REVIEW ARTICLE

Biological role of copper as an essential trace element in the human organism

Biologická role mědi jako základního stopového prvku v lidském organismu

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Summary

This paper presents an overview of the physiological properties of copper (Cu), an essential trace element playing an important role in the human metabolism, primarily as a cofactor of many metalloenzymes. The maintenance of Cu homeostasis is required for proper functioning of the human body. However, when the disturbance of Cu homeostasis occurs, strong pathological manifestations may develop. Wilson's disease and idiopathic toxicosis are examples of severe chronic liver diseases that are the results of genetic predisposition to the hepatic accumulation of copper. Conversely, congenital Menkes disease is manifested as serious Cu's nutritional deficiency. Although Cu is necessary for many life processes, it is also a powerful weapon used since the ancient times against many microorganisms. Finally, the theories of Cu antimicrobial and antiviral mechanisms of action are summarized, including contemporary and potential future utilizations in medical and non-medical fields of human life.
Key words: copper • metalloenzymes • copper toxicity • copper deficiency • copper-related diseases • copper applications

Souhrn

Tento článek popisuje přehledem fyziologických vlastností mědi (Cu) jako základního stopového prvku hrajícího důležitou roli v metabolismu člověka, a to především jako kofaktor mnoha metaloenzymů. Pro správnou funkci lidského těla je zásadní potřeba udržovat homeostázu Cu, protože při jejím narušení dochází k silným patologickým projevům. Příklady těžkých vrozených onemocnění jater, při kterých dochází k výraznému hromadění mědi v játrech, jsou Wilsonova choroba a idiopatická toxikóza. Naopak, vrozené onemocnění Menkesova choroba se projevuje závažným nedostatkem Cu v organismu. Ačkoliv je Cu nezbytná pro mnoho životních procesů, představuje také silnou zbraň používanou od starověku proti mnoha mikroorganismům. Nakonec jsou v příspěvku shrnuty teorie antimikrobiálního a antivirového působení Cu spolu s přehledem současných a možných budoucích využití v medicínských i nemedicínských oblastech lidského života.
Klíčová slova: měď • metaloenzymy • toxicita mědi • nedostatek mědi • nemoci spojené s mědí • aplikace mědi

Introduction

Copper (Cu), a redox active metal, is an essential trace element in humans and animals and it is involved in a number of physiological and biochemical processes as a cofactor of numerous metalloenzymes[1–3]. These catalyze a large number of enzymatic processes – cellular respiration, biosynthesis of neurotransmitters and peptide hormones, protection against free radicals, cross-linking of elastin, collagen and keratin[4]. Cu is also essential for iron homeostasis and thus indirectly affects hematopoiesis and participates in blood coagulation and angiogenesis[5–7].

In biological systems, Cu is predominantly present in the oxidised form of Cu^{2+} (cupric) ion. The ability of copper to accept and donate electrons reversibly plays the main role in the disposal of free radicals from the organism[8].

The Cu's body content is about 70–80 mg[9]; of which 10% is distributed in the plasma and blood elements and 90% in tissues. The Cu blood concentration is slightly different by gender; the male values range from 0.614 to 0.970 mg/L, in women from 0.694 to 1.030 mg/L. Cu concentration increases with age in healthy men, but not in women. In male smokers the blood Cu amount significantly decreases[9, 10]. The average intake of Cu by adults varies from 0.6 to 1.6 mg/d, a higher intake is needed during pregnancy and breastfeeding[11].

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Besides Cu indispensability for the basic life processes of most organisms, it is also important as a potent antimicrobial weapon against invading pathogens.

The finding that Cu is used by the innate immune system is a relatively recent discovery. The Cu appears to play a unique role in nutritional immunity by acting as a component of the antimicrobial arsenal produced by cells of the innate immune system[12, 13]. Although the exact mechanism of Cu antimicrobial effect is not fully understood, the benefit has been used throughout human civilization, from ancient Egyptian and Greek civilizations to the present time. Therefore, the Cu biocidal effect has become of scientific interest especially due to increasing antibiotic resistance against commonly used antibiotics[14].

