

REVIEW

Cardiac Sigma Receptors – An Update

T. STRACINA¹, M. NOVAKOVA¹¹Department of Physiology, Faculty of Medicine, Masaryk University, Brno, Czech Republic

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Summary

More than four decades passed since sigma receptors were first mentioned. Since then, existence of at least two receptor subtypes and their tissue distributions have been proposed. Nowadays, it is clear, that sigma receptors are unique ubiquitous proteins with pluripotent function, which can interact with so many different classes of proteins. As the endoplasmic resident proteins, they work as molecular chaperones – accompany various proteins during their folding, ensure trafficking of the matured proteins between cellular organelles and regulate their functions. In the heart, sigma receptor type 1 is more dominant. Cardiac sigma 1 receptors regulate response to endoplasmic reticulum stress, modulates calcium signaling in cardiomyocyte and can affect function of voltage-gated ion channels. They contributed in pathophysiology of cardiac hypertrophy, heart failure and many other cardiovascular disorders. Therefore, sigma receptors are potential novel targets for specific treatment of cardiovascular diseases.

Key words

Sigma receptor • Heart • Chaperone • Endoplasmic reticulum stress

Corresponding author

M. Novakova, Department of Physiology, Faculty of Medicine, Masaryk University, Kamenice 5, 625 00 Brno, Czech Republic.
E-mail: majka@med.muni.cz

A brief history – from an enigmatic binding site in the brain to ubiquitous receptor and molecular chaperone

Sigma receptors were first reported in the central nervous system by Martin and co-workers in 1976

(Martin *et al.* 1976). The authors believed that sigma receptor represents an opioid receptor subtype, which mediates psychomimetic and stimulatory behavioral effects of N-allylnormetazocine (SKF-10047) in chronic spinal dog. Subsequent binding studies in guinea pig and rat showed that binding profile of sigma receptor differs from any other known subtype of opioid receptor as well as other receptor classes (Su 1982, Tam 1983). Therefore, the sigma receptor was defined as novel receptor type (Su 1982).

Two subtypes of sigma receptor

Further research led to differentiation among at least two subtypes of sigma receptors. Based on their diverse ligand selectivity and stereospecificity, association with signal transduction mechanism and/or enzyme function, tissue distribution, subcellular localization, and apparent molecular mass, existence of sigma receptor type 1 (sigma 1 receptor) and type 2 (sigma 2 receptor) has been proposed and confirmed (Hellewell and Bowen 1990, Quirion *et al.* 1992, Torrence-Campbell and Bowen 1996). The sigma receptor originally described by Su (1982) was recognized as the sigma 1 receptor (Hellewell and Bowen 1990).

Since the molecular structure of the sigma 1 receptor was not known till 1996, various sigma ligands were employed in the studies of distribution and cellular functions of sigma receptors. Selective ligands (e.g. 1,3-di(2-tolyl) guanidine (DTG), SA 4503, (±)-PPCC, BD 1047) as well as clinically used drugs which exert affinity to sigma receptors (e.g. haloperidol, fluvoxamine, sertraline, amitriptyline) have played crucial role in the research. Based on their different binding profiles, sigma receptors were classified as

follows (Quirion *et al.* 1992): sigma 1 receptors exert high affinity to dextromethorphan, (+)-pentazocine, (+)-NANM, and carbetapentane; sigma 2 receptors bind these compounds with low affinity. Haloperidol and DTG, two mostly used sigma ligands in 1980s and 1990s, show affinity for both sigma subtypes (Kushner and Zukin 1994). Moreover, sigma subtypes exert different stereoselectivity for benzomorphans: sigma 1 receptor exhibits higher affinity for dextrorotatory benzomorphans and, in contrast, sigma 2 receptor exhibits equal or higher affinity for the levorotatory benzomorphans (Hellewell and Bowen 1990).

Sigma 1 receptor – molecular structure

Research on cellular localization(s) and function(s) of sigma receptors was significantly facilitated by description of molecular structure of the sigma 1 receptor. The sigma 1 receptor was first purified and cloned from guinea pig liver in 1996 (Hanner *et al.* 1996). The amino acid sequence was structurally unrelated to then known mammalian proteins (Hanner *et al.* 1996). Subsequently, the receptor was cloned from various tissues, both animal and human ones (Kekuda *et al.* 1996, Seth, Leibach, and Ganapathy 1997, Prasad *et al.* 1998, Seth *et al.* 1998, Mei and Pasternak 2001). Mei and Pasternak (2001) reported that predicted structure of rat sigma 1 receptor is highly homologous with murine (93.3 %), guinea pig (93.7 %) and human (96.0 %) sigma 1 receptor. Many structural models of the receptor were postulated (Su and Hayashi 2003, Laurini *et al.* 2011, Schmidt *et al.* 2016, Laurini *et al.* 2017). Most of them described sigma 1 receptor as membrane receptor with two transmembrane domains (Laurini *et al.* 2017). It was reported that ligand-binding region of sigma 1 receptor is similar to an active site of cupin family proteins, oligomeric bacterial and fungal enzymes, and plant seed storage proteins (Hanner *et al.* 1996, Schmidt *et al.* 2016). One of them is the yeast sterol C8-C7 isomerase, enzyme essential for ergosterol synthesis and cell proliferation (Moebius *et al.* 1997). In spite of structural homology, sigma 1 receptor binding region exerts no enzymatic activity. In addition, Mishra and co-workers reported, that sigma 1 receptor can be found either in monomeric or oligomeric forms in living cells in the presence and/or absence of various ligands (Mishra *et al.* 2015).

