

Inflammation during Obesity – Pathophysiological Concepts and Effects of Physical Activity

Entzündung und Adipositas – pathophysiologische Konzepte und Effekte körperlicher Aktivität

Summary

- › **The prevalence of obesity** is continuously rising worldwide. Obesity is the result of a lasting metabolic surplus which leads to pathological expansion of adipose tissue (AT). Beside a subset of apparently metabolically-healthy obese individuals, the majority of obese subjects develop an increased risk for type 2 diabetes mellitus (T2D), coronary heart disease (CHD), and several other "western world" diseases. In these individuals, AT expansion is associated with metabolic stress responses in adipocytes followed by the induction of signals of innate immune response.
- › **Downstream, these processes** are followed by translocation of NfκB into the nucleus, leading to the expression of various inflammatory cytokines and chemokines in AT. Infiltrating leukocytes amplify inflammation leading to a "spill-over" to the blood stream. Beside the negative effects of inflammatory mediators on endothelial function, inflammation is transferred to various other organs and tissues like liver, muscle, gut, and brain.
- › **Regular physical activity** increases energy turnover followed by a decrease of visceral fat mass. Subsequently, metabolic stress and its inflammatory consequences are reduced. Beside the metabolic effects, exercise also directly affects humoral and cellular immune activation. Inflammatory processes in AT are diminished followed by a reduced spill-over of inflammation to the blood stream. Exercise training is also effective in reducing pathophysiological consequences of obesity locally in tissues like muscle, gut, and brain.

KEY WORDS:

Adipose Tissues, Cytokines, Leukocytes, Physical Activity, Immune System, Adipocytes

Introduction

Several „western world“ diseases such as type 2 diabetes mellitus (T2D) or coronary heart disease (CHD) are associated with the high prevalence of obesity which continues to rise worldwide (12). Obesity is the result of a long time metabolic surplus which leads to a pathological expansion of adipose tissue (AT). AT expansion is caused mainly by an enlargement of pre-existing fully differentiated adipocytes

Zusammenfassung

- › **Die Prävalenz der Adipositas** steigt weltweit stetig an. Die pathologische Gewichtsüberschreitung ist dabei das Resultat einer langfristig positiven Energiebilanz. Neben eine Subgruppe metabolisch gesunder Adipöser entwickelt der Großteil der betroffenen Patienten Risikofaktoren für metabolische Erkrankungen, wie dem Diabetes Typ II, und Herz-Kreislauf-Erkrankungen. In diesen Patienten geht die massive Expansion des Fettgewebes mit metabolischem Stress in Adipozyten einher, der zu einer Aktivierung von Signalwegen der angeborenen Immunabwehr führt.
- › **Die folgende Translokation** des Transkriptionsfaktors NfκB induziert die Expression zahlreicher inflammatorischer Zytokine und Chemokine, die zur verstärkten Infiltration des Fettgewebes durch Leukozyten führt. Die sich auf diese Weise selbst verstärkende Entzündungsreaktion des Fettgewebes tritt ins Gefäßsystem über, in dem das Blut als Transitweg die Entzündungssignale ans Gefäßendothel und andere Organe und Gewebe, wie Leber, Gehirn, Muskel und Darm, heranträgt. Die hier resultierenden sekundären Entzündungsprozesse, die lokal auch spontan als Folge der Adipositas entstehen können, kennzeichnen die Adipositas als systemisch inflammatorische Erkrankung.
- › **Regelmäßige körperliche Aktivität** erhöht den Energieverbrauch und kann das viszerale Fettgewebe reduzieren. In der Folge kommt es zu einer geringeren Aktivierung metabolischer Stresssignale und deren entzündlichen Konsequenzen. Darüber hinaus hat regelmäßige körperliche Aktivität auch direkten Einfluss auf die aktivierte humorale und zelluläre Immunabwehr. Entsprechend reduziert sportliches Training inflammatorische Prozesse im Fettgewebe, wodurch auch systemisch anti-entzündliche Effekte erzielt werden. Gleichzeitig wirkt körperliche Aktivität auch gegen die lokalen pathologischen Konsequenzen der Adipositas in Organen und Geweben wie zum Beispiel im Muskel, dem Darm und dem Gehirn.