The Cu antibacterial effect (e.g. against *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Enterococcus faecalis, Bacillus subtillis*), the antifungal effect (e.g. against *Candida albicans*, etc.)[15, 16], antiviral (against bronchitis virus, polio virus, herpes simplex virus and HIV-1[17–20] and spermicidal activities[21] have been demonstrated in many studies.

Despite the extreme sensitivity of microorganisms to Cu, humans exposure is considered safe, as it is demonstrated by the widespread use of long-term Cu intrauterine devices by women[22–24].

This article discusses the overview of physiological effects of Cu, the mechanisms involved in maintaining the Cu homeostasis as well as the pathophysiological states associated with this trace element. Moreover, Cu antimicrobial and antiviral effects are described, including contemporary and potential future utilizations in the fight against serious pathogens.

The physiological importance of copper

Copper homeostasis

Cu homeostasis is a highly coordinated process on the intracellular and intercellular level involving the processes of intestinal absorption, distribution, efflux from cells and biliary excretion[25].

The absorption of Cu in the body depends mainly on its chemical form; the highly soluble Cu compounds are readily absorbed. The factors inhibiting the absorption of Cu from the intestinal lumen and simultaneously reducing its general bioavailability tend either to reduce its intraluminal solubility or to provoke competitive interactions with the Cu transport through the mucosa[26]. Presence of many components can affect its absorption. Fibre, phytate[27, 28], vitamin C[29, 30], fructose[31, 32] and other sugars decrease the bioavailability of Cu, but only at their highly elevated intake (fibre > 50 g/day; sugars > 35% of energy; ascorbic acid > 1500 mg/day). During normal diet, it is unlikely to affect the Cu utilization. Zinc and cadmium are the most powerful competitive inhibitors of Cu absorption[33]. Conversely, a high level of protein intake (above 100 g/day) enhances Cu bioavailability[27].

The Cu absorption takes place in the small intestine either by diffusion or using transport proteins 1-DMT1 or 1-CTR1 (1-DMT1 is the divalent metal transporter, 1-CTR1 is the Cu^{2+} specific transporter). The DMT1 binds iron and other divalent metals, such as Cu, manganese, etc. The Cu affinity for DMT1 is relatively low. The transporter CTR1 plays the key role in Cu uptake[4, 25].

In human cells, Cu is utilized in several cell compartments, and its intracellular distribution is regulated in response to metabolic demands and changes in cell environment[34]. The reduction Cu^{2+} to Cu^{+} ions is necessary for the transport across cell membranes[35]. The CTR1 is found in two cell locations: at the plasma membrane and in intracellular vesicles. The CTR1 distribution between these two compartments is cell-specific. A significant fraction of CTR1 in enterocytes is intracellular and is located in the vicinity of the apical membrane[4, 36]. The Cu transported across the apical membrane by CTR1 in intestinal enterocytes