Recently, evidence of the full crystal structure was reported (Schmidt *et al.* 2016). According to X-ray data, the solid-state structure of the sigma 1 receptor reveals a trimeric organization with a single

transmembrane domain for each protomer (Schmidt *et al.* 2016). The cytosolic domain of each of the three protomers contains a β -barrel fold with the ligand-binding region at its center. Such structure is substantially different from the two-transmembrane domain model proposed on the basis of biochemical, molecular, *in silico*, and NMR data (Laurini *et al.* 2011, Laurini *et al.* 2017). As Laurini *et al.* (2017) postulated, differences may arise from various factors, such as structure determination methods and experimental conditions used. Moreover, the protein may adopt different structures under solid and solution states. More studies are needed to prove structural details of sigma 1 receptor protein.

Sigma 1 receptor – ligands

The classification of sigma ligands as agonists and antagonists is mainly based on animal studies. Agonists are defined as ligands that induce hyperlocomotion or other physiological responses through binding to sigma receptor, while antagonists are ligands that block or blunt this response (Martin *et al.* 1976, Schmidt *et al.* 2016). Various endogenous substances, such as progesterone, dihydroepiandrosterone, sphingosine and its derivatives, and *N,N*-dimethyltryptamine, exert certain affinity to sigma 1 receptor (Patterson *et al.* 1994). Although these substances can bind to sigma 1 receptor under experimental conditions, up to now none of them has been reported to act as endogenous sigma 1 ligand. Nine years ago, Fontanilla *et al.* (2009) indicated *N,N*-dimethyltryptamine as endogenous sigma 1 regulator. However, relevant doubts were recently cast on this suggestion (Nichols 2018) and the endogenous ligand still seems to be undiscovered. The precise structure of the ligand-binding region may shed light on this problem.

Sigma 1 receptor – localization and function

The sigma 1 receptor is involved in a wide range of physiological functions and pathophysiological processes in nervous system, such as neurodegenerative diseases, neuropathic pain, depression and cocaine addiction (Su *et al.* 2016). It has been localized in several regions of the central nervous system as well as in peripheral nervous system and numerous non-neural tissues. According to immunohistochemical studies in rat, high density of sigma 1 receptor was found in olfactory bulb, several hypothalamic nuclei, septum, central grey, certain motor nuclei of the hindbrain, and dorsal horn of spinal cord (Alonso *et al.* 2000, Bouchard and Quirion

1997). Among non-neural tissues, high density of the sigma 1 receptor was found in the immune, endocrine and reproductive systems and in the digestive tract (Wolfe *et al.* 1989, Hellewell *et al.* 1994), as well as in the heart (Ela *et al.* 1994, Novakova *et al.* 1995).

Intracellular localization of sigma 1 receptor has been intensively studied. Various localizations were reported among different cell types and various stages of cell differentiation. The primary region, where sigma 1 receptor is located, is endoplasmic reticulum membrane associated with mitochondria (Hayashi and Su 2007). Sigma 1 receptor acts here as molecular chaperone. By interaction with various proteins, it promotes survival of the cell by regulation of calcium signaling, enhancing the endoplasmic reticulum signaling to nucleus and attenuating response to oxidative stress (Boehning *et al.* 2003, Mori *et al.* 2013, Su *et al.* 2016). Nevertheless, translocation of sigma 1 receptor was reported repeatedly after sigma ligand stimulation or cellular stress (Hayashi and Su 2007, Mavlyutov and Ruoho 2007). Hayashi and Su proved translocation from lipid-enriched sites of the endoplasmic reticulum to the endoplasmic reticulum-associated reticular network upon stimulation by psychoactive drugs in NG108-15 cells (Hayashi and Su 2003). Johannessen and co-workers reported inhibition of sodium voltage-gated channel Na_v1.5 by sigma 1 ligands in mouse cardiomyocytes (Johannessen *et al.* 2009). Voltage-gated sodium channels are resident plasma membrane channels and such inhibition suggested the co-operation of sodium channel with sigma 1 receptor on plasma membrane. Translocation to plasma membrane was proved repeatedly in neuronal tissue and was previously reviewed (Su *et al.* 2010). Recently, translocation to nuclear envelope was reported after haloperidol treatment in differentiated NG-108 cells (Kubickova *et al.* 2018). Mavlyutov and co-authors determined precise intracellular localization of sigma 1 receptor in retinal neurons using electron microscopy (Mavlyutov *et al.* 2015). In photoreceptor cells, predominant presence of sigma 1 receptor in the nuclear envelope and in the subsurface endoplasmic reticulum cisternae was found (Mavlyutov *et al.* 2015). Authors suggested mechanism of sigma 1 receptor action possibly different from that determined in other cell types.

It is generally accepted that the sigma 1 receptor works as a ubiquitous pluripotent modulator in the mammalian cells and interacts with many proteins (e.g. receptors, ion channels, enzymes, chromatin-remodeling factors) in various intracellular locations (Su *et al.* 2016).