SCHLÜSSELWÖRTER:

Fettzellen, Zytokine, Leukozyten, körperliche Aktivität, Immunsystem, Adipozyten

due to the storage of excess energy as fat. While several studies confirmed the existence of a subset of apparently metabolic healthy obese (MHO) individuals, the majority of obese subjects develop a status of metabolic stress which is followed by the activation of the innate immune system (34). The result is the development of a chronic low-grade inflammatory status which has been established as an

REVIEW

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1. LEIBNIZ UNIVERSITY HANNOVER,
Department of Sports Science,
Hannover, Germany



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CORRESPONDING ADDRESS:

Prof. Dr. Karsten Krüger
Institute of Sports Science
Department Exercise and Health
Leibniz University Hannover
Am Moritzwinkel 6, 30167 Hannover, Germany
✉ : karsten.krueger@
sportwiss.uni-hannover.de

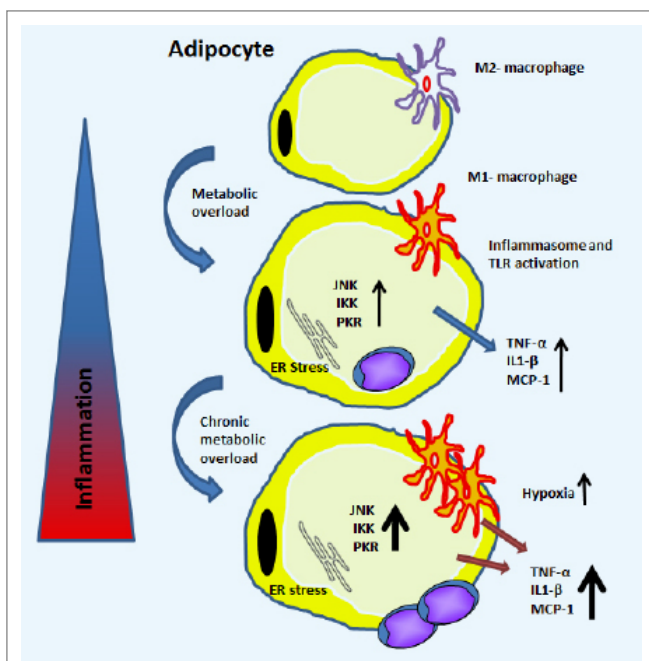


Figure 1

Consequences of a prolonged metabolic overload in metabolic tissues. IKK=Inhibitor of κ kinase; JNK=C-jun N-terminal kinase; PKR=Protein kinase R; TNF=Tumor necrosis factor; IL=Interleukin; MCP=Monocyte chemoattractant protein TLR=Toll-like receptors; ER=Endoplasmatic reticulum.

important predictor of risk for cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), colon cancer, breast cancer, dementia and depression. The current review summarizes the current knowledge about I) the development of inflammation in response of a metabolic overload II) the systemic and local inflammatory processes during obesity, and III) how exercise therapy mechanistically impacts inflammation by its anti-inflammatory properties (18).

Metabolic Disorders Trigger Inflammation

The excessive consumption of nutrients is suggested to be per se a trigger of inflammation. Interestingly, the first signals of inflammation during experimental induction of obesity originate from metabolic cells such as adipocytes and liver cells. In these cells, the metabolic overload engages pathways which are involved in propagating cellular stress and inflammatory signals by activation of I κ B kinase (IKK), c-jun N-terminal kinase (JNK), and protein kinase R (PKR). The phosphorylation I κ B results downstream in the dissociation of I κ B α from NF- κ B, which subsequently migrates into the nucleus and activates the expression of several inflammatory genes (1, 14, 36).

Additionally, the NLRP3-inflammasome and the Toll-like receptors (TLRs) of the innate immune system are activated in fat tissue and livers of obese individuals. It was shown that the regular consumption of unsaturated fatty acids contribute to the activation of both sensor-pathways. Both receptors as well as endoplasmatic reticulum stress induce downstream the induction of inflammatory cytokine production by adipocytes such as TNF- α , IL-1 β , IL-18, as well as several chemokines. Subsequently, a self-energizing inflammatory process is initiated by the chemotactic recruitment of leukocytes, which invade into the metabolic tissue. These data implicate that metabolic stress induces an inflammatory switch in adipocytes which seems to be a key event for the connection between metabolism and inflammation (33).