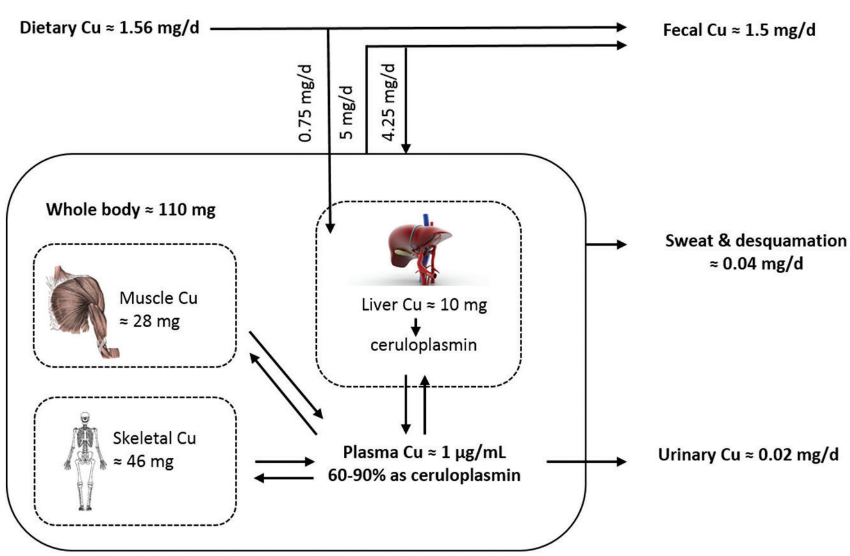

Fig. 1. Metabolism of Cu[41]

is shuttled to the ATP7A (Cu-transporting P-type ATPase) and pumped into the portal circulation for further utilization and to the liver, which is the major Cu storage organ[37]. In the liver, kidney, placenta, and mammary gland, the basolateral plasma membrane is the predominant CTR1 location[28–39] and it transports Cu from circulation by, mostly, retrieving Cu from specific carriers[40].

The ATP7A plays crucial role in moving Cu across many other polarized cell layers including the placenta and the blood-brain barrier to ensure adequate Cu concentration for the proper foetus development and especially of the brain. The ATP7A is also important for the delivery of Cu to nascent proteins in the Golgi apparatus. In mammals, ATP7A is expressed in many tissues except the liver. In the liver and several other tissues, ATP7B (homologous Cu-transporting ATPase) is important for loading Cu on the ceruloplasmin (ensuring peripheral Cu distribution). The ATP7B also mobilizes excess Cu into the bile to prevent tissue Cu overload. Cu excretion is almost exclusively by faeces, resulting from biliary excretion (70%); the rest is unabsorbed Cu and Cu from desquamation mucosal cells. The urine excretion is negligible[25] (see Fig. 1).

The most important Cu-containing metalloenzymes necessary for physiological processes of humans include the following ones:

• *Cu-Zn superoxide dismutase* (Cu-Zn SOD) is the most abundant extracellular metalloenzyme, responsible for the removal of superoxide anions (highly toxic reactive oxygen species) and for its transformation to hydrogen peroxide (H_2O_2) for further disposal (by catalase and glutathione peroxidase). It is a ubiquitous and highly stable enzyme consisting of two subunits. Each subunit has a Cu and Zn site. Cu ions are bound on the four imidazole histidine residues; Zn stabilizes the protein structure. The brain, liver and renal cortex contain the high tissue amount of the Cu-Zn SOD[4, 6].

• *Lysyl oxidase* is a key enzyme of the collagen and elastin synthesis and maturation. It catalyses the connective tissue formation by cross-linking between collagen fibres and elastin. Lysyl oxidase is a multimeric protein composed of 32 kDa subunits, requiring Cu for its activity[11].

• *Cytochrome-c oxidase* sits within the inner mitochondrial membrane. It has four redox-active metal sites, two heme sites (hemes a and a3), and two Cu sites (CuA and CuB)[11]. The cytochrome-c oxidase is the terminal electron acceptor of the respiratory chain and reduces molecular oxygen (O_2) to water. In addition, it pumps protons from the inside to the outside of the membrane, thereby a proton gradient across the membrane is formed[42, 43].

• *Dopamine β-hydroxylase* is indispensable for the conversion of dopamine to norepinephrine in the adrenal ganglion and noradrenergic neurons. The presence of the Cu and ascorbic acid (as an oxygen transport coenzyme) is essential for its activity[44].

• *Tyrosinase* is a transmembrane cuproenzyme, which catalyzes the oxidative conversion of tyrosine by many metabolic pathways to melanin pigment[45].

