α_1-ARs have a role in the numerous physiological states and neurological disorders that are associated with the central NE system.

Expression of α_1-ARs in brain

The specific localization of the α_1-AR subtypes in the brain has been hindered by the lack of subtype-selective antibodies and ligands. Early receptor binding or autoradiography studies indicated that α_1-ARs are located throughout the brain (104). Later, *in situ* hybridization studies suggested that the α_1-AR subtypes may be differentially expressed in the brain (105); however, these studies, while more accurate, are not quantitative due to mRNA transportation. Unfortunately, the lack of high affinity antibodies to the α_1-AR subtypes has prevented reliable immunohistochemistry findings (106).

The pharmacology of the α_1-ARs is very similar between human and rodents; however, the distribution is different (107). While there are comparable densities of α_1-ARs in the thalamus and cortex of rodents and humans, the density of α_1-ARs is much higher in the hippocampus of humans compared with rodents, especially in the CA3 region and dentate gyrus (107). Moreover, α_{1A}- and α_{1B}-ARs are differentially distributed in the human hippocampus, with the α_{1A}-AR concentrated in the CA3 and the α_{1B}-AR concentrated in the dentate gyrus (108).

To circumvent the lack of selective antibodies and ligands to determine the cellular localization of the α_1-ARs, transgenic mice were developed, which overexpress either the α_{1A}- or α_{1B}-ARs, fused with an enhanced green fluorescent protein (EGFP). Using this transgenic tagged-GPCR approach, it was determined that α_{1A}- and α_{1B}-ARs exhibit a similar expression pattern in the CNS (109,110). Both receptors are expressed in the amygdala, cerebellum, cerebral cortex, hippocampus, hypothalamus, midbrain, pontine olivary nuclei, trigeminal nuclei, and spinal cord. Both receptors were also found in the same cell types including neurons, GABAergic interneurons, and NG2 oligodendrocyte progenitors. Interestingly, neither α_{1A}- nor α_{1B}-ARs were found in astrocytes or cerebral vascular smooth muscle, cells previously thought to express α_1-ARs. Using transgenic KO mice for the individual α_1-AR subtypes, the distribution of α_1-ARs in the brain has been determined to be ~55% α_{1A} (111), 35% α_{1B} (112), and 10% α_{1D} (113).

Neural actions of α_1-ARs

Identification of the effects mediated by α_1-AR subtype has also been hindered by the lack of subtype-selective ligands. The α_1-ARs are generally stimulatory and found on postsynaptic cell bodies. α_1-ARs can increase the excitation mediated by glutamate or acetylcholine (114) and prime excitatory synapses (115). Furthermore, they have been found to directly enhance neurotransmitter release from presynaptic terminals (116), as well as to modulate GABAergic (117) and glutamatergic inputs (118). Their stimulatory actions have often been attributed to a decrease in cellular resting conductance (119,120), but may also involve an increase in calcium. α_1-ARs may also affect many CNS functions via non-neuronal mechanisms as they are also expressed in glia. α_1-AR activation has been found to increase calcium release in Bergmann glial cells (121).

α_1-ARs in neurogenesis

Recent evidence suggests that α_1-ARs are involved in the neurogenic effects of NE. Increasing brain NE levels has been found to enhance the proliferation of neural progenitor cells (NPCs) (122), while depleting NE decreases NPC proliferation *in vivo* (123). Stimulating α_1-ARs has also been shown to induce the proliferation and migration of embryonic NPCs *in vitro* (124,125). Using transgenic EGFP-tagged and CAM mouse models, we found that α_{1A}-AR are expressed in neural stem cells (NSCs) and/or transient amplifying progenitors (TAPs) *in vivo* and that the chronic stimulation of these receptors increases neurogenesis (126). Moreover, we have found that treating adult normal (nontransgenic) mice with the mildly selective α_{1A}-AR agonist, cirazoline, also increases

neurogenesis. Interestingly, although we found that α_{1B} - ARs also appear to be expressed on NSCs, chronic activation of these receptors did not increase neurogenesis. Indeed, CAM α_{1B}-AR mice display an age-dependent neurodegeneration (127). Our finding that stimulating α_{1A}-AR increases neurogenesis may have significant implications for many normal and pathological neurological processes.

