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Research Article

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Research progress of relations between exercise training and obese chronic inflammatory

Yan Wang

Institute of Physical Education, Henan Polytechnic University, Jiaozuo, China

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ABSTRACT

Obesity can be considered as a chronic, systemic low-grade inflammation state induced by different inflammatory cytokines. The chronic inflammation in obesity may be a result of hypoxia in adipose tissue, macrophage infiltration to vascular wall and endocytoplasmic reticulum stress. Studies have shown that long-time regular exercise training can lower the levels of inflammatory markers and reduce the inflammation in obesity. Exercise training may reduce chronic inflammation by promoting the release of muscle-derived IL-6, increasing the total adipose tissue oxygenation, inhibiting the macrophage infiltration, reducing the number of pro-inflammatory monocots, down regulating the Toll-like receptor expression, increased the number of regulatory T cells. It will provide new ideas for the clinical treatment of chronic inflammation through further investigating the molecular mechanisms by which exercise training reduces chronic, systemic inflammation in obese individuals.

Key words: Obesity, exercise and fitness, biological factors, genetic variation

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INTRODUCTION

Chronic inflammation is the important risk factor of some chronic disease, like cardiovascular disease, type 2 diabetes mellitus [1, 2] and so on. Researches have reported that obesity can increase the concentrations of the organism's inflammatory marker and proinflammatory cytokine [3], and it is thought that this change could be the immanent cause of higher risk of some clinical metabolic disease that caused by the increase of adipose tissue. Studies in recent years find that exercise training can resist chronic inflammation and reduce the risk of disease and further clarify that the specific mechanism of exercise training's resistance to chronic inflammation contributes to the clinic treatment of obese chronic inflammation. This article summarizes the formation mechanism of obese chronic inflammation and the influence and possible mechanism of action of exercise training to obese chronic inflammation.

CHRONIC INFLAMMATION AND OBESITY

Inflammation is a defensive reaction of a living tissue with blood vascular system to damage factors. There are two immunization routes in the inflammatory course of reaction. One is innate immune pathway and the other is specific immune pathway. When the inflammatory response happens, engine body will secret a mass of inflammatory factors like tumor necrosis factor-α ,TNF-α , Interleukin-6,IL-6, C-reactive protein, CRP and so on to protect their own. Inflammation is an important defensive reaction for organism to resist the harmful stimulus in the outside world. It is advisable for normal immunity to have limited inflammatory response, but the continuous chronic inflammation caused by the body's insufficient removal activity is harmful. When in chronic inflammation, the proinflammatory factors in the plasma (such as TNF, IL-6, IL-1), anti-inflammatory factors (such as IL-10) and cytokine antagonists (solubleIL-1receptor antagonist,slL-1ra), etc tend to rise to 2 to 3 times of the normal value, with slight increase of Europhile granulocyte and natural killer cells at the same time[4].

Hotamisligil et al. proposed that obesity is a systemic low-grade chronic inflammatory condition induced by

different inflammatory factors [5]. And the main organ for the obese to release inflammatory factor is adipose tissue. Nearly all the obese people have higher inflammatory medium produced and secreted by the adipose tissue [6]. In most cases, obesity also can cause endothelium dysfunction, damage the blood vessel endothelium, lead to the accumulation of macrophage in vascular intimae, release more inflammatory medium [7] and eventually induce the chronic inflammation.

THE FORMATION MECHANISM OF OBESE CHRONIC INFLAMMATION

Oxygen Deficit of Adipose Tissue

Study shows that increased adipose tissue can lead to oxygen deficit. The possible reasons are as follows. First, the angiogenesis of adipose tissue in obese individuals and the genetic expression and protein synthesis of vascular endothelial growth factors (VEGF) in their adipose tissue are reduced and the capillary density of the adipose tissue decreases [8, 9]. But the over expression of VEGF and increasing angiogenesis can prevent hypoxia and insulin resistance related to obesity [10, 11]. Then the vasoconstriction of the obverse's adipose tissue increases [12]. In obese condition, the circulation concentration of angiotensinogen and angiogenesis Ⅱ closely related to vasoconstriction increases and the expression in adipose tissue also increases [13]. In addition, the blood flow volume in the obverse's adipose tissue significantly decreases [14]. Studies have found that oxygen deficit can activate the recruitment of inflammatory cells, increase the ratio of proinflammatory macrophage of type M1 and M2 in the adipose tissue, and thus accelerate the local and systemic inflammatory response. A recent study reported that compared with the thin, the overweight and the obese have lower oxygen content and higher inflammatory response in adipose tissue and there is a negative correlation between tissue inflammatory response and oxygen content. This suggests that oxygen deficit of adipose tissue may be an important mechanism resulting in inflammation of human body's adipose tissue.