• *Ceruloplasmin (*CP*, α-2-globulin)* as a single polypeptide chain (about 120 kDa with 12 kDa carbohydrate) is the main plasma Cu-transporting protein (carrying up to 90% of Cu), responsible for Cu delivery to cells and excretion of Cu from the body[11]. As CP is one of the positive protein reactants of the acute phase, the increased CP plasma concentration occurs during pathological conditions, such as inflammation, infection or injury[46]. However, it appears that the regulation of CP expression is controlled not only just by inflammatory cytokines, but also through the hypoxia-inducible factor, which is linked to iron metabolism[47]. Higher concentrations of CP are associated with the development of atherosclerosis[4, 6]. The other important roles of CP are the antioxidant, amine oxidase and ferroxidase activities (the oxidation of Fe^{2+} to Fe^{3+} before binding to transferrin)[11].

Copper toxicity

Although Cu is an essential element in biology, it can be also a potentially dangerous and its dysregulation can lead to the development of many adverse health effects, including liver and kidney damage, anaemia, immunotoxicity and developmental toxicity[48].

Fortunately, acute and chronic Cu toxicity occurs relatively rarely; as a result of an accident, occupational diseases, environmental pollution or congenital metabolic disorders of Cu[49].

The most knowledge about the mechanisms of Cu-mediated biological damage comes from studies with DNA[50, 51]. Cu^{2+} ions bind specifically to DNA[52], preferably to guanosine residues[51]. The products of these reactions include single and double DNA strand breaks as well as base modification, the main product being 8-oxo-2'-deoxyguanosine[50, 51, 53, 54].

Moreover, Cu^{2+}, as heavy metal ions, catalyse the generation of reactive oxygen species (ROS) and cause cellular damage[51, 55] via depletion of enzyme activities through lipid peroxidation and reaction with nuclear proteins and DNA[56]. One of the most important metal-mediated mechanisms of the formation of free radical generation is by a Fenton-type reaction. Superoxide ion and hydrogen peroxide can interact with Cu, via the metal catalysed Haber–Weiss/Fenton reaction to form OH radicals[57].

$Cu^{+} + H_2O_2 \rightarrow Cu^{2+} + OH^{-} + \cdot OH$ Fenton reaction

$Cu^{2+} + \cdot O_2 \rightarrow Cu^{+} + O_2$ Haber ─ Weiss

However, Cu-mediated DNA damage is only partially inhibited by free-radical scavengers[51, 55]; thus ROS formation is not the main way leading to biological damage.

Similar as Cu excess, severe deficiency of Cu also affects, directly or indirectly, the components of the oxidant defence system and as a result it increases ROS formation leading to oxidative damage of lipids, DNA, and proteins[58].

Chronic exposure

Chronic Cu toxicity is primarily manifested in the liver (as liver cirrhosis) with episodes of haemolysis and with disorders of the immune system. The damages of the renal tubules, brain and other organs are the other accompanying symptoms and they may progress up to coma, liver necrosis, circulatory collapse and death.

The dialysis patients using devices with Cu tubing, workers using Cu pesticides and infants during long-term intravenous total parenteral nutrition[49)] are the risk groups for the development of chronic Cu toxicity. The patients with chronic liver disease can be also potentially susceptible to Cu[25)]. Many of the chronic toxic effects of Cu are associated with oxidative damage of membranes of macromolecules[59)]. Excessive Cu intake participates in the development of Cu toxicity also indirectly, through interaction with other nutrients (for example anaemia due to interference of Cu with iron transport)[25)].

Dermal exposure is not associated with systemic toxicity, but occasionally in susceptible individuals it may cause allergic reactions[22)].

Acute exposure

Acute intoxication can be caused by single or multiple ingestion of drinking water with an elevated Cu content (3–6 mg/L). The main acute symptoms are nausea, vomiting and gastric irritation. It is unclear whether these symptoms are a result of an acute Cu irritation or metal bitter taste of Cu. The progression of symptoms such as abdominal pain and headache, nausea, dizziness, vomiting, and diarrhoea, tachycardia, respiratory difficulties, haemolytic anaemia, haematuria, massive gastrointestinal bleeding, damage and failure of the kidney and liver was observed after an intentional or accidental ingestion of high concentrations of Cu salts (20–70 g)[25, 49)].