However, different methodological approaches were employed in abovementioned studies. Therefore, many questions concerning sigma 1 receptor localization and functioning remain unanswered.

Sigma 1 receptor in the heart

Contrary to other tissues, the first report on the presence of sigma receptors in the heart muscle was focused on sigma 2 type (Dumont and Lemaire 1991). Based on specific binding activity of the prototypic sigma receptor ligand [3H]-DTG, Dumont and Lemaire concluded that sigma 2 receptors are present on the rat heart membrane preparations. As reported later, the majority of sigma receptors (75 %) in the rat heart is represented by sigma 1 receptors (Novakova *et al.* 1995). Therefore, numerous studies were focused on cardiac sigma 1 receptor in various experimental models.

Sigma 1 receptor gene and regulation of its expression

Sigma 1 receptor is coded by SIGMAR1 gene (GeneCards[®]: Human Gene Database). In mouse, it was recognized on chromosome 4, in rat on chromosome 5. In human, the gene is located on the shorter arm of chromosome 9. Polymorphisms and mutations in SIGMAR1 in human population were identified and their association with neurodegenerative and psychiatric diseases have been reported (Luty *et al.* 2010, Al-Saif, Al-Mohanna, and Bohlega 2011, Huang *et al.* 2011, Mandelli *et al.* 2017). Up today, there is no evidence of association of SIGMAR1 variants with cardiovascular disorders.

In human genome, more than 20 regulatory regions for SIGMAR1 gene were identified. Only a few regulating mechanisms of SIGMAR1 expression are clear yet. Nevertheless, numerous factors, which affect expression of sigma 1 receptor in heart, have been reported in various models. Novakova *et al.* (2007) found that sigma 1 receptors in rat heart are upregulated by aging as well as by various stress factors, such as immobilization and cold environment. In mice, upregulation was caused by hypoxia (Novakova *et al.* 2007). Sigma 1 receptors are upregulated also by long-term exposure to prototypic sigma ligand haloperidol in heart of rat (Novakova *et al.* 2010) and guinea pig (Stracina *et al.* 2015). Specific regulatory mechanisms of these phenomena have not been identified yet.

The first evidence of a specific transcriptional factor regulating sigma 1 expression was brought by

Mitsuda and coworkers (Mitsuda *et al.* 2011). They reported that sigma 1 receptor can be upregulated by escalated endoplasmic reticulum stress by the PERK/ATF4 pathway. Activation of the pathway leads to amelioration of cell death signaling. Recently, key role of miRNA-297 in sigma 1 expression regulation during cardiomyocyte hypertrophy was reported (Bao *et al.* 2017). Regulation by other microRNAs has been also proposed (Su *et al.* 2016).

Cellular function of sigma 1 receptor

Sigma 1 receptors are expressed in atrial and

ventricular cardiomyocytes of both rat and guinea pig (Novakova *et al.* 2010, Stracina *et al.* 2015) as well as in intracardiac neurons (Zhang and Cuevas 2005). Function of the sigma 1 receptor, as a molecular chaperone, is based on interaction with various proteins. Due to intensive research of sigma receptors in neuronal system, a lot of protein-protein interactions have been identified in neuronal models (Pabba 2013, Su *et al.* 2016). Based on direct or indirect evidence, many of them can be applied in cardiomyocytes, too; in others, we can presume that the interactions are analogous. Key protein interactions are shown in Figure 1.

