A HYPOTHESIS ABOUT THE FUNCTION OF NEUROMELANIN AS A BASIC INFORMATION CARRIER IN THE DEVELOPED HUMAN BRAIN(COMPL.,COR.LAST)

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Abstract

The most common vision about the function of neuromelanin is correlated withits neuroprotective properties at present. But, in the last decades, there are hypotheses that its role in the human brain is more complicated and connected with a genetically controlled process of reversible transmitting and modulating the nervous impulses. We advance the hypothesis that neuromelanin plays an important role in the process of learning, especialy for the long-term memory. We propose a chemical pathway for the information accumulation in the polymeric neuromelanin molecules. This is made in dependence with the postsynaptic potentials and the properties of the neuronal enzymatic systems, especialy in the human brain.

Keywords: *human brain, neuromelanin, dihydroxyindole, postsynaptic potentials*

Introduction

The common vision about the function of neuromelanin in a few parts of the human brain is its role as a neuroprotector preventing the catecholaminergic neurons from oxidative damage and binding the excessive amounts of transition metals, especialy iron. However, there are conclusions during the last years that it may be has additional functions especialy in human brain (as it is found in very small quantities in the brain of non-human primates and is absent in lower species), and differs from peripheral melanins [1]. On the other side it was found that skin and ocularmelanins are chemicaly different. The substantia nigra melanin is not only biological garbage, but its melanogenesis is a fundamental and genetically controlled process. It is also suggested that substantia nigra melanin acts as a semiconductortransmiting and modulating the nervous impulses in a reversible way. It is known also that substantia nigra melanin is absent in newborn babies and in scarced quantities in patients with Parkinson's disease [2].

Here we advance the hypothesis that neuromelanin (probably, especialy in substantia nigra) plays an important role in the process of learning, increases its amount with ageing, while decreasing in the old aged suffering from Alzheimer's and Parkinson's disseases [3, 5], probably destroyed to lipofuscin [4] and probably also to nigral Lewy bodies.

Origin of the hypothesis

Melanins (eumelanin and pheomelanin) as exact final structures are unclear yet. The same is the situation about the melanogenesis. The reason is that there are many possible intermediates with many possible reactive positions. A lot ofposible synthesis pathways and the compositions of the final products are proposed. On the other side, according to [5], the

neuromelanin particles are composed by a core of pheomelanin, surrounded with an eumelanin envelope in ratio 1:3. Nevertheless, most of researchers agree, that the basic starting compound(s) for the production of eumelanin are 5,6-dihydroxyindole (DHI) and/or 5,6-dihydroxyindole-2-carboxylic acid (DHICA). There are two possible pathways to reach these compounds from L-DOPA-with or without initial decarboxylation of L-DOPA.

When L-DOPA is decarboxylated to dopamine the stages to DHI are as follows: dopamine is oxidized by the action of a few possible enzymes, different from tyrosinase, to dopamine semiquinone, which can be transformed by dissproportianation to dopamine and dopamine quinone or additionaly oxidized by oxygen (reduced to superoxide anion radical) to dopamine quinone. Another possibility is the direct oxidation of dopamine to dopamine quinone by tyrosinase. Dopamine quinone produced by rapid rearrangement converts to leucoaminochrome, which rapidly is oxidized by oxygen to aminochrome. DHI is produced from aminochrome by slow rearrangement. The next step-the oxidation of DHI to indole-5,6-quinone will be commented further in the text. Because of the difference in the reaction rates of the described processaminochrome accumulates, and by many different ways is toxic for the neuron [5]. In this article the alternative route (without decarboxylation of L-DOPA) is not commented.

When L-DOPA is not decarboxylated the stages are as follows [6]: L-DOPA is oxidized by tyrosinase (EC.1.14.18.1) to dopaquinone, which spontaneously converts to cyclodopa (leucodopachrome), which dissproportionates to L-DOPA and dopachrome. The last product can be converted to DHI (spontaneously) or by the action of dopachrometautomerase (EC.5.3.2.3) to DHICA, which could be directly used in melanogenesis or be converted to DHI by DHICA decarboxylase [7]. (Notes: for the first route L-DOPA is decarboxylated to dopamine by L-DOPA decarboxylase; in the presence of cysteine or glutathione a part of dopamine quinone, respectively dopaquinone react to end products of type of benzothiazines, which differ from corresponding indole analogues only by an additional sulfur atom. These are used in the melanogenesis of the pheomelanins).