Copper deficiency

In humans, serious Cu deficiency is rare. However, unrecognized or marginal Cu deficiency (< 1 mg / day) may be widespread. The cause can be either inadequate dietary intake (primary Cu deficiency) or inadequate Cu absorption (secondary Cu deficiency). Also some heavy metals in foods can compete with Cu absorption and decrease its absorption[2)].

The group with potential risk of Cu deficiency includes the genetically susceptible population: newborns with low birth weight, infants fed cow's milk, pregnant and lactating mothers, patients receiving total parenteral nutrition (when Cu intake is lower than 0.1 mg Cu/kg body weight/day), individuals with malabsorption syndrome, diabetics, alcoholics, people with eating disorders and also vegetarians[25)].

The symptoms of Cu deficiency (accompanied by a reduction of Cu concentration in serum and of CP level) are abnormalities of the bone marrow, neutropenia and mainly hypochromic microcytic anaemia, which is resistant to iron treatment[25)]. The other symptoms include the growth disorders and also an increased incidence of infections due to the Cu necessity for the production of interleukin-2 by lymphocytes during infection[60)] and hypopigmentation of hair. Deficits of the nutrients during pregnancy can result in gross structural malformations in the conceptus, and persistent neurological and immunological abnormalities in the offspring[61)].

Interference of the oxidant defence system components and consequently increased ROS production and oxidative damage to lipid, DNA and proteins was demonstrated due to Cu deficiency in the animals and cell culture models[25, 61)].

A decrease of SOD activity and an increase of superoxide anions has been shown in Cu deficient rats[62, 63)]. In addition, it is postulated that a decrease in cytochrome-c oxidase activity and oxidative inactivation of complex I (NADH: ubiquinone oxidoreductase) contribute to increased production of ROS in Cu deficient animals[64)]. Increased lipid peroxidation has been observed in Cu deficient plasma, liver, heart, aorta, and erythrocytes[65, 66)].

Congenital disorders of copper metabolism

Menkes disease and Wilson's disease are the most frequent diseases of Cu metabolism. Menkes disease is manifested as serious Cu´s nutritional deficiency, while Wilson's disease as copper toxicosis[25)].

Menkes disease

Menkes disease is a rare disease linked to the X chromosome, caused by mutation of the gene encoding ATP7A, Menkes ATPase (Cu-transporting ATPase)[2)]. ATP7A (protein in the trans-Golgi network) is the enzyme responsible for Cu incorporation into cuproenzymes (at a low Cu level), and for the efflux of Cu excess from the cells from the trans-Golgi network to the plasma membrane (at high Cu intracellular levels). Menkes disease mainly occurs in boys, and is often fatal in early childhood[25)]. The typical symptoms are mental retardation, neurological abnormalities and degeneration of connective tissue (due to a lack of several Cu dependent enzymes needed for brain development)[2)].

A decreased activity of *cytochrome-c oxidase* leads to a serious neurological disorder too. *Tyrosinase* deficiency causes a lack of melanin, which is manifested by hypopigmented hair with a steel appearance, and brittle and frizzy hair ("curly hair syndrome") due to the lack of an unidentified cuproenzyme required for cross-linking of keratin[25)].

The treatment is performed by intravenous Cu administration, but Cu cannot be transported to the brain. Nevertheless, early diagnosis and daily injection of Cu-histidine intraperitoneally and intrathecally into the central nervous system could prevent neurodegeneration and prolong life[25)].

Wilson's disease

Wilson's disease is a rare autosomal recessive disorder of Cu metabolism, caused by mutation of the gene encoding enzyme ATP7B – Wilson ATPase on a chromosome 13[2)]. ATP7B enzyme is mainly found in the liver, where it is primarily responsible for Cu delivery to cuproenzymes and for Cu biliary efflux.

