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Тұжырым

Реакклиматизация кезеңінде шиеленіскен бұлшықет жүктемесі кезінде спортшылардың қызметтік қозғалмалылығына таудағы жаттықтырулар біркелкі емес әсер етеді.

Summary

Train in mountain is proving repeated influence at functional mobilization of sportsmen on effort freight muscle in period reacclimatization.

УДК 576.3.32:615.014.425

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DIFFERENTIAL CYTOTOXIC EFFECTS OF HEAVY METALS ON THE NF kB SIGNAL PATHWAY AND EFFECT OF ANTIOXIDANT

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NF-κB is a multiprotein complex that is known to activate a great number of genes involved in the early cellular defense reactions of higher organisms and acts as transcription factor. NF-kB is composed of with one 50-kD (p50) and one 65-kD (p65) polypeptide [1,2,3]. Within nonstimulated cells, NF-kB resides in the cytoplasm in an inactive complex coupled with the inhibitor protein IkB. Pathogenic stimuli cause phosphorylation and the release of IkB. NF-kB then enters the nucleus, binds to DNA control elements, and induces the synthesis of mRNA. A unique and puzzling feature of NF-kB is that its activation is triggered by a great variety of agents, including the cytokines interleukin- 1 and tumor necrosis factor, viruses, double-stranded RNA, endotoxins, phorbol esters, UV light, and ionizing radiation. Further, genes with the NF-kB promoter sites encode cytokines, growth factors, cell adhesion molecules, and immuno receptors [3,4].

In view of its broad range of possible stimuli and target genes, it is not surprising that NF-kB is considered a crucial regulator of the immune system. Evidence also suggests that NF-kB plays a significant role in oncogenesis [2]. Evidence that H_2O_2 and not other forms of ROS served as messengers for NF-kB activation also came from genetic experiments. As mentioned earlier, steady-state levels of H_2O_2 and O^{2-} in a cell are determined by the activity of antioxidant enzymes like catalase and Cu/Zn-SOD among others. Specifically, overexpression of the catalase gene will result in decreased intracellular H_2O_2 levels while overexpression of SOD results in increased dismutation of O^{2-} to H_2O_2 [5].

NF-κB is found in almost all animal cell types and is involved in cellular responses to stimuli such as stress, cytokines, free radicals, ultraviolet irradiation, oxidized LDL [2,5]., and bacterial or viral antigens. NF-κB plays a key role in regulating the immune response to infection. Consistent with this role, incorrect regulation of NF-κB has been linked to cancer, inflammatory and autoimmune diseases, septic shock, viral infection, and improper immune development [4,6]. Active NF-κB turns on the expression of genes that keep the cell proliferating and protect the cell from conditions that would otherwise cause it to die via apoptosis. Defects in NF-κB it's a result in increased susceptibility to apoptosis leading to increased cell death [6]. This is because NF-κB regulates anti-apoptotic genes especially the TRAF1 and TRAF2 and thereby checks the activities of the caspase family of enzymes which are central to most apoptotic processes [6,7].

Heavy metal ions can be released by corroding metallic implants into the surrounding tissue. When they enter blood vessels some of them are carried by proteins like albumin and can be taken up by endothelial cells lining the vessels [7].

Nickel has been extensively studied with respect of gene induction. Nickel has been found to alter the expression of a surprisingly large number of genes. These include inactivation of senescence genes, inactivation of the antiangionetic thrombospondin gene by induction of the activating transcription factor [8], silencing of a telomer marker gene, induction of the hypoxia-regulated gene cap 43 and others. Several of these genes are involved in the control of mitogenesis, and these findings provide a hypothesis for the stimulation of cell proliferation in nickel [9].

Baeuerle and co-workers investigated the activation of NF-kB by the cytokine tumor necrosis factor alpha (TNF-α) in mouse keratinocyte cell clones which contain stably integrated extra genes for catalase and SOD, resulting in higher levels of enzymatic activities [8,9]. Consistent with an important role for H2O2 but not O2, catalase-overexpressing cells had decreased NF-kB activation. Aminotriazole, a catalase inhibitor, restored a normal response. SOD-overexpressing cells showed a hyper induced NF-kB activation, possibly resulting from an enhanced conversion of O_2 into H_2O_2 [10,11,13,14].