Macrophage Infiltration

It is found at present that most of the obese exist injury of vascular endothelial cells. In the formative period, the endothelial cells will express endothelial cell adhesion molecule (ECAM), including vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) and so on, and these molecules can selectively attract and infiltrate leukocytes in circulation. At the same time, the vascular endothelial cells also release monocot chemo attractant protein-1 (MCP-1) and macrophage colony-stimulating factors (M-CSF) to recruit monocots in blood and stimulate the latter to differentiate into different types of macrophage in blood vessels and these macrophage in turn release proinflammatory cytokine, like IL-1, IL-6, TNF-α etc, which develops into local inflammatory response. And this local inflammatory response then stimulates other types of cells, such as endothelial cells, smooth muscle cells and so on to produce proinflammatory cytokine, which eventually makes the inflammatory response confined to endothelium dysfunction area expand to the systemic inflammatory response.

Endoplasmic Reticulum

Obesity can make the body's tissue especially adipose tissue increase demand for endoplasmic reticulum, lead to the structure changes of adipose tissue, increase protein and lipid synthesis and metabolic disorders of intracellular nutrient substance and energy. Endoplasmic reticulum stress then triggers unfolded protein response (UPR), which is realized mainly through three kinds of Tran membrane proteins, including protein kinase R-like endoplasmic reticulum kinase (PEAK), inositol requiring-1 (IRE-1) and activating transcription factor-6 (ATF-6). Studies have reported that the PRRK phosphorylation of ob/ob genotype obese mice is much higher than the wild type mice. PEAK can directly degrade the inhibiting factor IkB protein of nuclear factor kB (NF-kB), so as to stimulate NF-kB inflammatory pathway, which can induce transcription of inflammatory genes, increase the inflammatory factors and thus lead to chronic inflammation of adipose tissue.

POSSIBLE MECHANISM OF EXERCISE TRAINING'S RESISTANCE TO CHRONIC INFLAMMATION

Promote Release of Myogenic IL-6

Cytokines in circulation under quiescent condition mainly come from leukocyte, adipose, liver and cerebrum. And under acute high-duty exercises, the IL-6 released by skeletal muscle can instantly get 100 times than quiescent condition. Though IL-6 released by muscle is instantaneous, it can help leukocytes increase secretion of IL-10, IL-1 interleukin-1 receptor antagonist (IL-1RA) and other anti-inflammatory cytokines. IL-1 RA can inhibit the proinflammatory effects of IL-1β and peripheral IL-10 can reduce the adaptive immune response and reduce the damage of tissue caused by inflammation. Moreover, myogenic IL-6 can also inhibit the upstream key biological activity of proinflammatory cytokines, TNF-α. However, IL-6 at the same time is the main cytokine stimulating the liver's secretion of CRP, therefore, it itself is also regarded as a proinflammatory factor. So whether myogenic IL-6 has anti-inflammatory effects need further research. It is worth noticing that the rise of IL-6 in acute exercise condition is related to the exercise intensity. And when taking low or moderate intensive exercises, IL-6 will not rise. However, the current study suggests that even when taking low or moderate exercises, some metabolic risk factors including inflammatory markers will also reduce. This also illustrates that there are many ways for exercise training

to reduce obese chronic inflammation.

Increase the Oxygen Content of Adipose Tissue

First of all, exercise training can promote angiogenesis of adipose tissue. Studies show that nine-week exercise training can increase the density of adipose tissue's vascular endothelial cells in viscera (epididymis) of the male rat, and improve the gene expression level of vessel matrix cells' VEGF and VEGF receptor 2 in adipose tissue. Another study reports the influence of exercise training to VEGF genetic expression and VEGF protein level in subcutaneous fat tissue of rats. Compared with the control group, six-week exercise training increased VEGF genetic expression in the adipose tissue of the rat but the protein levels remained the same. Secondly, exercise training can reduce the vasoconstriction of animals' other tissue/ organ. The past study suggests that exercise training can reduce the mass content related to vasoconstriction in several crucial tissues/organs. For example, exercise training can reduce the expression level of angiotensinogen in rat's brain tissue. Under the obese condition, the adipose tissue is an important source to produce and cause vasoconstrictor biotic factors in tissues. Moreover, exercise training can also increase the blood supply in the animal's adipose tissue as the animal researches show that exercise training can increase the blood supply in the rat's adipose tissue. In this experiment, the 15-week swimming training make the blood supply of rat's subcutaneous and visceral adipose tissue increase, which could be caused by the increase of total blood volume after exercise training? Aerobic exercise can increase the blood volume and appetency of hemoglobin's, thus make the absolute oxygen content of blood increase. In conclusion, exercise training can increase the oxygen content of the adipose tissue and as oxygen deficit of adipose tissue is the vital mechanism causing obese chronic inflammation, exercise training can prevent obese chronic inflammation from happening and developing.

