REVIEW ARTICLE | Iranian Biomedical Journal 28 (2 & 3): 59-70 March and May 2024

Effect of Cold Adaptation on the State of Cardiovascular System and Cardiac Tolerance to Ischemia/Reperfusion Injury

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OPEN ACCESS

Received: December 5, 2022
Accepted: August 8, 2023
Published online: August 9, 2023

Citation:
Voronkov NS, Popov SV, Naryzhnaya NV, Prasad NR, Petrov IM, Kolpakov VV, Tomilova EA, Sapozhenkova EV, Maslov LN. Effect of Cold Adaptation on the State of Cardiovascular System and Cardiac Tolerance to Ischemia/ Reperfusion Injury. *Iran biomed J* 2024; 28(2 & 3): 59-70.

ABSTRACT

Despite the unconditional success achieved in the treatment and prevention of AMI over the past 40 years, mortality in this disease remains high. Hence, it is necessary to develop novel drugs with mechanism of action different from those currently used in clinical practices. Studying the molecular mechanisms involved in the cardioprotective effect of adapting to cold could contribute to the development of drugs that increase cardiac tolerance to the impact of ischemia/reperfusion. An analysis of the published data shows that the long-term human stay in the Far North contributes to the occurrence of cardiovascular diseases. At the same time, chronic and continuous exposure to cold increases tolerance of the rat heart to ischemia/ reperfusion. It has been demonstrated that the cardioprotective effect of cold adaptation depends on the activation of ROS production, stimulation of the β_2-adrenergic receptor and protein kinase C, MPT pore closing, and K_{ATP} channel. ***DOI: 10.61186/ibj.3872***

Keywords: Acclimatization, Cold temperature, Heart, Ischemia, Reperfusion

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INTRODUCTION

Hospital mortality in patients with STEMI is 4.6%-7.5% , which has not decreased in recent years[1-4]. Moreover, drugs that have been approved for clinical use and are capable of preventing reperfusion injury of the heart with high efficacy are not currently available[5,6]. During recent years, the attention of investigators has greatly been drawn to the study of the molecular mechanisms of the cardioprotective effect of pre- and post-conditioning, believing that this knowledge contributes to the development of drugs that increase cardiac tolerance to reperfusion injury[7]. The study of the trigger and molecular mechanisms underlying the infarct-reducing effect of cold adaptation can contribute to the identification of molecular targets for developing novel cardioprotective drugs.

List of Abbreviations:
AMI: acute myocardial infarction; **AMPK:** AMP-activated protein kinase; **AR:** adrenergic receptor; **AT_1:** angiotensin II type 1; **BP:** blood pressure; **CAO:** coronary artery occlusion; **CHD:** coronary heart disease; **CVD:** cardiovascular disease; **ET-1:** endothelin-1; **FGF:** fibroblast growth factor; **IRI:** ischemia-reperfusion injury; **K_{ATP}:** ATP-sensitive K^+-channels; **MDA:** malondialdehyde; **mitoK_{ATP}:** mitochondrial ATP-sensitive K^+ channel; **MPT:** mitochondrial permeability transition; **mTOR:** mammalian target of rapamycin; **NOS:** nitric oxide synthase; **PKA:** protein kinase A; **PKC:** protein kinase C; **PPARγ:** peroxisome proliferator-activated receptor γ; **ROS:** reactive oxygen species; **STEMI:** ST-segment elevation myocardial infarction; **TNF-α:** tumor necrosis factor-α; **TR:** thyroid hormone receptor; **TRPV1:** transient receptor potential vanilloid 1; **α7nAChR:** α7 nicotinic acetylcholine receptor

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INFORMATION SOURCES

The National Library of Medicine's PubMed (https://pubmed.ncbi.nlm.nih.gov/) was searched to acquire information on the subject of the article. About 3000 abstracts were studied, and 1200 full-text articles on cold adaptation and cold exposure were identified. Also, 62 articles were found in Russian on cold adaptation and exposure in Russian libraries. The duration of searching was about six months (from April 2022 to October 2022), and a total number of 172 papers were included in this review.

COLD AND HUMAN

Effect of cold environment on the state of the cardiovascular system in the Far North population

The health of people who came to work in Norilsk and Dikson, cities located above the Arctic Circle, was investigated in an earlier study[8]. In 1964, it was documented that healthy residents of Norilsk had higher BP than those living in Central Asia[9]. A persistent BP increase has been also observed in migrants living in the Far North. However, arterial hypertension was much less common in the indigenous population of the northern regions of Russia[10]. The incidence of hypertension among migrants in the Far North raises with increasing the length of residence in the Arctic area, reaching 61% in people living in this region for more than 15 years[11]. Moreover, a higher prevalence of hypertension was observed among the shift workers than the rest of the Russian population[12]. In addition, an increase in the incidence of AMI cases and the mortality rate from CVD was found among the newcomer population of the Far North, while in the indigenous inhabitants of this region who lead a traditional lifestyle, AMI was relatively rare[10]. The incidence of CHD in people aged 50-59 years living in the Arctic for less than 10 years was reported as 25%, but this rate increased to 45% for those who had been living in the Far North for more than 10 years ($p < 0.001$). Therefore, long-term residence in the Arctic is considered a risk factor for the occurrence of CHD[8]. At the same time, the incidence of CHD was lower among the indigenous population, leading a traditional lifestyle, than those residents of the middle latitudes of the Union of Soviet Socialist Republics[8]. According to Turchinskiĭ, aboriginals of the Arctic who have preserved the traditions and lifestyle of their ancestors, practically experienced no hypertension[8]. However, Yakuts living in the city of Yakutsk in the Arctic region had a high incidence of CHD and hypertension[13]. The incidence of AMI among migrants arriving in the Far North increased sharply after 7 to 10 years[8]. In Norilsk, 24% of AMI patients are comprised of young people aged less than 44 years old[14]. Mortality from CVD among the male population of Yakutsk aged 20-54 years is 38.4% of the total mortality[15], which is significantly higher than the rate reported in South/Middle Russia[16]. Atherosclerotic lesion of the aorta and atherosclerosis of the coronary arteries in Yakutsk are more common in the newcomers than in the indigenous population[15]. The incidence of CVD in the Siberian Federal District, compared to Russia, is also higher as a whole[17]. Melnikov[18] found that in Novosibirsk (a Southern Siberian city), the average age of individuals who died from CVD was 59 years old, and among the inhabitants of Mirny (Yakutia, Russia) and Yakutsk, this indicator was 52 and 55 years, respectively. Danish researchers have shown that CVD mortality among the Greenland population is two times higher than that of Danish people[19].

Seasonal variations in morbidity and mortality of patients with CVD

Approximately 10% more cases of AMI were observed in winter or spring than in summer in Virginia[20], and approximately 53% more AMI cases were reported in winter than in the summer in Massachusetts[21]. There was a negative correlation between hospital admissions of patients with acute coronary syndrome and mean daily temperature in Athens (Greece)[22]. In Hungary, a peak period of the incidence of AMI was found during spring[23], while the minimum number of events was recorded during summer. This pattern was also identified in Germany, London (UK), Yekaterinburg (Russia), Northern Ireland, and Finland[24-28]. According to Barnett et al., in cold periods, the rate of coronary event increases more in populations living in warm climates than those living in cold climates[29]. High ambient temperatures can also increase mortality from CVD (Fig. 1)[30]. Increased AMI morbidity and mortality during the cold season are associated with the activation of the adrenergic system[31], an elevation in blood viscosity, and an enhancement in platelet aggregation (Fig. 2)[32].

Effects of cold on the cardiovascular system

Adverse effects of cold adaptation on the cardiovascular system

One of the main negative effects of cold adaptation is hypertension. BP increases after prolonged exposure to cold in animals[33,34] and in humans (Fig. 2)[17,35]. In animals, when adapting to cold (1-4 ºC), cardiac hypertrophy develops[34]. There are also data on cardiac hypertrophy in humans during chronic cold exposure[35]. It has been observed that left ventricular hypertrophy develops after continuous cold exposure (4 °C; 4 weeks) without a change in the right ventricle weight[34]. Similarly, intermittent cold exposure (4 °C; 1.5 or 8 h daily; 4 weeks) did not induce cardiac hypertrophy[34].