α_1-ARs in locomotion

Although the dopaminergic-striatal pathways are considered the primary mechanism for controlling locomotion and motor activity in the CNS, α_1-ARs activated by NE may also be involved (128,129). Postsynaptic excitatory α_1-ARs have been shown to modulate midbrain dopamine cell activity (130). α_1-ARs have also been found to increase the tonic firing of principal neurons in the substantia nigra pars reticulate (131). The output of the basal ganglia and motorrelated behaviors may be significantly impacted by this increase in excitability. *In vivo* pharmacological evidence suggests that α_{1B}-ARs are involved in the motor activity and spontaneous movement (132). Consistent with this finding, α_{1B}-AR KO mice do not display fear-motivated exploratory behavior (133). Mice lacking α_{1B}-AR also exhibit decreased psychostimulant-induced locomotor hyperactivity (134) that correlated with reduced psychostimulant-induced dopamine release in the nucleus accumbens (135). In contrast, the α_{1A}-AR may mediate the facilitation of α-motor neuron activity in the rat spinal cord (136). In summary, the α_{1B}-AR may be involved in controlling locomotion and motor activity, which is relevant to locomotor disorders.

α_1-ARs in neurodegeneration

In contrast to long-term α_{1A}-AR activation, chronic α_{1B} - ARs stimulation appears to cause an age-progressive apoptotic neurodegeneration (127). Transgenic mice that systemically overexpress the α_{1B}-AR display an age-dependent neurological disorder similar to multiple system atrophy (127) characterized by autonomic dysfunction, Parkinsonism, and ataxia. Histological examination reveals that α_{1B}-AR overexpression causes a synucleinopathy marked by the aggregation/formation of α-synuclein inclusion bodies and interneuron loss in the cerebellum and hippocampus, as well as degeneration of spinal cord cell columns (137). Consistent with the finding that α_{1B}-AR activation induces a Parkinson-like syndrome, mice lacking α_{1B}-ARs (KO) do not show this neurodegenerative phenotype. In fact, α_{1B}-AR KO mice appear to live a normal, albeit longer life than the α_{1A}-AR KO mice (138).

α_1-ARs in cognitive function and neuroplasticity

The function of α_1-ARs in learning and memory has not been clearly defined and is controversial. Most *in vivo* studies suggest that activating α_1-ARs improves memory while blocking α_1-ARs impairs cognition (139–141). Other studies have reported that α_1-ARs inhibit memory (142–144). These differences may be due to species-specific differences or to differential regulation by α_1-AR subtypes. Recently, we found that chronic α_{1A}-AR stimulation improves cognitive function (145; manuscript submitted), whereas long-term α_{1B}-AR activation impaired learning and memory (unpublished findings). Furthermore, we found that treating normal mice with a selective agonist increased both spatial and declarative memory processes, while α_{1A}-AR KO mice have diminished cognitive function. The mechanism for these actions is not known for certain. However, neurogenesis has been shown to enhance certain forms of learning and memory, while neurodegeneration generally impairs cognitive function.

α_1-AR dysfunction is implicated in the pathogenesis of Alzheimer's disease (AD). For example, polymorphisms in the α_{1A}-AR are associated with AD susceptibility (146). Brain tissue from aged transgenic AD mice displays increased α_1-ARs in cerebral cortices (147).

Increasing α_1-AR activation in the medial prefrontal cortex improves cognitive function of rats (148). In AD patients, α_1-AR binding is significantly reduced in the prefrontal cortex (149,150). Furthermore, α_{1A}-AR mRNA expression is decreased in the prefrontal cortex in patients with dementia (151). These results suggest that increasing α_{1A}-AR activity may delay or alleviate AD symptoms.

