APŽVALGINIAI STRAIPSNIAI

Structure and function of β_3-adrenergic receptors

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Summary. *β-adrenergic receptors have been subdivided into three types: β_1-, β_2- and β_3-adrenergic receptors. β_1-adrenergic receptors are predominant in the heart, β_2-adrenergic receptors – in the respiratory system, and β_3-adrenergic receptors – in the adipose tissues. However, since 1989, when β_3-adrenergic receptor was cloned, numerous biochemical and functional studies have confirmed its presence in various species and tissues, including the heart. Unlike β_1- and β_2-adrenergic receptors, it has been shown that β_3-adrenergic receptors possess the cardiodepressant effects in human ventricles, what did not fit to its stimulatory properties of adenylyl cyclase in other tissues. In this regard, the role of β_3-adrenergic receptors in the regulation of cardiac function may be of great importance in pathological conditions and remains undetermined, so far. In this review brief characterization of β_3-adrenergic receptors, concerning their structure, function and possible pathophysiological role is provided.*

History

Sympathetic stimulation induces a number of physiological effects, such as modulation of heart rate, vascular tonus, bronchospasm, glucose and lipid metabolism, etc. A. M. Lands et al in 1967 (1) subdivided the β-adrenergic receptor (β-AR) mediated effects into β_1- and β_2- on the basis of the rank order of potency of epinephrine and norepinephrine in different tissues. The receptors mediating responses in the heart were designated β_1 and the receptors mediating vasodepressor activity and bronchodilatation were designated β_2. However, in some tissues, like white and brown adipose tissue (WAT and BAT, respectively) and digestive tract, the β-AR-mediated effects such as lipolysis, oxygen consumption and smooth muscle relaxation were not compatible with the sole involvement of β_1- and β_2-adrenoreceptors (2–4). This led to the hypothesis for the existence of a third β-AR, mediating thermogenesis in BAT and lipolysis in WAT (5), which finally has been cloned by L. J. Emorine et al in 1989 (6).

Structure

β_3-AR differs from β_1- and β_2-AR subtypes by its molecular structure and pharmacological profile (7). Human β_3-AR shares 51% and 46% identity with β_1- and β_2-AR amino acid sequences, respectively (while there is 54% homology between β_1- and β_2-AR amino acid sequences). β_3-AR is activated by selective pharmacological agonists (SR 58611, BRL 37344, CGP 12177), which have little effect on β_1- and β_2-ARs (see Table 1). The homology between human, bovine, monkey, hamster, guinea pig, mouse and rat β_3-ARs (80–90%) is considerably higher than that between different β-ARs subtypes (8).

β_3-ARs, as well as β_1- and β_2-ARs, belong to the G-protein coupled receptors characterized by seven transmembrane domains (TM) of 22–28 amino acids, and having three intracellular and three extracellular loops (Fig. 1). The N-terminus of all three β-ARs is extracellular and glycosylated. The C-terminus is intracellular, but unlike in β_1- and β_2-ARs, has no sites for phosphorylation by protein kinase A (PKA) and β-adrenoceptor kinase (βARK). The disulphide bond between Cys110 in the 2nd and Cys189 in the 3rd extracellular loops (indicated by S-S) is essential for ligand binding and activity of the receptor. Cys361 residue in the fourth intracellular domain is palmitoylated. Palmitoylation has been shown to mediate the adenylyl cyclase stimulation by agonist-bound receptor, possibly by promoting the insertion of several adjacent residues in the membrane (9) and thus forming an additional intracellular loop resulting in an active conformation for G protein coupling. β_3-ARs together