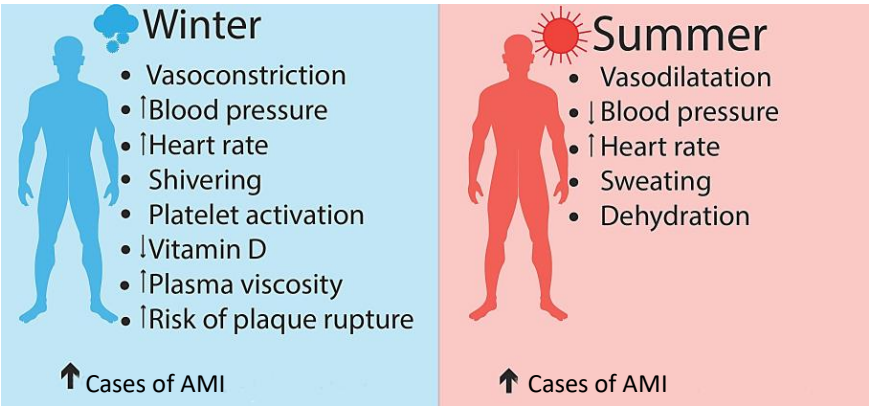

Fig. 1. Reasons behind the increased AMI in cold and warm conditions.

Our data coincide with those of a research group in USA[36-38]. They found that long-term cold exposure (5 ± 2 ºC; 8 weeks) induced an increase in the left ventricular weight without alterations in the right ventricular weight. In addition, cardiac hypertrophy was reversible and disappeared four weeks after the cessation of cold exposure. Importantly, mild cold adaptation (8 ± 1 ºC; 5 weeks) did not affect the weight of the left ventricle[39]. All the above data clearly show that the adverse effects of cold adaptation depend on its severity, and thus the ambient temperature for adaptation should carefully be taken into account.

Role of aldosterone, angiotensin-II, and endothelins in the adverse effects of cold adaptation

It has been documented that aldosterone, angiotensin-II, and endothelins play an important role in the development of hypertension. Moreover, they can be involved in the development of cardiac hypertrophy[40-45]. It has also been reported that a 17-day ski trip in the Far North at temperature ranging from -30 to -40 °C causes a two-fold elevation in the plasma aldosterone concentration[46]. However, some investigators were unable to detect an increase in the plasma aldosterone concentration in the rats following cold exposure (5 °C; 3 weeks)[38] and cold adaptation (4 °C; 14 days)[47], though the plasma aldosterone level increased after seven days of cold exposure (4 °C)[47]. Repeated cold water immersions (three times a week for six weeks) did not alter the plasma aldosterone concentration in male swimmers in winter[48], which is likely due to the fact that the exposure was not intense enough to induce an increase in the plasma aldosterone level. Repeated cold exposure (4 °C; 1 h daily; 19 days) induced an increase in plasma aldosterone concentration in rats[49]. Cold exposure (5 ± 2 °C; 4 weeks) also induced hypertension and cardiac hypertrophy in rats. Daily administration of spironolactone prevented the development of hypertension, but not cardiac hypertrophy[50]. Adenoviral delivery of renin antisense inhibited the development of hypertension after adaptation to cold (6.7 ± 2 °C; 1, 3, and 5 weeks) in rats[51]. The recombinant adeno-associated virus carrying short-hairpin small-interference RNA for the mineralocorticoid receptor was administered to mice during cold exposure (6.7 °C; 32 days)[33]. This adenoviral construct prevented a cold-induced increase in BP. The mentioned data indicate that aldosterone

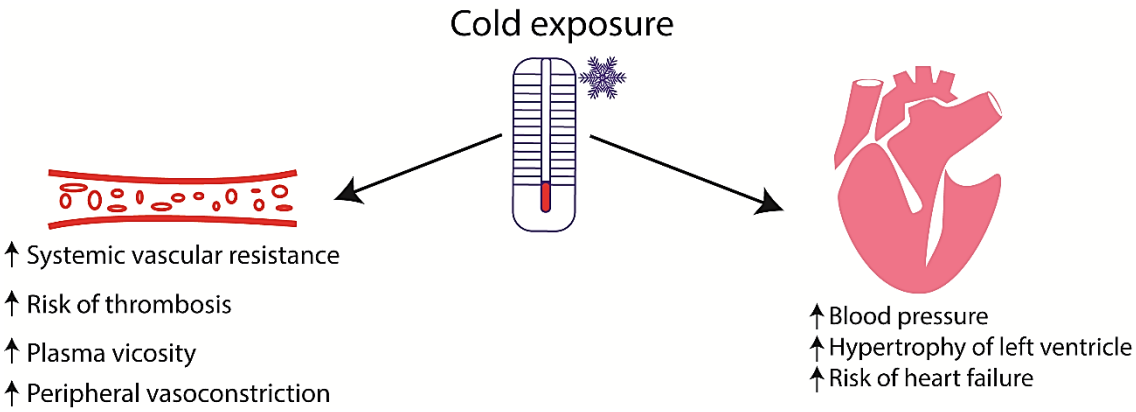

Fig. 2. Blood circulation and heart and responses to cold exposure.

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is involved in the development of cold-induced hypertension, but not cardiac hypertrophy. In 1993, Cassis found that cold exposure (4 °C; 7 days) had no effect on the plasma angiotensin II level in rats[52], but later in 1998, he and his colleagues discovered that cold exposure (4 °C; 7 days) led to an increase in the plasma concentration of angiotensin II in these animals[53]. Shechtman et al. also demonstrated that treatment with captopril could prevent cold-induced hypertension (5 ± 2 °C; 4 weeks) in rats, whereas it has no effect on cardiac hypertrophy[54]. Treatment with the AT_1 receptor antagonist losartan was found to prevent cold-induced hypertension (5 ± 2 °C, 3 weeks) in rats but did not abolish the development of cardiac hypertrophy[55]. Pressor response to a bolus injection of angiotensin-II increased in cold-adapted rats (5 ± 2 °C; 3 and 4 weeks)[56]. These data were confirmed by other investigators who found that cold adaptation enhanced the responsiveness of tail arteries to angiotensin II in rats[57]. It was shown that cold exposure (5 °C; 5 weeks) did not increase BP in angiotensinogen gene-knockout mice[58]. The above-mentioned evidence convincingly shows that angiotensin-II is involved in the development of cold-induced hypertension through the activation of the AT_1 receptor. ET-1 is a potent vasoconstrictor. It was demonstrated that cold exposure (6.7 ± 2 °C; 1, 3, and 5 weeks) increased BP and also ET-1 level in the heart and mesenteric arteries in rats[59]. However, investigators did not find any alteration in the concentration of ET-1 in plasma. In a study performed by Chen et al., cold exposure doubled the expression of ET_A receptor protein, while the expression of the ET_B receptor decreased by 90%, in the heart of cold-exposed rats. Cold exposure also increased the ET_A/ET_B receptor ratio in the heart by about 60-fold[59]. In another investigation by Zhang et al., wild-type and ET_A receptor knockout mice were exposed to cold (4 °C) for 2 and 5 weeks. They found that cold adaptation induced severe cardiac fibrosis in wild-type mice, and ET_A receptor knockout abolished these negative manifestations of cold adaptation[60]. Consequently, endogenous ET-1 could be involved in cardiac fibrosis through the activation of ET_A receptors. Endogenous catecholamines do not seem to play a role in the development of cold-induced hypertension, as pressor response to a bolus injection of the α-AR agonist phenylephrine decreased in cold-adapted rats (5 ± 2 °C; 3 and 4 weeks)[56]. Chronic treatment with the α-AR antagonist prazosin had no effect on the development of cold-induced hypertension in rats (5 ± 2 °C; 3 and 4 weeks)[61]. As a result, endogenous catecholamines are not involved in cold-induced hypertension. It is possible that the activation of the ET_A receptor causes hypertension and cardiac hypertrophy after long-term cold exposure (Fig. 3).