There are some other physiological processes in AT during obesity which might also trigger inflammation. Some studies provided evidence that in expanded AT oxygen supply is insufficient. Accordingly, hypoxic conditions in AT seem to result in necrotic cell death. These data are supported by the findings of „crown-like structures“ in AT of obese individuals (3). These cell aggregates represent necrotic cells which are circuted by accumulated M1 macrophages which actively produce cytokines (3, 25) (Fig. 1).

Immune Cell Invasion

In AT of obese subjects, an increased number of macrophages can be found. Specifically, an increase of type M1 „proinflammatory“ macrophages was reported, while the number of M2 macrophages seems to decrease. The changes from M2 to M1 macrophages implicates a switch from a cell type, which is mainly anti-inflammatory and involved in repair and remodeling processes, to a cell type which is an important producer of proinflammatory cytokines, such as tumor necrosis factor (TNF)- α , interleukin (IL)-6, and monocyte chemoattractant protein (MCP)-1 (6). Accordingly, the increase of M1 macrophages was accompanied by a strong increase of cytokine expression. The abundance of M1 macrophages in visceral fat was shown to be inversely correlated with insulin sensitivity, suggesting that inflammatory processes are involved in the development of T2D. Beside macrophages, other immune cells like natural killer cells (NK cells), and lymphocytes increase in AT. Regarding lymphocytes, animal studies demonstrated an increased ratio of CD8+ to CD4+ cells and a decreased number of immunoregulatory T regulatory cells (Tregs). However, the specific contribution of these cells to the inflammatory milieu and its pathophysiological consequences are not yet known (11, 26) (Fig. 2).

Spill-Over to Systemic Inflammation

The inflammatory processes in AT are chronic and progressive. Thus, the continuous expression of a variety of cytokines, such as TNF- α , IL-1 β , CCL-2, MCP-1, and IL-18, is suggested to „spill over“ to other organs and tissues (23). Accordingly, the inflammation which develops locally in the expanding AT, becomes systemic through the release of numerous pro-inflammatory mediators into the blood stream. In blood, a wide cluster of inflammatory mediators (beside the above named) are chronically elevated in obese subjects like c-reactive protein (CRP), MCP-3, myeloperoxidase (MPO), vascular cell adhesion molecule-1 (VCAM-1), tissue inhibitor of metalloproteinase 1 (Timp-1), interferon gamma-induced protein 10 (IP-10), and macrophage inflammatory protein-1 (MIP-1) (23).

Blood is suggested to be a transit way for these inflammatory mediators which subsequently transports inflammatory signals to several other organs and tissues like liver, blood, vessels and endothelium, brain, muscle, and gut. Thus, obesity represents a systemic inflammatory disease affecting various organs which tend to express inflammatory signals themselves.

„Metaflammation“ and its Consequences

An important hallmark of the metabolic-induced inflammation found in obesity is that the inflammatory state is accompanied by a reduced metabolic rate. This contrasts a „classical“, non-sterile inflammation which is always associated with an increased local or systemic metabolism. Therefore, the metabolic-

induced sterile inflammation is designated as “metaflammation” or „meta-inflammation“ (14). Another feature of metaflammation is chronicity. While a non-sterile inflammation is regularly temporary and quickly resolved, metaflammation is progressive and remains unresolved over time (14).

Beside several organ specific effects of inflammation in obesity, a central pathophysiologic consequence of metaflammation is the progressive insulin resistance. In this regard, it was shown that JNK and IKK activation target the insulin receptor substrate 1 (IRS-1) for serine phosphorylation, which antagonizes the insulin receptor signaling cascade. Additionally, chronically increased levels of TNF- α are known to disturb insulin signaling in adipocytes and liver cells. While wildtype mice, which are fed a high fat diet, develop an insulin resistance, mouse models, which are

deficient for TNF- α , JNK, TLR2, or IKK ϵ , have beneficial effects on metabolisms after being challenged by high fat diets. However, actually several other inflammatory pathways and kinases are investigated, which might affect insulin signaling and contribute to the increasing prevalence of diabetes (15).

The important role of metabolic stress and AT inflammation for the development of metabolic disorders is supported by the concept of metabolic healthy obesity. While there is actually no general agreement on accepted criteria to define MHO, available data implicate that MHO have a distinct lower risk of diabetes type II, lower visceral fat mass, smaller adipocytes and only a slight infiltration by macrophages. Instead, they have more abdominal and subcutaneous fat tissue with no inflammatory characteristics (32).