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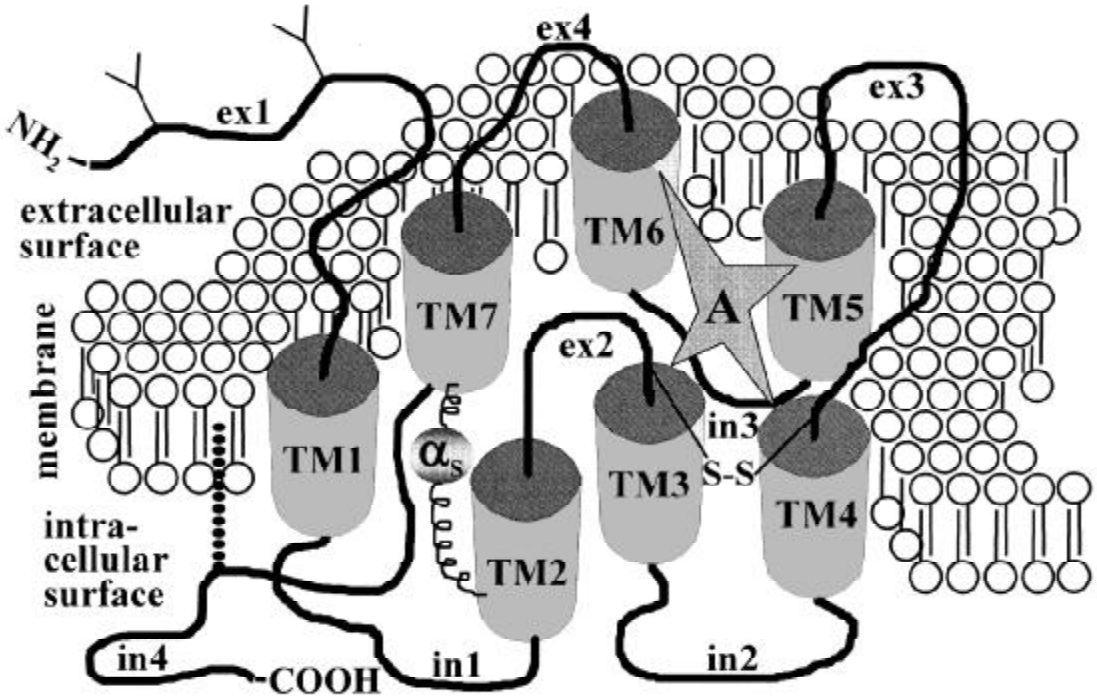

Fig. 1. **Structure of β_3-adrenergic receptor**

A – β_3-AR agonist; α_s – stimulatory subunit of G protein; TM – transmembrane domain; in – intracellular domain; ex – extracellular domain; S-S – disulphide bond; Y – N-glycosylation sites; ⚫ – palmitoylation site.

with α_1B receptors are the only in the family of adrenergic receptors having introns (10, 11). TM3, TM4, TM5 and TM6 are essential for ligand binding. TM2 and TM7 are involved in G_s activation (12).

Function

Like β_2-AR, which despite of its predominance in lung, was found in the heart of different species (13–15), β_3-ARs were identified in variety of tissues. They inhibit contractile activity of ileum and colon (16–18), modulate neuronal bronchomotor, inducing relaxation of airway smooth muscle (19), produce peripheral vasodilation, which is predominant in skin and fat (20, 21), reduces contractile force in human ventricular muscle (22), and stimulates L-type calcium current in human atrial myocytes (23). Until recently β_3-AR was shown to possess the same intracellular signaling pathway as β_1- and β_2-ARs, i. e. activation of adenylyl cyclase and cAMP-dependent phosphorylation. In human atrial myocytes the activation of β_3-AR leads to the phosphorylation of calcium channels and increase of I_{Ca} (Fig. 2a), while in the adipocytes they mediate lipolysis and thermogenesis (Fig. 2b). However, recent and at some degree controversial data show, that selective β_3-AR agonists exert negative inotropic effects on human ventricular muscles, and this is related with activation of inhibitory G_i proteins (22). Further studies of the same group showed that β_3-ARs in human ventricular muscle stimulated the production of nitric oxide (NO) through the activation of endothelial constitutive NO synthase (NOS), which has been shown to be present not only in the endothelial cells, but also in the ventricular myocytes (24). In this way, NO, having diffused from endothelial cells or produced right in the myocytes, exerts the generation of cGMP and successive inhibition of phosphodiesterase 3 (PDE3) and/or activation of PDE2, which can reduce the contraction force, stimulated through cAMP pathway (Fig. 2c). The stimulation of NO by β_3-AR agonists in the endothelial cells and its following diffusion to the myocytes should partially explain why β_3-AR agonists very potently and efficiently (maximal stimulation is equal to that of isoprenaline, nonselective agonist of β-AR, but is resistant to nadolol, β_1-, β_2-AR antagonist) stimulate I_{Ca} in the human atrial myocytes (23), but very weakly and transiently stimulate the contraction force of human atrial and ventricular muscles (our unpublished data). Such stimulation of the contraction force can be improved, by L-NMMA, an inhibitor of NO synthase. However, even then it still remains far from that of isoprenaline. The interpretation of the results, so far, is complicated by conf-

