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Pharmacology & Therapeutics 111 (2006) 652 – 673
Pharmacology & Therapeutics
www.elsevier.com/locate/pharmthera

Associate editor: P. Molenaar

β_3-Adrenoceptors in the cardiovascular system: Putative roles in human pathologies

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Abstract

The sympathetic nervous system is central for the neurohumoral regulation of the cardiovascular system and is largely involved in many cardiovascular diseases affecting millions of people around the world. It is classically admitted that β-adrenoceptors (β-AR) of the β_1 and β_2 subtypes mediate the effects of catecholamines on the force of contraction of cardiac muscle, and on the relaxation of vascular smooth muscle. However, the molecular characterization in 1989 of a third β-AR subtype, β_3, and later its identification in human heart has changed the classically admitted paradigm on the regulation of heart function by the β-adrenergic system. In blood vessels, β_3-AR, like β_1 and β_2, produced a relaxation. But at the present time, the physiological role of β_3-AR is not clearly identified. Thus, the purpose of this review is to summarize the pharmacological and molecular evidence supporting the functional roles of β_3-AR in cardiovascular tissues of various species, including humans. In addition, this review discusses the potential role of β_3-AR in several cardiovascular diseases and emphasizes their putative involvement as new therapeutic targets.

Keywords: β-adrenergic receptors; Heart; Vessels; Contractility; Heart failure; Hypertension

Abbreviations: β-AR, β-adrenoceptor; cAMP, cyclic adenosine monophosphate; BRL 37344, 4-[-[2-hydroxy-(3-chlorophenyl)ethyl-amino]propyl]phenoxyacetate; CHO, Chinese hamster ovary; CL 316 243, 5-(2-{[2-(3-chlorophenyl)-2-hydroxyethyl]-amino}propyl)-1,3-benzodioxole-2,2-dicarboxylate; cGMP, cyclic guanosine monophosphate; CGP 12177A, 4-[3-*t*-butylamino-2-hydroxypropoxy]benzimidazol-2-one; CFTR, cystic fibrosis transmembrane conductance regulator; eNOS, endothelial nitric oxide synthase; L-748,328, (*S*)-*N*-[4-[2-[[3-[3-(ami-nosulphonyl)phenoxy]-2-hydroxypropyl]-amino]ethyl]phenyl]benzenesulfonamide; L-748,337, (*S*)-*N*-[4-[2-[[3-[3-(acetamidomethyl)phenoxy]-2-hydroxypropyl]amino]ethyl]phenyl]benzenesulfonamide; L-NMMA, N^G-monomethyl-L-arginine monoacetate; NO, nitric oxide; PCR, polymerase chain reaction; PKA, cAMP-dependent protein kinase; SR 58611A, (*RS*)-*N*-[(25)-7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydronapht-2-yl]-(2)-2-(3-chlorophenyl)-2 hydroethanamide hydrochloride; SR 59230A, 3-(2-ethylphenoxy)-1-[(1*S*)1,2,34-tetrahydronapht-1-ylaminol]-(2*S*)-2-propanol oxalate; TGβ3, mice overexpressing human β_3-adrenoceptors in cardiomyocytes.

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0163-7258/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.pharmthera.2005.12.002

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1. Introduction

The sympathetic nervous system is central for the neurohumoral regulation of the cardiovascular system and is largely involved in many cardiovascular diseases affecting millions of people around the world. During the 1980s, the classification of β-adrenoceptors (β-AR) into 2 subtypes (β_1 and β_2) (Lands et al., 1967) was challenged. Thus, it is now known that 3 different subtypes, β_1-, β_2- and β_3-AR, could at least participate in the regulation of cardiovascular function. β_3-AR differs from β_1- and β_2-AR subtypes by its molecular structure and pharmacological profile. Its stimulation produces specific effects in the cardiovascular system. This review will present an overview of characteristics of β_3-AR and reports on the presence and the roles of β_3-AR in the cardiovascular system and their potential involvement in different pathologies.

2. Structure and characteristics of β_3-adrenoceptors

2.1. Gene

The gene encoding human β_3-AR was cloned in 1989 (Emorine et al., 1989). Since then, the gene has been cloned in rat, mice, bovine, monkey, dog (for review, see Strosberg, 1997), sheep and goat (Forrest & Hickford, 2000). Unlike the genes encoding β_1- and β_2-AR, the gene encoding β_3-AR contains introns. The existence of several exons raises the possibility of alternative splicing and thus of different receptor isoforms with putative distinct pharmacological properties. Among the different species previously cited, variations in length and amino acid content of the sequence of the C-terminus tail have been reported (Fig. 1).

In human, the gene is localized on chromosome 8. The number of exons and introns is controversial. The first structure proposed was 2 exons and 1 intron. The first exon of 1.7 kb has a high homology with rodents. It encodes for the first 402 amino acids of the receptor. The second exon encodes the last 6 amino acids of the C-terminus tail and the 3′ region not translated from the mRNA (Granneman et al., 1992, 1993; Van Spronsen et al., 1993). This structure of 2 exons and 1 intron has also been described in dogs and monkeys (Walston et al., 1997; Lenzen et al., 1998). Thus, 2 putative isoforms with various C-terminus tails could exist (Fig. 1): an isoform of 402 amino acids (isoform A) and an isoform with 6 additional amino acids (isoform C). Another structure with 3 exons and 2 introns has also been proposed for the human gene (Fig. 1; Levasseur et al., 1995). However, the alternative splicing site for the second exon seems to be not functional (Granneman et al., 1992) and strengthens the first hypothesis of a structure with 2 exons.

In rats and mice, the gene encoding β_3-AR contains 3 exons and 2 introns. The first exon of 1.4 kb encodes the first 388 amino acids. In rat, the second exon of 0.7 kb encodes the last 12 amino acids of the C terminus tail. In this species, 2 isoforms of β_3-AR could be expressed: A and B isoforms of 388 and 400 amino acids, respectively (Fig. 1; Van Spronsen et al., 1993). In mice, 2 sites in the exon 2 allow an alternative splicing leading to 2 isoforms, β_{3a} and β_{3b} (Evans et al., 1999). The β_{3b}-AR encoded by the alternately spliced mRNA has a C-terminus that has 17 amino acids following the sequence encoded by the first exon region compared to 13 in the known receptor (β_{3a}-AR) (Fig. 1). β_{3b}-AR mRNA is differentially expressed in mouse tissues, with levels relative to β_{3a}-AR mRNA highest in hypothalamus, cortex and white adipose tissue, and lower in ileum smooth muscle and brown adipose tissue (Evans et al., 1999).

2.2. Protein

The β_3-AR, as well as β_1- and β_2-AR, belongs to the G protein-coupled receptors characterized by 7 transmembrane