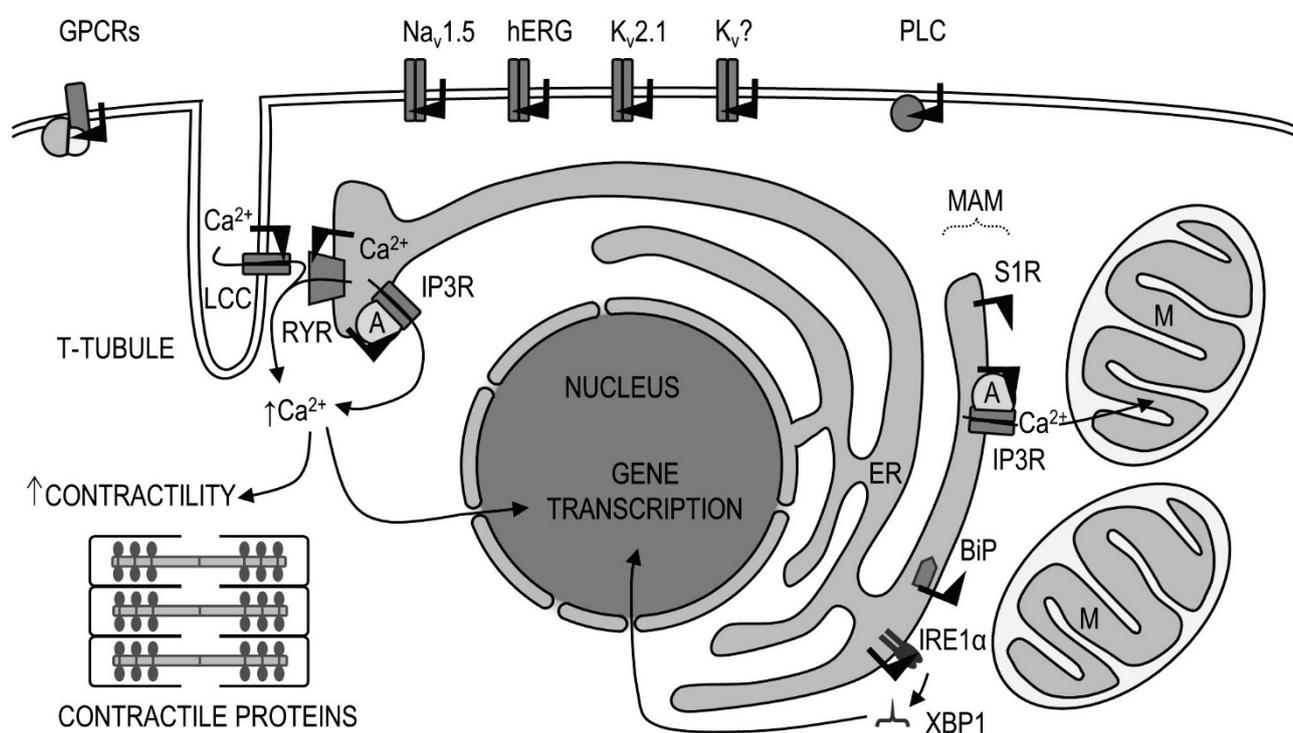


Fig. 1. The Sigma 1 Receptor Protein Interactions in Cardiomyocyte. Sigma 1 receptors are represented by black flags. They are primarily located on mitochondrion-associated endoplasmic reticulum membrane (MAM). Only key interactions related to the text are presented. All presented interactions were determined experimentally. For more information see corresponding chapters in the text. A – ankyrin B; BiP – binding immunoglobulin protein; Ca^{2+} – calcium ions; ER – endoplasmic reticulum; GPCRs – G protein-coupled receptors; hERG – human ether-a-go-go-related gene potassium voltage-gated channel; IP3R – inositol 1,4,5-trisphosphate receptor; IRE1 α – inositol requiring protein 1 α ; $\text{K}_v?$ – potassium voltage-gated channel ensuring transient outward potassium current; $\text{K}_v2.1$ – $\text{K}_v2.1$ potassium voltage-gated channel; LCC – L-type calcium voltage-gated channel; M – mitochondria; MAM – mitochondrion-associated endoplasmic reticulum membrane; $\text{Na}_v1.5$ – $\text{Na}_v1.5$ sodium voltage-gated channel; PLC – phospholipase C; RYR – ryanodine receptor; S1R – sigma 1 receptor in trimeric form; XBP1 – spliced X-box binding protein 1.

Interaction with endoplasmic reticulum membrane proteins – a modulation of calcium handling and dealing with endoplasmic reticulum stress

The endoplasmic reticulum plays an essential role in calcium handling, protein synthesis and folding, and lipid synthesis in the cell (Glembotski 2012). The endoplasmic reticulum calcium pool is important for contraction of cardiomyocyte as well as for signaling

within the cell. The first studies about effect of sigma ligands on the cardiomyocytes reported increased calcium influx which led to increased contractility (Ela *et al.* 1994, Novakova *et al.* 1995). It was suggested that sigma 1 receptor directly affects calcium channels or modulates potassium channels on plasma membrane (Ela *et al.* 1994). Subsequent study uncovered that sigma 1 ligands increase inositol 1,4,5-trisphosphate (IP3)

production in cardiomyocytes and observed increase of contractility depends on calcium stores in endoplasmic reticulum (Novakova *et al.* 1998). IP3 activates its receptor, a transmembrane glycoprotein complex primarily located on endoplasmic reticulum membrane. After the activation, IP3 receptor releases calcium from endoplasmic reticulum (Fig. 1). Three types of IP3 receptors affect cardiac function to various extent (Kockskämper *et al.* 2008). IP3 receptors type 1 and 2 represent important intracellular calcium channels in cardiomyocytes (Garcia and Boehning 2017). An overexpression of IP3 receptor types 1 and 2 were reported in rat and guinea pig heart after long-term exposure to sigma ligand haloperidol (Novakova *et al.* 2010, Stracina *et al.* 2015).

The chaperone activity of sigma 1 receptor on IP3 receptor, first described on Chinese hamster ovary cells with transfected receptors (Hayashi and Su 2007), was proven in cardiomyocytes (Tagashira *et al.* 2013). Besides IP3 receptors, an interaction with other important intracellular calcium channel, ryanodine receptor type 2, was discovered in cardiomyocytes. Tagashira *et al.* showed that sigma 1 receptors are associated both with ryanodine receptors type 2 and IP3 receptors type 2 in cardiomyocyte endoplasmic reticulum membrane (Tagashira *et al.* 2013). Sigma ligand pentazocine suppressed ryanodine receptor mediated calcium release from endoplasmic reticulum, which consequently led to decreased contraction force. Sigma 1 receptor stimulation also promotes mitochondrial calcium transport through IP3 receptor type 2 (Fig. 1) and in turn ATP production (Tagashira *et al.* 2013).