Consequently, an accumulation of Cu in hepatocytes occurs, leading to cirrhosis[2, 53)] and defective incorporation of Cu into CP. The result is an increased plasma concentration of unbound Cu and subsequent Cu accumulation in the extrahepatic tissues, especially in the kidney, brain and cornea – as Kayser Fleischer-rings (diagnostic marker of Wilson's disease)[2, 25)].

The neurological symptoms of the disease include the upper limbs tremor, slow movement and personality changes. Late complications are icterus and encephalopathy development, coagulation disorders, occasionally associated with intravascular coagulation and renal insufficiency[9, 25)].

In an early diagnosis, Wilson's disease can be treated by many different ways (using chelating agents, low income Cu diet and high intake of zinc supplements)[59)]. The antidote of choice is zinc (in form of $ZnSO_4$ or $(CH_3COO)_2Zn$); it partially blocks Cu absorption by induction of metallothionein, which binds Cu in the mucosal cells until they are not desquamated and eliminated[25)]. Moreover, zinc is fully effective, non-toxic, body's own substance. On the other hand, zinc exhibits a too slow effect especially in the acute phase of Cu toxicity with neurological symptoms. Therefore, chelating agents are used, including D-penicillamine, trientine (risk of toxicity) and tetrathiomolybdate. These create complexes with dietary protein and Cu, and make Cu to be non-toxic. Subsequently, patients are treated by maintenance zinc therapy[67)]. Concomitant dietary restrictions removing foods with high content of copper (for example chocolate, oysters and fungi) are required. With early diagnosis and treatment, these people can live a normal life[25)].

Idiopathic copper toxicosis

This rare disorder is a hereditary genetic disease of Cu metabolism, called also non-Indian childhood cirrhosis. It is characterized by abnormally high Cu levels in the liver, normal or elevated plasma concentrations of copper and CP, clinical onset of cirrhosis by 2 years of age, and death within 5 years.

Early initiated D-penicillamine treatment prevents fatal consequences and often renewed liver histology[49)].

Copper and neurodegenerative diseases

The disturbance of Cu homeostasis leading to oxidative stress and formation of free radicals contributes to the development of Alzheimer's disease and Creutzfeldt-Jakob disease[2)]. In Alzheimer's disease, we often encounter an increased Cu concentration in the cerebrospinal fluid, the Cu concentration in the plasma is either normal or elevated[59)]. Alzheimer's disease aetiology is associated with the accumulation of β-amyloid protein. Under normal conditions, its precursor binds Cu (in reduced state) and facilitates its transport across the entire length of the neuron (from the cell body to the surface of the axon and to the plasma membrane of the dendrites). In Alzheimer's disease, the function of β-amyloid protein precursor is impaired, leading to Cu oxidation in the presence of H_2O_2 and to production of free oxygen radicals. At the same time, β-amyloid protein precursor fragmentation occurs, these aggregate and damage the neurons by free oxygen radicals[2)]. In addition, Cu extracellularly accumulates in amyloid plaques, which leads[59)] to reduction of the cytochrome-c oxidase and superoxide dismutase activity. The consequences of these events are reduction of the key metabolic and defence mechanisms and damages to the neurons[2)].

In the case of Creutzfeldt-Jakob disease, another neuronal membrane protein (prion), allowing Cu entry by endocytosis, is damaged, the same as in the scrapie in humans and bovine spongiform encephalopathy (mad cow disease) in bovine animals too. As in the previous case, a protein conformational change alters its function. The structural change involves the transition of a natural α-helical prion into a β-leaf conformation that confers the pathogenic potential of the protein and simultaneously aggregates it. Moreover, the mutant prion possesses a markedly reduced ability for Cu transport, making neuronal cells susceptible to oxidative stress[2)].

The relationship between Cu and the development of Parkinson's disease is also described. Cu is associated with accelerated aggregation of α-synuclein protein in the formation of Lewy bodies[3, 68)]. Similarly, Cu has been shown to promote aggregation of mutant Huntington disease polyglutamine repeat proteins. If Cu dysregulation is a cause or a consequence of these neurodegenerative diseases is under considerable investigation[3)].