Heavy metal ions induce mechanisms of gene activation in endothelial cells as do proinflammatory mediators [11], indicating that corroding metal ion containing biomaterials can provoke inflammatory reactions by known, as well as by yet unknown, intracellular signaling pathways [11,12]. To study their involvement in the inflammatory response investigated heavy metal ion induced effects in cultured human vascular endothelial cells (HUVECs). $NiCl_2$ and $CoCl_2$ upregulate, especially in concentrations of 1 mM, the expression of adhesion molecules, as well as the cytokines IL-6 and IL-8 [15].

In addition, possible signal transduction mechanisms were elucidated. The HUVECs were treated with various selective inhibitory drugs followed by the incubation of metal ions before measuring the expression of the above-mentioned endothelial factors. Two protein kinase inhibitors (H-7 and H-8) strongly repressed Ni^{2+} and Co^{2+} enhanced expression. We showed that $NiCl_2$ and $CoCl_2$ activate the translocation of the transcription factor nuclear factor (NF)-KB into the cell nucleus and enhance its binding to a NF-KB consensus sequence as shown by mobility shift analysis [13,14,15]. Despite the repression of heavy metal induced adhesion molecule synthesis, did not detect any inhibition of NF-KB translocation by H-7 or H-8. Therefore, it must be concluded that heavy metal ions like Ni^{2+} and Co^{2+} activate two or more signal transduction pathways in endothelial cells. There is one pathway in which H-7 and H-8 sensitive protein kinases are involved and a second pathway leading to NF-KB activation, which is insensitive to H-7 and H-8 [14,15].

Chromate (VI) is the only carcinogenic metal species that directly generates reactive oxygen species by interaction with cellular reductants. Hydroxyl radicals, when generated in proximity to DNA, cause DNA strand breaks and oxidized bases. Besides causing direct gene mutations, Cr (VI)-evoked formation of $OH^{\bullet}$ radicals has been shown to activate nuclear factor-B which may stimulate inflammatory processes. In a commercial DNA array test system employing human hepatoma cells, chromate (VI) at low concentrations of 5 – 10 M induced the promoters for c-Fos, HSP70, GADD45, NF-B, p53, XRE and CRE [16].

To delineate the molecular mechanisms of NF-kB-mediated regulation of chromium (VI)-induced cell death, the signaling pathway leading to the activation of NF-kB was interrupted by stable transfection of a kinase mutated form of IkB kinase b (IKKb-KM). It was demonstrated a novel role for the NF-kB transcription factor in inhibiting chromium (VI)-induced cell death. Inhibition of NF-kB by IKKb-KM or IKKb gene deficiency resulted in a spontaneous cleavage of Bcl-xl anti-apoptotic protein due to the elevated caspase-3 activity. DNA microarray assay suggested a decreased expression of genes encoding anti-apoptotic proteins, cIAP1 and cIAP2, in the cells overexpression IKKb-KM. Chromium (VI) treatment of these NF-kB-inhibited cells induced necrotic-like cell death. Such chromium(VI)-induced cell killing could be partially inhibited by expression of exogenous cIAP1, an inhibitor of caspases, indicating non-caspase cytotoxic mechanisms may be involved in chromium(VI)-induced cell death. Indeed, combination of cIAP1 and the antioxidant, N-acetylcysteine, resulted in a significant inhibition of chromium(VI)-induced cell death of NF-kB-inhibited cells [17,16]. These results suggest that NF-kB is essential for inhibiting reactive oxygen species-dependent cytotoxicity. Such inhibition may involve up-regulation of the expression of anti-death proteins including cIAP1 that prevents spontaneous caspase activation and subsequent cleavage of Bcl-xl protein. In tumor cells, NF-κB is active either due to mutations in genes encoding the NF-κB transcription factors themselves or in genes that control NF-κB activity (such as IκB genes); in addition, some tumor cells secrete factors that cause NF-κB to become active. Blocking NF-κB can cause tumor cells to stop proliferating, to die, or to become more sensitive to the action of anti-tumor agents [16]. Thus, NF-κB is the subject of much active research among pharmaceutical companies as a target for anti-cancer therapy. Because NF-κB controls many genes involved in inflammation, it is not surprising that NF-κB is found to be chronically active in many inflammatory diseases, such as inflammatory bowel disease, arthritis, sepsis, asthma, among others [17,18]..