Cardioprotective effect of cold adaptation

Short-term cold exposure contributes to an increase in the level of catecholamines and is associated with an increase in oxygen demand in humans[36,62]. In addition, prolonged (seven weeks) cold exposure causes a rise in oxygen consumption in mice[63]. Therefore, it could be hypothesized that adaptation to cold would cause a decrease in cardiac tolerance to IRI. However, we found that continuous cold adaptation (4 °C; 4 weeks) increases the rat heart's tolerance to ischemia (45 min) and reperfusion (2 h)[34,64]. Our data also indicated that intermittent cold adaptation (4 °C, 8 h/day, 4 weeks) or intermittent cold exposure (4 °C, 1.5 h/day, 4 weeks) had no effect on cardiac tolerance to IRI[34]. A Czech research group found that chronic cold exposure (8 °C, 8 h/day for a week, followed by 4 weeks at 8 °C for 24 h/day) augments cardiac tolerance to ischemia (20 min) and reperfusion (3 h), and this effect persists for at least 14 days[39]. A Russian research group found that the infarct-limiting effect of cold adaptation is not associated with serum cortisol, corticosterone, T_3, and T_4 levels[34]. Cold exposure did not affect the appearance of peptic ulcers in the stomach or the involution of the thymus and spleen[34]. Continuous cold exposure induced a 40% increase in adrenal gland hypertrophy. Therefore, chronic cold exposure is not considered a form of stress. Both continuous and intermittent cold exposure cause an increase in brown fat weight, heart weight, and left ventricle weight, which are typical alterations for cold adaptation[65,66]. Tibenska et al. observed that the infarct-reducing effect of adaptation to cold is not accompanied by β_1-AR expression, PKA, the p-PKA level, and adenylyl cyclase activity[39]. Simultaneously, they found that cold adaptation increased the tolerance of cardiac mitochondria to Ca^{2+} overload, which may indicate the important role of the permeability transition pore (MPT pore) in the cardioprotective effect of cold adaptation[39]. There is evidence that chronic cold exposure (4 °C; 4 weeks) had no effect on the level of autophagy markers (p62, LC3II, and LC3I) in myocardial tissue of sham-operated mice[67]. However, the levels of these markers were altered in mice with abdominal aortic constriction after cold adaptation, indicating an enhancement of autophagy. It can be assumed that autophagy is involved in the cardioprotective effect of cold adaptation. Jankovic and colleagues found that cardiac tolerance to IRI increased with adaptation to hypoxia[68], and the specificity of cold adaptation was an increase in oxygen consumption[69,70]. In cold-adapted mice, oxygen consumption remains increased at room temperature (20 °C)[71]. However, it should be noted that cold exposure (4 °C; 10 days) does not affect heart's oxygen consumption[72]. Hypoxia-inducible factor-1α

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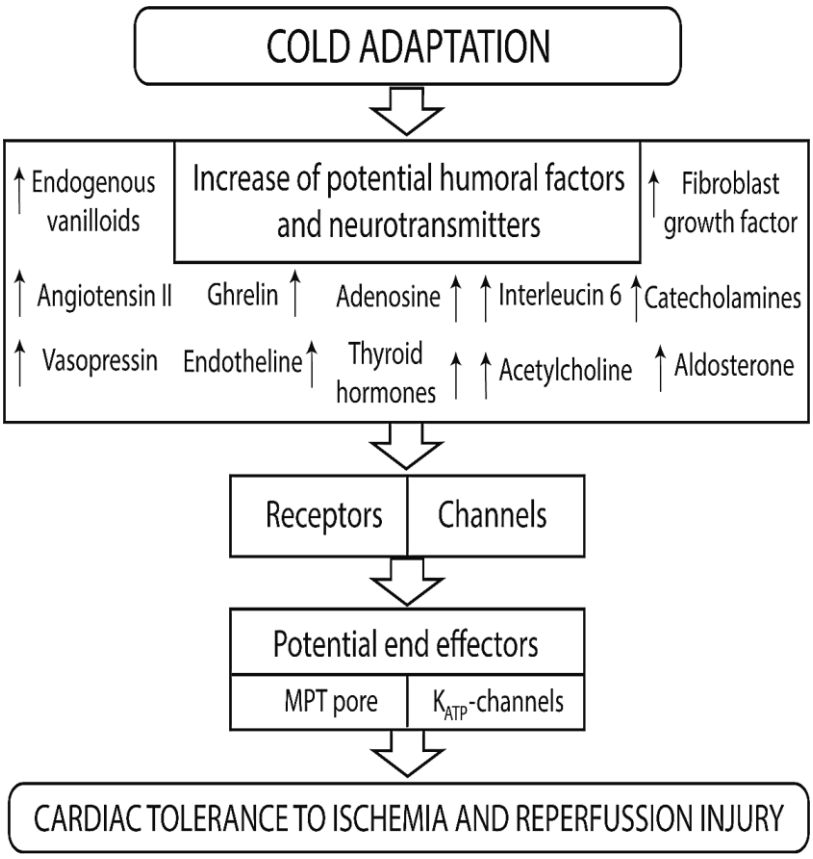

Fig. 3. Potential signaling pathways of cardiac tolerance to IRI during cold adaptation.

decreased in brown adipose tissue of rats after chronic cold exposure (4 ± 1 °C) for 12, 21, and 45 days[73], but not in white adipose tissue of rats after cold adaptation (4 ± 1°C, for 3, 7, 12, 21, and 45 days)[68]. Consequently, the molecular mechanism of the cardioprotective effect of cold adaptation must be different from the molecular mechanism of adaptation to hypoxia. Thus, the receptor and signaling mechanism of the infarct-reducing effect of cold adaptation have been still remained unclear. It is not known how cold adaptation affects cardiac contractility during reperfusion and influences programmed cell death during reperfusion (apoptosis, necroptosis, pyroptosis, and ferroptosis). We assume that the same receptors and signaling mechanisms involving in conditioning mediate the protective effect of cold adaptation[74,75-77].

Role of catecholamines in the cardioprotective effect of cold adaptation

Catecholamines and adrenergic receptors play an important role in cold adaptation[39,78]. Preliminary stimulation of β-AR increases cardiac tolerance to IRI (Fig. 3)[39,79], and the cardioprotective effect of ischemic preconditioning is associated with the activation of the α_1-AR[80]. It has been also shown that the release of endogenous catecholamines by tyramine prior to CAO increases cardiac resistance to IRI[81], and α_1-AR stimulation mimics the cardioprotective effect of ischemic preconditioning[82]. The cardioprotective and antiarrhythmic effects of the α_1-AR agonists are mediated via $G_{i/o}$-proteins and associated with the activation of PKC and opening of mitoK_{ATP}[82-84]. In addition, the cardioprotective effect of the β-AR agonist isoproterenol is mediated via the activation of PKC-δ[85]. The infarct-reducing effect of isoproterenol has been indicated to be dependent on the stimulation of β_1-AR[85]. However, there is evidence that the β_1-AR agonist denopamine, the β_1-, β_2-AR agonist isoproterenol, and the β_2-AR agonist formoterol decrease infarct size and improve cardiac contractility during reperfusion[86]. The antioxidant N-acetylcysteine eliminates the infarct-sparing effect of isoproterenol, but the mitoK_{ATP} channel blocker 5-hydroxydecanoate does not affect the cardioprotective effect of isoproterenol. These facts suggest that ROS are involved in the development of the cardioprotective effect of isoproterenol[86]. The above-mentioned studies indicate that the activation of α_1-AR, β_1-AR, and β_2-AR can increase cardiac tolerance to IRI. Since endogenous catecholamines are involved in the development of cold

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adaptation, it can be hypothesized that they also contribute to the development of the cardioprotective effect of cold adaptation. Tibenská and colleagues found that the infarct-reducing effect of cold adaptation does not depend on β_1-AR expression. However, it is probable that other ARs can be involved in the cardioprotective effect of cold adaptation. The same research group also demonstrated that the persisting infarct-limiting effect of chronic cold adaptation mediates via β_2-AR stimulation[87].

Role of thyroid hormones in the cardioprotective effect of cold adaptation

Thyroid hormones play a role in the cardioprotective effect of adapting to cold[66] and stimulate TRs: TRα and TRβ[88]. Data on the role of thyroid hormones in regulating cardiac tolerance to IRI are contradictory. It has been reported that thyrotoxicosis does not affect cardiac resistance to IRI, and hypothyroidism promotes a decrease in infarct size in rats[89]. In a study by Jeddi et al., the isolated hearts from hypothyroid rats were subjected to 30 minutes of global ischemia, followed by 120 minutes of reperfusion[90]. They results showed that hypothyroid rats's hearts were resistant to IRI. In Suarez et al.'s study, hypothyroidism contributed to a decrease in infarct size and reduced the release of lactate dehydrogenase and creatine kinase from the isolated heart. However, it was demonstrated that overexpression of endothelial TRα1 contributes to a 45% decrease in infarct size in mice[91]. In another study, pretreatment with thyroxine (25 μg/100 g/day subcutaneously) for two weeks increased the tolerance of the isolated rat heart to IRI[92]. Moreover, 3,5-Diiodothyropropionic acid, a T_3 analog that binds to the TRα and TRβ, reduced infarct size and attenuated inflammatory cardiac injury after permanent CAO in mice[93]. In an investigation conducted on the isolated perfused rat heart subjected to IRI, T_3 reduced infarct size[94]. The inconsistent data on the role of TRs in regulating cardiac tolerance to IRI seems to be linked to the presence of two TR (TRα and TRβ) subtypes. It is possible that the activation of one receptor enhances cardiac resistance to IRI, but stimulation of another TR aggravates IRI cardiac injury. In this regard, the selective TRα and TRβ antagonists could clarify the situation. Since thyroid hormones play an important role in cold adaptation, it can be assumed that they are involved in the infarct-reducing effect of adaptation (Fig. 3).

