Coordination Chemistry Reviews 371 (2018) 86–95

Contents lists available at ScienceDirect

Coordination Chemistry Reviews

journal homepage: www.elsevier.com/locate/ccr

Review

Copper imbalance in Alzheimer's disease: Overview of the exchangeable copper component in plasma and the intriguing role albumin plays

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ARTICLE INFO

Article history:
Received 13 September 2017
Received in revised form 22 March 2018
Accepted 21 May 2018

Keywords:
Alzheimer's disease
Copper
Exchangeable copper
Albumin
Glycated albumin
Ceruloplasmin

ABSTRACT

Essential metals are vital elements for human biology. Iron, copper, and zinc are all essential for life. Trace metal dyshomeostasis has been linked to cognitive deterioration and in particular to a disturbance in the regulation of copper (Cu), characterized by an increase in serum Cu not bound to ceruloplasmin (nCp-Cu also known as "free" copper). It is thought to play a role in the development of Alzheimer's disease (AD), the most common form of dementia. Copper homeostasis is finely regulated in our bodies and the expansion of exchangeable nCp-Cu is symptom of the breakdown of this homeostasis, which affects myriad biological pathways. If not structurally bound to enzymes or coordinated by proteins, copper generates free radicals via Haber-Weiss and Fenton reactions. Human Serum Albumin (HSA) is the most abundant serum protein and the main protein exchanging copper in the nCp-Cu pool. Copper coordinated by HSA is in equilibrium with copper coordinated by other small copper chelators circulating in the blood stream in a dynamic and exchangeable manner dependent on environmental osmolarity, oxidation state, pH and compounds' functions. Albumin is susceptible to glycation starting from Maillard reaction, carbohydrates, in particular glucose, form advanced glycation end-products (AGEs). AGE-albumin is one of this products. Free radicals and free metals in circulation accelerate this cross-linking of protein with carbohydrates. Modified albumins are also significantly less effective than native forms in avoiding the aggregation of Aβ, the main component of the amyloid plaques in the AD brain.

The current review aims to provide insight into the coordination chemistry of copper in plasma with a special glance toward the exchangeable copper coordinated by albumin, to explore how aberrant regulations of this interaction are linked to the aetiology of AD.

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https://doi.org/10.1016/j.ccr.2018.05.020
0010-8545/

1. Introduction

Alzheimer's disease (AD) is the most common form of dementia and one of the most socially costly diseases in all developed countries. According to the World Alzheimer report 2015 (alz.co.uk/research/world-report-2015) [1], 9.9 million new cases of dementia are established each year worldwide. The global cost of dementia reached US$ 818 billion in 2015. AD is a degenerative brain disease, with 60% to 80% of cases of dementia, characterized by a decline in memory, language and problem-solving and other cognitive skills all of which affect a person's ability to perform everyday activities. Among several hallmarks of AD there are plaques, microscopic clumps of a protein fragment called beta-amyloid (Aβ), and tangles, twisted microscopic strands of the tau protein. The principal pharmacologic approach to treatment that has been approved today is a symptomatic approach that does not significantly change the course of the illness [1]. Besides age and familiarity, modifiable risk factors include diabetes mellitus, midlife hypertension, midlife obesity, physical inactivity, depression, a major depressive disorder, smoking, and limited education. One of the potentially modifiable risk factors for cognitive decline is a failure of essential metal control. Essential metals are vital elements for humans: iron, copper, and zinc are all essential for life. Two-thirds of human proteins use iron, copper, zinc, selenium, manganese, and other metals. Thus, the biology of these metals affects our health. Trace metals are useful when kept under control, but the breakdown of their homeostasis often leads to diseases since they generate oxidative stress via Haber-Weiss and Fenton reactions.

Trace element dyshomeostasis has been linked to cognitive deterioration and to increased levels of the exchangeable component of circulating copper, defined as copper non-bound to ceruloplasmin (nCp-Cu, or "free" copper [2]). The component is thought to play a role in AD onset and progression [3]. It is defined as the copper pool travelling in the blood stream and is not bound to ceruloplasmin (Cp), which instead tightly binds 90–95% of plasma copper. It is possible to calculate the concentration of nCp-Cu by starting from the assumption (Walshe's formula [4]) that Cp binds 6 atoms of structural copper, which is equivalent to Cp's weight percentage (0.3% copper): [6 (atoms of Cu) *63 uma (Cu molecular weight)/132 kDa (Cp molecular weight)] * 100 = 0.3%; more details are available at j-alz.com/letterseditor/index.html#March2013. Equivalent data can be obtained calculating nCp-Cu from mg/L of Cp and considering the conversion of 3.15 μg/Cu for mg of Cp [5].

