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INDUCTION OF VASODILATION BY HYDROGEN PEROXIDE AND ITS APPLICATION IN EXERCISE SCIENCE

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ABSTRACT: Regular exercise or physical activity benefits the cardiovascular system, lowers mortality and morbidity, and is a particularly important factor for maintaining the health of blood vessels by improving the function of endothelial cells. Shear stress and increased metabolic rate caused by exercise induce vasodilation by generating endothelium-derived relaxing factors (EDRF) such as nitric oxide. In addition, some studies suggest that vasodilation is also induced by endothelium-derived hyperpolarizing factors (EDHF) and substances such as H_2O_2. Thus, we undertook this study to show that reactive oxygen species such as H_2O_2 that have not previously been investigated in the field of exercise science may induce vasodilation and an increase in blood pressure, and to provide information for application in the field of exercise science. In this review, we discuss reports on H_2O_2 published in the fields of basic science and exercise science while focusing on vasodilation induced by H_2O_2. H_2O_2 induces vasodilation by simultaneously increasing endothelial NOS (eNOS) and directly activating the Ca^{2+}- activated K^+ channels of vascular smooth muscle cells. A novel study should be conducted in the field of H_2O_2 as a factor of vasodilation via increased metabolic rate during exercise.

KEY WORDS: hydrogen peroxide, vasodilation, nitric oxide, nitric oxide synthase

Introduction

Regular physical activity benefits human health by reducing risk factors such as cardiovascular disease, cancer, and metabolic syndrome and by lowering mortality and morbidity [3,12]. Exercise is thought to have positive effects in countering cardiovascular diseases in general and vascular diseases, including hypertension, in particular [55]. Several studies have reported that exercise induces changes in blood pressure, lipid and glucose metabolism, neurohormonal factors, weight, and shear stress [1,34,57].

A number of studies in vascular physiology have reported that exercise induces normal vasodilation by improving the functions of endothelial cells [7,28,30].

Specifically, studies suggest that vasodilation is induced by the increase of nitric oxide (NO) resulting from increased shear stress during exercise. Such studies focused on the role of NO as an endothelium-derived relaxing factor (EDRF). Other studies have shed light on the role of endothelium-derived hyperpolarizing factors (EDHFs), especially hydrogen peroxide (H_2O_2), which are strong vasodilators [6,16,35].

The vasodilation response induced by H_2O_2 has not been studied thus far in the field of exercise science. Thus, the role of increased H_2O_2 as an oxidative stress inducer during exercise needs to be further examined with regards to its role in vasodilation and hypertension in studies on exercise physiology. This review, based on previous studies in basic science and exercise science, aims to illuminate the effect and role of H_2O_2, which increases during exercise, on vasodilation and to provide basic information to support experimental research on H_2O_2 and the vasodilation response during exercise. This review focuses on H_2O_2 and limits the discussion on other vasodilators to a minimum.

Overview of vasodilation by nitric oxide and H_2O_2

Vasodilation during exercise is determined by the composite action of a number of local vasoregulators and is a physiological response essential for the continuation of exercise. The increase of blood flow via vasodilation during exercise helps maintain a balance with the metabolic demand [9], contraction frequency of skeletal muscles [33], and muscular oxygen uptake [4]. In exercise physiology, sub-

stances such as NO, K^+ ion, H^+ ion, oxygen, and lactate are believed to be local vasodilators, but this review focuses exclusively on the vasodilation response caused by H_2O_2.

The role of NO in vasodilation

Before examining the vasodilation response of H_2O_2, we need to summarize the vasodilation response of NO. NO is the most well-known vasodilator and is generated by endothelial cells and skeletal muscle cells [9]. NO was first discovered by Furchgott and Zawadzki in 1980 [21] and has been classified as an EDRF ever since.

NO is a strong vasodilator that is produced during conversion of L-arginine to citrulline, which is mediated by Ca^{2+}-dependent activation of nitric oxide synthase (NOS) in endothelial cells [44]. According to Kinlay et al [27], weakened arterial compliance occurs after blockage of NO generation in healthy people, suggesting a close association between NO and vasodilation. Rowley [48] also observed frequent induction of hypertension in endothelial NOS (eNOS) knockout mice, and on the basis of that result, he suggested that NOS is correlated with vasodilation and peripheral resistance.

