Comment
ON THE 6-AMINONICOTINAMIDE ANTAGONISM OF DPN-DEPENDENT ENZYMATIC SYSTEMS

This short note is just a comment to a recent paper by Dietrich and colleagues (1), which appeared in this journal under the same title.

These authors have shown that the powerful niacin antagonist, 6-aminonicotinamide (6-AN), is capable of causing a marked regression of the 755 tumor in mice. They have also shown that this 6-AN is converted in vivo to a 6-AN analog of DPN or TPN, which is then postulated to become bound to available apo-dehydrogenases, producing, thus, unusual and ineffective holo-enzymes. It is supposed that in this antagonism inhibition probably occurs at the initial step of electron transport in the mitochondria, the unusual enzymes being incapable of functioning in the normal electron and hydrogen transfer reactions essential for the normal growth of the cell. This would result in the blocking of the oxidative phosphorylation with, as a consequence, an impaired synthesis of ATP, the selective toxicity to tumors being due (following the general conception developed by Dietrich and colleagues) to quantitative differences in the DPN content of the normal and malignant tissues, the faulty and normal pyridine nucleotides competing for the apo-dehydrogenases.

The hypothesis advanced by the quoted authors, concerning the inability of the 6-AN analogs of DPN or TPN to function as normal electron carriers, receives confirmation and explanation from recent theoretical studies on the relation between the electronic structure and the functioning of the respiratory coenzymes. Thus we have shown in a recent publication (4) that the oxidation-reduction mechanism of the respiratory enzymes, pyridine nucleotide enzymes or flavoproteins, may be related to the energies of the molecular electronic orbitals of the oxidized and reduced forms of the associated coenzymes: DPN or TPN, FMN or FAD. In each case a particularly low-lying empty orbital is associated with the oxidized form, and a particularly high-lying filled orbital is associated with the reduced form. The oxidized form must thus have a great tendency to accept electrons and the reduced form to give them up, the oxidation-reduction being accompanied by the appropriate instantaneous redistribution of these orbitals.

Quantitatively, the energies of the molecular electronic orbitals are of the general form $E_i = a + k_i \beta$, where $a$ and $\beta$ are, respectively, the coulomb and the exchange integrals of the molecular orbital method of quantum chemistry (5, 6). The orbitals are thus characterized by the values of $k_i$. In general, positive values of $k_i$ correspond to bonding orbitals, occupied by electrons in the ground state of the molecules, and negative values of $k_i$ to antibonding orbitals, occupied by electrons in the excited states. The smallest positive value of $k_i$ corresponds to the highest occupied molecular orbital; the smaller this value, the lower the ionization potential of the molecule and the greater its electron-donor properties. The smallest negative value of $k_i$ corresponds to the lowest empty molecular orbital; the smaller this value, the greater the electron-acceptor properties of the molecule (7).

TABLE 1

<table>
<thead>
<tr>
<th>Compound</th>
<th>DPN$^+$</th>
<th>DPNH</th>
<th>6-AN-DPN$^+$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy of the lowest empty molecular orbital</td>
<td>$-0.356$</td>
<td>$-0.915$</td>
<td>$-0.471$</td>
</tr>
<tr>
<td>Energy of the highest occupied molecular orbital</td>
<td>$1.052$</td>
<td>$0.298$</td>
<td>$0.735$</td>
</tr>
</tbody>
</table>

The corresponding columns of the table indicate the values of the coefficients $k_i$ of the energies of these two essential molecular orbitals in the oxidized and reduced forms of DPN, denoted DPN$^+$ and DPNH, respectively. Almost identical values would be obtained for TPN.

The relatively small value of the coefficient of the energy of the lowest empty molecular orbital in DPN$^+$ indicates high electro-affinity and accounts thus for the electron acceptor properties of this substance. In the same way the relatively small value of the coefficient of the energy of the highest filled molecular orbital in DPNH accounts for the great electron donor properties of this reduced form of the coenzyme.

The energies of these two essential molecular orbitals will of course be modified by any substitution occurring at the pyridine ring. The last column of the table indicates the results of the calcu-
lations for the 6-AN analog of DPN+. The calculations show that the substitution of an amino group at the 6-carbon atom of DPN+ involves an elevation of the energies of both the highest occupied and the lowest empty molecular orbitals. The essential result is of course the elevation (increase in the absolute value of $k$) of the lowest empty molecular orbital, since it is the energy of this orbital which determines the biological functioning of DPN+ as an electron acceptor. If the relatively important increase in the absolute value of $k$ for this orbital is taken into account, the amino substitution signifies an important diminution of the electron-acceptor properties of the substance, if not their entire disappearance.

Our theoretical conclusions correlate thus satisfactorily with the observations and hypothesis of Dietrich and his colleagues.

We may add that our point of view, correlating the electron donor and acceptor capacities of the respiratory coenzymes and of related substances with the energies of their highest filled and lowest empty electronic orbitals, has been verified very recently in a comparative study of the electron acceptor properties of riboflavin and related pteridines, carried out by E. Fujimori in the laboratory of Albert Szent-Gyorgyi (2). The calculations predict an elevation of the energy of the lowest empty orbital on passing from riboflavin to the related pteridines (7), an elevation which, as a matter of fact, should be of the same order of magnitude as the corresponding elevation on passing from DPN+ to its 6-AN analog. In agreement with this prediction the electron-acceptor capacity of the pteridines, as measured by their capacity to form complexes with tryptophan, is much smaller than the corresponding ability of riboflavin (3).

In conclusion, quantum-mechanical calculations show that the lowest empty molecular electronic orbital is placed much higher in the 6-aminonicotinamide analog of DPN+ than in DPN+ itself. Consequently, the faulty coenzyme does not possess the pronounced electron-acceptor properties of the true coenzyme and cannot thus function as an electron carrier in the respiratory chain. The anti-tumor activity of the antagonist may be considered, in agreement with the hypothesis of Dietrich and colleagues, as resulting from this loss of the electron-accepting capacity.

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REFERENCES


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