Pharmacological Reports
2013, 65, 1489–1497
ISSN 1734-1140

Review

α_1-Adrenergic receptor subtypes in the central nervous system: insights from genetically engineered mouse models

Irena Nalepa, Grzegorz Kreiner, Adam Bielawski, Katarzyna Rafa-Zabłocka, Adam Roman

Department of Brain Biochemistry, Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, PL 31-343 Kraków, Poland

Correspondence: Irena Nalepa, e-mail: nfnalepa@cyf-kr.edu.pl

Abstract:
α_1-Adrenergic receptors (α_1-ARs) are important players in peripheral and central nervous system (CNS) regulation and function and in mediating various behavioral responses. The α_1-AR family consists of three subtypes, α_{1A}, α_{1B} and α_{1D}, which differ in their subcellular distribution, efficacy in evoking intracellular signals and transcriptional profiles. All three α_1-AR subtypes are present at relatively high densities throughout the CNS, but the contributions of the individual subtypes to various central functions are currently unclear. Because of the lack of specific ligands, functionally characterizing the α_1-ARs and discriminating between the three subtypes are difficult. To date, studies using genetically engineered mice have provided some information on subtype-related functions of the CNS α_1-ARs. In this mini-review, we discuss several CNS processes where the α_1-ARs role has been delineated with pharmacological tools and by studies using mutated mice strains that infer specific α_1-AR subtype functions through evaluation of behavioral phenotypes.

Key words:
α_{1A} adrenergic receptor, α_{1B} adrenergic receptor, α_{1D} adrenergic receptor, genetic models, noradrenergic, antidepressant, phenotype

Abbreviations: AR – adrenergic receptor, CAM – constitutively active mutant, cAMP – cyclic adenosine monophosphate, CMS – chronic mild stress, CNS – central nervous system, CRF/CRH – corticotropin releasing factor/hormone; ECS – electroconvulsive shock, FST – forced swim test, GPCR – G-protein-coupled receptor, GRK – G-protein-coupled receptor kinase, HPA – hypothalamic-pituitary-adrenocortical, KO – knockout, MSA – multiple system atrophy, PCA – *p*-chloro-amphetamine, PKA – protein kinase A, PKC – protein kinase C, PLC – phospholipase Cβ, TCA – tricyclic antidepressant drug, TGFβ – transforming growth factor β3, TST – tail suspension test, WT – wild-type

Introduction

Noradrenaline is a neurotransmitter that plays an essential role in behavior and the regulation and function of the peripheral and central nervous system (CNS). The noradrenergic system modulates cognitive functions, such as arousal, attention, learning and memory [41]. Dysregulation of noradrenergic neurotransmission and abnormalities in brain adrenergic re-

ceptor signaling are associated with a variety of behavioral pathologies; affective and cognitive disorders, including attention-deficit/hyperactivity disorder (ADHD); stress- and/or anxiety-related disorders (e.g., posttraumatic stress disorder [PTSD] and depression) and drug abuse [1].

Physiological responses to noradrenaline and adrenaline are mediated by adrenergic receptors (AR), which are seven-transmembrane-spanning receptors that belong to the large G-protein-coupled receptor (GPCR) superfamily. The AR family is presently divided into three distinct receptor subclasses, β-, α_2- and α_1-AR, and each subclass comprises several subtypes. All three α_1-AR subtypes, α_{1A}, α_{1B} and α_{1D}, are coupled to Gq/11 and phospholipase Cβ (PLC), which stimulate phosphoinositide hydrolysis to produce two second messengers, diacylglycerol and inositol trisphosphate, followed by protein kinase C (PKC) activation and increased mobilization of intracellular Ca^{2+}. The α_1-ARs function as stimulatory receptors, and each subtype is encoded by a separate gene located on different chromosomes, has a distinct pharmacological profile and amino acid sequence and is differentially distributed [8, 37, 38].

The physiological responses mediated by α_1-ARs in the cardiovascular and peripheral nervous systems have been well studied. These receptors are involved in smooth muscle contraction, growth and differentiation. The α_1-AR subtypes are important for the modulation of vasoconstriction, blood pressure control and urinary tract contractility and have been previously characterized [4, 8, 15, 46] but are beyond the scope of this current review.

Central α_1-ARs modulate a large number of positive motivated behaviors and mediate aversive behaviors [44]. These receptors influence motor and exploratory activity, and in mice, central α_1-AR neurotransmission is required for behavioral activation to environmental changes and may act on sensorimotor and motivational processes [45]. The α_1-ARs mediate corticotropin releasing factor (CRF) secretion, can modulate the activity of the hypothalamic-pituitary-adrenocortical (HPA) axis and regulate behavioral stress responses. However, because subtype-selective pharmacological tools are absent, the contributions of each α_1-AR subtype to various central functions are currently unclear.

In this review, we briefly examine the different regulatory and cellular characteristics of α_1-ARs (*in vitro* studies using recombinant systems and transfected cells) and focus on the functional roles of α_1-AR subtypes in the CNS (*in vivo* studies employing pharmacological tools and genetically engineered mice).

α_1-Adrenoceptor signaling regulation and cellular function

The regulation of GPCR signaling occurs *via* a variety of dynamic control mechanisms, including phosphorylation and desensitization, protein-protein interactions, protein trafficking, and transcription. Because of GPCR desensitization, the intensity of a biological response wanes over time (reviewed in [26]). Similar to other GPCRs, the α_1-ARs may undergo homologous (phosphorylation by G-protein-coupled receptor kinases [GRKs]) or heterologous desensitization (phosphorylation by second messenger-activated protein kinases, such as PKC and protein kinase A [PKA]), arrestin-related internalization and endocytosis into clathrin-coated vesicles. Although such mechanisms are responsible for the regulation of α_1-AR signaling intensity, α_1-AR subtypes display divergent regulatory properties, and as demonstrated through previous work utilizing various recombinant systems, the rate of phosphorylation, desensitization and internalization in response to agonists differs between the receptor subtypes [5]. Such diversity may be linked, at least in part, with differential cellular localization of receptor subtypes and their access to agonists acting at the cell surface. The α_{1B}-AR, which is localized mainly on the plasma membrane, undergoes rapid desensitization and internalization in response to adrenergic agonists, but the α_{1A}-AR, which is localized both on the cell surface and intracellularly, displays a slower rate of internalization compared with the α_{1B}-AR. By contrast, the α_{1D}-AR is localized predominantly in intracellular vesicles, and the intracellular localization of α_{1D}-AR in unstimulated cells may be linked with its continuous internalization stemming from its constitutive activity [3, 38]. Therefore, these studies implicate the existence of additional mechanism(s) to regulate α_{1D}-AR function. Interestingly, the α_1-AR subtypes have been shown to form both homo- and hetero-oligomers. Heterodimerization, in particular, seems to regulate α_{1D}-AR function, as co-expression of α_{1D}-AR with the