Heliyon 6 (2020) e04360

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

The effect of hypothalamic peptides, neurohormone C and proline-rich peptide-1on the Ca^{2+}-handling system in heartin pathophysiological conditions

Artashes G. Guevorkian *

Department of Biochemistry, Yerevan State Medical University after MkhitarHeratsi, 2 Koryun St., Yerevan 0025, Armenia

ARTICLE INFO

Keywords:
Cell biology
Metabolite
Biochemistry
Organ system
Pathophysiology
Calcium-depot proteins
Crush syndrome
Heart
Hypothalamic peptides
Ischemia-reperfusion
Isoproterenol
Pancreatitis

ABSTRACT

Atthe Institute of Biochemistry named after H. Buniatyan we discovered and studied hypothalamic peptides with coronary dilatory and antioxidant activities:neurohormone C (NC) and proline-rich peptide-1 (PRP-1). Both NC and PRP-1 exhibit cardioprotective effects, in part by restoring the calcium affinity for calcium-binding membrane proteins in cardiomyocytes. This affinity is diminished in the sarcoplasmic reticulum and mitochondriawith myocardial damage, heart failure, pancreatic necrosis and crush syndrome caused by isoproterenol. The peptides can also destroy the four detected toxic peptides and myocardial depressant factor, and protect against ischemia-reperfusion injury. Further studies of these peptides may be promising for the treatment of patients at high risk of cardiovascular disease, regardless of pathology.

1. Introduction

Cardiovascular diseases ultimately lead to heart failure (HF), characterized by metabolic derangement underlying hemodynamic changes and myocardial damage. Such changes develop in one third of patients with atrial fibrillation (AF) [1, 2]. HF and AF are the leading cause of morbidity and mortality worldwide affecting more than 30 million people [3, 4]. A decrease in coronary blood flow during HF correlates with an increase in certain neurohormones, atrial and cerebral natriuretic peptides and cytokine (IL-6) with vasodilating effect, probably involved in compensatory mechanisms, which are not effective enough [5]. Coronary dilatory hypothalamic peptides, discovered and studied at the Institute of Biochemistry after H. Bunyanyan (NAS RA) can be used to protect the heart muscle [6, 7]. These are the neurohormones K, C and G, glycopeptides produced by limited proteolysis of specific protein-hormonal complexes in magnocellular neurosecretory cells (n. paraventricularis and n. supraopticus) [6]. Neurohormone C (NC), containing two vasoconstrictor and four vasodilator fractions, can be anchored by heart proteins and regulate cardiac hemostasis in precardiac and auricular regions [7]. Proline-rich peptide-1 (PRP-1) (primary structure: AGAPEPAE-PAQPGVY, molecular weight: 1475.26 Da) was also found in endocrine cells of hypothalamus. It is a C-terminal fragment of neurophysin II, a product of cleavage of prepro-vazopressin-neurophysin II [8]. Both NC and PRP-1 are involved in: competitive inhibition of cAMP and cGMP phosphodiesterases, regulation of protein synthesis and degradation, suppression oxidative stress, preventing histopathological changes in heart [6, 8]. Our results indicate other heart protection mechanisms involving these peptides. Disruption of intracellular Ca^{2+} homeostasis is the main cause of contractile dysfunction and arrhythmias in failing myocardium. It is associated with pathological changes in the expression and activity of Ca^{2+}channel proteins and proteins providing Ca^{2+}-controlled cell function [9]. The understanding of molecular mechanisms of aberrant Ca^{2+} handling can serve as basis for the development of new approaches in innovative treatments of cardiovascular diseases [4, 10]. Here we summarize our work on modulatingCa^{2+}homeostasis via NC and PRP-1 in heart in various pathological conditions.

* Corresponding author.
E-mail address: artashes_72@rambler.ru.

https://doi.org/10.1016/j.heliyon.2020.e04360
Received 25 February 2020; Received in revised form 26 May 2020; Accepted 26 June 2020