Role of ROS in the cardioprotective effect of cold adaptation

It is well known that ROS are involved in the cardioprotective effect of ischemic pre- and post-conditioning[95]. In a previous study, cold exposure (5°C; 1.5 h; 28 days) had no effect on the diene conjugates and MDA levels in the myocardium of rats. Moreover, catalase and superoxide dismutase activity increased in cardiac tissue of rats[96]. In another study, rats were subjected to cold exposure (5 °C; 5, 10, 15, and 49 days). The results demonstrated that cold exposure had no effect on the MDA level in myocardial tissue, and chronic cold exposure (4 °C; 4 weeks) had no effect on ROS generation in the myocardial tissue of sham-operated mice[67]. Other investigators have shown that cold adaptation (4 °C; 6 h during 14 days) leads to the increased ROS production in myocardial tissue of rats[97], and cold-weather field training increases the serum lipid hydroperoxides level in human[98]. In Schmidt et al.'s study, cold adaptation (4 °C; 6 months) promoted an increase in glutathione peroxidase activity in the rat heart without affecting glutathione reductase activity[99]. Selman et al. found that cold exposure (8 °C; 18 days) increased catalase activity in myocardial tissue of small mammals (*Microtus agrestis*) without altering superoxide dismutase activity[100]. Emirbekov et al. observed that cold adaptation (-5 °C; 3 h; during 20–25 days) decreased the MDA level in the myocardium and increased total antioxidant activity in the myocardial tissue of rats[101]. We found that a free radical scavenger, N-2-mercaptopropionylglycine, abolished the infarct-reducing effect of cold adaptation [unpublished data]. Thus, there is currently no convincing evidence that cold adaptation enhances or inhibits ROS production in animals without I/R cardiac injury or in animals with CAO and reperfusion.

Role of FGF, TNF-α, M-cholinergic, TRPV1, vasopressin, ghrelin, adenosine, and opioid receptors in the cardioprotective effect of cold adaptation

FGF is involved in the cardioprotective effect of ischemic pre- and post-conditioning[74]. Cold adaptation (4 °C; 15 days) induced an increase in the plasma FGF21 level in mice[102]; however, some investigators believe that cold adaptation (6 °C; 7 days) decreases the plasma FGF21 level in mice. Thus, the question of the involvement of FGF in the infarct-reducing effect of cold adaptation remains open. It has been reported that TNF-α is involved in the cardioprotective effect of adaptation to hypoxia[103]. There are two TNF-α receptors: TNF-α receptors I (TNFR-I, p55) and II (TNFR-II, p75)[104]. The activation of TNFR-I aggravates IRI[104], while the stimulation of TNFR-II enhances cardiac tolerance to IRI[103]. Cold adaptation (4 °C; 15 days) induced an increase in the plasma TNF-α concentration in mice[102]. Therefore, it is possible that TNF-α has involvement role in the cardioprotective effect of cold adaptation. It is known that α7nAChR is

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responsible for the cardioprotective effect of remote postconditioning[105], and the muscarinic receptor has a participation in the infarct-reducing effect of remote preconditioning[106]. Therefore, it can be assumed that these receptors are involved in the cardioprotective effect of cold adaptation. In a study by Manukhin et al., rabbits were exposed daily to severe cold condition (-10 °C; 6 h; 1-30 days), in which an increased sensitivity of blood vessels to acetylcholine was found. The authors suggested that cold adaptation can alter the characteristics of M-cholinergic receptors of blood vessels[107]. In this case, the cardioprotective effect of cold adaptation could be mediated via the activation of M-cholinergic receptors. Gorbunov and colleagues observed the involvement of the TRPV1 channel in the regulation of cardiac resistance to IRI. They have also observed that the TRPV1 activation increases cardiac tolerance to IRI due to calcitonin gene-related peptide release from afferent nerve endings[108]. It has been shown that chronic cold exposure (4 °C; 4 weeks) upregulates TRPV1 in the myocardial tissue of mice[67]. However, there are data that cold exposure (4 °C; 5 weeks) downregulates TRPV1 in the murine heart[60]. Consequently, the role of TRPV1 in the infarct-reducing effect of cold adaptation requires further study. Pretreatment with vasopressin has been demonstrated to decrease infarct size in rats[109], while chronic cold exposure has been found to increase the plasma level of vasopressin in guinea-pigs[110]. Therefore, vasopressin could be involved in the cardioprotective effect of cold adaptation. There is evidence that an uncharacterized pertussis toxin-insensitive receptor localized in guinea pig cardiomyocytes could play a role in cold adaptation[111]. This receptor, which is expressed in myocardial tissue, could be the PPARγ[112]. The activation of PPARγ enhances cardiac tolerance to IRI[113]. It has been demonstrated that cold exposure (4 ± 1 °C for 1, 3, 7, 12, 21, and 45 days) increases PPARγ expression in the skeletal muscle of rats[114]. If an increase in PPARγ expression is observed in myocardial tissue, this will enhance cardiac tolerance to IRI, suggesting the involvement of α7nAChR. In this regard, FGF, TNF-α, M-cholinergic, and PPARγ receptors are found to be involved in the cardioprotective effect of cold adaptation (Fig. 3).

Role of protein kinases, NOS, MPT pore, and K_{ATP} channels in the cardioprotective effect of cold adaptation

Chronic cold exposure (4 °C; 4 weeks) had no effect on the phosphorylated AMP-activated protein kinase (p-AMPK), p-mTOR kinase (mammalian target of rapamycin), in the myocardial tissue of sham-operated mice[67]. However, after cold adaptation, the levels of p-AMPK and p-mTOR altered in mice with abdominal aortic constriction. Cold adaptation (4 ± 1 °C; 3, 7, 12, 21, and 45 days) led to an increase in p-AMPKα expression in the white adipose tissue of rats[68]. It is well known that these kinases are involved in regulating cardiac tolerance to IRI[74]. Therefore, it can be assumed that they are involved in the cardioprotective effect of cold adaptation. The role of other kinases in cold adaptation remains unknown. We established that inducible NOS plays an important role in the infarct-reducing effect of adaptation to chronic hypoxia[115]. It has also been demonstrated that cold exposure enhances endothelial NOS expression in the brown adipose tissue of rats[116]. However, there is no data on the effect of cold adaptation on NOS expression in the heart. An earlier study has suggested that long-term cold exposure (5 ± 2 °C; 5 weeks) decreases the plasma nitrite and nitrate levels in mice[58]. These data indicate a reduction in NO production after cold adaptation. It has been known that MPT pore closure is involved in the cardioprotective effect of ischemic preconditioning and postconditioning[74]. Tibenska and colleagues obtained indirect evidence of the involvement of MPT pore in the cardioprotective effect of cold adaptation in rats[39]. There is evidence that K_{ATP} channels are also involved in the cardioprotective effect of pre- and postconditioning[74,75], as well as adaptation to continuous hypoxia[115]. We found that the K_{ATP} channel blocker, glibenclamide, abolished adaptation-induced cardiac tolerance to IRI [unpublished data] (Fig. 1).

CAN ANGIOTENSIN-II AND ENDOTHELINS INCREASE CARDIAC TOLERANCE TO IRI?