Given that α_1-ARs affect cognitive function, it is not surprising then that numerous studies have shown that α_1-ARs also affect plasticity in the hippocampus, a cortical structure critical for learning and memory. NE through α_1-AR activation has been shown to promote hippocampal long-term potentiation (LTP), an important synaptic mechanism underlying learning (140,152,153). α_1-ARs may also play a role in long-term depression (LTD) in the hippocampus (154). The role of the various α_1-AR subtypes in neuroplasticity is unknown.

α_1-ARs in depression and anxiety

The involvement of NE in depression is well-established. Although several studies have suggested that α_1-ARs are involved in the antidepressant effects of NE (155), the role of individual α_1-AR subtypes in mood is not well-defined. Recently, using transgenic mice, we showed that chronic α_{1A}-AR was associated with a significant decrease in depression-like behavior, whereas chronic α_{1B}-AR stimulation was prodepressant (156,157). Subsequently, we have shown that chronic α_{1A}-AR activation reduces anxiety and obsessive–compulsive-like behavior (158; manuscript submitted). The mechanism for these actions is not known. However, since considerable evidence links depression to neurogenesis, enhanced α_{1A}-AR-stimulated neurogenesis deserves serious attention as the mechanism. Increased α_{1A}-AR stimulated GABA release in the amygdala and other cortical structures could be involved in the anti-anxiety actions (159).

α_{1A}-ARs in epilepsy

NE has long been known to be potently anti- epileptogenic (see reviews in refs. 160,161). Numerous studies using different models of epilepsy have shown that the anticonvulsant effects are mediated in part by α_1-ARs (162–168). The underlying mechanism has not been clearly established. However, the activation of α_1-ARs has been shown to enhance tonic GABA-mediated inhibition in several regions of the brain including the piriform cortex (169), amygdala (170), medial septum (171), hippocampus (120), and frontal cortex (172). The increase in GABA release resulted from a direct α_1-AR-mediated decrease in a potassium conductance resulting in a depolarization of inhibitory GABAergic interneurons (120,172). This increase in GABA-mediated inhibitory tone, in turn, reduces epileptiform bursting in the hippocampus (173). This physiological response appears to be mediated by α_{1A}-ARs in the hippocampus (174,175) and amygdala (159), and may be impaired by stress (170), which reduces α_1-AR numbers.

The α_1-AR subtypes have both positive and negative roles in regulating seizure activity. Both CAM α_{1A}-AR and WT α_{1A}-AR mice under the control of the endogenous promoter demonstrate an antiepileptic phenotype with increased seizure thresholds to flurothyl, a chemoconvulsant (176; manuscript in preparation). In contrast, the CAM α_{1B}-AR mice exhibit decreased seizure thresholds to flurothyl. Moreover, CAM α_{1B}-AR mice develop a grand mal seizure disorder that appears to be a multifocal epilepsy (177). The mechanism underlying the seizures in the CAM α_{1B}-AR mice is not known, but may be due to NMDA/$GABA_A$ receptor dysregulation and apoptosis (178). Consistent with these findings, we have found that α_{1A}-AR KO mice often display spontaneous seizures, whereas α_{1B}-AR KO mice do not show this phenotype. Indeed, the lack of α_{1B}-ARs appears to confer some resistance to the neurotoxicity produced by seizures (179). Furthermore, α_{1B}-AR KO mice do not appear to develop the neurodegeneration associated with prolonged and severe seizures

(179). We also have evidence that chronic activation of the α_{1A}-AR, but not the α_{1B}-AR, protects the brain from apoptosis (178). Using transgenic mice, we found that the hippocampus expresses the highest amount of the α_{1A}-AR compared with other areas in the brain (110). We also discovered that both the overexpressed WT α_{1A}-AR and the CAM α_{1A}-AR mice have an increased density of hippocampal interneurons (180) and demonstrate protection from anoxia/trauma and hyperexcitability (145). Taken together, these results suggest that α_{1A}-AR activation is not only anti-epileptogenic, but neuroprotective.