Let’s look at the our proposal for the melanogenesis from DHI or DHICA. In [8] authors propose to utilize a year 1949 idea that the two molecules which are products of additional oxidation of DHI or DHICA (indole-5,6-quinone and indole-5,6-quinone-2-carboxylate) can be paired by Diels Alder reaction between 4 and 7 positions of the first molecule and 2 and 3 positions of the second molecule. The authors consider the possibility for additional oxidation to occur with a separation of carbon dioxide. Clearly, such a reaction needs an excess of oxygen. Let’s forget, for the time being, the toxicities of DHI and indole-5,6-quinone and consider a possible path of eumelanin melanogenesis. In [9] the authoraffirms that in indole-5,6-quinone position 4 is electrophilic, while position 2 in DHI is highly nucleophilic. But in [10] the author claims that positions 4 and 7 in indole-5,6-quinone are highly reactive. At the same time it was shown that, if positions 1 and 2 in DHI are methylated, the melanogenesis takes place [11].

Essence of the hypothesis

Proceeding from the abovementioned our proposal presents the melanogenesis as proceeding in four steps:

1. DHI bonds by its 3-rd position to the 4-th or 7-th position of indole-5,6-quinone. This forms two possible isomers.

2. The DHI part of the previous product is oxidized by two moles of cytochrome C to four possible isomers, exactly analogous to the Diels Alder products from [8].

3. In the previuos indole-5,6-quinone part of the dimer two protons (from 4-th and 7-th positions) migrate to the oxygen atoms with an aromatisation and formation of a part similar to DHI. In the other part two protons (from 2-nd and 3-rd positions) migrate to the oxygen atoms with an aromatisation and formation of a part similar to DHI, as well.

4. The product from the step 3 is oxidized by four moles of cytochrome C (or directly by complex IV) to a product combined by two parts similar to indole-5,6-quinone. But only one of them could bond additional DHI molecule.

Let's view the enthalpy changes for the first two steps. By use of programm OASIS from BTU-Bourgas [12] we found the next values for the heats of formation of componds included in these steps [kJ/mol]: DHI: -130,37 ; indole-5,6-quinone: +50,50 ; the four posible dimers as follows: -36,65 ;

-39,62 ; -40,88 ; -44,02. For cytochrome C in [13] we found E^0 ox/red= +0,22 V what corresponds to ΔG^0= - E^0*n*F = -42,45 kJ/2 moles(for 2 electron oxidation of DHI).We accept that $\Delta H^0=\Delta G^0$. The complete reaction is:

DHI + indole-5,6-quinone + 2*Cyt C/ox = dimer(1-4) + 2*Cyt C/red + 2*H^+

For the four isomeric dimers we calculated the enthalpy changes as follows [kJ/mol]:

+4,59 ; +1,62 ; +0,36 ; -2,78 .These values correspond to potential changes (for two electron process,mV) as follows: -23,80 ; -8,40 ; -1,87 ; +14,41. The total difference is 38,17 mV.

On the other hand it is known that synaptic potentials (except of the action potential) change gradually from approx. -45(EPSP) to -100 mV(IPSP). One must keep in mind, that E^0 for cytochrome C is at pH=7 (approximately physiologic) and, except of this, it corresponds to the midpoint of the equilibrium. On the other hand, cytochrome C is a small hemeproteine, highly water-soluble and loosely associated with the inner membrane of the mitochondrion. We think the equilibrium is shifted to CytC/ ox by the action of the complex IV (cytochrome C oxidase). It is a complicated process, but we assume it is controled mainly by the cytochrome A component. For the latter we find E^0= +0,29 V. As in previous case we found potential changes (mV) as follows: -93,80; -78,40; -71,87; -55,59.

Discussion of the hypothesis

We believe that an explanation could be found how neurons can rule the isomeric form of the every next unit in the growing neuromelanine chain. In reverse, the information could be read by the neurons, probably by use of semiconducting and magnetic properties of neuromelanin. It is very important to know, that the molecular mass of indole-5,6-quinone is 147 and every molecule in our model carries two bits of information, what (in equal masses) is approximately 8 times more than in dsDNA.

Notes:

1. The electrode potentials used and found mean midpoint potentials at approx. physiologic conditions, without to account for the mitochondrial pH gradient (pH=7)(12).

2. According to [14] human cytochrome c is identical only with that of chimpanzee and differs from that of Rhesus monkey by one mutation, from these of rabbit and mouse by 9 mutations etc. The complex IV is species specific, too. These changes determine the changes of the midpoint potentials and leaving the interval, where IPSP-EPSP could rule the isomeric composition of growing neuromelanin chain.

3. Since the present vision for the mechanism of memory is connected to thenotion for the role of axons-dendritic spines interactions, the article [15] could be very useful for the additional research in this field. We mean the next row of occurrences: axons-dendritic target spines (number and postsynaptic potentials)-sharf synapses-postsynaptic potentials (EPSP-IPSP)-transcription of memory data into neuromelanin.

4. As a last conclusion we assume that the formed neuromelanin is probably the most important material base of the Freud's doctrine of complexes.

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