Systemic and Local Effects of Metaflammation

The long term consequences of metaflammation are reflected by inflammatory processes in other organs and tissues. However, for some tissues it is not quite clear if they spontaneously develop an inflammation as a direct result of metabolic stress or if they develop secondary inflammatory characteristics due to an inflammatory spill-over from the blood (14).

Regarding the blood and the endothelium, it was previously mentioned that most obese individuals exhibit a systemic low grade inflammation represented by the increase of several inflammatory cytokines. Some of these cytokines are known to be vasoactive and their chronic elevations represent important risk factors for the development of cardiovascular diseases. Some inflammatory mediators are known to act directly on endothelial function by increasing the expression of endothelial adhesion markers such as ICAM-1 and reducing eNOS expression (26).

Recent studies demonstrated chronic elevations of lipopolysaccharides (LPS) in serum of many obese individuals. This low grade endotoxemia is suggested to be induced by inflammatory

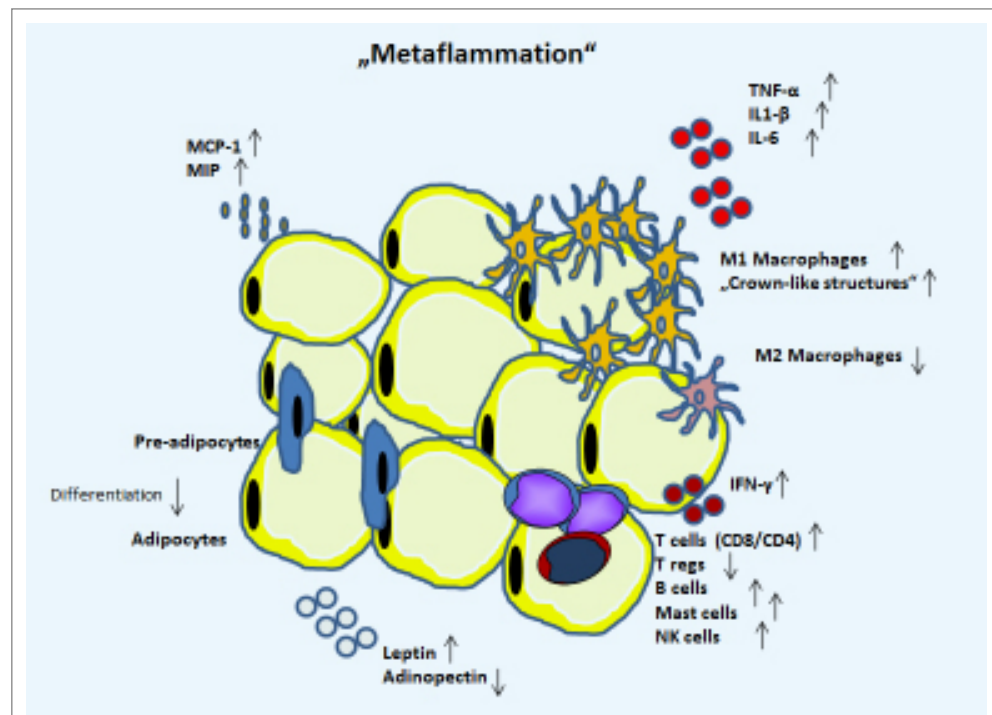


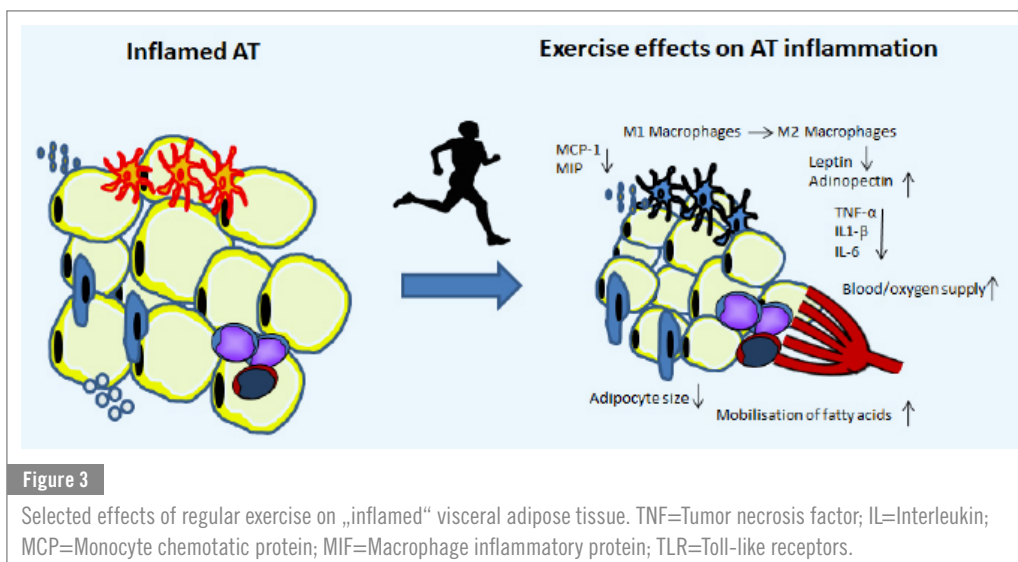
Figure 2

Immunological changes in an „inflamed“ visceral adipose tissue. TNF=Tumor necrosis factor; IL=Interleukin; MCP=Monocyte chemotactic protein; MIP=Macrophage inflammatory protein; TLR=Toll-like receptors; IFN=Interferone, Tregs=Regulatory T cells.

processes in the enteric nervous system and microbiota leading to a disturbed gut integrity. Regarding microbiota, obesity is accompanied by a reduction of the genetic diversity of the gut bacteria, resulting in an increased percentage of LPS, producing bacteria populations which subsequently exacerbate microbiota-associated inflammatory processes. It is also suggested that the production of some specific metabolites, like short chain fatty acids (SCFA), impact key metabolic pathways such as insulin signaling, incretin production as well as inflammation. Inflammatory processes might also directly affect the functional integrity of the tight junctions of the intestinal epithelium. The resulting gut barrier dysfunction represents an open door for microbes and microbial-derived LPS endotoxin to enter systemic circulation resulting in endotoxemia (34). However, the detailed mechanism of this obesity associated leaky gut are not yet known.

