MELANINS AND PARKINSON'S DISEASE

por

D. S. Galvão[1] and M. J. Caldas[2]

ABSTRACT – We have studied, using the Htckel n-electron approximation, a family of polymers descending from 5, 6, indolequinone, the most abundant monomers in melanins. Based on the presence of edge states that produces the appearance of deep midgap states acting as deactivator for free radicals, potentially citotoxic, we have built a model which is able to explain the presence of melanins in non-illuminated areas of the brain. Its relationship to the Parkinson's disease is discussed here, as well as a possible new class of chemicals to treat diseases involving hypomelanosis.

INTRODUCTION

Melanins are a class of biological pigments with the basic function of photoprotection. However the presence of these pigments in non-illuminated areas of the body leads to the postulation (Jellinger and Jirasek, 1971; McGiness, 1973) of other biological functions to them. There is evidence for a role of melanins in the etiology of Parkinson's disease and in the etiology of certain drugs-induced otopathies and retinopathies (McGiness, 1973). The simple most common anatomical finding in both idiopathic and post-encephalitic Parkinson's disease is the apparent destruction of melanin-containing cells in the substancia nigra and other pigmented areas of the brain (McGiness, 1973).

In this work we present a model, based on electronic structure calculations, that could explain the presence of these pigments in the brain and how it could be related to the Parkinson's disease.

We present in the next section a brief summary of relevant information on eumelanins; the techniques used in this work are described in section 3; and finally we present and discuss our results in section 4.

[1]-Instituto de Física, UNICAMP, CP 6165, Campinas, SP,Brasil.
[2]-Instituto de Física, USP, CP 20516, São Paulo, Brasil.

SURVEY OF PREVIOUS INFORMATION

In spite of many years of investigations the exact structure of eumelanins remains to be fully elucidated, but there are strong evidences (Swan, 1974) that the planar 5,6,indolequinone molecule (IQ) and/or the reduced forms semiquinone (SQ) and hydroquinone (HQ) (figure 1) compose the major part of the active material of the pigment.

Theoretical contributions for the electronic behavior of eumelanins date from 1960 when a speculative model (Longuet-Higgins, 1960) was suggested, picturing eumelanins as a linear-chain semiconducting polymer. This model received strong support from the work of Pullman and Pullman (Pullman and Pullman, 1961), where a large conjugation of the polymer was assumed.

Objections to the conjugated polymer model (CPM) came from magnetic resonance data. It is a well known fact (Blois et al., 1964) that melanins present a stable free radical Electron Paramagnetic Resonance (EPR) signal, and the analysis of these signals indicates that the unpaired spins are localized over one or at most two monomeric units or single molecules. This is in an apparent clear contradiction with a model of itinerant spins on extended band states, as supposed in the CPM. Recently, Galvão and Caldas (Galvão and Caldas, 1988) demonstrated that the presence of 'edge states' could remove the apparent contradiction with the EPR data.

METHOD

We used throughout the approach of Htckel *n*-electron Theory (HT). The reasons for this choice and the reliability of the method were discussed elsewhere (Galvão and Caldas, 1988, 1990).

We have made calculations for polymers with up to ten monomers units (110 heavy atoms) and for infinite chains (in the Bloch limit). All calculations were carried out within the same parameterization used by Pullman (Pullman and Pullman, 1961). We have introduced translational symmetry to study infinite chains still within the same parameterization. Band structure, density of states (DOS) and charge density were obtained using 1500 k-points equally spaced in the first Brillouin Zone, which is sufficient to provide a very good charge and bond order description. For the finite chains the discrete spectrum was Lorentzian enveloped and weighted to reproduce the DOS localized over a specific cell or monomeric unit.

RESULTS AND DISCUSSION

The molecule of IQ and/or SQ and HQ presents various possible active sites, giving rise to many possible polymerization paths, as indicated in figure 2. The relative occurrence of bonding sites in natural and synthetic eumelanins is an unsolved question.