In many cell lines, tumor promoters also induce activation of NF kB. NF kB is a rapidly induced stress- responsive transcription factor that functions to intensify the transcription of a variety of genes including cytokines, growth factors and acute response proteins and its activation has been shown to be linked to MAPK signaling pathways, especially p38 kinase 99 [18]. The mechanism for NF kB activation is well known. In its inactive form, NF kB is found in the cytosol bound to an inhibitory protein called inhibitory kappa B (IkB). When stimulated, IkB is phosphorylated, released from NF kB, and subsequently

degraded [19]. Following separation from IkB, NFkB is translocated into the nucleus where it activates gene transcription by binding to its distinct DNA sequence found in specific genes. NFkB activation is generally associated with initiation or acceleration of tumorogenesis and in JB6 cells, inhibition of NFkB was shown to block tumor promoter- induced cell transformation . Earlier evidence suggests that NFkB comprised of RelA- containing complexes has a significant anti- apoptotic role whereas complexes consisting of c-Rel or p50 possess pro – apoptotic properties [20]. The most common composition of NF kB is Rel A, and this may explain why the results of most studies indicate that activation of NF kB generally results in suppression of apoptosis whereas inhibition of NF kB can induce apoptosis. Arsenic has been shown to have varying effects on NF kB activity and DNA binding, including no effect [20,21], activation and inhibition of TNF α-induced activation. Therefore, because of its potential dual role in inhibiting or promoting apoptosis, NF kB may be an important key in determining whether arsenic acts as a carcinogenic agent or as an effective therapeutic agent. Arsenite (500 μM) was reported to prevent TNF α- induced NF kB activation by directly blocking the activity of the IkB kinase complex (IKK), which resulted in an inhibition of the phosphorylation and degradation of inhibitory kappa B alpha (IkBα). Previous studies by this group showed that lower arsenite concentration (0.5-5 μM) resulted in increased DNA synthesis and activation of NF kB in aortic endothelial cells. Recently these finding were supported by the observation that low arsenite concentrations (1-5 μM) were associated with cell proliferation whereas concentrations greater than 50 μM caused cell death [19,20,21]. In these studies, ERKs kinases were only activated by arsenite at the higher concentrations whereas 5 μM arsenite was sufficient to induce NF kB-dependent transcription. Others showed previously that even though arsenite activated MAPKs and AP-1, NF kB DNA binding or activation was not affected. Others have also shown that arsenite blocks IkB α phosphorylation and degradation induced by TNF, although the mechanism was not fully elucidated, the inhibition was not mediated directly by MAPKs. Recent evidence suggested that arsenite (≥ 12.5) inhibits TNF – α –induced NF kB and IKK activation by binding to Cys -179 in the activation loop of the IKK α and IKK β. Overexpression of IKK β protected NFkB from inhibition by arsenite strongly suggesting that IKK may be a critical target for arsenite. Recent data showed that combined exposure of ATL cells to arsenic and IFN – α has dramatic synergistic effects on both cell cycle arrest and induction of apoptosis in these cells. The apoptotic effect of arsenic was caused by an up- regulation of IkB – α, resulting in a sharp decrease in DNA binding of NF kB complexes and suppression of NF kB target genes due to the cytoplasmic retention of RelA. Similar to the effect on lymphocytes, sodium arsenite down regulates NFkB activity by inhibiting phosphorylytion and subsequent degradation of IkB α in CaCo-2 cell. Arsenite activated all major mitogen-acti- vated protein kinase pathways in various mammalian cell lines, which is explained by inhibition of the corresponding protein phosphatases. Arsenite caused enhanced binding of the mitogenic transcription factor AP-1 to DNA, and it activated the expression of the early genes c -fos, c -myc and egr -1, and of the stress genes gadd 153 and gadd 45.The activation of transcription factor AP-1 and the induction of some early genes supports the hypothesis that arsenic promotes neoplastic growth through stimulation of cell proliferation. In another study, effects of metals on gene expression regulated by 13 different promoters in a recombinant cell line were investigated. Arsenate was found to activate the promoters for MTIIA, GSTYa, HSP70, Fos, NFB, p53. This list includes several genes coding for cytoprotective proteins, namely metallothionein, glutathione-S-transferase, and some stress proteins [20, 21, 22]. Arsenic also interfered with the transcriptional activity of glucocorticoid receptor complexes, thereby decreasing the expression of genes that down regulate cell proliferation in favor of differentiation. Other authors observed that arsenite inhibited the activation of the transcription factor NF-B and the transcription of genes mediated by this factor. This effect was found to be caused by an inhibition of I-B kinase, an enzyme required for the phosphorylation and degradation of the inhibitor I-B. Because the dominant effect of NF-B seems to be growth inhibitory, the prevention of NF-B activation by arsenite points to a further link to the stimulation of cell proliferation in arsenic-induced carcinogenesis. Examples for genes induced by cadmium and to cause a sustained activation of mitogen-activated protein kinases that correlated with the induction of c -fos The latter effect was specific for cadmium, because six other metal ions tested were inactive [15,24].