The fraction of nCp-Cu represents an exchangeable pool of copper in plasma, still a matter of research. It is of relevance in neurological disorders [6] and other complex diseases, for example diabetes [7]. The analysis of copper binding components in blood serum/plasma is complex; fortunately, a comprehensive and updated review was published recently [8].

The current review aims at providing information about the coordination chemistry of copper in plasma proteins and compounds, with particular emphasis on the copper complexed by albumin, and to explore how the aberrant regulation of this interaction is linked to the aetiology of AD.

2. Copper in human physiology

Copper is an essential metal for all organisms. In the human body, copper appears in both oxidation states: Cu(I) and Cu(II). Copper absorbed from the diet (food, supplements and water) is mainly Cu(II), but in order for it to be absorbed in the intestine by the enterocyte's membrane it has to be reduced to Cu(I) via reductases. It is then exported from the enterocytes into the bloodstream through the Cu-ATPase ATP7A [9,10]. The central organ of the control of copper homeostasis is the liver. Through the portal vein, copper from the intestine enters the liver and reaches the hepatocyte. Excess copper is released in the bile and excreted through the stool [11]. To enter the hepatocyte through hCTR1 copper must be reduced to Cu(I) at the cell membrane via reductases. Then, in the cytoplasm, it can be distributed to the sites of utilization by chaperons and released to various enzymes and storage proteins [superoxide dismutase (SOD), metallothioneins, cytochrome *c*-oxidase (COX) into mitochondria]. Copper homeostasis and transport is fine-tuned because – even though it is crucial to the functionality of many human enzymes (for a wide review see [12]) – it is toxic in excess [13]. In fact, if not structurally bound to enzymes or coordinated by proteins (e.g. chaperons) or other molecules, copper can generate free radicals, even at very low concentrations. Free radicals, especially the hydroxyl radical ·OH, are produced when H_2O_2 reacts with Fe(II) and Cu(I) (Fenton reaction). They cause oxidative stress, which is involved in cellular degeneration and aging.

Copper distribution and handling in the body depend on coordination chemistry (for a comprehensive review on this topic, see [14]). Copper is handled by a sophisticated protein network that allows for the transport and export of the metal while avoiding accumulation. In their review, Rubino and Franz [14] explained the differences between the two classes of copper proteins: the first class is made up of proteins that use copper as a cofactor to perform biological functions such as electron transfer, reduction-oxidation (redox) reactions, and dioxygen transport (e.g.: Cp; Cu, ZnSOD; COX). The second class is made up of the so-called "copper trafficking proteins" that carry copper as cargo. They may be integral membrane proteins (e.g. ATPases), intracellular copper chaperones (Hah1/Atox; hCCS; cytochrome *c* oxidase copper chaperone Cox11, Cox 17; Sco1; Sco2), transcription factors, or regulatory proteins (COMMD1, XIAP). Another important distinction between these two classes of copper proteins is that while cuproenzymes perform the catalytic function and use the reduction of the copper core from Cu(II) to Cu(I), copper transport proteins avoid Cu(II)/Cu(I) redox cycles. The critical point is that, if copper is not used for a catalytic function (as in cuproenzymes), it can enter Cu(II)/Cu(I) redox cycles and produce hydroxyl radical (·OH) in a continuous manner. Therefore, biological cell conditions, such as chemical environments, pH and oxidation states are of critical importance in the ongoing effort to avoid toxic reactivity.

Another group of proteins or peptides involved in the binding of copper as well as of other d-block metals (iron and zinc) are the so called Intrinsically Disordered Proteins (IDPs), which have a non-defined 3D structure. Aβ, which is found in the brain of AD patients [15], belongs to the IDP group. The most abundant form of Aβ are Aβ40 and Aβ42, 40 and 42 amino acids long respectively. In general, the monomeric forms of these peptides are flexible with small α-helical or β-sheets secondary structures. Depending on the surrounding condition, they can fluctuate between different structures and can also form a partially folded structure. These proteins have a weak affinity for Cu(I/II) and Zn(II) with flexible interaction that adapts to different coordination sites: the fast copper-exchange reactions intrapeptidic and interpeptidic are very dynamic. This kinetics can influence the biological role: in fact,