We have calculated polymers built through uniform bonding, following the paths imposed by the dimers #1 to #4 in figure 2. For a question of limited space we have chosen only one structure to discuss in detail, the #S2 (polymer type #2, with semiquinone units).

We present in figure 3(a) the DOS of the infinite chain, where the well-defined gap around E= (zero in the scale of the figure) is seen. We compare this DOS with the Local DOS (LDOS) in figure 3(b) at the internal cell of the decapolymer S2, to show the similarity of the curves. This indicates that the decapolymer is a good representation of the infinite chain. In figure 3(c) we plot the LDOS at the end cell of the decapolymer (the 'defect cell'): we clearly see the introduction of a deep midgap defect level, empty in the neutral charge state, and thus able to accept two electrons. This is a very localized defect state, no trace of it is found already at the neighboring cell.

The edge-states are equivalent to localized deep-level defects in normal semiconductors, and thus they act ae edge-states are equivalent to locap for electrons. Considering the charge localization and midgap location of the energy level, the electron remain trapped (stabilized) at the defect centers. This mechanism could explain the presence of melanins in the brain. The capture and stabilization of electrons by the edge states could be an efficient mechanism of cellular defense against (deactivating process) free radicals (potentially citotoxic), produced or not by ionizing radiation.

In the Parkinsonians a relative overabundance of excited-states species or free radicals were observed in the melanized areas of the brain (McGiness, 1973). Besides that an abnormal high electronic density was also observed in these areas (Moses, 1966), as it would be expected if a mechanism as described above exists.

Another important point is the role of structural disorder present in synthetic melanins, but not confirmed in natural samples. Preliminary calculations using sophisticated techniques to treat disorder in polymers (Galvão et al., 1989; dos Santos et al., 1990) have demonstrated that the presence of limited disorder increase enormously the efficiency of the mechanism of electronic capture and thus the cellular defense.

The chemicals used in diseases involving hypomelanosis are generally based on the administration of 3,4,dihydrophenylalanine (DOPA), a precursor of melanins, but that presents many collateral effects. The utilization of compounds derived from 5,6,indolequinone (that according to our results are involved in the process of cellular defense) opens the possibility of a new class of designed-drugs, that are expected to present few collateral effects as they are much more closer to natural pigments found in the body than DOPA. This possibility is under

investigation.

ACKNOWLEDGMENTS

The authors wish to thank the Brazilian Agencies CNPq and FAPESP for financial support.

REFERENCES

Blois, M.S., B. Zahland and J.E. Maling, 1964, Biophys. J., 441, 471.
dos Santos, D.S. Galvão and B. Laks, 1990, Sol. Stat. Commun. 4741, 215. ,
Galvão, D.S. and M.J.Caldas, 1988, J. Chem. Phys. 4881, 4088.
Galvão, D.S., D.A. dos Santos, B. Laks, C.P. de Melo and M.J. Caldas, 1989, Phys. Rev. Lett. 4631, 786. ,
Galvão, D. S. and M.J. Caldas, 1990, J. Chem. Phys. 92, 2630; idem - in press.
Jellinger, K. and A. Jirasek, 1971, Acta Neurop. Berl., 4171, S5, 3.
Longuet-Higgins, H.C., 1960, Arch. Biochem. Biophys., 86, 231.
McGiness, J., 1973, J. Theor. Biol., 39, 667 (1973).
Moses, H.L., 1966, Anat. Rec., 155, 167
Pullman, A. and B. Pullman, 1961, Bioch. Biophys. Acta, 54, 384.
Swan, G.A., 1974, Fort. Chem. Org. Natur., 31, 522.

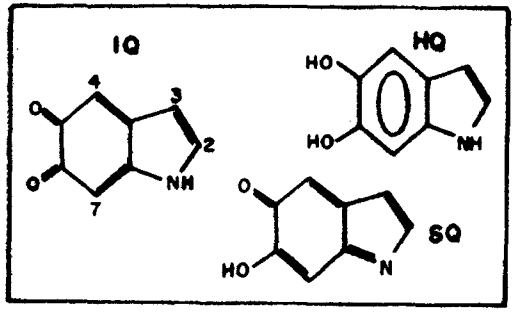

Fig. 1 - Schematic representation of the molecule of 5,6,indolequinone (IQ), semiquinone (4SQ1) and hydroquinone (HQ); the active sites are indicated in IQ.