Cross-talk between endoplasmic reticulum and mitochondrion is important for maintaining homeostasis in both organelles. Impairment of endoplasmic reticulum luminal homeostasis leads to misfolding or unfolding of proteins. An accumulation of unfolded proteins is known as endoplasmic reticulum stress (Glembotski 2007). Protein synthesis and folding are controlled by endoplasmic reticulum protein quality control mechanisms and accumulation of unfolded proteins is sensed by endoplasmic reticulum stress sensors: inositol requiring protein 1 α (IRE1 α), protein kinase RNA-like ER kinase (PERK) and transcriptional factor 6 (ATF6) (Liu *et al.* 2016). In these processes, endoplasmic reticulum resident proteins take important part. Endoplasmic reticulum stress activates a complex signaling pathway to deal with the misfolded and unfolded proteins, which is referred as the unfolded

protein response. The rate of general translation is reduced and the expression of endoplasmic reticulum resident protein chaperones and protein foldases is increased to restore homeostasis. However, if the unfolded protein response is unsuccessful, endoplasmic reticulum stress causes cell dysfunction and apoptotic pathways are activated (Biala and Kirshenbaum 2014). Recently, potential function of sigma 1 receptor in regulating normal mitochondrial organization and size in the heart was reported in sigma 1 receptor knockout mouse model (Abdullah *et al.* 2018).

Sigma 1 receptor, as the endoplasmic reticulum resident protein, has been found to promote cellular survival by regulating specific endoplasmic reticulum stress sensors at the mitochondria-associated membrane region under endoplasmic reticulum stress in various cellular models (Hayashi and Su 2001, Hayashi and Su 2007, Wu and Bowen 2008, Mitsuda *et al.* 2011, Mori *et al.* 2013). Reported sigma 1 receptor dependent protective signaling pathways significantly differ in various cell types. Recently, sigma 1 receptor was reported as an essential component of the unfolded protein response pathway eliciting cellular protection in cardiomyocytes (Alam *et al.* 2017). Alam *et al.* (2017) described that sigma 1 receptor regulates C/EBP-homologous protein expression in association with activation of the inositol requiring kinase 1 α and spliced X-box binding protein 1 (IRE1 α /XBP1) pathway (Fig. 1). The IRE1 α /XBP1 pathway is the most conserved branch of the unfolded protein response in mammals and is important for cardiomyocyte viability and contractile function (Wang *et al.* 2014).

Numerous implications may be proposed from currently known sigma 1 receptor functions on endoplasmic reticulum membrane. However, there are a lot of unanswered questions. The answers may bring some new insights into endoplasmic reticulum and mitochondrion coordination and consequently into pathophysiology of many heart diseases.

Interaction with voltage-gated ion channels – a modulation of action potential of cardiomyocytes

Generally, three main groups of voltage-gated ion channels are present in working cardiomyocytes: sodium voltage-gated channels conduct sodium current, responsible for membrane depolarization; calcium voltage-gated channels conduct calcium current, which contributes to the plateau phase of action potential; and potassium voltage-gated channels conducting potassium

currents, which ensures returning the depolarized membrane to a resting state. There is direct or indirect evidence, that sigma 1 receptor modulates all main ion currents in cardiomyocytes.

Inhibitory effect of haloperidol on activated sodium current was reported in human atrial cardiomyocytes and in rat ventricular cardiomyocytes (Crumb *et al.* 2006, Tarabova *et al.* 2009). Johannessen *et al.* (2009) described modulation of Na_v1.5 channels by sigma 1 receptors in. They showed that level of Na_v1.5 channel inhibition by selective sigma 1 ligands depends on number of sigma 1 receptors on plasma membrane, however non-specific ligands, such as haloperidol, inhibit Na_v1.5 channel also on cells with no sigma 1 receptors. As a possible explanation of above result, direct effect of non-selective ligands on ion channels as well as modulation *via* sigma 2 receptors were proposed (Johannessen *et al.* 2009). Modulation of Na_v1.5 channels by sigma ligands can be inhibited by progesterone (Johannessen *et al.* 2011). The sigma 1 receptor has been reported to modulate sodium channels Na_v1.2, Na_v1.4 and Na_v1.5 also in non-cardiac cells (Balasuriya *et al.* 2012, Gao *et al.* 2012).

Effect on calcium current was reported by Ela *et al.* (1994) who described increased influx of calcium into the neonatal rat cardiomyocyte after sigma 1 receptor stimulation. Twelve years after, sigma 1 ligand haloperidol was reported as mild to moderate blocker of the L-type calcium channel (Tarabova *et al.* 2009). It was proven that inhibitory effect is independent on channel splice variant (cardiac or vascular). The modulation of calcium current by sigma 1 receptor was also reported in non-cardiac cells (Brent *et al.* 1996, Tchedre *et al.* 2008). In retinal ganglion cells, direct interaction of L-type calcium channel with sigma 1 receptor was proven by coimmunoprecipitation assay (Tchedre *et al.* 2008).

Potassium channels are the most diverse group of voltage-gated channels (Perney and Kaczmarek 1991). Potassium repolarizing current on cardiomyocytes consists of several components. In rat ventricular cardiomyocytes, haloperidol was reported as an effective inhibitor of one of them (Bebarova *et al.* 2006). Haloperidol inhibits transient outward potassium current (I_{to}) and significantly decelerates its recovery. Based on whole-cell patch-clamp recordings, direct modulation of potassium channels by sigma 1 receptor was suggested in isolated intracardial neurons (Zhang and Cuevas 2005). In dose-dependent manner, sigma ligands reversibly block delayed outward rectifying potassium channels,

increase conductance of calcium-sensitive potassium channels and inhibit M-current.

