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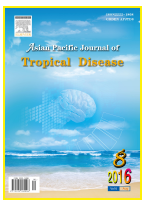

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Neural effects in copper deficient Menkes disease: ATP7A-a distinctive marker

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ABSTRACT

Menkes disease, also termed as "Menkes's syndrome", is a disastrous infantile neurodegenerative disorder originated by diverse mutations in cupric cation-transport gene called ATP7A. This gene encodes a protein termed as copper transporting P-type ATPase, essential for copper ion transport from intestine to the other parts of our body along with other transporters like copper transporter receptor 1 and divalent metal transporter 1. The copper transportation is vital in the neuronal development and synthesis of various enzymes. It is found to be an appreciated trace element for normal biological functioning but toxic in excess. It is essential for the metallation of cuproenzymes which is responsible for the biosynthesis of neurotransmitters and other vital physiological mechanisms. Copper is also actively involved in the transmission pathway of N-methyl-D-aspartate receptors and its subsequent molecular changes in neural cells. The expression of *ATP7A* gene in regions of brain depicts the importance of copper in neural development and stabilization. Studies revealed that the mutation of *ATP7A* gene leads the pathophysiology of various neurodegenerative disorders. This review focused on the normal physiological function of the gene with respect to their harmful outcome of the mutated gene and its associated deficiency which detriments the neural mechanism in Menkes patients.

1. Introduction

Menkes disease is a genetic disorder which impairs the copper metabolism and affects the copper levels in the body. Patients with Menkes disease have poor copper absorption in small intestine which is insufficient for the biological needs. These patients also have altered influx of copper through both blood brain barrier and placental barrier[1-3]. It is a genetic neurodegenerative disease in newborns due to mutation of X-linked gene ATP7A. The consequence of this genetic alteration results in the abnormal cellular transport of copper and elicits poor or improper activities of copper-dependent enzymes[4]. The incidence of this syndrome is estimated to be around 1 in 100 000 newborns. The disease principally affects male infants. Menkes disease occurs when the body is unable to regulate the metabolism of copper intake from food. Copper accumulates at abnormally low levels in the liver and brain, but higher than normal levels in the kidney and intestinal lining and other parts of the body. Generally the birth of affected infant occurs prematurely. Even though they seem to be healthy at birth and grow normally for 1 to 2 months, the symptoms appear gradually thereafter and the life span do not exceed not more than 3 years. It is characterized by deterioration of nervous system, flaccid muscles, convulsions, lack of flourishes (growth at expect rate). It also appears hypothermia and atypical, twisted, dull colored and brittle hair which is kinky and breaks easily. Additional signs and symptoms include weak muscle tone (hypotonia), sagging facial features, developmental delay and intellectual disability[5]. Usually the patients have expanded nerve damage in brain grey matter. This can also direct arteriosclerosis or occlusion of artery and decline the bone strength prone to bone fracture[4,6].

2. History of Menkes disease

In 1930s, veterinary scientists in Australia explained the role and importance of copper in mammalian neurodevelopment through demyelinating disease in ataxic lambs[4]. During pregnancy when the mother lambs fed on grass in copper scarce grazing land, leads to porencephaly, brain cavitation and cerebral demyelination of their progenies. In 1972 Danks and his colleagues identified Menkes kinky hair syndrome was arised from the paucity of copper which can lead to anomalous and inconsistent neural development in humans[4]. The basement of this research was the recognition of

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the hair of infants seems similar to that of brittle wool of Australian sheep raised on copper deficient soil. Menkes and colleagues after a research on an Irish American family, they proposed the basis was due to a X-linked recessive inheritance[7]. A copper transporting P-type ATPase (*ATP7A* gene) was identified in 1993 as the major causative factor for the syndrome by positional cloning[8].

3. Copper in human body

Copper is a little-appreciated trace element present in all the tissues which is essential for biological processes, but surplus leads to toxicity. Copper is crucial for abundant physiological activities like development of vascular and connective tissues, iron mobility, endogenous antioxidant activity, generation of dermal, hair and retinal pigments *etc.* It is an inevitable element in neuroendocrine peptide amidation, biosynthesis of catecholamines and also in electron transport chain function[9].

About 95% of the copper present in blood plasma is found firmly bound in a protein complex called ceruloplasmin and rest loosely bound to albumin. Copper is present in all the tissues including brain. In brain it is distributed more in synaptic membranes, hippocampus, basal ganglia, cerebellum and cerebellar granular neurons. It maintains the strength and genesis of myelin sheath covering of nerves. In central nervous system enzymes such as cytochrome c oxidase, ceruloplasmin, copper superoxide dismutase, dopamine hydroxylase, peptidylglycine α-amidating monooxygenase (PAM) and tyrosinase highly depends on copper in for their functioning and synthesis[9,10]. It is indirectly implicated in the pathogenesis of various neurological disorders. It is necessary for the synthesis of phospholipids and involved in the oxidation of fatty acids. The gastrointestinal tract absorbs copper ions which is present in dietary content and also present in secretions of both pancreas and liver[11].