The increase in shear stress and acetylcholine (ACh) level during exercise is known to play an important role in the mechanism of vasodilation induced by NO during exercise, and blood vessels are dilated by repolarization and the activation of K^+ channels of vascular smooth muscle cells (VSMCs), the activation of soluble guanylate cyclase (sGC), and the inhibition of myosin light-chain kinase (MLCK) [53]. A number of human and animal studies suggest that increased eNOS in endothelial cells induced by exercise causes increased NO generation [51], which in turn has positive effects during exercise [13,49,58]. Therefore, exercise increases NO generation and bioavailability by enhancing the expression and activation of eNOS. Figure 1 summarizes the increase of NO and the mechanism of vasodilation during exercise.

H_2O_2 as a candidate endothelium-derived hyperpolarizing factor

Exercise is an effective non-pharmacological therapy for the regulation of vasodilation and blood pressure because it improves the function of endothelial cells, and it is effective in inducing the normal functions of blood vessels. In contrast, exercise increases the metabolic rate of cells when compared to cells at rest and consequently increases oxidative stress. Overproduction of reactive oxygen species (ROS) during exercise increases oxidative stress inducing negative effects in the human body; however, the excess amount of ROS products of OH^-, H_2O_2, O_2^-, and $ONOO^-$ suppress the antioxidant defence system, which in turn decreases the oxidative stress.

However, it is unreasonable to emphasize only the negative effects of H_2O_2 in vascular physiology since H_2O_2 is considered a candidate EDHF and can likely act as an important regulator of vasodilation and blood pressure, which are among the positive effects of exercise.