The relationship between the sigma 1 receptor and hERG (human ether-a-go-go-related gene) potassium channel has been studied intensively. The hERG channels are responsible for the rapid component of delayed rectifier current I_{Kr}. Haloperidol was reported to block the hERG channels expressed in *Xenopus* oocytes (Suessbrich *et al.* 1997) and in human embryonic kidney cells (HEK 293) (Martin *et al.* 2004, Katchman *et al.* 2006). In the leukemic K562 cell line, the regulating function of sigma 1 receptors on hERG expression was clarified (Crottès *et al.* 2011). The sigma 1 receptor modulates the hERG current density in the presence of sigma ligands. However, the direct interaction between sigma 1 receptor and hERG in the plasma membrane is not sigma 1 ligand dependent, it is reduced by cholesterol depletion. Coimmunoprecipitation study proposed that sigma 1 receptors located in lipid rafts (Balasuriya *et al.* 2014) potentiate the hERG subunit's translocation from endoplasmic reticulum to Golgi apparatus (Crottès *et al.* 2011). Altogether, sigma 1 receptor binds to hERG channel in endoplasmic reticulum and facilitates hERG maturation and trafficking. Su *et al.* (2016) suggested that sigma 1 receptor might exert chaperoning activities in endoplasmic reticulum to facilitate proper protein sorting to their final destinations. However, such relationship of sigma 1 receptor with other proteins (except of hERG) has not been proven yet.

The effect of many clinically used sigma ligands on cardiac action potential and electrocardiogram parameters was observed in various experimental models. Besides used experimental model and tested ligand, the studies usually vary in dosage and route of administration. In clinical studies, patients are usually treated by more than one drug and drugs interactions may make interpretation of obtained results more difficult. Moreover, sigma 1 ligands may affect various ion channels as well as various receptor systems in the same time. Also, direct action of the ligand on ion channel should be taken in consideration. Potential receptor-independent inhibition of the K_v2.1 channel by sigma ligands was recently reported (Liu *et al.* 2017). In sum, the reported effects of sigma 1 ligands on ion channels seem to be inconsistent and most of the specific mechanisms of sigma 1 receptor interactions with ion channels are unclear.

Other protein interactions – another pieces of incomplete mosaic

It may be expected that sigma 1 receptor interacts – besides abovementioned – with numerous other proteins in cardiomyocytes. Among others, interaction with opioid receptors, NMDA receptors and dopamine receptors has been reported in neuronal models (Mei and Pasternak 2002, Navarro *et al.* 2010, Balasuriya *et al.* 2013). However, action of these receptor systems in the heart is not fully understood and only indirect evidence of interaction with cardiac sigma 1 receptor has been reported and the mosaic of cardiac sigma 1 receptor actions stays incomplete.

Role of sigma 1 receptor in pathophysiology of cardiovascular diseases

Our current knowledge about physiological functions of cardiac sigma 1 receptors are still incomplete and their pathophysiological roles are largely unknown. Only a few studies have been focused on the expression and function of sigma 1 receptors in cardiovascular disorders. Recently, significant roles of sigma 1 receptors in cardiac hypertrophy and heart failure have been proposed. Moreover, many of clinically used sigma 1 ligands exert cardiovascular side effects.

Cardiac hypertrophy and heart failure

It is well known, that endoplasmic reticulum stress is important agent in pathophysiology of many cardiovascular diseases, such as hypertension, atherosclerosis, myocardial infarction, and cardiac hypertrophy which ultimately result in heart failure (Liu *et al.* 2016). Cardiac hypertrophy is caused by pressure/volume overload or overactivation of neurohumoral systems, such as the renin-angiotensin-aldosterone system. It is initiated as an adaptive response, but if the process is uncontrolled and prolonged, it may lead to heart failure and eventually to death (Shimizu and Minamino 2016). Moreover, increased myocardium mass may lead to decreased tolerance of heart to ischemia (Hlaváčová *et al.* 2017).

As discussed above, activation of sigma 1 receptors leads to amelioration of endoplasmic reticulum stress. Sigma 1 ligands may therefore protect the heart from hypertrophy. Cardioprotective role of the sigma 1 receptors was also reported after stimulation by dehydroepiandrosterone in ovariectomized rats, which leads to activation of the Akt-eNOS pathway (Bhuiyan and Fukunaga 2009). On the other hand, inhibition of Akt

pathway by endogenous oxidative stress may lead to autophagy of cardiomyocytes (Wang *et al.* 2018). In addition, exposure to sigma 1 antagonist haloperidol aggravates hypertrophy by impairment of mitochondrial calcium signaling in cardiomyocytes (Shinoda *et al.* 2016) and stimulation of sigma 1 receptors restores abnormal mitochondrial calcium mobilization and ATP production (Tagashira *et al.* 2013, Tagashira *et al.* 2014). Recently, miR-297 was proposed as a novel regulator of sigma 1 receptor in cardiomyocyte hypertrophy (Bao *et al.* 2017). Up-regulation of miR-297 increases the activation of XBP1 and ATF4 pathways *via* targeting sigma 1 receptor, which promotes cardiomyocyte hypertrophy. However, the precise mechanism by which sigma 1 receptor induces this action has not been described yet.