Copper and cancer

In cancer, Cu (and simultaneously CP) concentrations are almost always significantly increased (2–3 times), while concentrations of zinc, iron and selenium are significantly decreased[69)].

Serum Cu concentrations correlate with tumour development, its size, occurrence, progression and recurrence and it can be said that the malignant tumours have often higher Cu concentrations[2, 70)]. ROS production and oxidative stress are probably the major mechanisms involved in the development of cancer[59)]. Moreover, Cu induces proliferation and migration of endothelial cells by activating various angiogenic factors (e.g., endothelial growth factor, basic fibroblast growth factor, tumour necrosis factor, and interleukin 1). As a result, new blood vessels are formed, because tumours require a rich supply of oxygen and nutrients. The formation of new bloodstream can be reversed by chelating agents[2)], such as D-penicillamine, tetrathiomolybdate, clioquinol and trientine, which are antiangiogenic agents still in clinical trials[69)].

In cancer, the level of plasma CP positively correlates with the stage of disease, and it can be said that malignant tumours have often higher Cu concentrations[70)].

Antimicrobial and antiviral activity of copper

Although Cu is necessary for many life processes, it is also a powerful antimicrobial weapon against many microorganisms. For over a hundred years it is used as a bactericidal and fungicidal agent. Cu antimicrobial activity is also utilized by the immune cells of eukaryotes. Many studies have shown that activated macrophages accumulate Cu within the phagosome that captures and prohibits microbial attack. In addition, levels of ATP7A protein are increased and Cu is transferred from the secretory space into the phagosome, resulting in a parallel increase of the levels of phagosomal Cu concentration.

These observations suggest responsibility of ATP7A for the increase in phagosomal Cu concentrations during infection[12, 13, 71)].

Several reports demonstrate that bacterial cells upregulate the expression of Cu ATPases during infection in dependency on metalloregulatory transcription factors of Cu, resulting in their ability to export Cu. Observing that bacterial pathogens actively exclude intracellular accumulation of Cu or alter the distribution of Cu in mammalian hosts suggests that the Cu status is a key battleground during infections[12)].

Biocidal mechanism of copper

The exact mechanisms of the biocidal effect of Cu are a source of ongoing investigation. It is assumed that the cause of cell death is multifactorial rather than the result of a single universal mechanism[72)]. A key property of Cu which significantly contributes to its toxic effect is its ability to accept and donate single electrons as it changes the oxidation state between Cu^{+} and Cu^{2+}. This allows Cu to act as a catalyst for the generation of ROS, such as hydroxyl radicals and superoxide anions. These ROS have a potential to cause oxidative damage to proteins, nucleic acids and lipids (including those in the cell membrane). The formation of ROS is the main mechanism of the Cu antibacterial effect[73)].

Free Cu ions may compete with zinc or other metal ions for important binding sites on proteins, leading to conformational change and the loss of protein function[74, 75)].

In addition, Cu ions can lead to the depletion of the sulfhydryl groups, for example in cysteines or glutathione in cytoplasmic enzymes needed to make branched-chain amino acids[76)].

Bacteria have developed a number of protection mechanisms against the toxic effects of Cu ions: extracellular Cu ion sequestration, relative impermeability of the outer and inner bacterial membrane to Cu ions, Cu absorbing metallothionein-like proteins in the cytoplasm and periplasm, and active cell mediated secretion[75)].

However, when they exceed a certain level of Cu and an exposure time (they are different between organisms), they cannot cope with Cu overload and can die. Due to the multifactorial death mechanism of Cu and especially its non-specific mechanism of damage their tolerance to Cu is relatively low. The bacterial Cu resistance systems do not usually provide protection but only prolong their survival[75)].

Cu possesses a potent antiviral (virucidal) activity. The inactivation of the enveloped or non-enveloped, single- or double-stranded DNA or RNA viruses by Cu and Cu compounds has been reported in many studies[18, 20, 77–79)].