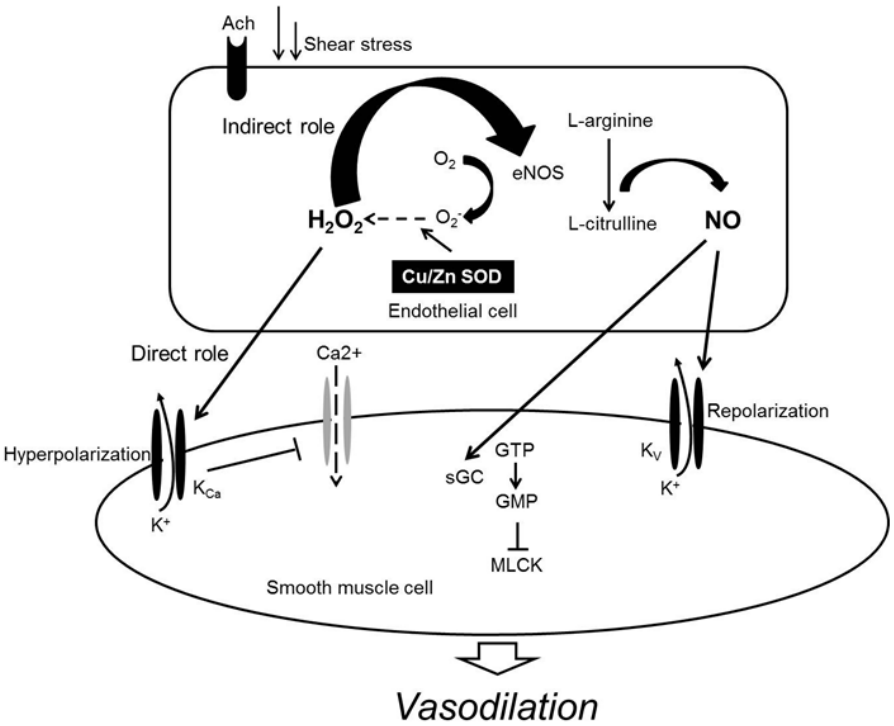

FIG. 1. SUMMARY OF THE MECHANISM OF DIRECT AND INDIRECT VASODILATION BY H_2O_2:
INCREASING H_2O_2 DURING EXERCISE INDUCES THE ENHANCED EXPRESSION OF ENOS IN ENDOTHELIAL CELLS AND A CONCOMITANT INCREASE IN NO GENERATION AND VASODILATION AS DEPICTED IN FIGURE 1. INCREASING H_2O_2 IN ENDOTHELIAL CELLS DURING EXERCISE DILATES BLOOD VESSELS BY ACTIVATING CA^{2+} – ACTIVATED K^+ CHANNELS IN VASCULAR SMOOTH MUSCLES AND CONSEQUENTLY INDUCES HYPERPOLARIZATION OF RESTING MEMBRANE POTENTIAL.
Note: → activation, ⊣ inactivation or inhibition. Ach: acetylcholine; eNOS: endothelial nitric oxide synthase; NO: nitric oxide; Kv: voltage gated K^+ channels; KCa: Ca^{2+} activated K^+ channels; sGC: soluble guanylate cyclase; GTP/GMP: guanosine triphosphate/guanosine monophosphate; MLCK: myosin light chain kinase

EDHF was first discovered by Feletou and Vanhoutte [16] and Chen et al. [6] in 1988. EDHF was so named because it induces hyperpolarization of the membrane potential in VSMCs. Various animal and human studies have established H_2O_2 as a candidate EDHF and reported that non-NO, non-prostaglandin (PGI_2)-mediated vasodilation is inhibited by catalase in agonist and flow-induced vasodilation [32,37,59].

H_2O_2 has no charge as a non-radical substance, is a more stable oxide than other ROS, and passes through cell membranes relatively easily [54]. H_2O_2 generated inside cells regulates cellular signalling by acting as a second messenger [5]. It is generated mainly when a superoxide anion is dismutated to H_2O_2, a reaction that is catalysed by superoxide dismutase (SOD), and in special situations (disease, cardiovascular disease, metabolic syndrome, etc.) H_2O_2 produces hydroxyl radicals easily [46]. It is known that cytotoxicity becomes stronger when H_2O_2 is generated as a hydroxyl radical. According to previous reports, H_2O_2 is generated via cellular signalling in endothelial cells.

In endothelial cells, eNOS, cyclooxygenase (COX), lipoxygenases, cytochrome P-450, epoxygenases, and NAD(P)H generate both superoxide anion and H_2O_2 [18,26], and H_2O_2 reportedly acts as a vasodilator [15]. H_2O_2 is believed to regulate flow-induced vasodilation [41] and auto-regulation of the coronary artery [59].

In addition to its direct effects on vasodilation, H_2O_2 is known to induce vasodilation indirectly. The exact mechanism of H_2O_2 induced vasodilation has not been clarified yet, but here we propose a number of possibilities based on previous studies.

Indirect vasodilation effect of H_2O_2: Synergistic effects on eNOS expression

The indirect vasodilation effect of H_2O_2 can be explained by its connection to NO generation. To explain the enhanced endothelial functions caused by exercise, a number of studies invoke the possibility of a synergistic effect that H_2O_2, which increases during exercises, has on NO generation.

According to Lauer et al. [31], the increase of H_2O_2 during exercise does not induce an increased expression of eNOS in catalase-overexpressing transgenic mice. However, they did confirm an increase in the H_2O_2 and myocardial eNOS levels in the aorta and left ventricle. These results suggest the possibility that the increase of H_2O_2 may act synergistically to enhance vasodilation caused by eNOS and NO during exercise. Moreover, Drummond et al. [14] reported that H_2O_2 is an essential regulator of eNOS transcription.

Thengchaisri et al. [55] reported that the restoration of coronary vasodilation during exercise in Yucatan miniature swine models with coronary artery occlusion is associated with the activation of NOS and that H_2O_2 plays an important role in this response. In particular, these researchers observed the restoration of vasodilation at physiological H_2O_2 concentrations of 0.3–10 m.