Cardiovascular adverse effects of clinically used sigma 1 ligands

Many sigma 1 ligands are used in clinical practice for treatment of various diseases (Table 1). Some of them exert cardiovascular side effects. The spectrum of the effects varies from frequent mild blood pressure change (hypotension or hypertension) to sporadic life-threatening ventricular arrhythmias, which may lead to sudden cardiac death.

It is out of scope of this review to pose all the sigma 1 ligands, in which cardiovascular adverse effects have been reported. Among all, cardiovascular side effects of the prototypic sigma 1 ligand haloperidol are the most controversial: haloperidol-induced QT prolongation is comparable to other antipsychotics; however, haloperidol treatment significantly increases a risk of ventricular arrhythmias and sudden cardiac death (Leonard *et al.* 2013, Leucht *et al.* 2013, Wu *et al.* 2015). In animal studies, reported effects of haloperidol seem to be consistent. Haloperidol provokes QT interval prolongation and cardiac arrhythmias, such as torsades de pointe. In isolated rat hearts, exposure to haloperidol leads to premature ventricular contractions. Incidence of arrhythmias was significantly lowered after repeated haloperidol administration, which suggest desensitization of sigma 1 receptor (Fialova *et al.* 2009). In rats, increased expression of sigma 1 receptor was detected in all heart chambers after long-term haloperidol administration (Novakova *et al.* 2010). QT prolongation and increase of sigma 1 receptor expression in cardiac atria were reported in guinea pigs after long-term haloperidol administration (Stracina *et al.* 2015). Expressions of IP3 receptor type 1 and 2 were also

increased in the atria only. Acute haloperidol exposure causes slowing of intraventricular conduction and lengthening of repolarization in anesthetized guinea pigs (Mortl *et al.* 2003).

Antipsychotic drug haloperidol is a nonselective ligand, which acts as a sigma 1 receptor antagonist as well as a dopamine D2 and D3 receptor antagonist (Hayashi and

Su 2004). Haloperidol can also interact with other receptor systems. Moreover, haloperidol exerts significant cytotoxicity (Raudenska *et al.* 2013). Altogether with considerable variability in experimental methods, dosage and route of administration in the studies, it is difficult to propose a role of sigma 1 receptors in the observed cardiovascular effects of haloperidol.

Table 1. Clinically used drugs with affinity to sigma 1 receptor.

Drug category	Sigma 1 ligand	References
<i>Analgesics</i>	Pentazocine	Zhang and Cuevas 2005
<i>Anesthetics</i>	Ketamine	Robson <i>et al.</i> 2012
<i>Anticonvulsants and Antiepileptic Agents</i>	Lamotrigine, Phenytoin	Cobos <i>et al.</i> 2005
<i>Antidepressants</i>	Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Opipramol, Sertraline	Hashimoto 2009, Albayrak and Hashimoto 2017
<i>Antidiarrheals</i>	Loperamide	Sánchez-Fernández <i>et al.</i> 2014
<i>Anti-Parkinson and Anti-Dementia Drugs</i>	Amantadine, Donepezil, Memantine	Peeters <i>et al.</i> 2004, Albayrak and Hashimoto 2017
<i>Antipsychotics</i>	Fluphenazine, Gevotroline, Haloperidol, Nemonapride, Perphenazine, Remoxipride, Risperidone, Trifluoperazine	Schuster <i>et al.</i> 1995
<i>Antitussive Agents</i>	Dextromethorphan, Dimemorphan, Pentoxyverine,	Nguyen <i>et al.</i> 2014
<i>Psychostimulants</i>	Methylphenidate	Zhang <i>et al.</i> 2012
<i>Psychoactive Substances</i>	Cocaine, Ibogaine, Methamphetamine, Phencyclidine	Navarro <i>et al.</i> 2013, Chao <i>et al.</i> 2017

Sigma 1 receptor as a cross-link between mental and cardiovascular disorders

Epidemiological studies have demonstrated a close relationship between depression and cardiovascular diseases (Trebatická *et al.* 2017). Cardiovascular diseases can lead to severe depression (Gottlieb *et al.* 2004). Among cardiovascular diseases, the strongest association with depression has been reported in ischemic heart disease and after myocardial infarction (Schleifer *et al.* 1989). Inversely, depression can lead to significant increase in the risk of developing heart failure and is independently associated with increased cardiovascular morbidity and mortality (Rumsfeld *et al.* 2003).

In 2012, Ito *et al.* suggested that decreased brain sigma 1 receptor expression contributes to the

relationship between heart failure and depression in a mouse model of pressure overload. As a part of link between depression and cardiovascular diseases, brain-derived neurotrophic factor (BDNF) was discussed as an important agent. It was shown that the BDNF-TrkB pathway plays a role in the pathophysiology of cardiovascular diseases as well as depression and interaction between sigma 1 receptor and the BDNF-TrkB pathway was discussed (Hashimoto 2013). Bhuyian *et al.* (2013) proposed a hypothesis of sigma 1 receptor mediated protective mechanism in cardiomyocyte, which may explain protective effect of selective serotonin uptake inhibitors on heart failure progression. In mouse model of myocardial infarction, decreased expression of brain sigma 1 receptor was reported (Ito *et al.* 2013). Brain sigma 1 receptor stimulation improves mental

disorder and cardiac function in mice after myocardial infarction. Recently, it was reported that heart failure-induced depression in mice is mediated by corticosteroids through reduced sigma 1 receptor expression in the brain (Shinoda *et al.* 2016).