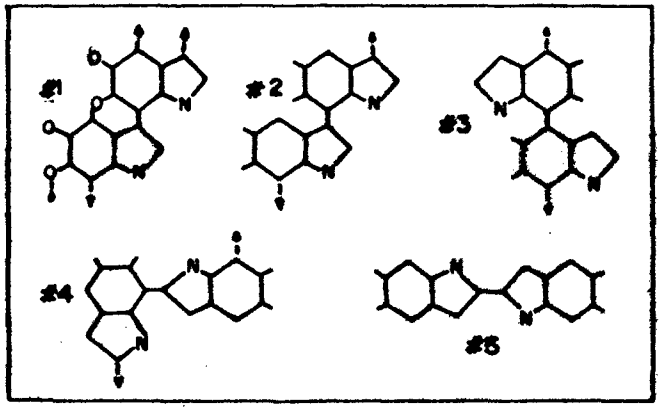

Fig. 2 - Schematic representation of the + dimers and polymerization directions. Polymers are studied in the three redox + forms (no particular form is assumed).

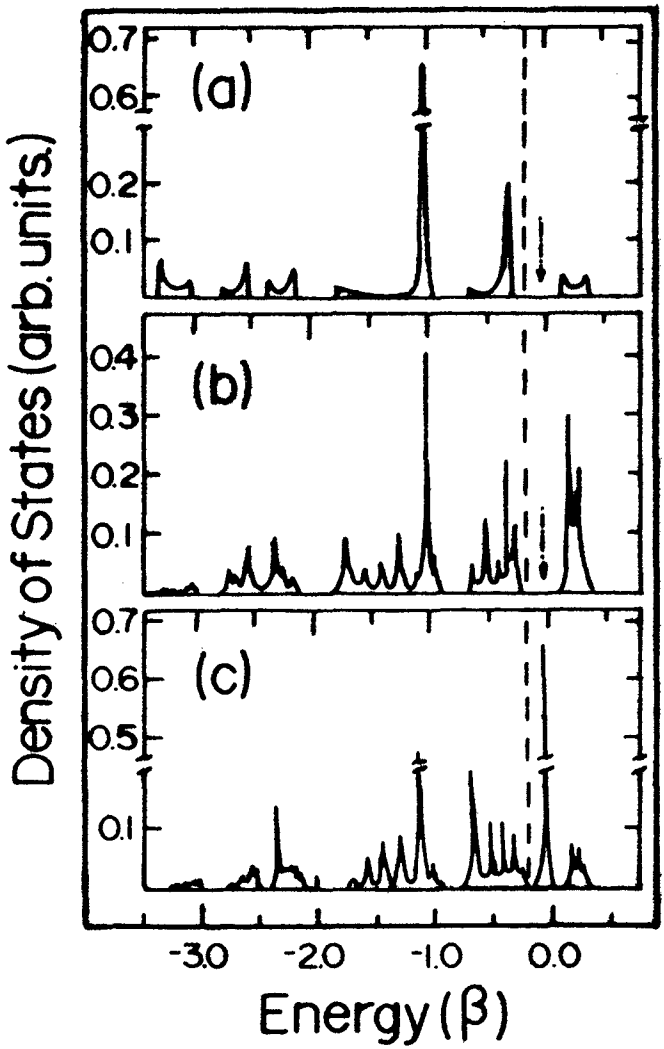

Fig. 3 - Density of States (DOS) for (a) unit cell of infinite polymer; (b) Local DOS for internal cell of decapolymer; and (c) Local DOS for end-cell of decapolymer, the (discrete) spectrum was Lorentz ian-enveloped and weighted to reproduce the DOS localized over the specific cell or monomeric unit. Dashed line separates occupied from unoccupied states. Arrows in (a) and (b) indicate location