The cardioprotective effect of angiotensin II during ischemia and reperfusion of the heart has been well-documented[117,118]. Angiotensin II acts through two receptors: AT_1R and AT_2R. Evidence has revealed that the infarct-reducing effect of angiotensin II acts via G protein-independent signaling through the AT_1 receptor[117]. The cardioprotective effect of stimulating the AT_1 receptor has been confirmed by Nuñez's group[118-120]. However, the blockade of the AT_1 receptor enhances cardiac tolerance to IRI in mice[121]. In 1996, it was shown that endothelin-1 can mimic ischemic preconditioning against infarction in the isolated rabbit heart through the activation of the ETA receptor and stimulation of PKC[122]. Endothelin-1 protects the isolated rat heart against IRI via the activation of the ET_A receptor, stimulation of PKC, and opening of the mitoK_{ATP} channel[123]. Recently, it has been shown that endogenous endothelin-1 and the ETA receptor are involved in the cardioprotective effect of remote preconditioning in rats[124]. However, it has been displayed that the selective ET_A receptor antagonist

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BQ123, can also increase cardiac tolerance to reperfusion in rabbits[125]. Based on the above-mentioned studies, it is reasonable to hypothesize that endothelin-1 and angiotensin II can play a role in the cardioprotective effect of cold adaptation (Fig. 3).

CONCLUSION

Analysis of the published data indicates that cold adaptation increases the incidence of developing hypertension, coronary artery disease, and AMI in human. Moreover, long-term exposure to cold condition causes hypertension, cardiac hypertrophy, and cardiac tolerance to IRI in rats. Cold-induced hypertension is mediated via the activation of aldosterone, AT-1, and ET_A receptors. It appears that the activation of AT-1 and ET_A receptors causes cardiac hypertrophy after long-term cold exposure. TRPV1, adrenergic, thyroid, MR, ET_A, AT_1, PPARγ, α7nAChR. FGF, TNF-α, and M-cholinergic receptors could be involved in the cardioprotective effect of cold adaptation. It is assumed that antioxidants, protein kinases, MPT pore, and K_{ATP} channels contribute to the development of cold adaptation, which triggers cardiac tolerance to IRI.

DECLARATIONS

Acknowledgments

The authors did not use artificial intelligence (AI)-assisted technologies in the production of submitted work.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

All authors reviewed the results and approved the final version of the manuscript.

Authors' contributions

NSV: contributed to the acquisition, analysis, and interpretation of data, as well as to the conception, writing, and typing of the article, and preparation for printing; SVP, NVN, and IMP: contributed to the acquisition, analysis, or interpretation of data, as well as to the conception or design. NRP, VVK, EAT, and EVS: revised the manuscript critically. LNM: devised the project, the main conceptual ideas of the article, final approval of the content for publication of this manuscript.

Data availability

The data supporting the findings of this study are within the manuscript.

Competing interests

The authors declare that they have no competing interests.

Funding

This article was prepared with the support of the Ministry of Science and High Education of the Russian Federation [the state assignment no. 122020300042-4].

Supplementary information

The online version does not contain supplementary material.

REFERENCES

1. Menees DS, Peterson ED, Wang Y, Curtis JP, Messenger JC, Rumsfeld JS, et al. Door-to-balloon time and mortality among patients undergoing primary PCI. N Engl J Med. 2013; 369(10):901-9.
2. Fabris E, Kilic S, Schellings DAAM, Berg JMT, Kennedy MW, Houwelingen KGV, et al. Long-term mortality and prehospital tirofiban treatment in patients with ST elevation myocardial infarction. Heart. 2017; 103(19):1515-20.
3. Vaidya SR, Devarapally SR, Arora S. Infarct related artery only versus complete revascularization in ST-segment elevation myocardial infarction and multi vessel disease: a meta-analysis. Cardiovasc Diagn Ther. 2017; 7(1):16-26.
4. Olier I, Sirker A, Hildick-Smith DJR, Kinnaird T, Ludman P, Belder MAD, et al. Association of different antiplatelet therapies with mortality after primary percutaneous coronary intervention. Heart. 2018; 104(20):1683-90.
5. Maslov LN, Barbarash OL. Pharmacological approaches to limiting the infarct zone size in patients with acute myocardial infarction: Analysis of clinical data. Eks Klin Farmakol. 2018; 81:34-41.
6. Maslov LN, Popov SV, Mukhomedzyanov AV, Derkachev IA, Ryabov VV, Boshchenko AA, et al. Pharmacological approaches to limit ischemic and reperfusion injuries of the heart: analysis of experimental and clinical data on P2Y12 receptor antagonists. Korean Circ J. 2022; 52(10):737-54.
7. de Miranda DC, de Oliveira Faria G, Hermidorff MM, dos Santos Silva FC, de Assis LVM, Isoldi MC. Pre- and post-conditioning of the heart: an overview of cardioprotective signaling pathways. Curr Vasc Pharmacol. 2021; 19(5):499-524.
8. Turchinskiĭ VI. Cardiological aspects of human adaptation in the Far North. Vestn Akad Med Nauk SSSR. 1979;6:23-32.
9. Zubri GL, Klimov EA. On arterial pressure in the population of Noril'sk. Sov Med. 1964; 27:135-8.

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[DOR: 20.1001.1.1028852.2024.28.2.1.8]
[DOI: 10.61186/ibj.3872]