Not only depression can affect cardiovascular functions. QT interval prolongation was reported in drug-free patients suffering from schizophrenia (Fujii *et al.* 2014). Authors suggested a role of potassium channels inhibition in both disorders. QT prolongation was also found in rat neurodevelopmental model of schizophrenia (Stracina *et al.* 2016). As the sigma 1 receptors are ubiquitous molecular regulators, their contribution to link between schizophrenia and QT prolongation may be based on their pluripotent chaperone activity. However, this issue needs further investigation.

Neurodegenerative diseases

Association of sigma 1 receptor with various neurodegenerative diseases (e.g. amyotrophic lateral sclerosis, Huntington's disease, Alzheimer disease, Parkinson disease) was intensively studied (Cai *et al.* 2017). During last decade, disease-causing mutations in sigma 1 receptor gene (SIGMAR1) were associated with juvenile amyotrophic lateral sclerosis (ALS) and juvenile distal hereditary motor neuropathy in humans (Al-Saif *et al.* 2011, Li *et al.* 2015). As Mavlyutov and co-authors reviewed, sigma 1 receptor knockout mouse did not develop ALS (Mavlyutov *et al.* 2015). However, sigma 1 receptor knockout in mouse SOD-1 model of ALS led to a faster onset of disease and decreased longevity (Mavlyutov *et al.* 2013). Recently, sensory and autonomic nervous system dysfunction in ALS was described (Nolano *et al.* 2017, Vucic 2017). Impaired neuronal regulation of cardiac function in ALS patients was reported previously (Dalla Vecchia *et al.* 2015). It is not clear, if such impaired regulation may lead to cardiovascular disease progression. In Huntington's disease, association of neurodegeneration and cardiac malfunction was proved (Critchley *et al.* 2018). However, possible role of sigma 1 receptor has not been studied in such consequences yet. The proper molecular mechanisms of neuro-cardio link in neurodegenerative diseases need to be uncovered.

Sigma 2 receptor

Sigma 2 receptor is one of the most poorly understood proteins in cell biology today. While sigma 2

receptor has not been cloned yet, its exact molecular structure is not known so far. It was suggested that the sigma 2 receptor is identical with the progesterone receptor membrane component 1 (Xu *et al.* 2011). However, Chu *et al.* (2015) reported that both these proteins are different binding sites derived from independent genes. According to binding studies, high density of sigma 2 receptors are present in cerebellum, motor cortex, substantia nigra, hippocampus (Bouchard and Quirion 1997), in lungs, liver, kidneys (Hellewell *et al.* 1994), and in cells with high proliferation rate, such as tumor cells (Xu *et al.* 2011). Because of overexpression in many types of tumors, sigma 2 receptors have been intensively researched in the field of tumor biology, cancer diagnostics and treatment (van Waarde *et al.* 2015). Radiolabeled sigma ligands have been developed and are used for diagnostic imaging using positron emission tomography and single photon emission computed tomography. Sigma 2 receptors have been also explored as a possible target for anticancer drug delivery. Moreover, cytotoxic and anticancer effects of sigma 2 ligands have been reported (Zeng *et al.* 2012). Nevertheless, specific functions of sigma 2 receptors in tumor as well as other cells stay unclear.

According to our best knowledge, there is only one relevant study dealing with sigma 2 receptor action in the heart. Monassier and co-workers reported that sigma 2 agonist inhibits inwardly rectifying potassium channels in the heart (Monassier *et al.* 2007).

Many studies have reported close and overlapping pharmacological and biochemical properties of sigma 1 and sigma 2 receptors. Therefore, sigma 2 receptors might also act as a molecular chaperones (Su *et al.* 2016). However, proper description of role of sigma 2 receptor needs further investigation.

Future perspectives

Although numerous studies have been focused on the effects of cardiac sigma 1 receptors, many pieces of the mosaic of their functions are missing. A major step forward to better understanding of cardiac sigma 1 receptor function would be the identification of the endogenous ligand(s) responsible for the action of sigma 1 receptors under physiological as well as pathological conditions. This step might be promoted by precise structural model of the receptor. Knowledge of the crystal protein structure opens new possibilities in design and preparation of novel highly specific sigma 1

ligands. Such ligands will help in research of new therapeutic strategies. In the heart disorders associated with protein misfolding, sigma 1 receptor-dependent activation of IRE1 α -XBP1s pathway may preserve myocyte viability and contractile function (Alam *et al.* 2017). In cardiac hypertrophy treatment, rescuing the decreased expression of sigma 1 receptor through miR-297 inhibition may be beneficial (Bao *et al.* 2017). And other perspectives will appear as the further investigation will shed new light onto the topic.

Conflict of Interest

There is no conflict of interest.

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