1.1. The effect of hypothalamic peptides on isoproterenol-induced heart damage

Release of catecholamines into the blood is accompanied by an increase in their level in the rat myocardium, and leads to damage, which also develops after exposure to isoproterenol, a synthetic sympathomimetic, non-selective β-adrenoceptor agonist [11]. Isoproterenol is used in reproducible and well-characterized model of cardiac hypertrophy, since it increases the need for oxygen in myocardium, reduces effective coronary perfusion and has a harmful effect on heart, i.e. arrhythmias, loss of myocytes and fibrosis, with progression to HF [12]. We found that radioactively labeled isoproterenol is not evenly distributed, and pronounced radioactivity is detected in areas of greatest damage to cardiomyocytes, which leads to myocardial infarction (MI) (confirmed by electrocardiography, biomarkers, histopathological changes, etc.) [13]. Administration of NC restores the reduced protein synthesis in the outer and inner membranes and mitochondrial matrix of heart muscle cells, protects from isoproterenol-induced biochemical and histopathological changes in rat myocardium [14]. In addition, NC, as a vasodilator, can improve cardiac blood and lymph flow, reducing necrotic areas of the heart [15]. We found that isoproterenol-induced necrotic myocardial damage is accompanied by a loss of calcium-binding properties of cardiomyocyte proteins, especially in sarcoplasmic reticulum (SR), which is responsible for the storage of Ca^{2+} [16]. The loss of calcium affinity was determined in 5 acidic proteins (3 proteins with Mr 60–80 kDa and 2 proteins with Mr20-30 kDa), in cardiac calsequestrin2 (CASQ2, Mr 55 kDa), which is the only known protein with cyclic storage and delivery of calcium [17]. Isoproterenol does not affect the calcium-binding ability of Ca^{2+}-ATPase (Mr 100 kDa), but facilitates the binding of calcium to the 32 kDa membrane protein in SR, which usually does not have affinity for calcium ions, but acquires it as a result of transition from alkaline form to acidic form, determined by modeling of its tertiary structure with a specially designed program (software development) [13, 16]. It should be noted that the loss of calcium-binding ability of CASQ2 can cause significant damage, while upon binding Ca^{2+}, CASQ2 is able to polymerize and hold up to ~40 Ca^{2+} per CASQ2 polymer, maintaining a high content of SR Ca^{2+} and a relatively low content of free luminal Ca^{2+} [17]. It is of importance, because cardiomyocyte contraction is mediated by Ca^{2+}-induced Ca^{2+} release with participation of SR-localized ryanodine receptor 2 (RyR2), directly affected by luminal Ca^{2+} and indirectly by CSQ2, which is localized close to RyR2 channels and is involved in direct structural interaction with RyR2 [18,19]. Impairment of contractility, cardiac arrhythmias, and HF can be caused by impaired intracellular Ca^{2+}-handling, occurring mainly at the SR level and Ca^{2+}leakage through RyR2 channel, which contributes Ca^{2+}depletion in SR and depolarization of cardiomyocytes, triggering fatal arrhythmias [20].

Interestingly, we found that calcium binding ability is lost in the same SR proteins and mitochondrial proteins of cardiomyocytes after pancreatic necrosis and long-term muscle crush injury (crush syndrome, CS), which are also accompanied by heart damage and MI (see below). In these cases, the administration of therapeutic doses of NC can also protect the myocardium from damage, regardless of whether it is caused by isoproterenol or acute pancreatitis, and/or CS. Thus, NC can modulate calcium levels in mitochondria and SR in cardiomyocytes, restoring calcium affinity for calcium-binding proteins, especially CSQ2, and completely inhibiting the calcium binding capacity of 32 kDa membrane protein [13, 21]. It can be assumed that the beneficial effect of NC on cardiac output is probably related to its effect on the accumulation of intracellular calcium by Ca^{2+}-binding proteins involved in the regulation of Ca^{2+}release through RyR2, luminal Ca^{2+}concentrations due to interactions between CSQ2 and RyR2 transmitted via anchor proteins junctin and/or triadin [22].

Thus, NC can regulate the level of intracellular calcium, increasing its binding to proteins and preserving its pool in heart cells. The concentration of calcium serving as an inhibitor of cAMP and cGMP phosphodiesterases also increases, stimulating myocardial contractility and supporting cardiac function after heart attack, decompensated congestive heart failure, cardiogenic shock, etc. It should be noted that the advantage of phosphodiesterase inhibitors is the combination of positive inotropy with vasodilation, although their long-term use, increasing the calcium content, can lead to arrhythmias and sudden cardiac death [23]. These negative consequences can be prevented by using NC to lower calcium levels and increase the ability of cardiomyocyte proteins to bind calcium.

It is noteworthy that Ca^{2+} released from the stores of the sarcoplasmic/endoplasmic reticulum and extracellular pools of Ca^{2+} can accumulate in the cytosol and mitochondria of cardiomyocytes and lead to an overload of Ca^{2+} and, ultimately, to an opening of mitochondrial permeability transition pore followed by mitochondrial dysfunction, apoptosis and necrosis and death of heart cells [24]. Moreover, mitochondria are the main source of cellular production of reactive oxygen species (ROS), and the opening of mitochondrial permeability transition pore affects the mitochondrial ROS signaling [25]. The efflux of ROS from mitochondria of heart cells is dynamically regulated by Ca^{2+} and ADP, and can be used to develop approaches for prevention of HF [26]. NC can protect from deleterious mechanisms underlying heart damage and HF by modulating the level of Ca^{2+} in SR and mitochondria of cardiomyocytes.