3.3 Inhibit Infiltration of Macrophage to Adipose Tissue

Peripheral blood mononuclear cells migrating to the inflammatory areas and transforming into macrophages which infiltrate tissue is a vital part of the continuous inflammatory tissue. And the migration and infiltration of peripheral blood mononuclear cells require the participation of adhesion molecules. Under physiological conditions, endothelial cells do not express adhesion molecules. The damaged endothelial cells, however, will express and release adhesion molecules, like ICAM-1, VCAM-1 and selecting and so on, which then attract the peripheral blood mononuclear cells to migrate and infiltrate the tissues. Exercise training can increase the number of vascular endothelial precursors differentiate from stem cells which can form the marrow, and improve the regeneration capacity of the blood vessel endothelium. In addition, regular exercise can also increase the blood flow volume and shear stress of the blood, which can reduce the adhesion molecules expressed and released by vascular endothelial cells. Studies show that the expression level and circulation concentration of VCAM-1 and P-selectin in endothelial cells really decline significantly after exercise training. Moreover, after mononuclear macrophage is activated in different ways, it can polarize into two different cell types: M1 macrophage and M2 macrophages. The M1 macrophage can produce IL-6, TNF and other proinflammatory factors while M2 macrophage can produce anti-inflammatory factors. The inflammatory adipose tissue will selectively recruit M1 macrophages and induce the type M2 anti-inflammatory macrophages to transform into M1 proinflammatory macrophages. And exercise training can inhibit this kind of transformation and reduce the infiltration to adipose tissue of M1 macrophage.

Reduce the Number of Proinflammatory Mononuclear

Long term chronic health effect can not only bring down the levels of proinflammatory factors, but also can reduce the number of the proinflammatory monocots. There are two types of monocots in human blood, one classic monocot and the other proinflammatory monocot. Though the proinflammatory monocots only make up 10% of the monocytes, they are the main sources of TNF-α and other proinflammatory cells and the key factor leading to systemic inflammatory response. After a acute high-duty exercise, proinflammatory monocots will increase instantly and return to normal level the moment the body stops exercising. But regular exercises can reduce the number of proinflammatory monocytes in circulation under quiescent condition. Research shows that compared with those who regularly exercise, those who do not regularly exercise have higher proinflammatory monocytes, but the number of this kind of monocytes will reduce to the same level as those who exercise regularly after 12-week regular exercise training. Moreover, exercise training can make peripheral monocytes reduce the release of proinflammatory cytokines and increase the anti-inflammatory cytokines.

Reduce the Expression of Toll-like Receptor

Toll-like receptor (TLR) is a highly conserved transmembrane protein involved in nonspecific immunity and plays a crucial role in recognizing micro-organism pathogen and endogenous danger signal. Activate TLR can increase the expression and secretion of proinflammatory factors, so TLR is very important in mediating the systemic inflammatory response. Researches show that compared with those who do not often exercise, the blood monocytes of those who exercise regularly have weaker inflammatory response to the stimulation of endotoxin in vitro and it is detected that the expression level of the TLR4 of these cells is reduced. And the low expression level of TLR then

reduce the production of proinflammatory factors. However, long-term regular exercise can promote steatolysis, increase concentration of free fatty acid in plasma which is the legend of TLR2 and TLR4 and from this we can speculate that exercise can cause cascade reaction by activate TLRs. But there is no evidence to support this deduction at present and recent researches all show that after a secular motion, the proinflammatory cytokines produced by monocytes under the stimulation of LPS will reduce significantly.

Increase the Number of Regulatory T Cells

Regulatory T cells are a group of lymphocytes capable of negative regulation of the body's immunoreaction and often play a vital role in maintaining tolerance and avoiding excessive immunoreaction which would damage the organism. CD4 + CD25 + regulatory T cells can specifically express the P3 forkhead transcription factor and inhibit immunoreaction, without which would cause autoimmune response and increase immunoreaction to foreign antigens. Studies show that 12-week regular shadowboxing exercise can increase the number of regulatory T cells in body's circulation. And after separating the peripheral blood mononuclear cells in this experiment to culture in vitro, it is found that under the stimulation of exo-antigens, the expressions of cytokines, transforming growth factor-β and IL-10 produced by regulatory T cells will increase and both of the cytokines are anti-inflammatory factors which contribute to resisting inflammatory response. However, in an experiment using exercise mouse model, after random allocation to the mice, the study did some moderate exercise and high-duty exercise training respectively to them and then detected the number of regulatory T cells in circulation. It turned out that the regulatory T cells significantly increased only in the high-duty exercise training mice with reduction of proinflammatory factors and increase of anti-inflammatory factors. These results suggest that the anti-inflammatory effect may be stronger after high-duty exercises. All in all, exercise training can increase the number of regulatory T cells in circulation which can release the anti-inflammatory factors to resist chronic inflammation.

CONCLUSION

An increasing number of findings support that there are correlations between exercise level and chronic inflammation and using exercise training to treat the obese chronic inflammation has gained encouraging results. By promoting release of myogenic IL-6, increasing the oxygen content of adipose tissue, inhibiting infiltration of macrophage to adipose tissue, reducing the number of proinflammatory mononuclears, reducing the expression of Toll-like receptors, increasing the number of regulatory T cells and so on, exercise training can resist obese chronic inflammation. Further researches need to preferably clear the dose-response relationship between exercise training and the inflammatory cascade reaction and further illustrate the molecular mechanism of exercise training to resist systemic obese chronic inflammation.

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