10. Orekhov KV. Ekstremal'nye faktory Kraĭnego Severa i voprosy zdorov'ia naseleniia étogo raĭona. Vestn Akad Med Nauk SSSR. 1979; 6:73-82.
11. Skavronskaia TV, Leus AI, Fedoseeva LA, Kumanovskaia TA, Preobrazhenskiĭ DV. Prevalence of hypertension among gas industry employees in Far North. Kardiologiia. 2005; 45(3):84.
12. Krivoschekov SG, Sobakin AK, Fomin AN. Estimation of functional state and labour efficiency of shift workers in conditions of the Far North. Int J Circumpolar Health. 2004; 63 Suppl 2:349-52.
13. Petrov RA, Rybkin IA. [Ischemic heart disease and arterial hypertension in Yakutsk (clinico-epidemiologic study)]. 1977; 17(3):63-70.
14. Turchinskiĭ VI, Sakharova SS. [Characteristics of clinical course of myocardial infarct in young persons under conditions of an industrial city in the Far North]. Kardiologiia. 1979; 19(5):39-45.
15. Alekseev VP, Ivanov KI, Konstantinov VV, Zhdanov VS, Akimova AI, Osipova ON, et al. [Epidemiology of ischemic heart disease and peculiarities of atherosclerosis in male residents of Yakutsk]. Ter Arkh. 2001; 73(1): 12-8.
16. Oganov RG, Maslennikova GI. [Prevention of cardiovascular diseases-real way to improvement of demographic situation in Russia]. Kardiologiia. 2007; 47(1):4-7.
17. Tikhonov DG, Nikolaev VP, Sedalischev VI. [Some problems of pathogenesis and clinical symptoms of atherosclerosis (coronary heart disease, hypertension) in the far north]. Ter Arkh. 2011; 83(1):63-9.
18. Melnikov VN. Life span of people who died from cardiovascular diseases in Siberia: a comparative study of two populations. Int J Circumpolar Health. 2003; 62(3):296-307.
19. Bjerregaard P, Dyerberg J. Mortality from ischaemic heart disease and cerebrovascular disease in greenland. Int J Epidemiol. 1988; 17(3):514-9.
20. Ornato JP, Peberdy MA, Chandra NC, Bush DE. Seasonal pattern of acute myocardial infarction in the national registry of myocardial infarction. J Am Coll Cardiol. 1996; 28(7):1684-8.
21. Spencer FA, Goldberg RJ, Becker RC, Gore JM. Seasonal distribution of acute myocardial infarction in the second national registry of myocardial infarction. J Am Coll Cardiol. 1998; 31(6):1226-33.
22. Panagiotakos DB, Chrysohoou C, Pitsavos C, Nastos P, Anadiotis A, Tentolouris C, et al. Climatological variations in daily hospital admissions for acute coronary syndromes. Int J Cardiol. 2004; 94(2-3):229-33.
23. Kriszbacher I, Bódis J, Csoboth I, Boncz I. The occurrence of acute myocardial infarction in relation to weather conditions. 2009; 135(1):136-8.
24. Shiue I, Perkins DR, Bearman N. Hospital admissions of hypertension, angina, myocardial infarction and ischemic heart disease peaked at physiologically equivalent temperature 0 °C in Germany in 2009–2011. Environ Sci Pollut Res. 2016; 23(1):298-306.
25. Donaldson GC, Robinson D, Allaway SL. An analysis of arterial disease mortality and BUPA health screening data in men, in relation to outdoor temperature. Clin Sci(Lond).1997; 92(3):261-8.
26. Donaldson GC, Tchernjavskii VE, Ermakov SP, Bucher K, Keatinge WR. Winter mortality and cold stress in Yekaterinburg, Russia: Interview survey. BMJ. 1998; 316(7130):514-8.
27. Crawford VLS, McCann M, Stout RW. Changes in seasonal deaths from myocardial infarction. QJM. 2003; 96(1):45-52.
28. Näyhä S. Environmental temperature and mortality. Int J Circumpolar Health. 2005; 64(5):451-8.
29. Barnett AG, Dobson AJ, McElduff P, Salomaa V, Kuulasmaa K, Sans S. Cold periods and coronary events: an analysis of populations worldwide. J Epidemiol Community Heal. 2005; 59(7):551-7.
30. Urban A, Kyselý J. Application of spatial synoptic classification in evaluating links between heat stress and cardiovascular mortality and morbidity in Prague, Czech Republic. Int J Biometeorol. 2018; 62(1):85-96.
31. Marchant B, Donaldson G, Mridha K, Scarborough M, Timmis AD. Mechanisms of cold intolerances in patients with angina. J Am Coll Cardiol. 1994; 23(3):630-6.
32. Keatinge WR, Coleshaw SRK, Cotter F, Mattock M, Murphy M, Chelliah R. Increases in platelet and red cell counts, blood viscosity, and arterial pressure during mild surface cooling: Factors in mortality from coronary and cerebral thrombosis in winter. Br Med J. 1984; 289(6456):1405-8.
33. Sun Z, Bello-Roufai M, Wang X. RNAi inhibition of mineralocorticoid receptors prevents the development of cold-induced hypertension. Am J Physiol Circ Physiol. 2008; 294(4):H1880-7.
34. Tsibulnikov SY, Maslov LN, Naryzhnaya NV, Ivanov VV, Bushov YuV, Voronkov NS, et al. Impact of cold adaptation on cardiac tolerance to ischemia/reperfusion. Role of glucocorticoid and thyroid hormones. Gen Physiol Biophys. 2019; 38(3):245-51.
35. Gapon LI, Shurkevich NP, Vetoshkin AS. [Structural and functional changes in the heart and 24-hour arterial pressure profile in patients with arterial hypertension in the Far North]. Klin Med (Mosk). 2009; 87(9):23-9.
36. Shechtman O, Papanek PE, Fregly MJ. Reversibility of cold-induced hypertension after removal of rats from cold. Can J Physiol Pharmacol. 1990; 68(7):830-5.
37. Freegly MJ, Shechtman O, Bergen P van, Reeber C, Papanek PE. Changes in blood pressure and dipsogenic responsiveness to angiotensin II during chronic exposure of rats to cold. Pharmacol Biochem Behav. 1991; 38(4):837-42.
38. Bergen P Van, Fregly MJ, Papanek PE. Effect of a reduction in sodium intake on cold-induced elevation of blood pressure in the rat. Proc Soc Exp Biol Med. 1992; 200(4):472-9.
39. Tibenska V, Benesova A, Vebr P, Liptakova A, Hejnová L, Elsnicová B, et al. Gradual cold acclimation induces cardioprotection without affecting β-adrenergic receptor-mediated adenylyl cyclase signaling. J Appl Physiol. 2020; 128(4):1023-32.
40. Drawnel FM, Archer CR, Roderick HL. The role of the paracrine/autocrine mediator endothelin-1 in regulation

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[DOR: 20.1001.1.1028852.2024.28.2.1.8]
[DOI: 10.61186/ibj.3872]

of cardiac contractility and growth. Br J Pharmacol. 2013; 168(2):296-317.
41. Ennis I, Aiello E, Cingolani H, Perez N. The autocrine/paracrine loop after myocardial stretch: mineralocorticoid receptor activation. Curr Cardiol Rev. 2013; 9(3):230-40.
42. Feniman De Stefano GMM, Zanati-Basan SG, De Stefano LM, Silva VROE, Xavier PS, Barretti P, et al. Aldosterone is associated with left ventricular hypertrophy in hemodialysis patients. Ther Adv Cardiovasc Dis. 2016; 10(5):304-13.
43. Frangogiannis NG. Fibroblasts and the extracellular matrix in right ventricular disease. Cardiovasc Res. 2017; 113(12):1453-64.
44. Seo K, Parikh VN, Ashley EA. Stretch-induced biased signaling in angiotensin II Type 1 and apelin receptors for the mediation of cardiac contractility and hypertrophy. Front Physiol. 2020; 11:181.
45. Wang L, Tan A, An X, Xia Y, Xie Y. Quercetin dihydrate inhibition of cardiac fibrosis induced by angiotensin II in vivo and in vitro. Biomed Pharmacother. 2020; 127:110205.
46. Krylov IF, Tigranian RA. [Hormonal metabolic status of the human body under the conditions of the Far North]. Kosm Biol Aviakosm Med. 1986; 20(5):85-8.
47. Bligh Tynan ME, Bhagwat SA, Castonguay TW. The effects of chronic cold exposure on diurnal corticosterone and aldosterone rhythms in sprague-dawley rats. Physiol Behav. 1993; 54(2):363-7.
48. Janský L, Vybíral S, Trubačová M, OkrouhlÍk J. Modulation of adrenergic receptors and adrenergic functions in cold adapted humans. Eur J Appl Physiol. 2008; 104(2):131-5.
49. Obut TA, Saryg SK, Ovsukova MV, Dementeva TU, Obut ET, Erdinieva TA. Effect of dehydro-epiandrosterone sulfate on aldosterone level during stress exposures: role of μ-opioid receptors. Bull Exp Biol Med. 2012; 152(6):696-8.
50. Baron A, Riesselmann A, Fregly MJ. Effect of chronic treatment with clonidine and spironolactone on cold-induced elevation of blood pressure. Pharmacology. 1991; 43(4):173-86.
51. Wang X, Sun Z, Cade R. Prolonged attenuation of cold-induced hypertension by adenoviral delivery of renin antisense. Kidney Int. 2005; 68(2):680-7.
52. Cassis LA. Role of angiotensin II in brown adipose thermogenesis during cold acclimation. Am J Physiol Metab. 1993; 265(6 Pt 1):E860-5.
53. Cassis L, Laughter A, Fettinger M, Akers S, Speth R, Burke G, et al. Cold exposure regulates the renin-angiotensin system. J Pharmacol Exp Ther. 1998; 286(2):718-26.
54. Shechtman O, Fregly MJ, Van Bergen P, Papanek PE. Prevention of cold-induced increase in blood pressure of rats by captopril. Hypertension. 1991; 17(6 Pt 1):763-70.
55. Fregly MJ, Rossi F, Bergen P, Brummermann M, Cade JR. Effect of chronic treatment with losartan potassium (DuP 753) on the elevation of blood pressure during chronic exposure of rats to cold. Pharmacology. 1993; 46(4):198-205.
56. Fregly MJ, Brummermann M. Effect of chronic exposure to cold on vascular responsiveness to phenylephrine and angiotensin II. Pharmacology. 1993; 47(4):237-43.
57. Shechtman O, Sun Z, Fregly MJ, Katovich MJ. Increased tail artery vascular responsiveness to angiotensin II in cold- treated rats. Can J Physiol Pharmacol. 1999; 77(12):974-9.
58. Sun Z, Cade R, Zhang Z, Alouidor J, Van H. Angiotensinogen gene knockout delays and attenuates cold-induced hypertension. Hypertension. 2003; 41(2):322-7.
59. Chen GF, Sun Z. Effects of chronic cold exposure on the endothelin system. J Appl Physiol. 2006; 100(5):1719-26.
60. Zhang Y, Li L, Hua Y, Nunn JM, Dong F, Yanagisawa M, et al. Cardiac-specific knockout of ET(A) receptor mitigates low ambient temperature-induced cardiac hypertrophy and contractile dysfunction. J Mol Cell Biol. 2012; 4(2):97-107.
61. Fregly MJ, Rossi F, Sun Z, Tümer N, Cade JR, Hegland D, et al. Effect of chronic treatment with prazosin and L-arginine on the elevation of blood pressure during cold exposure. Pharmacology. 1994; 49(6):351-62.
62. Armstrong DW. Metabolic and endocrine responses to cold air in women differing in aerobic capacity. Med Sci Sport Exerc. 1998; 30(6):880-4.
63. Mineo PM, Cassell EA, Roberts ME, Schaeffer PJ. Chronic cold acclimation increases thermogenic capacity, non-shivering thermogenesis and muscle citrate synthase activity in both wild-type and brown adipose tissue deficient mice. Comp Biochem Physiol A Mol Integr Physiol. 2012; 161(4):395-400.
64. Tsibulnikov SY, Maslov LN, Ivanov VV, Naryzhnaya NV, Tsibulnikova MR. [Infarct-limiting effect of adaptation to continuous cold exposure]. Ross Fiziol zhurnal Im IM Sechenova. 2016; 102(11):1363-8.
65. Maslov LN, Naryzhnaia NV. [Impact of long-term adaptation to cold on the state of cardiovascular system]. Ross Fiziol Zh Im I M Sechenova. 2015; 101(5):525-37.
66. Tsibulnikov S, Maslov L, Voronkov N, Oeltgen P. Thyroid hormones and the mechanisms of adaptation to cold. Hormones. 2020; 19(3):329-39.
67. Lu S, Xu D. Cold stress accentuates pressure overload-induced cardiac hypertrophy and contractile dysfunction: Role of TRPV1/AMPK-mediated autophagy. Biochem Biophys Res Commun. 2013; 442(1-2):8-15.
68. Jankovic A, Korac A, Buzadzic B, Otasevic V, Stancic A, Vucetic M, et al. Endocrine and metabolic signaling in retroperitoneal white adipose tissue remodeling during cold acclimation. J Obes. 2013; 2013: 937572.
69. Zhao ZJ, Chi QS, Cao J, Wang DH. Seasonal changes of body mass and energy budget in striped hamsters: The role of leptin. Physiol Biochem Zool. 2014; 87(2):245-56.
70. Kinoshita K, Ozaki N, Takagi Y, Murata Y, Oshida Y, Hayashi Y. Glucagon is essential for adaptive thermogenesis in brown adipose tissue. Endocrinology. 2014; 155(9):3484-92.
71. Egecioglu E, Anesten F, Schéle E, Palsdottir V. Interleukin-6 is important for regulation of core body