1.2. The effect of hypothalamic peptides on heart damage following pancreatic necrosis

Acute pancreatitis (AP) is associated with a number of metabolic disorders, including hypocalcemia, which correlates with clinically significant changes in hemodynamics, associated cardiac damage and impaired myocardial contractility, also observed in AP models [27]. The exact mechanism of myocardial damage that develops in AP is still unclear, but in clinical practice it is necessary to identify AP patients with a high risk of cardiovascular disease in order to determine the treatment strategy [28]. Despite the differences in pathophysiology of AP between various animal models and humans, some common changes are observed: early activation of proteases, release of inflammatory mediators, enhanced permeability in vascular and epithelial tissues, apoptosis and necroptosis, abnormal calcium signaling in the acinar cells, etc. [29]. We used a rat model of AP induced by local hypothermia of pancreas, which is characterized by diffuse necrotic myocardial damage and myocardial infarction. We then studied the processes 3 h after the onset of AP associated with vascular necrosis (edematous hemorrhagic AP), 24 and 72 h after the onset of AP associated with hemorrhagic pancreatic necrosis, and 7, 14 and 21 days after the onset of AP associated with chronic pancreatitis, characterized by symptoms of sclerosis and lipomatosisof organs, respectively, corresponding to reparative, chronic, and chronic recurrent stages of pancreatitis [30, 31]. AP is accompanied by increased secretion of catecholamines in blood and elevated level of norepinephrine in heart, contributing to myocardial damage, similar to isoproterenol-induced HF and MI, resulting in 25–35% of mortality from AP [32].

At the necrotic stage of AP we observed a loss in the ability of cardiomyocyte membrane proteins to bind calcium in mitochondria and SR, including CSQ2, accompanied by compensatory binding of calcium to 32 kDa protein [13, 30, 31]. Calcium depletion and hypocalcemia cause a total destruction of cardiomyocyte SR that is much more common in patients with persistent organ failure in AP [33]. We have shown that NC can protect the heart muscle from damage, possibly due to the fact that it completely restores the affinity of calcium for calcium-binding proteins, especially at the end of the necrotic stage of AP, in addition to helping reduce amylase and trypsin levels and restore mast cell ability to regulate histamine levels which increase significantly in the pancreas and plasma of AP rats [13].

Surprisingly, the effective dose of PRP-1 (10^{-6} M) administered to rats intraperitoneally 24 and 48 h after the onset of experimental pancreatic necrosis, protected against heart damage, rapidly repairing

necrotic areas and calcium affinity for calcium-binding proteins in cardyomyocytes [34] (Figure 1). Although, both PRP-1 and NC can increase the incorporation of radioactive precursors into the proteins of cardiomyocytes, especially at the chronic recurrent stage, they do not influence the expression of calcium-binding proteins, the ability of which to bind calcium, can probably be restored by several mechanisms, regardless of synthesis de novo [6, 8, 13]. This is especially important because calcium plays a key role in converting edematous pancreatitis into necrotic pancreatitis [35]. Excess of calcium in cardiomyocytes may cause uncoupling of mitochondrial respiratory system and oxidative phosphorylation, leading to energy deficiency and impairment of myocardial contractility with a decrease in the strength of contractions and contracture formation [36].

Experimental AP is characterized not only by redox dysregulation and progression of ischemia and ion channel dysfunction, but also by the depressing effect of pancreatic toxins, which affect the cardiac contractility associated with diastolic myocardial dysfunction [37]. So, myocardial depressant factor (MDF, a toxic octapeptide, released into the blood from ischemic pancreas) can reduce myocardial contractility and cause damage to heart muscle in AP and various shocks [38]. An increase in MDF is accompanied with an increase in activity by 8–12 times of serum alpha-amylase, a marker of pancreatic dysfunction [13, 39]. Even a single injection of an effective dose of NC can reduce alpha-amylase activity by 80–85% and destroy MDF in blood and myocardium in the acute stage of AP (the first 3 h of pancreatic inflammation) [13, 21]. Moreover, an effective dose of PRP-1 has a similar effect to NC, suppressing both MDF and alpha-amylase in serum during pancreatic necrosis [35].