4. Copper absorbtion and distribution

The copper was present in food as cupric (Cu^{2+}) form and it can be absorbed only as cuprous (Cu^{+}) form via luminal membrane of the enterocyte of duodenum. Before uptake the reduction may occur in the acidic environment of stomach, but more preferably from the action of cytochrome b ferric/cupric reductase and/or cytochrome b reductase 1 found on the intestinal cell membrane. The enzyme reductase localized in the duodenal brush border surface called the Steap proteins a family of metalloreductases[12,13]. The absorption across apical membrane is accomplished by a homotrimer carrier protein called copper transporter receptor 1 (CTR1). Various cell lines and *in vivo* studies have revealed the localization of CTR1 in the apical membrane as well as intracellular vesicular compartments in the cytosol of intestinal cells[14]. Studies showed that CTR1 is the primary protein which takes part in the import of copper in diet across the intestinal microvilli. In addition to this, a divalent mineral cation transporter (DMT 1 or DCT 1) also serves as copper transporter[15].

Within the enterocyte, copper is bound to amino acids (especially histidine and cysteine), glutathione, and/or other proteins. The fate of copper in enterocyte may be: i) stored and/or sequestered; ii) utilized for enterocytic functions; iii) transported into blood stream through cytosol.

Recent cell culture studies characterized CTR2 a homolog of CTR1 which also play a role in intracellular copper homeostasis[16]. Copper gets transported through a protein CTR2 and stored temporarily in the cytosolic vesicles. Mobilization of copper into portal blood from vesicles via albumin (bound loosely) and higher affinity towards α-2 macroglobulin[15,17]. Some have suggested that the metallothionein will function as a storage protein for copper particularly in neonates with elevated copper level whose biliary elimination process is underdeveloped. But presently there was no clear evidence for any specialized protein for copper storage as like ferritin for iron[18]. The absorption of copper via various mechanisms was given in Figure 1.

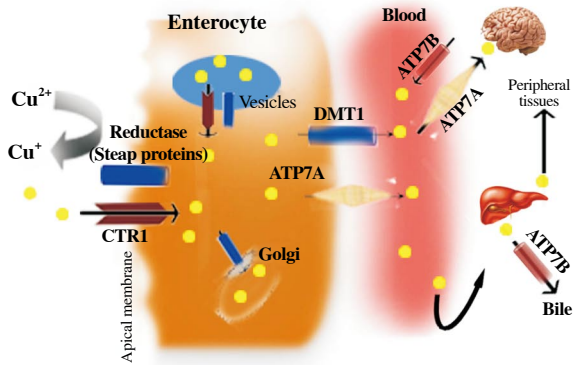

Figure 1. The dietary copper absorbed via CRT1 through the apical membrane of enterocyte was being stored in the vesicles and released whenever necessary. Released copper was then transported through ATP7A and partially by DMT1. It then crossed the blood brain barrier through the transporter ATP7A for neural mechanism in the brain and excess copper was pooled back into the blood via ATP7B. The transport to peripheral tissues was undertaken by hepatic circulation and excreted into bile through ATP7B.

The influx of copper is facilitated through CTR1 and DMT1 which do not need energy or a potential (proton) gradient, whereas efflux needs energy and it is accomplished by adenosine triphosphate hydrolysis. The protein coded with ATPases enzymes (ATP7A and ATP7B) are known to participate in copper transport mechanisms. The transfer of copper ions to the intracellular trans face of Golgi bodies in cuproenzymes biosynthesis requires the protein ATP7A. Based on extensive works done on experimental animal models, it is well developed that the human copper status depends on the concentration of ATP7A and its encoding mRNA[19]. The second one named as ATP7B which is extensively involved in hepatic copper homeostasis and localized in brain, kidney, placenta and mammary tissue. It mainly takes part in exit mechanism of copper whereas defect in this protein or mutation leads to copper retention disorder (Wilson's disease). The ATP7B gene is mainly expressed in the liver where it is responsible for biliary excretion of Cu.

5. Copper in central nervous system

For the critical function to be take place in central nervous system, copper serve as a cofactor for the transfer of electrons by the cuproenzymes for processes like cellular respiration, antioxidant defense mechanisms, and peptide amidation and also for the biosynthesis of various neurotransmitters.