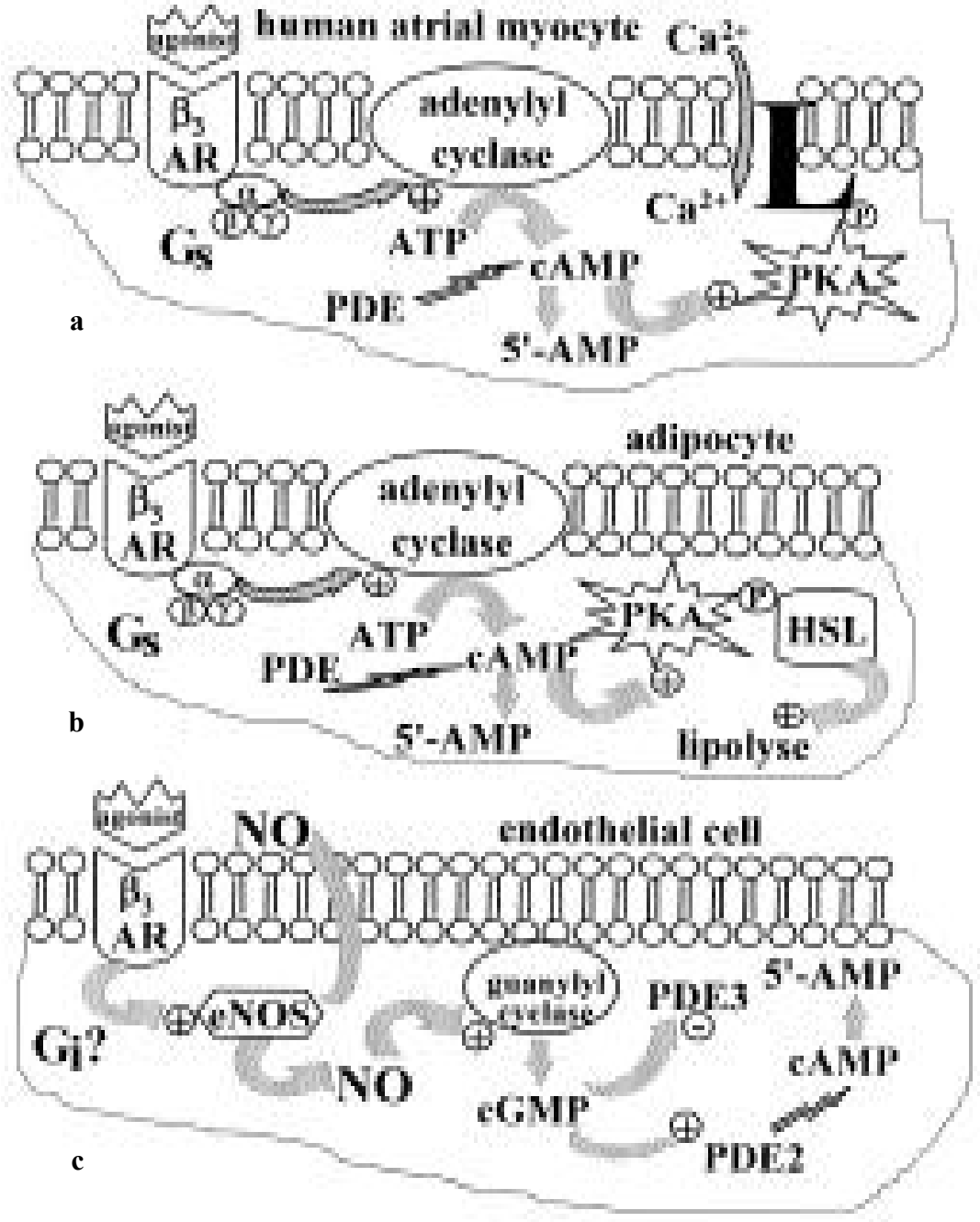

Fig. 2. **Function of β_3-adrenergic receptor (β_3-AR)**

In human atrial myocytes (A) and adipocytes (B) β_3-AR is coupled to stimulatory G proteins (G_s), and stimulates L-type calcium current or lipolysis, respectively. In endothelial cells (C) β_3-ARs seem to be coupled to endothelial nitric oxide synthase (eNOS), possibly through inhibitory G proteins (G_i) and stimulate production of nitric oxide NO. PKA – cAMP dependent protein kinase; PDE – phosphodiesterase, hydrolysing cAMP to 5'-AMP; HSL – hormone sensitive lipase; α, β, γ – subunits of G protein; L – L-type calcium channel, permitting the entrance of calcium ions into the cell. Phosphorylation (P) by PKA increases open probability of the channel.

licting data on expression of mRNA for β_3-ARs in the heart. Although the expression of a β_3-ARs in human myocardium was recently demonstrated both at the level of mRNA (22, 25) and protein (26–28), however, was not detected by others (29).

Pharmacology

Cloned functional β_3-ARs were characterized in Chinese hamster ovary (CHO) cells expressing only this β-AR subtype. These studies were based on stimulation of adenylyl cyclase, measurement of cAMP accu-

Table 1. **Properties of three human β-adrenergic receptors**

Receptor	β_1-AR	β_2-AR	β_3-AR
Number of amino acids	477	413	408
Introns	–	–	2
Phosphorylation by PKA and βARK	Yes	Yes	No
Most potent catecholamine	Noradrenaline	Adrenaline	Noradrenaline
Selective agonist	Xamoterol Dobutamine	Zinterol Procaterol	BRL 37344, CGP 12177