Fukai et al. [20] suggested that the removal of superoxide anions by the activation of extracellular SOD (ec-SOD) is an important mechanism in the increase of NO induced by H_2O_2 during exercise. The increase of H_2O_2 during exercise can be explained by a mechanism wherein coenzyme Q radicals are combined with oxygen molecules during the synthesis of ATP and, as a result, superoxide anions increase and are simultaneously dismutated to H_2O_2 [17]. Therefore, superoxide anions are considered an essential source for the generation of H_2O_2 during exercise.

The hypothesis that the increased generation of H_2O_2 in patients with coronary artery disease can act as a compensatory mechanism for reduced bioavailability of NO may reflect the vasodilation characteristic of H_2O_2 [41]. Therefore, H_2O_2 increase during exercise needs to be studied further from the viewpoint of vascular physiology not only for its negative roles in oxidative stress, but also as a positive factor that supports NO generation via exercise-enhanced endothelial cell functions. Figure 1 summarizes the indirect vasodilation effect of H_2O_2.

Direct vasodilation by H_2O_2: the role of H_2O_2 as an EDHF

In the previous section, we illuminated the indirect role of H_2O_2 in NO generation. Research on the direct effect of H_2O_2 on vasodilation can explain its role as a strong EDHF. EDHF is a hyperpolarization factor isolated from endothelial cells that hyperpolarize the membrane potential of VSMCs. Moreover, EDHF is thought to cause vasodilation because vasodilation induced by acetylcholine is observed even in the skeletal muscular arteries of eNOS knockout mice [24], confirming that vasodilation can be induced by factors other than EDRF.

Direct vasodilation in response to H_2O_2 is observed in bovine pulmonary arteries [8], bovine coronary arteries [25], cat cerebral arteries [19], and porcine coronary arteries [2,23]. However, there are contradictory reports that suggest that H_2O_2 induces contraction in canine basilar arteries [60] and rat aorta [50,52]. This discrepancy may result from differences in tissue, animal species, the trophic state of animals, or oxidative stress level at rest, and requires further research.

Some researchers have reported that the EDHF-mediated vascular response is inhibited by Ca^{2+}-activated K^+ (K_{Ca}) channel blockers [36,39]. K^+ channels regulate the resting membrane potential and basal vascular tone [43]. Activation of K^+ channels induces hyperpolarization and inhibits the activation of Ca^{2+} channels (blood vessels possess an L-type Ca^{2+} channel) and consequently induces vasodilation [10]. K_{Ca} channels, a super-family of K^+ channels, are activated by depolarization and an increase of Ca^{2+} in cells [38] and induce hyperpolarization and vasodilation because of their high conductance [42,45].

A study by Matoba et al. [36] uncovered H_2O_2 as a potential EDHF. These researchers examined the acetylcholine concentrations in response to different treatments in a group simultaneously treated with indomethacin, a COX inhibitor, L-NNA, an eNOS inhibitor, and catalase, and compared them to the concentrations observed in another group treated with indomethacin and L-NNA alone. They observed a significant decrease in the vasodilation response of

the group treated with the above-mentioned 3 drugs. These results suggest the possible existence of a vasodilator besides COX and NO and, considering the decrease in vasodilation caused by catalase, implicate H_2O_2 as that vasodilator. Furthermore, since treatment with a high concentration of KCl solution mimics treatment with catalase, the vasodilation response of H_2O_2 may be closely related to K^+ channels. Among the studies that support this result, Cohen and Vanhoutte [11] reported a vasodilation response of H_2O_2 and the inhibition of vasodilation by a K_{Ca} inhibitor in the mesenteric arteries of endothelium-denuded mice. Matoba et al. [36,37] obtained similar results using human mesenteric arteries. Hayabuchi et al. [23] observed the activation of K_{Ca} channels directly by H_2O_2 or dependent on cGMP from electro-physiological recordings by using patch-clamping and reported that in addition to direct activation of K^+ channels, H_2O_2 affects cellular signalling. Their results suggest that H_2O_2 induces the hyperpolarization of VSMCs by directly altering the K_{Ca} channel molecules.