The activation of mitogenic signaling pathways offers an attractive hypothesis of cadmium carcinogenesis, which in synergy with the inhibition of DNA repair and in antagonism with the stimulation of cytoprotective mechanisms by cadmium, may explain the complex organ specifity in cadmium carcinogenesis [25]..

The steady-state levels of ROS are determined by the rate of reactive oxygen species (ROS) production and their clearance by scavenging mechanisms. Certain antioxidative enzymes including SOD, glutathione peroxidase, catalase, and thioredoxin are potent ROS scavengers but occur in cells only at relatively low concentrations.

The same is true for nonenzymic antioxidants. Amino acids and proteins are also ROS scavengers. Amino acids are less effective than the classical antioxidants on a molar basis, but their cumulative intracellular concentration is 0.1 M [20].

Chemical antioxidants act by donating an electron to a free radical and converting it to a nonradical form. Likewise, such reducing compounds can terminate radical chain reactions and reduce hydroperoxides to less reactive derivatives. However, chemical antioxidant defense is a double-edged sword. When an antioxidant scavenges a free radical, its own free radical is formed. Many antioxidants can act as prooxidants by reducing non radical forms of oxygen to their radical derivatives, particularly if redox cycling occurs. The exact mix of pro-and antioxidant properties of a reducing compound is a complex interaction involving pH, relative reactivities of radical derivatives, availability of metal catalysts, and so forth. Anti-or pro-oxidant properties of sulfhydryl compounds depend upon pH, those of beta-carotene upon oxygen concentration [25,20,26]. Likewise, uric acid, probably a significant antioxidant in higher primates participates in a Fenton-type reaction with peroxide — a property which may be important in the etiology of gouty inflammatory disease [26].

ROS are useful as signalling molecules and in animal and plant host defense, but on the other hand they cause cellular damage if produced in an uncontrolled manner [27]. Therefore there is a need to remove ROS, and many enzymic and nonenzymic mechanisms are present in cells to achieve this. Superoxide ions can be removed, to form hydrogen peroxide, by the enzyme SOD. The cytosolic form contains Cu and Zn (Cu Zn–SOD), while a mitochondrial form contains Mn (Mn–SOD). H_2O_2 can be removed by glutathione peroxidase or catalase, both of which are heme -containing enzymes [26]. However, besides enzymes, many dietary components have antioxidant capacity, capacity, including b-caroten, ascorbate (vitamin C) and a-tocopherol (vitamin E). Therefore, when considering how far ROS will travel, or in which part of the cell ROS will act, one has to consider that cells and organelles alike are well protected from the presence of ROS by a variety of means [26]. Heme proteins play a major role in various biological functions, such as oxygen sensing, electron transport, signal transduction, and antioxidant defense enzymes. Most of these reactions are carried out by redox reactions of heme iron. As the heme is not recycled, most cells containing heme-proteins have the microsomal mixed function oxygenase, heme oxygenase, which enzymatically degrades heme to biliverdin, carbon monoxide, and iron [27]. However, the red cell with the largest pool of heme protein, hemoglobin, contains no heme oxygenase, and enzymatic degradation of the red cell heme occurs only after the senescent red cells are removed by the reticuloendothelial system. Therefore, only nonenzymatic heme degradation initiated when the heme iron undergoes redox reactions in the presence of oxygen-producing ROS takes place in the red cell. Unlike enzymatic degradation, which specifically attacks the α-methene bridge, ROS randomly attack all the carbon methene bridges of the tetrapyrrole rings, producing various pyrrole products in addition to releasing iron [27,26].

The antioxidant and pro-oxidant behavior of flavonoids and the related activity-structure relationships were investigated by Cao's group [21,27], using the oxygen radical absorbance capacity assay. Both the antioxidant and the copperinitiated prooxidant activities of a flavonoid depend upon the number of hydroxyl substitutions in its backbone structure, which has neither antioxidant nor prooxidant action [25,27].