Beside the gut, also muscle tissue is affected by the chronic elevation of inflammatory mediators in the circulation. It is suggested that both circulating inflammatory cytokines as well as non-esterified fatty acids (NEFA) activate NF- κ B and STAT3 pathways followed by increased activation of the ubiquitin proteasome system. These catabolic signals lead to a combination of sarcopenia and obesity, a state called sarcopenic obesity. Such processes are intensified by the increased storage of intramuscular lipids and their derivatives which are known to induce mitochondrial dysfunction characterized by impaired β -oxidation capacity and increased formation of reactive oxygen species (4, 30).

Actually, there are some studies showing that metaflammation also exerts effects on bone marrow and hematopoiesis. Accordingly, it was shown that obese inflammation induces a remodeling in the bone marrow niche which affects hematopoietic stem cells. These cells, which represent progenitors of all myeloid, lymphoid, and erythroid lineages, are affected by an inflammatory micro-environment leading to detrimental



changes of the hematopoietic system. It is suggested that immune cells are inflammatory primed, leading to more circulating cells, which exhibit a pro-inflammatory phenotype (10).

Although the direct link between brain inflammation and increased adiposity is still unclear, some studies provide evidence for a critical role for inflammatory processes and related alterations in brain structure, cognitive functions, and behaviour. In this regard, Papenberg and colleagues investigated the impact of high levels of peripheral inflammatory cytokines on gray-matter volumes in older sedentary adults. Results showed that inflammation exacerbated negative effects on brain and cognition, and this was particularly pronounced in more inactive older adults (28). Animal studies showed that peripheral low grade inflammation induces neuroinflammation due to multiple pathways leading to microglia activation, neuronal cell death and sickness behaviour. It is therefore highly possible that adiposity-driven inflammation contributes to the development of depressive disorders and their growing prevalence (36).

Effects of Exercise on Metaflammation

It is well known that regular exercise training has systemic and local anti-inflammatory effects, which might be important mechanisms to protect against the development of several chronic diseases.

A major effect of an active lifestyle is to increase energy demands followed by a decrease of visceral fat mass. In this regard, exercise is known to mobilize fatty acids followed by a reduction in adipocyte size, and increases blood flow and oxygen supply in adipose tissue (14, 34). Recent studies proved that exercise training induces a transition from white adipose tissue (WAT) to brown fat, a process that has beneficial metabolic and cardiac effects. It is suggested that myokine released from contracting muscles during exercise, induces the activation of PPAR γ which affects browning of WAT (3).