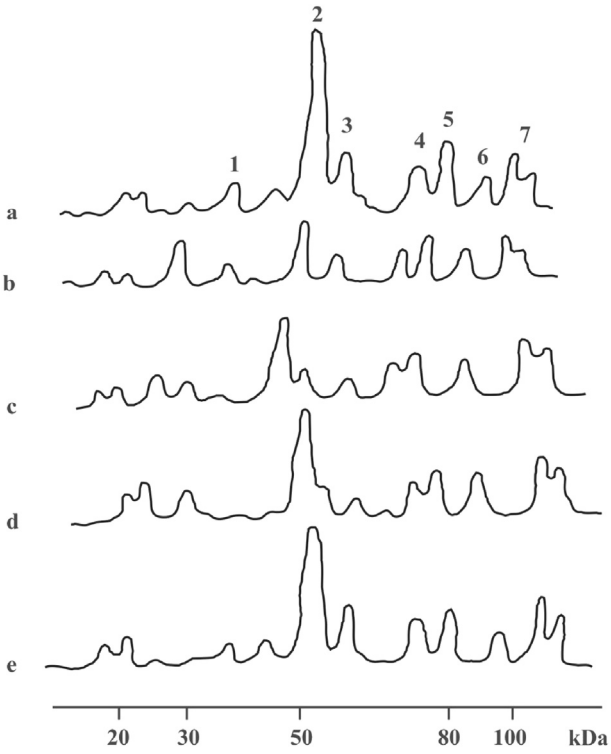

Figure 1. Effect of proline rich peptide-1 (PRP-1) on the calcium binding to the cardiomyocyte SR membrane proteins in the dynamics of *pancreatic necrosis (PN)*. 1, 3, 4, 5, 6 - acidic proteins; 2 - *calsequestrin*; 7 - two subunits of Ca2+-ATPase. (a) control; (b) early stage of PN - the 24th h after PN initiation; (c) reparative stage of PN - the 7th day of PN/PRP-1 treatment; (d) chronic stage of PN - the 14th day of PN/PRP-1 treatment; (e) chronic recurrent stage of PN - the 21st day of PN/PRP-1 treatment. *Notes.* $^{45}CaCl_2$ *was administered prior to initiation of PN and its binding was assessed after SDS-PAGE separation of the cardiomyocyte SR membrane proteins. PRP-1 was injected 24 and 48 h after the PN initiation.*

1.3. The effect of hypothalamic peptides on heart damage following crush syndrome

Myocardial damage is developed in our model of experimental muscle crush injury culminating in crush syndrome, which often leads to death due to extreme hypovolemic shock, hypocalcemia, hyperkalemia, metabolic acidosis, acute renal failure, etc. [40, 41]. Decompression is accompanied by restoring blood flow in the damaged limbs and by release of toxic compounds, including peptides, formed during anaerobic proteolysis of myoglobin, which penetrate into the blood, causing toxemia and systemic pathological changes [42]. The combination of peritoneal dialysis and massive fluid resuscitation is used to reduce lactic acidosis, serum levels of myoglobin and K^+ and myoglobin-derived toxic peptides, which protect against tissue damage increasing the survival of animals with long-term crush injuries [43]. We revealed four toxic peptides resulting from anaerobic cleavage of muscle myoglobin after long-term compression (more than 2–5 h), accompanied by ischemia and necrosis, resulting in MI and cardiac arrest [44]. One of these peptides is nonapeptide, which completely coincides with MDF except additional C-terminal L-arginine, which enhances penetration of the peptide into the tissues, in particular, the myocardium [45]. Clinical data also show an accumulation of MDF and nonapeptide in myocardium 24–48 h after AP and/or 24 h after decompression (reperfusion) in crush syndrome, and are associated with the death of people from myocardial infarction. MDF released during pancreatic necrosis and/or during decompression in crush syndrome cannot cross the blood-brain barrier, but penetrates the brain after N-terminal arginylation [35]. This “re-uptake”mechanism works also for other small peptides formed in crush syndrome, which, crossing the BBB in the form of "arginine proteins" cause neurodegenerative lesions in the nervous tissue [35, 46]. N-terminal arginylation of proteins occurs in all eukaryotic cells, and arginylated proteins are rapidly ubiquitinated and degraded by serine proteases, which can be inhibited by endogenous molecules with a molecular weight from one to five thousand [47].

Damage to cardiomyocytes is induced in crush syndrome in the early stage of decompression, but not during compression [48]. We found histomorphological changes in the heart in early period of decompression (2–48 h), which are accompanied by a decrease in calcium-binding ability of membrane proteins in SR of cardiomyocytes, including CSQ2, and these processes are strikingly similar to those observed with pancreatic necrosis [40]. An effective dose of PRP-1 (10^{-6} M), administered at the end of compression and after an hour, significantly ameliorates the heart damage caused by pancreatic necrosis and/or crush syndrome and protects against harmful processes, sufficiently modulating the calcium-binding properties of Ca^{2+}-binding proteins in the cardiomyocytes, and also destroying MDF, nonapeptide and other toxic peptides derived from myoglobin [44]. It can be assumed that there is a possible interaction between NC and PRP-1, since they use similar mechanisms of heart protection for the same pathologies, but this requires further study (Figure 2).