Selective antagonist	CGP 20712A Metoprolol	ICI 118551	SR 59230A
G protein	G_s	G_s	G_s, G_i
Effector	Adenylyl cyclase	Adenylyl cyclase	Adenylyl cyclase, NO synthase
Tissue where receptor is predominant	Heart	Lungs	Adipose tissue

PKA – cAMP dependent protein kinase; βARK – β-adrenergic receptor kinase; NO – nitric oxide.

Table 2. **Pharmacological characteristics of the human β_1-, β_2-, and β_3-ARs expressed in Chinese hamster ovary cells**

Ligand	β_1-AR			β_2-AR			β_3-AR		
β-AR agonists:	K_i (nM)	K_{ac} (nM)	IA	K_i (nM)	K_{ac} (nM)	IA	K_i (nM)	K_{ac} (nM)	IA
(-)Noradrenaline	24100	0.8	–	11800	36	–	475	6.3	1.00
(-)Adrenaline	18900	2.7	–	4320	2.2	–	20650	49	1.00
(-)Isoproterenol	2020	0.19	1.08	254	2.5	1.01	620	3.9	0.90
BRL37344	1750	112	1.30	1120	177	0.80	287	15	1.11
SR58611A	38500	12000	0.96	187	36	0.87	6640	25	1.23
SM11044	18100	190	1.50	4100	62	1.03	1300	84	0.98
β_3-AR agonists / β_1-, β_2-AR antagonists:									
Bucindolol	0.2	antagonist	–	0.1	antagonist	–	23	7.0	1.01
ICI201651	549	antagonist	–	2860	antagonist	–	85	20	1.14
CGP12177A	0.9	antagonist	–	4.0	antagonist	–	88	139	0.68
Pindolol	3.4	antagonist	–	2.3	antagonist	–	11	153	0.55
Nadolol	40	antagonist	–	14	antagonist	–	636	1120	0.80
β-AR antagonists:									
(-)Bupranolol	1.7	antagonist	–	0.4	antagonist	–	50	antagonist	–
ICI118551	120	antagonist	–	1.2	antagonist	–	257	antagonist	–
CGP20712A	1.5	antagonist	–	1800	antagonist	–	2300	antagonist	–
Selective β_3-AR antagonist:									
SR59230A*	–	–	–	–	–	–	~100[#]	antagonist	–