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[DOR: 20.1001.1.1028852.2024.28.2.1.8]
[DOI: 10.61186/ibj.3872]

temperature during long-term cold exposure in mice. Biomed Rep. 2018; 9(3):206-12.
72. Ketzer LA, Arruda AP, Carvalho DP, de Meis L. Cardiac sarcoplasmic reticulum Ca 2^+ -ATPase: heat production and phospholamban alterations promoted by cold exposure and thyroid hormone. Am J Physiol Circ Physiol. 2009; 297(2):H556-63.
73. Vucetic M, Otasevic V, Korac A, Stancic A, Jankovic A, Markelic M, et al. Interscapular brown adipose tissue metabolic reprogramming during cold acclimation: Interplay of HIF-1α and AMPKα. Biochim Biophys Acta. 2011; 1810(12):1252-61.
74. Heusch G. Molecular basis of cardioprotection: signal transduction in ischemic pre-, post-, and remote conditioning. Circ Res. 2015; 116(4):674-99.
75. Yellon DM, Downey JM. Preconditioning the myocardium: from cellular physiology to clinical cardiology. APS. 2003; 83(4):1113-51.
76. Maslov LN, Tsibulnikov SY, Prokudina ES, Popov SV, Boshchenko AA, Singh N, et al. Trigger, signaling mechanism and end effector of cardioprotective effect of remote postconditioning of heart. Curr Cardiol Rev. 2019; 15(3):177-87.
77. Tsibulnikov SY, Maslov LN, Gorbunov AS, Voronkov NS, Boshchenko AA, Popov SV, et al. A review of humoral factors in remote preconditioning of the heart. J Cardiovasc Pharmacol Ther. 2019; 24(5):403-21.
78. Maslov LN, Vychuzhanova EA. The role of the sympathoadrenal system in adaptation to cold. Neurosci Behav Physiol. 2016; 46(5):589-600.
79. Asimakis GK, Inners-Mcbride K, Conti VR, Yang CJ. Transient beta adrenergic stimulation can precondition the rat heart against postischaemic contractile dysfunction. Cardiovasc Res. 1994; 28(11):1726-34.
80. Minatoguchi S, Uno Y, Kariya T, Arai M, Wang N, Hashimoto K, et al. Cross-talk among noradrenaline, adenosine and protein kinase C in the mechanisms of ischemic preconditioning in rabbits. J Cardiovasc Pharmacol. 2003; 41 Suppl 1:S39-47.
81. Bankwala Z, Hale SL, Kloner RA. Alpha-adrenoceptor stimulation with exogenous norepinephrine or release of endogenous catecholamines mimics ischemic preconditioning. Circulation. 1994; 90(2):1023-8.
82. Tsuchida A, Liu Y, Liu GS, Cohen MV, Downey JM. Alpha 1-adrenergic agonists precondition rabbit ischemic myocardium independent of adenosine by direct activation of protein kinase C. Circ Res. 1994; 75(3):576-85.
83. Karliner JS, Honbo N, Epstein CJ, Xian M, Lau YFC, Gray MO. Neonatal mouse cardiac myocytes exhibit cardioprotection induced by hypoxic and pharmacologic preconditioning and by transgenic overexpression of human Cu/Zn superoxide dismutase. J Mol Cell Cardiol. 2000; 32(10):1779-86.
84. Ravingerová T, Pancza D, Ziegelhoffer A, Styk J. Preconditioning modulates susceptibility to ischemia-induced arrhythmias in the rat heart: The role of α-adrenergic stimulation and K(ATP) channels. Physiol Res. 2002; 51(2):109-19.
85. Yabe KI, Ishishita H, Tanonaka K, Takeo S. Pharmacologic preconditioning induced by beta-adrenergic stimulation is mediated by activation of protein kinase C. J Cardiovasc Pharmacol. 1998; 32(6):962-8.
86. Salie R, Moolman JA, Lochner A. The mechanism of beta-adrenergic preconditioning: roles for adenosine and ROS during triggering and mediation. Basic Res Cardiol. 2012; 107(5):281.
87. Tibenská V, Marvanova A, Elsnicová B, Hejnova L, Vebr P, Novotný J, et al. The cardioprotective effect persisting during recovery from cold acclimation is mediated by the β2-adrenoceptor pathway and Akt activation. J Appl Physiol. 2021; 130(3):746-55.
88. Saponaro F, Sestito S, Runfola M, Rapposelli S, Chiellini G. Selective thyroid hormone receptor-beta (TRβ) agonists: new perspectives for the treatment of metabolic and neurodegenerative disorders. Front Med. 2020; 7:331.
89. Seara FAC, Maciel L, Barbosa RAQ, Rodrigues NC, Silveira ALB, Marassi MP, et al. Cardiac ischemia/reperfusion injury is inversely affected by thyroid hormones excess or deficiency in male Wistar rats. PLoS One. 2018; 13(1):e0190355.
90. Jeddi S, Zaman J, Zadeh-Vakili A, Zarkesh M, Ghasemi A. Involvement of inducible nitric oxide synthase in the loss of cardioprotection by ischemic postconditioning in hypothyroid rats. Gene. 2016; 580(2):169-76.
91. Suarez J, Wang H, Scott BT, Ling H, Makino A, Swanson E, et al. In vivo selective expression of thyroid hormone receptor α1 in endothelial cells attenuates myocardial injury in experimental myocardial infarction in mice. Am J Physiol Regul Integr Comp Physiol. 2014; 307(3):R340-6.
92. Kumar A, Taliyan R, Sharma PL. Evaluation of thyroid hormone induced pharmacological preconditioning on cardiomyocyte protection against ischemic-reperfusion injury. Indian J Pharmacol. 2012; 44(1):68-72.
93. Abohashem-Aly AA, Meng X, Li J, Sadaria MR, Ao L, Wennergren J, et al. DITPA, a thyroid hormone analog, reduces infarct size and attenuates the inflammatory response following myocardial ischemia. J Surg Res. 2011; 171(2):379-85.
94. Lieder HR, Braczko F, Gedik N, Stroetges M, Heusch G, Kleinbongard P. Cardioprotection by post-conditioning with exogenous triiodothyronine in isolated perfused rat hearts and isolated adult rat cardiomyocytes. Basic Res Cardiol. 2021; 116(1):27.
95. Krylatov AV, Maslov LN, Voronkov NS, Boshchenko AA, Popov SV, Gomez L, et al. Reactive oxygen species as intracellular signaling molecules in the cardiovascular system. Curr Cardiol Rev. 2018; 14(4):290-300.
96. Bozhko AP, Gorodetskaia IV. [Importance of thyroid hormones in the realization of the protective effects of cold adaptation]. Patol Fiziol i Eksp Ter. 1994; 4:29-32.
97. Wang X, Che H, Zhang W, Wang J, Ke T, Cao R, et al. Effects of mild chronic intermittent cold exposure on rat organs. Int J Biol Sci. 2015; 11(10):1171-80.
98. Schmidt MC, Askew EW, Roberts DE, Prior RL, Ensign WY, Hesslink RE. Oxidative stress in humans training in a cold, moderate altitude environment and their response