1.4. The effect of proline-rich peptide-1 on ischemia-reperfusion injury

Ischemic events in the heart are the most common cause of HF, and are characterized by insufficient blood supply, depletion of energy reserves, changes in membrane potential and fluidity, impaired homeostasis, etc., which can lead to MI and localized necrosis [49]. Reperfusion is the only treatment recommended to reduce infarct size after the acute MI, although ischemia-reperfusion (IR) can cause systemic inflammation and oxidative stress contributing to complicated situation in the clinic, such as cardiac arrest with successful reanimation, as well as ischemic events in brain and heart leading to highmortality [50, 51]. Bioactive peptides may have a protective effect against IR injury, they exhibit low toxicity and immunogenicity and are often more selective for their target than ordinary small organic molecules [52, 53]. Our findings show that PRP-1 can also be used to reduce biochemical and morphological changes

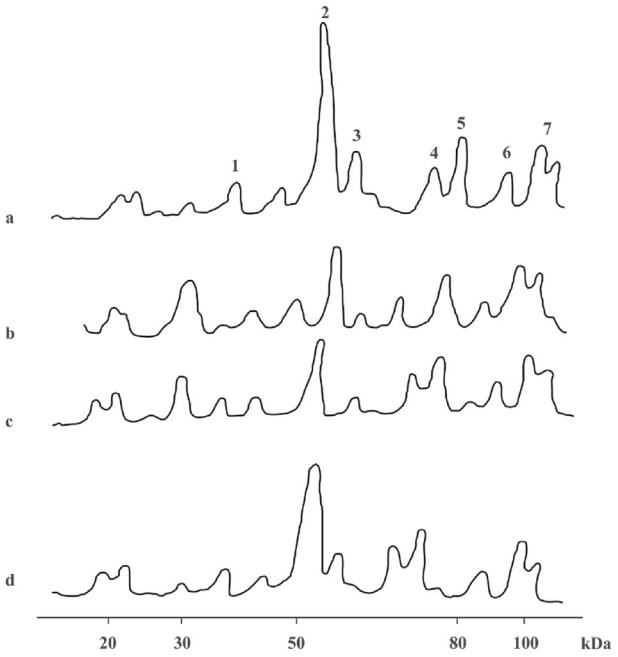

Figure 2. Effect of proline rich peptide-1 (PRP-1) on the calcium binding to the cardiomyocyte SR membrane proteins in the dynamics of crush syndrome. (a) control; (b) 2 h decompression; (c) 4 h decompression/PRP-1 treatment; (d) 48 h decompression/PRP-1 treatment. *Notes. prior to initiation of muscle crush injury $^{45}CaCl_2$ was administered and its binding assessed after SDS-PAGE separation of the cardiomyocyte SR membrane proteins. PRP-1 was injected immediately at the end of compression and an hour later.*

associated with pathological cardiac remodeling, including, development and progression of ventricular dysfunction, arrhythmias, as well as ventricular rupture and aneurysm, leading to death [54]. The diffuse and granular immunoreactivity of PRP-1 is determined in the muscle fiber network of sinoatrial node of human heart, and can affect cell death, inflammation and oxidative stress, regulating the expression of cytokines (TNF-α, IL-1 and IL-6), caspase activity, lipid peroxidation, energy metabolism, glucose utilization, calcium transport, etc. [8]. It is important, because oxidative stress (in particular, lipid peroxidation), inflammatory response, necrosis, apoptosis and other mentioned processes can contribute to the development of MI [55].

Open-chest model of myocardial IR injury is the most acceptable and suitable model for the reproduction of human MI and screening of pharmacological activity of various compounds [56, 57]. Using this model, we demonstrated that post-ischemic administration of an effective dose of PRP-1 significantly reduces *in vivo* necrotic area of myocardial infarction, caused by temporary occlusion of coronary artery in rats, as well as it improves cardiac hemodynamics and coronary circulation, by increasing the left ventricular ejection fraction, which is an indicator of efficiency of pumping into the systemic circulation [58]. PRP-1 significantly reduces the levels of superoxide anion and malondialdehyde in early period of reperfusion (up to 40–45% and 20–25%, respectively), as well as inhibits the activity of myeloperoxidase and the accumulation of neutrophils in heart tissues, attenuating inflammation and necrosis and restoring contractile activity of rat myocardium after 24 h reperfusion [59]. In addition, PRP-1 can activate catalase, stimulate energy metabolism and inhibit the activity of phospholipase A2 providing a membrane-stabilizing effect [8]. Of note, elevated levels of lipoprotein-associated phospholipase A2 are detected early after MI and are strongly and independently associated with mortality. Overall, PRP-1 inhibits oxidative and inflammatory processes that cause IR damage, and ultimately supports cardiac function, which indicates an urgent need for PRP-1 studies for its use in acute treatment of patients with MI.