5.1. Central copper transport

The exact and precise mechanism of copper uptake and

consumption by human brain is not yet well described. From several studies CTR1, ATP7A, ATP7B and DMT1 are highly expressed in the polarized brain capillary endothelial cells of blood brain barrier[20,21]. The basolateral surfaces of polarized cells of choroid plexus localize ATP7A for the transport of fresh copper to the brain where the blood-cerebrospinal fluid barrier is mainly located. The mammalian epithelial cells of choroid plexus express fivefold level of ATP7A than ATP7B and this confirms the transport of copper occurs via ATP7A is more[22]. These ATPases (ATP7A and ATP7B) are membrane proteins that hydrolyse ATP for the active transport of cations across cellular membranes. The protein ATP7A delivers the copper to copper-dependent enzymes in the trans-Golgi network of the neural cells and ATP7B takes away excess Cu^{2+} back to the blood from the brain[23].

An *in situ* brain perfusion study revealed that the expression of mRNAs encoding for CTR1 and ATP7A were more in choroid plexus than in brain capillaries and parenchyma. But the ATP7B is primarily expressed more in brain capillaries. The authors suggest that the regulatory site of Cu in the cerebrospinal fluid is mainly achieved by blood-cerebrospinal fluid barrier[20]. After crossing blood-cerebrospinal fluid barrier, the cation forms complex with small amino acid molecules and albumin of cerebrospinal fluid. Then they enter into the cytoplasm of neurons through the importers CTR1 and divalent mineral cation transporter 1. Here the metal is transferred to metallochaperones[24]. This transfer mechanism facilitates the metallation of enzymes which was abundantly expressed in whole regions of vertebrate brain. The enzymes include ceruloplasmin, hephaestin, Cu/Zn superoxide dismutase 1, cytochrome c oxidase, dopamine-β-hydroxylase, PAM and tyrosinase. For the regulation of metal homeostasis ATP7A constitutively cycles between intracellular trans-Golgi network and plasma membrane of neural cells[25,26].

5.2. ATP7A protein trafficking in neuronal cells

Besides facilitating copper transport through blood brain barrier and blood-cerebrospinal fluid barrier for metalation of cuproenzymes, the trafficking of ATP7A protein also plays other diverse vital tasks in the nervous system. The trafficking of ATP7A is elevated in the response of increased copper load and is reversed when copper concentrations are lowered[23]. Meskini and his colleagues established that, an augmented expression of ATP7A was observed in neurons and their extending axons prior to synaptogenesis in an injury stimulated neurodevelopmental model. This report supported the contribution of the protein in neurogenesis and axon extension[27]. From the mottled brindled mouse model of Menkes disease the same researchers further showed that the homeostasis of neuronal development requires regulated expression of ATP7A[27,22].

Synaptic N-methyl-D-aspartate (NMDA) receptor activation causes a reversible ATP7A trafficking to axonal and dendritic process in the hippocampal glutamatergic neurons[28]. After glutamate binds with receptor it initiates the entry of calcium through the channel and also favors copper expulsion[29]. This trafficking and copper efflux was found to be impaired in mottled brindled mice. The NMDA mediated calcium uptake might be competitively inhibited by the synaptic release of copper and modulated the activation of calcium dependent cascades that contribute to a neuroprotective action[29]. Schlief *et al.*[28] proved the role of Menkes ATPase in the availability of NMDA receptor-dependent mechanism and releasable pool of copper in the hippocampus. Deleterious and abnormal glutamatergic activation can be happen by impaired ATP7A function. NMDA receptor stimulation leads to a sudden and reversible trafficking of ATP7A. It implies that there is a direct relation between the neuronal activation and copper homeostasis in the nervous system[11]. In particular, copper acts as a neuro protective and reduces the cytoplasmic Ca^{2+} levels significantly followed by NMDA receptor activation.

In noradrenergic neurons ATP7A takes a key role in the consumption of copper for biosynthesis of transmitters and its neuronal discharge. The sympathetic neuronal vesicles contains a specialized enzyme called dopamine-β-hydroxylase which is essential for the conversion of dopamine to norepinephrine and such biochemical reaction proceeds only with the presence of copper[30]. ATP7A protein provides copper to dopamine-β-hydroxylase and a series of nonepinephrinergic receptors, and its transporters deals with the reuptake and/or binding following synaptic release. Also impaired ATP7A mutation found to cause distal motor neuron disease and disrupts the requirement of this protein in cholinergic neurons for PNS maintenance and functions[31].