K_i – inhibition constant (binding competition); K_{act} – activation constant (adenylyl cyclase stimulation); IA – intrinsic activity of the agonist, relative to noradrenaline induced maximal cAMP stimulation; [#] – equilibrium dissociation constant for human colonic β_3-AR. All data are reported by N. Blin et al (41), except * – reported by F. De Ponti et al (42).

mulation and direct or competitive binding with β-AR ligand [^{125}I]-iodocyanopindolol. From these studies, the following properties of the β_3-AR were recognized: low affinity for conventional β-AR antagonists, including radioligands; low stereoselectivity indices for agonists and antagonists enantiomers; low affinity of reference agonists; high potency of a novel class of compounds initially described as potent activators of lipolysis and thermogenesis in WAT and BAT of rodents; partial agonist activity of several antagonists of β_1- and β_2-ARs (30).

Pharmacological studies of β_3-ARs have allowed classifying the ligands into following groups:

1. β-AR agonists, selective for β_3-AR;
2. β_3-AR agonists / β_1- and β_2-AR antagonists;
3. Nonselective β_1-, β_2-, β_3-AR antagonists;
4. Selective β_3-AR antagonists.

The pharmacological properties of β_3-AR are summarized and compared to those of β_1- and β_2-AR in Table 2.

Pathophysiological role

Each type of β-ARs is mainly expressed in certain tissues. β_1-ARs are predominant in the heart and are the target of β-AR antagonists. β_2-ARs are predominant in the respiratory system and are the target of β-AR agonists inducing bronchorelaxation. β_3-ARs are expressed primarily in adipose tissues and may be important in regulation of body weight. However, all three β-ARs are present in the human heart in not estimated proportion. Depending on the pathophysiological state (31) and the age (32) the density of β_1-ARs is reduced. In heart failure, increased sympathetic activity leads to down regulation of cardiac β_1- and β_2-ARs due to their phosphorylation by PKA and βARK (Table 1). In contrast, the density of β_3-ARs, which lack the sites for phosphorylation by both kinases, in left ventricle increases 2–3 times (27). In such circumstances the significance of β_3-ARs in regulation of heart function, particularly their I_{Ca} stimulatory properties, could greatly increase. On the other hand, the inhibitory effect of β_3-ARs in the ventricles could serve as protector from myocardial overload in conditions of increased sympathetic activity, since they are being activated with higher concentrations of physiological catecholamines than β_1- or β_2-ARs. Moreover, this cardiodepressant property could help in myocardial ischemia to reduce oxygen consumption and save the resources of high-energy phosphates.

Unfortunately, almost all, what we can say today about pathophysiological role of this receptor, is only a consideration. Selective agonists of β_3-AR are just in preclinical studies. The limitation for experimental studies is the absence of really selective antagonists for this receptor. However, the new findings concerning β_3-AR promise that coming decade will give many answers to the questions, which we can not resolve so far.