2. Conclusion

Our findings show that hypothalamic peptides, neurohormone C and proline-rich peptide-1 can protect from heart failure by affecting the intracellular mechanisms of myocardial damage. They restore the impaired calcium-binding ability of membrane proteins in sarcoplasmic reticulum and mitochondria of cardiomyocytes and destroy toxic peptides, including myocardial depressant factor, thereby providing higher safety of cardiomyocytes, improving cardiac hemodynamics and coronary circulation, and protecting against myocardial infarction caused by isoproterenol, and/or pancreatic necrosis and crush syndrome. PRP-1 exerts also a dose-dependent cardioprotective effect against ischemia-reperfusion injury, suppressing oxidative stress, reducing inflammation and necrosis, and restoring myocardial contractility. Further studies of these peptides may be promising for the treatment of patients at high risk of cardiovascular disease, regardless of pathology.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

References

[1] Z.V. Wang, D.L. Li, J.A. Hill, Heart failure and loss of metabolic control, J. Cardiovasc. Pharmacol. 63 (2014) 302–313.
[2] G. Savarese, L.H. Lund, Global public health burden of heart failure, Card. Fail. Rev. 3 (2017) 7–11.
[3] S.S. Chugh, R. Havmoeller, K. Narayanan, et al., Worldwide epidemiology of atrial fibrillation: global burden of disease 2010 study, Circulation 129 (2014) 837–847.
[4] M. Luo, M.E. Anderson, Heart failure compendium. Mechanisms of altered $Ca^{2}+$ handling in heart failure, Circ. Res. 113 (2013) 690–708.
[5] I. Coma-Canella, A. Macías, N. Varo, et al., Neurohormones and cytokines in heart failure. Correlation with coronary flow reserve, Rev. Esp. Cardiol. 58 (2005) 1273–1277.
[6] A.A. Galoyan, Biochemistry of Novel Cardioactive Hormones and Immunomodulators of Functional System Neurosecretory Hypothalamus – Endocrine Heart, NaukaPublishers, Moscow, 1997.
[7] R.M. Srapionyan, A.A. Galoyan, Cardioactive protein-hormonal complexes of brain and heart, Neurochem. Res. 35 (2009) 912–916.
[8] A.A. Galoyan, Brain Neurosecretory Cytokines: Immune Response and Neuronal Survival, Kluwer Academic/Plenum Publishers, New York, 2004.
[9] N.C. Denham, C.M. Pearman, J.L. Caldwell, et al., Calcium in the pathophysiology of atrial fibrillation and heart failure, Front. Physiol. 9 (2018) 1380.
[10] A.T. Roe, M. Frisk, W.E. Louch, Targeting cardiomyocyte Ca^{2+} homeostasis in heart failure, Curr. Pharmaceut. Des. 21 (2015) 431–448.
[11] K.E. Kotchi, T. Weisselberg, P. Röhnert, et al., Nitric oxide inhibits isoprenaline-induced positive inotropic effects in normal, but not in hypertrophied rat heart, Naunyn-Schmiedeberg's Arch. Pharmacol. 357 (1998) 579–583.
[12] P. Krenek, J. Kmecova, D. Kucerova, et al., Isoproterenol-induced heart failure in rats is associated with nitric oxide-dependent functional alterations of cardiac function, Eur. J. Heart Fail. 11 (2009) 140–146.
[13] G.A. Kevorkian, Regulatory Effect of the Neurohormone "C" on Myocardial Metabolism in Isoproterenol Damage and Pancreatic Necrosis, Doctoral thesis, Yerevan, 1998.
[14] G.A. Kevorkian, A.S. Kanayan, L.H. Voskanian, et al., Synthesis of mitochondrila proteins following isoproterenol-induced damage in rat myocardium, Med. Chem. Issues. 35 (1989) 79–83.