In contrast, Rogers et al. [47] reported that H_2O_2 induced vasodilation by activating 4-aminopyridine-sensitive (voltage-gated K^+ channel blocker) Kv channels in the coronary arteries of dogs, suggesting that H_2O_2 produced during exercise can potentially prevent myocardial ischaemia.

An interesting report reveals that treatment with quercetin, a flavonoid with known antioxidant effects, activates K_{Ca} channels by generating H_2O_2 in VSMCs [10], suggesting that, in addition to endothelium-dependent vasodilation, H_2O_2 generated in VSMCs is directly involved in vasodilation. However, further research is required to better understand the vasodilation response of H_2O_2 to non-endothelial cells. The findings presented above demonstrate that direct vasodilation by H_2O_2 occurs via the activation of K_{Ca} channels. Figure 1 summarizes the mechanism of direct vasodilation by H_2O_2.

Application of H_2O_2 in exercise science

Exercise causes stress in our bodies that in turn induces the activation of reduction-oxidation (redox) pathways resulting in the increased generation of oxide in response to the rising metabolic rate. Unfortunately, however, increased H_2O_2 during exercise is mostly viewed negatively, as a source of oxidative stress, and vasodilation induced by H_2O_2 has not been viewed as an important topic in the area of exercise science. The negative effects of H_2O_2 cannot be neglected according to the research of Kumar et al. [29] that suggests the possibility of decreasing the vasodilatation response by the eNOS reducing activity promoter H_2O_2 . In addition to the negative effects of H_2O_2, Wegwood and Black [56] reported that reduced expression of eNOS is due to the production of H_2O_2 caused by endothelin A receptor in the pulmonary artery. Thus, the role of H_2O_2 has been described to have contradictory characteristics of regulation in vasoconstriction and vasodilation. These characteristics can be dependent on the regulation of exercising muscle and skin blood flow, and also cause high blood pressure when H_2O_2 plays a negative role in blood vessels.

Although numerous studies have reported that exercise interventions enhance vascular compliance and health by improving the functions of endothelium in patients with vascular diseases such as hypertension, most of these studies focus on NO. Various basic studies suggest either an association or independence between NO and H_2O_2. Therefore, exercise science requires further, in-depth research on how H_2O_2 increase during exercise affects blood vessels.

Research by Goto et al. [22] suggests that the cycling of 50% VO_{2max} induced the increase of flow-mediated blood flow in conditions inhibiting the generation of eNOS and that exercise improves endothelium-dependent hyperpolarization in type 2 diabetic rats [40]. These results emphasize the importance of further investigations in the roles of EDHF including H_2O_2 in exercise science. Thus, we conclude with caution that H_2O_2 is a key player in cardiovascular research including its role as a regulator of hypertension during exercise.

The relationship between H_2O_2 and increased metabolic rate and vasodilation during exercise is a consistent topic to be studied. In particular, further study of the role of H_2O_2 is needed in terms of exercise muscle and increase in skin blood flow.

Conclusion

Vascular response to exercise and H_2O_2 is still an interesting unexplored topic in the area of exercise science. On one hand, increased oxidative stressors such as H_2O_2 can be negative byproducts of the response to exercise, and on the other hand, they can act as positive factors regulating vasodilation and peripheral vascular resistance during exercise. It appears that H_2O_2 is rarely described as a negative by-product, because it has been known for a long time that ROS fulfil many important cellular functions such as signal transduction, cellular proliferation and apoptosis.

Considering that H_2O_2 is accepted as a strong candidate of EDHF and is a major factor for the expression of eNOS along with the direct activation of K_{Ca} channels in VSMCs, it should be recognized as a positive by-product of the physiological response to exercise.

This effect of H_2O_2 can also potentially explain the relation between exercise and blood pressure regulation. However, there are many issues yet to be addressed by researchers in the area of exercise science. Areas that have potential for intensive research include the intensity and type of exercise required to induce the positive effects of H_2O_2 on blood vessels; the role of H_2O_2 in arteries of different sizes (diameter, conduit, and resistance arteries); and the balance of H_2O_2 with intrinsic antioxidants, in particular, the mechanism of blood-vessel and blood-pressure regulation by H_2O_2 generated during exercise.

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