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[DOR: 20.1001.1.1028852.2024.28.2.1.8]
[DOI: 10.61186/ibj.3872]

to a phytochemical antioxidant supplement. Wilderness Environ Med. 2002; 13(2):94-105.
99. Terblanche SE, Masondo TC, Nel W. Effects of chronic cold exposure on the activities of cytochrome c oxidase, glutathione peroxidase and glutathione reductase in rat tissues (Rattus norvegicus). Comp Biochem Physiol B Biochem Mol Biol. 2000; 127(3):319-24.
100. Selman C, McLaren JS, Himanka MJ, Speakman JR. Effect of long-term cold exposure on antioxidant enzyme activities in a small mammal. Free Radic Biol Med. 2000; 28(8):1279-85.
101. Emirbekov EZ, L'vova SP, Gasangadzhieva AG. [Effect of repeated cold stress on intensity of lipid peroxidation and tissue antioxidant system]. Bull Exp Biol Med. 1998;125(4):339-41.
102. Bal NC, Maurya SK, Pani S, Sethy C, Banerjee A, Das S, et al. Mild cold induced thermogenesis: are BAT and skeletal muscle synergistic partners? Biosci Rep. 2017; 37(5):BSR2017108
103. Chytilová A, Borchert GH, Mandíková-Alánová P, Hlaváčková M, Kopkan L, Khan MAH, et al. Tumour necrosis factor- α contributes to improved cardiac ischaemic tolerance in rats adapted to chronic continuous hypoxia. Acta Physiol. 2015; 214(1):97-108.
104. Flaherty MP, Guo Y, Tiwari S, Rezazadeh A, Hunt G, Sanganalmath SK, et al. The role of TNF-α receptors p55 and p75 in acute myocardial ischemia/reperfusion injury and late preconditioning. J Mol Cell Cardiol. 2008; 45(6):735-41.
105. Li HX, Cui XL, Xue FS, Yang GZ, Liu YY, Liu Q, et al. Inhibition of glycogen synthase kinase-3β is involved in cardioprotection by α7nAChR agonist and limb remote ischemic postconditionings. 2018; 38(5):BSR20181315.
106. Mastitskaya S, Marina N, Gourine A, Gilbey MP, Spyer KM, Teschemacher AG, et al. Cardioprotection evoked by remote ischaemic preconditioning is critically dependent on the activity of vagal pre-ganglionic neurones. Cardiovasc Res. 2012; 95(4):487-94.
107. Manukhin BN, Anan'ev VN, Kichikulova TP, Anan'eva ON. M-cholinergic response of arterial pressure in rabbit small intestine blood vessels during cold adaptation. Dokl Biol Sci. 2003; 391:312-4.
108. Gorbunov AS, Maslov LN, Jaggi AS, Singh N, Petrocellis LD, Boshchenko AA, et al. Physiological and pathological role of TRPV1, TRPV2 and TRPV4 channels in heart. Curr Cardiol Rev. 2019; 15(4):244-51.
109. Nazari A, Sadr SS, Faghihi M, Azizi Y, Hosseini M-J, Mobarra N, et al. Vasopressin attenuates ischemia-reperfusion injury via reduction of oxidative stress and inhibition of mitochondrial permeability transition pore opening in rat hearts. Eur J Pharmacol. 2015; 760:96-102.
110. Z Zeisberger E, Roth J, Simon E. Changes in water balance and in release of arginine vasopressin during thermal adaptation in guinea-pigs. Pflügers Arch. 1988; 412(3):285-91.
111. Takagi S, Kihara Y, Sasayama S, Mitsuiye T. Slow inactivation of cardiac L-type $Ca2^+$ channel induced by cold acclimation of guinea pig. Am J Physiol. 1998; 274(2): R348-56.
112. Fliegner D, Westermann D, Riad A, Schubert C, Becher E, Fielitz J, et al. Up-regulation of PPARγ in myocardial infarction. Eur J Heart Fail. 2008; 10(1):30-8.
113. Zhong C Bin, Chen X, Zhou XY, Wang XB. The role of peroxisome proliferator-activated receptor γ in mediating cardioprotection against ischemia/reperfusion injury. J Cardiovasc Pharmacol Ther. 2018; 23(1):46-56.
114. Stancic A, Buzadzic B, Korac A, Otasevic V, Jankovic A, Vucetic M, et al. Regulatory role of PGC-1α/PPAR signaling in skeletal muscle metabolic recruitment during cold acclimation. J Exp Biol. 2013; 216(Pt 22):4233-41.
115. Tsibulnikov SY, Maslov LN, Naryzhnaya NV, Ma H, Lishmanov YB, Oeltgen PR, et al. Role of protein kinase C, PI3 kinase, tyrosine kinases, no-synthase, KATP channels and MPT pore in the signaling pathway of the cardioprotective effect of chronic continuous hypoxia. Gen Physiol Biophys. 2018; 37(5):537-47.
116. Kikuchi Utsumi K, Gao B, Ohinata H, Hashimoto M, Yamamoto N, Kuroshima A. Enhanced gene expression of endothelial nitric oxide synthase in brown adipose tissue during cold exposure. Am J Physiol Regul Integr Comp Physiol. 2002; 282(2):R623-6.
117. Hostrup A, Christensen GL, Bentzen BH, Liang B, Aplin M, Grunnet M, et al. Functionally selective AT 1 receptor activation reduces ischemia reperfusion injury. Cell Physiol Biochem. 2012; 30(3):642-52.
118. Nuñez RE, Javadov S, Escobales N. Critical role of angiotensin II type 2 receptors in the control of mitochondrial and cardiac function in angiotensin II-preconditioned rat hearts. Pflugers Arch Eur J Physiol. 2018; 470(9):1391-403.
119. Nuñez RE, Castro M, Javadov S, Escobales N. Angiotensin II and ischemic preconditioning synergize to improve mitochondrial function while showing additive effects on ventricular postischemic recovery. J Cardiovasc Pharmacol. 2014; 64(2):172-9.
120. Nuñez RE, Javadov S, Escobales N. Angiotensin II-preconditioning is associated with increased PKCε/PKCδ ratio and prosurvival kinases in mitochondria. Clin Exp Pharmacol Physiol. 2017; 44(12):1201-12.
121. Lange SA, Wolf B, Schober K, Wunderlich C, Marquetant R, Weinbrenner C, et al. Chronic angiotensin II receptor blockade induces cardioprotection during ischemia by increased PKC-ε expression in the mouse heart. J Cardiovasc Pharmacol. 2007; 49(1):46-55.
122. Wang P, Gallagher KP, Downey JM, Cohen MV. Pretreatment with endothelin-1 mimics ischemic preconditioning against infarction in isolation rabbit heart. J Mol Cell Cardiol. 1996; 28(3):579-88.
123. Bugge E, Ytrehus K. Endothelin-1 can reduce infarct size through protein kinase C and KATP channels in the isolated rat heart. Cardiovasc Res. 1996; 32(5):920-9.
124. Zhang M, Gu WW, Hong XY. Involvement of endothelin 1 in remote preconditioning-induced cardioprotection through connexin 43 and Akt/GSK-3β signaling pathway. Sci Rep. 2018; 8(1):10941.
125. Tamareille S, Terwelp M, Amirian J, Felli P, Zhang XQ, Barry WH, et al. Endothelin-1 release during the early phase of reperfusion is a mediator of myocardial reperfusion injury. Cardiology. 2013; 125(4):242-9.

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[DOR: 20.1001.1.1028852.2024.28.2.1.8]
[DOI: 10.61186/ibj.3872]