[15] R.M. Srapionyan, Neurospecific protein-hormonal complexes, Physiol. Sci. Advances. 27 (1996) 21–31.
[16] A.G. Guevorkyan, Properties of new Ca^{2+}-binding protein from sarcoplasmic reticulum membranes during acute pancreatitis, Med. Sci. Arm. 38 (1998) 35–39.
[17] C. Manno, L.C. Figueroa, D. Gillespie, et al., Calsequestrin depolymerizes when calcium is depleted in sarcoplasmic reticulum of working muscle, Proc. Natl. Acad. Sci. USA 114 (2017) E638–E647.
[18] W. Chen, R. Wang, B. Chen, et al., The ryanodine receptor store-sensing gate controls Ca2+ waves and Ca2+-triggered arrhythmias, Nat. Med. 20 (2014) 184–192.
[19] A. Handhle, C.E. Ormonde, N.L. Thomas, et al., Calsequestrin interacts directly with the cardiac ryanodine receptor luminal domain, J. Cell Sci. 129 (2016) 3983–3988.
[20] R. MarksA, Calcium cycling proteins and heart failure: mechanisms and therapeutics, J. Clin. Invest. 123 (2013) 46–52.
[21] G.A. Kevorkian, A.A. Galoyan, A.S. Kanayan, et al., Acute pancreatitis and myocardium: the influence of neurohormone “C”, J. Appl. Cardiol. 5 (1995) 212–219.
[22] A.F. Dulhunty, E. Wium, L. Li, et al., Proteins within the intracellular calcium store determine cardiac RyR channel activity and cardiac output, Clin. Exp. Pharmacol. Physiol. 39 (2012) 477–484.
[23] T. Ahmad, P.E. Miller, M. McCullough, et al., Why has positive inotropy failed in chronic heart failure? Lessons from prior inotrope trials, Eur. J. Heart Fail. 21 (2019) 1064–1078.
[24] R. Harisseh, M. Abrial, P. Chiari, et al., A modified calcium retention capacity assay clarifies the rolesof extra-and intracellular calcium pools in mitochondrial permeability transition pore opening, J. Biol. Chem. (2019) jbc.RA119.009477.
[25] J.Q. Kwong, J.D. Molkentin, Physiological and pathological roles of mitochondrial permeability transition pore in heart, Cell Metabol. 21 (2015) 206–214.
[26] M. Kohlhaas, A.G. Nickel, C. Maack, Mitochondrial energetics and calcium coupling in heart, J. Physiol. 595 (2017) 3753–3763.
[27] P.A. Banks, T.L. Bollen, C. Dervenis, et al., Acute pancreatitis classification working group. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus, Gut 62 (2013) 102–111.
[28] R. Pezzilli, A. Barassi, G. Melzid’Eril, Cardiovascular alterations associated with acute pancreatitis, Pancreat. Disord. Ther. 2 (2012) 3, e118.
[29] F.S. Gorelick, M.M. Lerch, Do animal models of acute pancreatitis reproduce human disease? Cell. Mol. Gastroenterol. Hepatol. 4 (2017) 251–262.
[30] A.S. Kanayan, N.K. Permyakov, R.K. Khandanyan, et al., The combined pathology of the pancreas and heartmusclewith myocardial infarction and acute destructive pancreatitis, Arch. Pathol. 5 (1996) 56–61.
[31] N. Hazra, M. Gulliford, Evaluating pancreatitis in primary care: a population-based cohort study, Br. J. Gen. Pract. 64 (2014) e295–301.
[32] A.G. Guevorkian, Alterations in calcium-binding properties of sarcoplasmic reticulum membrane proteins folowing cardiac injury, Int. J. Biochem. Res. Rev. 3 (2014) 1–10.
[33] T. Peng, X. Peng, M. Huang, et al., Serum calcium as an indicator of persistent organ failure in acute pancreatitis, Am. J. Emerg. Med. 35 (2017) 9782016982.
[34] A.G. Guevorkyan, Kh. AlchujyanN, H.M. Mikaelyan, et al., Beneficial effects of hypothalamic proline-rich peptide-1 on heart failure associated with experimental pancreatic necrosis and crush syndrome, Eur. Chem. Bull. 5 (2016) 259–265.
[35] W. Zhou, F. Shen, J.F. Miller, et al., Evidence for altered cellular calcium in pathogenetic mechanisms of acute pancreatitis in rats, J. Surg. Res. 60 (1996) 147–155.
[36] O.V. Maslov, A.A. Vinokurov, V.V. Alabovsky, Stimulation of mitochondrial oxygen uptakeintensityinheart by penetrating calcium to myocardium through Na +-Ca2+ exchange, Bull. VSU. 1 (2010) 94–98.
[37] A.V. Ershov, V.T. Dolgikh, The effect of pancreatogenic factors on contractility and metabolism of isolated rat heart, Siber. Med. J. 6 (2015) 63–68.
[38] A.M. Lefer, Pathophysiologic role of myocardial depressantfactor as a mediator of circulatory shock, Klin. Wochenschr. 60 (1982) 713–716.
