EDITORIAL

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Jelkmann W, Thevis M. Could Nickel Become a Novel Erythropoiesis-Stimulating Compound for Cheating Athletes? Dtsch Z Sportmed. 2016; 67: 253-254.

Could Nickel Become a Novel Erythropoiesis-Stimulating Compound for Cheating Athletes?

Könnte Nickel ein neues erythropoietisch wirksames Dopingmittel werden?

Rude and violent behavior in sports is sometimes called "nickelig" in German language. Ironically, recent evidence suggests that nickel may be misused in sports (19). Nickel belongs to group 10 of the current IUPAC (International Union of Pure and Applied Chemistry) periodic classification of elements. It shares properties with iron and cobalt, the latter being a prohibited substance according to the regulations of the World Anti-Doping Agency (WADA) (7, 21). Under experimental conditions, ionic nickel can induce hypoxia-like responses, possibly promoting red blood cell production (1). This knowledge calls into question whether the recent detection of a nickel-enriched product claiming performance-enhancing properties, is indicative of attempts to undermine current human and animal doping controls (19, 20).

The Hypoxia Inducible Transcription Factors (HIFs)

The erythropoietin gene (EPO) is controlled by the hypoxia-inducible transcription factors (HIFs). HIFs are heterodimeric proteins composed of α- and β-subunits. There are different HIF-α subunits. HIF-1α is rather ubiquitously expressed, with HIF-1 (HIF-1α/HIF-1β) playing important roles in metabolic processes, such as glucose metabolism (15). In contrast, HIF-2α is restricted to specific cell types, including renal and extra-renal cells producing EPO, and endothelial cells producing vascular endothelial growth factor (VEGF) (9). Hence, HIF-2 (HIF-2α/HIF-1β) promotes erythropoiesis and angiogenesis. Distinct prolyl residues of the HIF-α subunits are hydroxylated in an O_2-pressure-dependent manner by specific enzymes, the prolyl-4-hydroxylase domain proteins (PHD-1, -2 and -3). PHDs are iron- and 2-oxoglutarate-dependent dioxygenases. Prolyl hydroxylated HIF-α is immediately ubiquitinated by the so-called SCF complex (S-phase kinase-associated protein 1, Cullin, F-box containing complex) to undergo immediate proteasomal degradation. Salnikow et al. were the first to demonstrate that nickel exposure activates HIF-1 (13). Subsequent studies have shown that Ni^{2+} does not only stabilize HIF-1α but also HIF-2α (11). Nickel is less potent than cobalt as a HIF-stabilizer (4).

Several hypotheses have been proposed to explain the stabilization of HIF-α by nickel. Ni^{2+} can enter cells via the divalent metal transporter-1 (DMT1) and thereby compete with Fe^{2+} for entry into cells (2). Of note, however, simple competitive inhibition of the HIF-α PHDs has been considered unlikely (4). It has been suggested that divalent metals such as Ni^{2+} or Co^{2+} may stabilize HIF-α by binding to Cullin-2 (8).

Effects of Nickel on EPO Production

Almost 40 years ago the group of Hopfer discovered that the intra-renal injection of nickel compounds (αNi_3S_2, NiO, NiS_2, βNiS, Ni dust) produces an increase in circulating EPO and erythrocytosis in rats (6). The intra-renal injection of Ni_3S_2 was also effective in guinea pigs but not in in hamsters or gerbils, indicating significant species-specificity (18). Importantly, $NiCl_2$ proved to increase EPO mRNA expression and EPO production in the human hepatoma cell line, Hep3B (5). The intraperitoneal infusion of $NiCl_2$ failed to stimulate EPO production in rats (17). Likewise, the subcutaneous injection of nickel failed to stimulate renal EPO mRNA expression in mice (10).

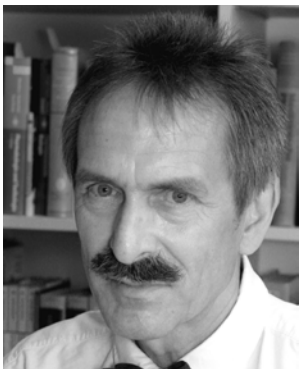
Note, here, that dietary nickel was found to increase the blood hemoglobin concentration and to cause pulmonary hypertension in broiler chickens (12). No such effect has been reported with respect to increased nickel supplementation in mammals. It can be stated that the effect of Ni^{2+} differs from that of Co^{2+}, as the latter clearly stimulates EPO synthesis and erythropoiesis following oral administration (7).

Effects of Nickel on Other HIF-Dependent Genes

HIFs do not only stimulate erythropoiesis, but are involved in a number of other processes which protect the cells from oxygen and glucose deprivation. More than 1000 HIF target genes have been identified so far (15). For example, hypoxia, nickel, and cobalt stimulate VEGF expression in osteoblast cell cultures by a similar mechanism (16). GeneChip analysis of mouse embryonic fibroblasts exposed to Ni^{2+} has demonstrated increased expression of genes involved in glucose metabolism, including glycolytic enzymes and genes responsible for glucose transport (14).

Conclusion

Nickel can stimulate HIF-dependent processes. However, there are no data in support of the assumption that nickel can stimulate EPO production when administered systemically (oral, subcutaneous, or intravenous routes). Actually, nickel is contained in numerous food products including corn, nuts, fruits, tea, etc. and thus an integral part of the human diet. Increased nickel supplementation, however, can ›



Prof. Dr. med. Wolfgang Jelkmann
Institute of Physiology, University of Lübeck

Prof. Dr. Sportwiss. Mario Thevis
Center for Preventive Doping Research – Institute of Biochemistry, German Sport University Cologne

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CORRESPONDING ADDRESS:
Wolfgang Jelkmann, M.D.
Professor of Physiology, Institute of Physiology, University of Luebeck
Ratzeburger Allee 160
23562 Luebeck, Germany
: wolfgang.jelkmann@uni-luebeck.de

cause severe side effects. Extensive nickel consumption can result in allergic reactions and (irreversible) nickel sensitivity, digestion problems, increased red blood cell counts, kidney failure and cancer, primarily lung cancer (3). These facts alone should discourage athletes from a potentially deleterious doping practice with nickel. In addition, anti-doping laboratories have established methods for detection of transition metals including nickel in biological samples (19, 20).

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