The cuproenzymes (such as cytochrome c oxidase, superoxide dismutase 1, and PAM), copper chaperones (copper chaperones, ATP7A, ATP7B, *etc.*) and copper transporters were expressed in mouse spinal cord[32]and normal motor neuron requires copper for its pathological functions[33]. The case reports of ATP7A related distal motor neuropathy combined with peripheral neuropathy confirmed the importance of copper in motor neurons[33-35]. Till the date the clinical and biochemical data findings of patients with ATP7A related distal motor neuropathy have not shown any associated symptoms like hair, skin or joint abnormalities, abnormal blood copper and catecholamine profile, defective renal tubular function which are regarded as the prime symptoms reported in patients with mutations at the ATP7A locus in Menkes disease[36,37].

5.3. Contribution of Cu-ATPases in neural functions

Cu-ATPases possess an inevitable responsibility in the development and maintenance of physiological and biochemical functions of the central nervous system. Brain magnetic resonance imaging revealed that cerebral atrophy, derangement in myelin sheath formation of nerve axons more over demyelination and abrasion of intracranial blood vessel walls were often detected in patients with Menkes disease[38]. The expression of ATP7A on various regions of the brain showed its distinctive physiological role in relation with copper (Table 1).

5.4. Neural defects in ATP7A mutation

ATP7A protein was expressed in the cell bodies of developing neurons and this expression afterward shift to its axons and attains peak before synaptogenesis. The entire growth and maturation of a neuron needs ATP7A protein expression, on the other hand, mutation and/or its paucity contributes to the physical as well as biological characteristics of neurodegenerative disorders in Menkes patients[27]. Hence the abnormal copper metabolism might act directly on grey or white matter. Its prime effect might setback the central nervous

Table 1

Showing the existence of ATP7A protein in various regions of central nervous system in relation with their specific physiological role. Various functions of ATP7A depend on the region and take part in development and maintenance of neurons.

Brain region	Physiological role
Ependymal cells of choroid plexus	Regulates the molecules concentration in cerebrospinal fluid[39]
Microvascular cells	Transport mechanism[40]
Astrocytes, microglia, tanycytes, endothelial cells, and neurons	Proper functioning and myelination[22]
Oligodendrocytes	mRNA stability for myelin components[41]
Intracranial vessels	Prevent demyelination[42]
Olfactory system	Delivery of copper to PAM[43]
Purkinje neurons	Reversed frequent tonic seizures and ataxia[44,27]
Cell bodies and axons	Synapse formation and plasticity[45]
Cerebellum	Compensates for the lack of ATP7B in copper delivery to ceruloplasmin[46]

system development and its allied functions[47].

A copper-dependent enzyme PAM was essential in cleavage of the carboxy-terminal glycine residue from several precursors of neuroendocrine peptide such as cholecystokinin, gastrin, vasoactive intestinal peptide, thyrotropin-releasing hormone, calcitonin, corticotropin-releasing hormone, and vasopressin. The bioactivity of these precursors will get diminished around 100 to 1 000 folds in comparison with amidated mature forms[48].

Tyrosinase is a copper derived biocatalyst essential for the synthesis of melanin. Impaired hair and skin pigmentation in patients with Menkes kinky hair disease is due to the insufficiency of this enzyme in the brain[49]. Altered PAM biosynthesis also exhibits the above characteristic feature by turn down the activity of the alpha-amidated compound known as melanocyte-stimulating hormone. PAM deficiencies have further significant and extensive pathological symptoms that expressed for the Menkes phenotype[50].

Decline in Cu/Zn superoxide dismutase in Menkes disease may prone to the formation of oxygen free radicals and initiate oxidative chain reaction which was postulated to cause neurotoxic effects, moreover produce localized damage in brain. These types of oxidative reactions have been put forward for the etiology of neurodegenerative disorders like Parkinson disease[51]. Mutations in the Cu/Zn superoxide dismutase gene have been linked with amyotrophic lateral sclerosis (a motor neuron disease).

Myeloid precursor protein is a copper-binding protein, which is predominantly located at the synapse in neuronal cells. ATP7A-assisted copper transport possesses a pivotal function in calcium transport process which is found to have a direct relation to Alzheimer's disease[52].

The expression of the anti-apoptotic protein B-cell lymphoma 2 plays a fundamental role in brain development and morphogenesis during infancy. There was a remarkable decrease in B-cell lymphoma 2 level and cytochrome c released from mitochondria into the cytosol. It elicits that the down-regulation of B-cell lymphoma 2 can cause neurodegeneration triggered by mitochondrial damage due to copper depletion throughout brain development in the neonates[53].

Conflict of interest statement

We declare that we have no conflict of interest.

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