[39] H.G. Beger, B.M. Rau, Severe acute pancreatitis: clinical course and management, World J. Gastroenterol. 13 (2007) 5043–5051.
[40] G.A. Kevorkian, G.L. Marukhyan, L.N. Arakelyan, et al., Influence of hypothalamic proline-rich peptide on the level of [14C] glucose utilization during crush syndrome, Neurochem. Res. 26 (2001) 829–832.
[41] O.S. Better, Rescue and salvage of casualties suffering from crush syndrome after mass disasters, Mil. Med. 164 (1999) 366–369.
[42] F.X. Huber, L. Herzog, E. Werle, et al., Crush syndrome in polytrauma – octreotide in a newthrapeutic concept, Clin. Nephrol. 52 (1999) 392–394.
[43] X.L. Zhou, S.Z. Ni, D. Xiong, et al., Fluid resuscitation with preventive peritoneal dialysis attenuates crush injury-related acute kidney injury and improves survival outcome, Scand. J. Trauma Resusc. Emerg. Med. J. 27 (2019) 68.
[44] A.G. Guevorkyan, A.S. Kanayan, G.S. Chailyan, et al., Influence of hypothalamic cytokine PRP on protein synthesis in brain subcellular compartments in crush syndrome, Cent. Nerv. Syst. Agents Med. Chem. 11 (2011) 184–188.
[45] K. Takada, T. Kanda, K. Ohkawa, et al., Ubiquitin and ubiquitin-protein conjugates inPC12h cells: changes during neuronal differentiation, Neurochem. Res. 19 (1994) 391–398.
[46] M. Yu, G. Chakraborty, M. Grabow, et al., Serine protease inhibitors block N-terminal arginylation of proteins by inhibiting the arginylation of tRNA in rat brains, Neurochem. Res. 19 (1994) 105–110.
[47] S. Liu, Y. Yu, B. Luo, et al., Impact of traumatic muscle crush injury as a cause of cardiomyocyte-specific injury: experimental study, Heart Lung Circ. 22 (2013) 284–290.
[48] S. Javadov, The calcium-ROS-pH triangle and mitochondrialpermeability transition: challenges to mimic cardiac ischemia-reperfusion, Front. Physiol. l6 (2015) 83.
[49] C. Lazzeri, A. Peris, Assessment and treatment of ischemia-reperfusioninjury: the real challenge of uncontrolled donation after circulatory death, Resuscitation 141 (2019) 207–208.
[50] P. Neary, H.P. Redmond, Ischemia-reperfusion injury and the systemic inflammatory response syndrome, in: P.A. Grace, R.T. Mathie (Eds.), Ischemia-Reperfusion Injury, Blackwell Science, London, 1999, pp. 123–136.
[51] P. Boisguerin, J.M. Giorgi, S. Barrère-Lemaire, CPP-conjugated anti-apoptotic peptides astherapeutic tools of ischemia-reperfusion injuries, Curr. Pharmaceut. Des. 19 (2013) 2970–2978.
[52] D. Wu, J. Wang, H. Wang, et al., Protective roles of bioactive peptides during ischemia-reperfusion injury: from bench to bedside, Life Sci. 180 (2017) 83–92.
[53] P.S. Azevedo, B.F. Polegato, M.F. Minicucci, et al., Cardiac remodeling: concepts, clinical impact, pathophysiological mechanisms and pharmacologic treatment, Arq. Bras. Cardiol. 106 (2016) 62–69.
[54] B. Ouyang, Z. Li, X. Ji, et al., The protective role of lutein on isoproterenol-inducedcardiac failure rat model through improving cardiac morphology, antioxidant status via positively regulating Nrf2/HO-1 signaling pathway, Pharm. Biol. 57 (2019) 529–535.
[55] K.S. Hayashida, I. Sano, K. Ohsawa, et al., Inhalation of hydrogen gas reduces infarct sizein the rat model of myocardial ischemia–reperfusion injury, Biochem. Biophys. Res. Commun. 373 (2008) 30–35.
[56] Q. Zhang, J. Xiang, X. Wang, et al., Beta(2)-adrenoceptor agonist clenbuterol reduces infarct size and myocardial apoptosis after myocardial ischemia/reperfusion in anaesthetized rats, Br. J. Pharmacol. 160 (2010) 1561–1572.
[57] A.G. Guevorgyan, Hypothalamic proline-rich peptide-1 protects against myocardial ischemia-reperfusion injury, Eur. Chem. Bull. 6 (2017) 49–53.
[58] M. Cikes, S.D. Solomon, Beyond ejection fraction: an integrative approachfor assessment of cardiac structure and function in heart failure, Eur. Heart J. 37 (2016) 1642–1650.
[59] Y. Gerber, J.P. McConnel, A.S. Jaffe, et al., Lipoprotein-associated phospholipase A2 and prognosis after myocardial infarction in the community, Arterioscler. Thromb. Vasc. Biol. 26 (2006) 2517–2522.