Beside these various metabolic processes exercise also alters humoral and cellular inflammatory signals in AT. Murine studies demonstrated that regular exercise reduces the release of various chemokines, such as MCP-1, from AT leading to a reduced infiltration of leukocytes. This effect is supported by the reduction of ICAM-1 expression in tissues and the vascular endothelium after regular exercise training. Recently, it was demonstrated that regular exercise reverses the switch from M2 to M1 macrophages in a mouse model of high fat diet.

However, the mechanisms inducing these phenotype switches are intensively discussed. Attenuation of metabolic stress might increase adipocyte-specific gene and protein expression such as AMPK and PGC-1 α which are known to enhance β -oxidation and mitochondrial biogenesis in AT. Both processes are known to limit local oxidative stress, mitochondrial dysfunction, and ER stress, followed by a decreased induction of inflammatory signals (13, 19).

An important immunologic effect of exercise training

is also represented by the reduced expression of TLRs on monocytes, macrophages, and within tissues. In detail, the expression of TLR1, TLR2, and TLR4 are reduced after both acute bouts of exercise as well as after regular exercise training on immune cells, in AT, and liver (34) (Fig. 3).

Another important mediator of the anti-inflammatory effects of exercise is suggested to be the release of IL-6 from the contracting skeletal muscle. After acute bouts of prolonged exercise a marked systemic increase of IL-6 is observed which might have several metabolic and immunologic functions (30). In contrast to a chronic slight increase of IL-6 during various pathophysiologic conditions, the transient rise in circulating IL-6 in response to exercise evokes the increased expression of circulating anti-inflammatory cytokines such as IL-10 and IL-1 receptor antagonist (IL-1RA). While IL-1RA reduces the pro-inflammatory effects of IL-1 β , IL-10 generally seems to downregulate several functions of the adaptive immune response (21, 29, 30).

Increased levels of circulating cortisol and adrenaline are the result of an activation of the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system (SNS). Cortisol, which is also stimulated by IL-6 release, exerts several anti-inflammatory effects on various immune cell subpopulations. Similarly, catecholamines have been shown to downregulate the expression of several pro-inflammatory cytokines in immune cells (13).

Another anti-inflammatory effect of exercise is represented by altered proportions of circulating monocyte subpopulations. Regular physical activity was shown to increase the percentage of so called classical monocytes (CD14^{hi}CD16⁻) expressing low levels of TLR4. In contrast, an inactive lifestyle promotes an increased percentage of non-classical (CD14^{low}CD16⁺ or CD14^{hi}CD16⁺) monocytes expressing high levels of TLR4 on their surface. Furthermore, exercise inhibits TNF- α production of monocytes via adrenergic mechanisms (9).

Local Effects of Exercise

Recently, some studies provided evidence that regular physical activity modifies gut microbiota during inflammatory states of obesity. Accordingly, exercise seems to promote microbial diversity associated with increases of health-beneficial gut bacteria populations. However, it is not clear which populations are modified and how these changes are mediated. Current data implicate that manipulation of gut microbiota by modifying

diet or exercise habits are powerful tools in the future to prevent or treat obesity-associated diseases (4, 8).

Regarding muscle, it is well known that in particular resistance training is an effective therapy against anabolic processes in inflammatory diseases. The upregulation of the mTOR pathway activates Akt, induces protein synthesis, and causes downregulation of the ubiquitin-proteasome system (31).

In blood vessels, the greater laminar shear stress increases NO production and its release by the endothelium. Furthermore, regular physical activity has been shown to increase the anti-oxidant defense capacity by up-regulation of a variety of anti-oxidants like superoxide dismutase (SOD). Another mechanism

to improve vascular function is assumed to be the mobilisation of endothelial progenitor cells (EPCs) by exercise. These cells are suggested to contribute to the maintenance of endothelial function by adhering to the vessel wall and differentiation into mature endothelial cells. Furthermore, EPCs may promote endothelial repair and proliferation by paracrine signaling (18, 20, 27).