In general, the more hydroxyl substitutions, the stronger the antioxidant and prooxidant activities. The flavonoids that contain multiple hydroxyl substitutions showed antiperoxyl radical activities several times stronger than Trolox, an α-tocopherol analogue [21,22,23]. Alpha-Lipoic acid, which plays an essential role in mitochondrial dehydrogenase reactions, has recently gained considerable attention as an antioxidant. Lipoate, or its reduced form, dihydrolipoate, reacts with ROS such as O^{2-}, hydroxyl radicals, hypochiorous acid, peroxyl radicals, and singlet oxygen. It also protects membranes by interacting with vitamin C and glutathione, which may in turn recycle vitamin E [23, 24, 26]. In addition to its antioxidant activities, dihydrolipoate may exert prooxidant actions through reduction of iron. Alpha- lipoic acid administration has been shown to be beneficial in a number of oxidative stress models such as is chemi are perfusion injury, diabetes (both α-lipoic acid and dihydrolipoic acid exhibit hydrophobic binding to proteins such as albumin, which can prevent glycation reactions), cataract formation, HIV activation, neurodegeneration, and radiation injury. Furthermore, lipoate can function as a redox regulator of proteins such as myoglobin, prolactin, thioredoxin and NF-κB transcription factor [24].

Uric acid and its monoanion urate, is traditionally considered to be a metabolically inert end-product of purine metabolism in man, without any physiological value [25]. However, this ubiquitous compound has proven to be a selective antioxidant, capable especially of reaction with hydroxyl radicals and hypochlorous acid, itself being converted to innocuous products (allantoin, allantoate, glyoxylate, urea, and oxalate). There is now evidence for such processes not only in vitro and in isolated organs, but also in the human lung in vivo. Urate may also serve as an oxidisable cosubstrate for the enzyme cyclooxygenase [25,26]. Ferulic acid

is a ubiquitous plant constituent that arises from the metabolism of phenylalanine and tyrosine. It occurs primarily in seeds and leaves both in its free form and covalently linked to lignin and other biopolymers. Due to its phenolic nucleus and an extended side chain conjugation, it readily forms a resonance stabilized phenoxy radical which accounts for its potent antioxidant potential. UV absorption by ferulic acid catalyzes stable phenoxy radical formation and thereby potentiates its ability to terminate free radical chain reactions. By virtue of effectively scavenging deleterious radicals and suppressing radiation-induced oxidative reactions, ferulic acid may serve an important antioxidant function in preserving physiological integrity of cells exposed to both air and impinging UV radiation [27].

Many natural products (including anti-oxidants) that have been promoted to have anti-cancer and anti-inflammatory activity have also been shown to inhibit NF-κB. That applies to the discovery and use of agents that can block NF-κB for therapeutic purposes [26, 27].

Recent work by Karin, Ben-Neriah and others has highlighted the importance of the connection between NF-κB, inflammation, and cancer, and underscored the value of therapies that regulate the activity of NF-κB [23,25].

The importance of metals and other reactive oxygen species on NF-kB activation is further supported by studies demonstrating that activation of NF –kB by nearly all stimuli can be blocked by antioxidants, including N-acetyl cysteine (NAC), thiols, green tea, polyphenols and vitamine E [27].

Among the wide spectrum of antioxidant facilities such as tocopherol, carotin, vitamin C, selenium and other- succinic acid – natural metabolite of cycle Krebs acids proved well. Studying of protective action of succinic acid can be used for preventive treatment against different disease, even cancer.

Thus, the purpose of our further studying is to define protective action of succinic acid on human and animal cells.

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Резюме

Рассмотрены различные пути активации тяжелыми металлами сигнальных путей транскрипционного фактора NF-кВ. NF- кВ является важным регуляторным элементом, определяющим пролиферацию, выживание, дифференцировку и апоптоз клеток. Активация факторов транскрипции тяжелыми металлами, приводит к изменению экспрессии нескольких сотен генов, и соответственно, активности многих метаболических процессов. Многие антиоксиданты имеют анти-раковый, противовоспалительный эффект, что также было показано в ингибировании транскрипционного фактора NF-kB, которые применяются для терапевтических целей.

Summary

Ауыр металдардың транскрипциялық NF-kB ядролық фактордің қоздыратын әр түрлі сигнал жолдары көрсетілген. NF-kB транскрипциялық фактор жасушадағы маңызды реттеуші элемент болып табылады, ол жасушаның пролиферациясын, тірі қалуын және апоптозды анықтайды. NF-kB транскрипциялық фактордың ауыр металдармен активтендіргенде көптеген гендерді түрлендіреді, соған сәйкес әр түрлі метаболикалық процестерді активтендіреді. Анықталған көптеген антиоксиданттар қатерлі ісікке және ісіп қызару процесіне қарсы эффектілігі көрсетілген, сол NF-kB транскрипциялық фактордың блокадалау жолдарында көрсетілген мұны терапевтік мақсатта қолданылады.