Cu^{2+} ions may inactivate viruses in a number of ways by binding electron donor groups on proteins or nucleic acids[80)]. The results are a spiral structure breakdown of nucleic acids and their denaturation. In the single chain DNA, the Cu binding site occurs on average in every third nucleotide. Moreover, formation of ROS can affect the peptide backbone of the capsid proteins of the virions[81)].

The viruses generally have no copper tolerance[74)]. Moreover, researchers Sagripanti et al., demonstrated, specifically in the *Herpes simplex* virus, the Cu enhanced antiviral effect with the following reducing agents in the order: ascorbic acid >> hydrogen peroxide > cysteine[19)].

Health related copper applications

Copper and copper-based compounds, due to their potent biocidal properties, are currently used in several

Table 1. Current and future potential applications of copper and copper compounds in the medical area

Medical usage of copper	
Wound healing	copper containing wound dressings[82, 83)]
Mucosal administration	copper-containing dental cement in dentistry[84, 85)] copper intrauterine devices in gynecology[86, 87)] nasal spray with copper[88)]
	alginate particles cross-linked by copper in gynecology[89)] – *in research*
Internal administration	treatment of rheumatoid arthritis[90, 91)] treatment of Menkes desease[25)] treatment of cancer[92)] – *in research*

medical and in many nonmedical areas, which affect human health (see Table 1, 2).

Although copper is widely used in many areas of human life, the main disadvantages of copper medical uses are: inapplicability in systemic infections, mainly due to its potential toxicity after orally administration and its price[74].

Conclusion

In conclusion, copper is an essential mineral for human life and its homeostasis is strictly maintained by many physiological processes. Although the Cu safety is often discussed, potent biocidal properties against microorganisms destine its widespread use in many areas related to human health. Many of these utilizations (for example intrauterine devices, dental cement) are already being commonly used. Therefore, it is expected that other novel approaches using Cu antimicrobial properties could bring new positive effects on health and life of humans. These new technologies, using for example non-soluble copper compounds into polymeric yarns, from which many textile and other consumer products for protection health workers and patients are produced, are in the research phase. Also, use of copper surfaces leading to the contact killing of pathogenic microorganisms in hospitals, followed by reduction of nosocomial infections occurrence, offers a great potential to the future. Reduced antibiotic consumption is ultimately a huge benefit. Nevertheless, in spite of the fact that Cu is a very attractive active material used for maintaining and even improving human health, its use should be very carefully considered, especially with regard to its possible toxic effects at the cellular and tissue level.

Conflicts of interest: none.

Table 2. Current and future potential applications of copper and copper compounds in with health related areas

Other usage of copper	
Reduction of nosocomial infections	Hospital surfaces with metallic copper, for example door knobs, bed rails and toilet seat using hospital soft surfaces[93–96], like sheets, patient robes and pajamas[17] and nurse clothing[17, 97, 98] – effect based on the contact killing Disinfection of contaminated cloths with biocides based on copper[74]) – *in research*
Components of textiles	Copper-impregnated fabrics with acaricidal effect, for example mattresses, quilts, carpets and pillows[17, 99] In form of socks for the prevention and treatment of fungal foot infections (athlete's foot)[100]
Protective equipment using by first responders and laboratory personnel	Latex gloves[17], masks, disposable robes[74] – *in research*
Quality Control of drinking water	In the form of copper pipes[74] Using copper-silver ionization[101–103]
Cosmetics	Copper-containing ointments[104]
Food industry	In food processing, storage and transportation as copper containing surfaces and packs[105–107]
Antiviral filters	Antiviral respiratory masks that reduce the risk of infection[17, 108] Blood and breastmilk filtration devices[78] – *in research*
Agriculture	The control of downy mildew on grapes and green slime in farm ponds, rice fields, irrigation and drainage canals, rivers, lakes and swimming pools[109] Fungicide for wood preservation[110] Potent molluscicides[111]
Painting	Self-disinfecting surfaces, for the reduction of microbial biofilm formation in ships[112–114]

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