Recently, some data have shown that the pleiotropic responses of exercise extend to the bone marrow during obesity and inflammation. Here it was shown that exercise induces remodeling processes by decreasing overall bone marrow adiposity and alter the inflammatory status. In bone marrow niches, the function of hematopoietic progenitor cells is positively stimulated by up-regulating hematopoiesis and reducing inflammatory characteristics on residing and mobilized bone marrow progenitors (10).

Some recent studies showed that exercise exerts anti-inflammatory and anti-oxidative effects during conditions on neuroinflammation. Barrientos and colleagues have demonstrated an inhibition of inflammatory signals in rats performing regular exercises. Other studies supported these findings by showing a reduced activation of microglia cells and a stimulation of cerebral BDNF production inducing neuroprotection (2) (Fig. 4).

Taken together, current knowledge implicates that obesity induced inflammation is initiated by metabolic stress which might spill over from the AT to other tissues. Accordingly, an important strategy to prevent the development of inflammatory processes during obesity is to reduce metabolic perturbations by balancing the energy intake, reducing intake of saturated fatty acids and choosing appropriate activity levels. For therapeutic purposes, exercise training represents an effective therapeutic intervention, which targets both metabolic as well as immunologic processes resulting in a decrease of metaflammation. ■

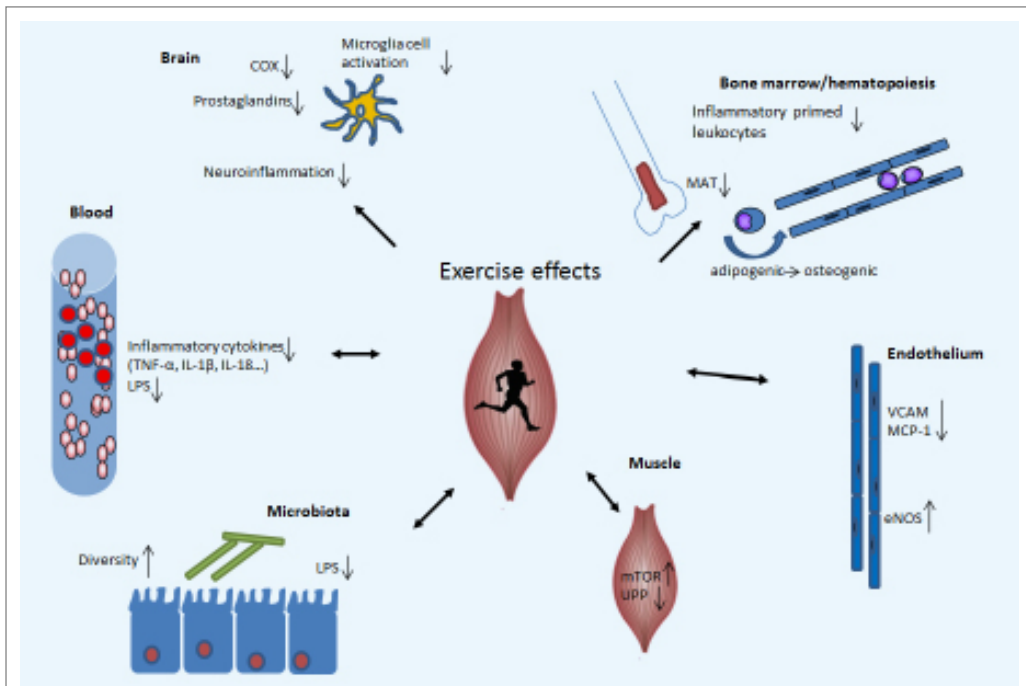


Figure 4

Systemic and local anti-inflammatory effects of regular exercise on selected organs and tissues. MAT=Marrow associated adipose tissue; TNF=Tumor necrosis factor; IL=Interleukin; MCP=Monocyte chemotatic protein; UPP=Ubiquitin proteasome pathway; eNOS=Endothelial nitric oxide synthase; COX=Cyclooxygenases; LPS=Lipopolysaccharides.

Conflict of Interest

The authors have no conflict of interest.

- Akt=Protein kinase B
- BDNF=Brain-derived neurotrophic factor
- IL=Interleukin
- IFN=Interferone
- MCP=Monocyte chemotatic protein
- MIP=Macrophage inflammatory protein
- NO=Nitric oxide
- TNF=Tumor necrosis factor
- TLR=Toll-like receptors
- Tregs=Regulatory T cells

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