Putative β_4-adrenergic receptor

How to reconcile the contradictory reports about the inhibition of contraction force of human ventricular muscles and stimulation of I_{Ca} in human atrial myocytes by the same β_3-AR agonists? It seems, that the simplest explanation is that cardiodepressant effect is reached via β_3-ARs, but the stimulation of I_{Ca} is produced through activation of fourth β-adrenergic receptor (33, 34). It has been shown, that in mice lacking a functional β_3-AR gene (β_3-AR knock-out) non-conventional β_3-AR agonist CGP12177, having β_1- and β_2-AR antagonistic properties, still caused cardiostimulant effects that were not different from the effects in atria of wild-type mice (35). Evidence has also been provided for the existence of fourth β-AR in the human atrium, where it has been shown to be coupled to G_s-adenylyl cyclase system (36). In addition, earlier it has been shown, that expression of mRNA for β_3-AR in human atria is negligible (29). This can serve as an argument, that β_3-AR agonists stimulated I_{Ca} in human atrial myocytes, as mentioned above (23), not through β_3- but via putative fourth β-AR. The final answer could be given by the molecular cloning of β_4-AR. However, the absence of it led to new intriguing hypotheses, based on experimental evidences. Recently A. A. Konkar et al (37) have shown that aryloxypropanolamines, such as CGP12177 and LY362884, originally developed as β_3-AR agonists, can stimulate adenylyl cyclase activity through β_1-AR, expressed in CHO cells. Interestingly, both compounds exhibited a biphasic effect on β_1-AR. Low concentrations of either of them potently blocked isoproterenol-induced stimulation of β_1-AR, whereas higher concentrations of these compounds stimulated β_1-AR. These results suggest that catecholamines and aryloxypropanolamines interact with distinct active conformations of the β_1-AR: a state that is responsive to catecholamines and is blocked with high affinity by CGP12177 and LY362884, and a novel state that is activated by aryloxypropanolamines but is resistant to blockade by standard β-AR antagonists, such as propanolol. That means, that above described putative fourth β-AR is just propanolol resistant conformation of β_1-AR. In contrast, our own experiments, performed

on rat ventricular myocytes, predominantly expressing β_1-ARs, did not reveal any stimulating conformation of β_1-AR by aryloxypropanolamines (23). In the concentration range from 1 nM to 10 μM, CGP12177 had no effect on L-type calcium current, but with high affinity blocked the isoprenaline-induced stimulation of I_{Ca}, as it was supposed to act as β_1-/β_2-AR antagonist.

Another explanation of cardiodepressant effects of β_3-ARs recently was provided by R. F. Bosch et al (38). They found that in guinea pig ventricular myocytes BRL37344, a selective β_3-AR agonist, or isoprenaline in the presence of atenolol and ICI118551 to block the β_1- and β_2-ARs, inhibits I_{Ks} (while isoprenaline alone stimulates this current), modifying in this way the duration of action potential. Such an effect may partly explain the inhibitory action of β_3-AR on heart function in this species (39). Surprisingly, when KvLQT1/MinK channels, which underline I_{Ks} current, were heterologously coexpressed with the human β_3-AR subunit in Xenopus oocytes, isoprenaline increased I_{Ks} (40) indicating that the β_3-adrenergic receptor can change its signaling pathway from a stimulatory to an inhibitory one depending on the cellular context. In line with these experiments, the stimulation of β_3-ARs by BRL37344 was found to decrease the amplitude and action potential duration in human endomyocardial biopsies (22).

Thus, the signaling pathways mediated by β_3-AR agonists in human heart remain unclear and further studies are needed to address the precise role of cardiac β_3-AR in cardiac physiology and physiopathology.

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β_3-adrenerginiai receptoriai: struktūra ir funkcija

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Raktažodžiai: β_3-adrenerginis receptorius, struktūra, funkcija, farmakologija, širdis.

Santrauka. β-adrenerginiai receptoriai (β-AR) skirstomi į tris tipus: β_1-, β_2- ir β_3-AR. Širdyje dominuoja β_1-AR, β_2-AR – kvėpavimo sistemoje, β_3-AR – riebaliniuose audiniuose. Tačiau nuo tada, kai 1989 metais β_3-AR buvo klonuotas, daugybė biocheminių ir funkcinių tyrimų patvirtino jo egzistavimą daugelyje įvairių gyvūnų bei žmogaus audinių, iš jų ir širdyje. Skirtingai negu β_1- ir β_2- adrenerginiai receptoriai β_3-AR gali slopinti žmogaus širdies skilvelių susitraukimo jėgą, o tai yra nesuderinama su jo savybe stimuliuoti adenililciklazę. Taigi patologinėmis sąlygomis β_3-AR vaidmuo, reguliuojant širdies veiklą, gali būti labai svarbus ir iki šiol labai mažai ištirtas. Šiame apžvalginiame straipsnyje trumpai apibūdinamos struktūrinės bei funkcinės β_3-adrenerginių receptorių savybės.

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