α_1-AR subtypes in mental illness

Heightened or excessive NE activity has been associated with schizophrenia, mania, and PTSD (reviewed in 142). The α_1-AR subtypes may have both positive and negative roles in these mental illnesses. α_1-AR antagonism has been recognized as a potential mechanism of antipsychotic action since the discovery that many antipsychotics block α_1-ARs (181). For example, the atypical antipsychotic clozapine has a high affinity toward these receptors (182). Many sources cite the antagonism of the α_{1A}-AR subtype as mediating this antipsychotic action though the data may not support this claim sufficiently, as the conclusions were based on studies performed in the peripheral nervous system while studying side effects (183) or not actually focused on the α_1-AR subtypes (184). The binding affinities of clozapine for α_{1A}- and α_{1B} -ARs are not significantly different (185,186); however, the observed α_1-AR up-regulation that occurs with clozapine treatment is mainly in areas of high α_{1B}-AR expression (187). In addition, the atypical antipsychotic risperidone has 120-fold antagonist selectivity for the α_{1B}-AR in the hippocampus (185). Furthermore, risperidone increases survival of hippocampal NSCs in a ketamine-induced model of schizophrenia (188). These results suggest that α_{1B}-ARs are involved in schizophrenia and antagonism of the α_{1B}-AR, but not the α_{1A}-AR, may be mediating part of atypical antipsychotic action. Interestingly, single nucleotide polymorphisms in the α_{1A}-AR promoter region have been found in an isolated population with schizophrenia (189).

Antagonism of the α_1-ARs is also used to treat the nightmares and sleep disturbances associated with PTSD. Recent evidence suggests that excessive PKC activation in the prefrontal cortex may be involved in PTSD as well as bipolar disorder (190). Antagonists and/or antipsychotics that block α_1-AR-mediated PKC activity have shown some benefit in treating these disorders. The level of RGS4, a small protein that inhibits PKC activity, is reduced in schizophrenia (191). RGS4 has also been linked genetically to schizophrenia and bipolar disorder (192–195). Interestingly, RGS4 is suggested to interact with α_{1B}-ARs, whereas RGS2 proteins will directly interact with α_{1A}-ARs, but not with α_{1B}-ARs or α_{1D}-ARs (196). Taken together, these findings suggest that α_{1A}-ARs and α_{1B}-ARs may play different roles in these mental illnesses. Studies are currently being conducted to determine the effects of chronic α_{1A}-AR and α_{1B}-AR activation on these mental illnesses.

Neuro summary

Although the role of α_1-ARs in the CNS has been the least understood historically, recent evidence suggests that many of their actions are mediated differentially by α_{1A} - ARs and α_{1B}-ARs. Chronic α_{1A}-AR stimulation increases neurogenesis, enhances learning and memory, and improves mood. It may also protect the brain from anoxia and traumatic injury, seizures, and age-dependent neurodegeneration. Therapeutic strategies to selectively activate the α_{1A}-AR subtype and/or only block α_{1B}-ARs may be neuroprotective, and therefore may be useful for treating a number of neurological disorders.

Epilogue

Our latest research indicates that chronic activation of the α_{1A}-AR, but not the α_{1B}-AR, increases life span (138; manuscript submitted). Using our transgenic α_1-AR and KO mice,

we found that both the CAM α_{1A}-AR and overexpressed α_{1A}-AR EGFP mice live significantly longer (>10%) than their normal littermates. Unlike many other mouse models of longevity, these mice are of normal body size and mobility. In contrast, the CAM α_{1B}-AR and overexpressed α_{1B}-AR EGFP mice have a shorter life span than their normal littermates. Furthermore, we found that α_{1A}-AR KO mice do not live as long as α_{1B}-AR KO mice. Taken together, these results suggest that the cardiac and neuroprotection afforded by the α_{1A}-AR translates into increased longevity.

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