CHEMICAL PROTECTION AND SENSITIZATION TO IONIZING RADIA - TION: MOLECULAR INVESTIGATIONS

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INTRODUCTION

Chemical radioprotection and radiosensitization are the phenomena induced by the presence of certain chemical compounds, which reduce or enhance respectively the effect of ionizing radiation on living organisms. Such substances are either naturally present or may be artificially introduced in the living cells. When these phenomena occur in complex biological systems, they are a synthesis of many processes of physical, chemical and biological nature. The study of the mecahnisms of chemical radioprotection and radiosensitization could also aim at a better understanding of how radiation acts on cells and tissues.

Chemical radioprotectors are interesting for the possible application in health protection of both professionally exposed workers and patients treated by radiation for diagnostic and therapeutic reasons. Although the initial enthusiasm has been not paid by the success of finding the "anti-radiation pill", the problem is so important that such studies are still up to date.

Chemical radiosensitization has boomed in the last years for its potential application in the radiotherapy of tumours since even a modest increase of radiosensitivity of neoplastic cells results in a better therapeutic treatment.

The main classes of radioprotective and radiosensitizing drugs include compounds with respectively reducing and oxidizing properties towards the radiation induced radicals derived from biological molecules. Both processes of radioprotection and radiosensitization occur by means of complicated mechanism, whose the very early stages correspond to very fast reactions. The mechanism of action of such substances can be investigated by means of radiation chemical techniques, i.e. pulse radiolysis (1). Briefly pulse radiolysis uses a short intense pulse of radiation to induce the initial physical-chemical damage and fast recording technique (i.e. absorption kinetic spectrophotometry with oscillographic output) are used to investigate the short-lived

chemical species produced, and to follow their subsequent pathway.

CHEMICAL RADIOPROTECTION.

Chemical radioprotection is still an important field of research in radiobiology at all levels of biological complexity. Different types of substances, including aliphatic alcohols, sulphur or selenium containing compounds etc., offer radioprotection "in vitro" and "in vivo". The most important class of radioprotective substances includes the sulphur-compounds. These compounds can act by different mechanisms: protection by mixed-disulfide formation protection by radical scavenging and protection by the hydrogen transfer mechanism. Of particular interest is the repair model by the hydrogen transfer mechanism, originally proposed by Alexander and Charlesby (2), and further applied to biological systems by Howard Flanders (3). According to this hypothesis, the radioprotection offered by -SH compounds is due to their ability to repair the radical damage of the target molecule by hydrogen donation from the -SH group. This reaction is in competition with the damage fixation produced by oxygen.

Adams and coll. (4,5) have directly observed by pulse radiolysis radical repair reactions such as:

$$. CH_2OH + RSH \longrightarrow CH_3OH + RS^{\cdot}$$

In solution containing excess RSH, the radical anion $RSSR^-$ formed from $RS^{\cdot}$ in the equilibrium reaction:

$$RS^{\cdot} + RS^- \rightleftharpoons RSSR^-$$

absorbs strongly at 410 nm and can be used to monitor the reaction.

A great number of rate constant for such repair reactions have been determined and they are generally lower than rate constants for the reactions of the same radicals with oxygen. If the previous model is correct, one should think that the -SH compounds are present at relatively high concentration in the cell in order to show radioprotection. An important molecule ubiquitously present in the cells at relatively high concentration is the tripeptide glutathione.

Radiation chemical data obtained in this Laboratory (6, 7) show that the -SH group is responsable of all chemical

events occurring in the molecule. Moreover the transfer of hydrogen atom from glutathione to carbon radicals has been demonstrated in model systems and appears to be the most probable mechanism of protection.

Repair of nucleic acid radicals by -SH compounds has not been observed directly by pulse radiolysis and it remains to be demonstrated directly that hydrogen transfer is a mechanism of protection in cellular systems.

CHEMICAL RADIOSENSITIZATION

The effect of oxygen in enhancing radiation damage in most biological systems, has been known for many years and fundamental and clinical work on both animal and human tumours has demonstrated the importance of anoxic regions in tumours as limiting factors in radiotherapy. ANy chemical agent which acts similarly to oxygen on the biological response to radiation is of potential value in radiotherapy. Nowdays some strongly electron-affinic compounds have been shown to be the most interesting radiosensitizers in view of the large number of investigations at fundamental level and for the promising pilot clinical studies still in progress (8).

They include quinones, dicarbonyl compounds, aromatic ketones, nitrofurans and nitroimidazoles. The radiosensitizing ability of these compounds is related to their electron-affinity and to their structure, in which the oxidizing property is due to the stabilizing effect of electron delocalization by resonance. Pulse radiolysis experiments have shown that these compounds are efficient oxidizing agents and can transfer electron rapidly and quantitatively from free radicals derived from different substrated including purines, pyrimidines, nucleic acids and amino acids. These experiments demonstrate that such sensitizers are more electron affinic than target molecules and give support to the electron-trapping model for the sensitization phenomenon proposed by Adams (9). The model suggests that, following direct ionization in the target molecule, thermalised electrons migrate to some electron trapping sites in the molecule. In the presence of electron affinic compounds, electron transfer reaction from the ionized molecule to the radiosensitizers could occur in competition with the internal charge recombination. The final result is an irreversible chemical damage to the critical molecule.

CONCLUSION

The purpose of this communication is to illustrate some significant examples of the application of radiation chemistry to chemical radioprotection and radiosensitization. The results demonstrate the important role played by molecular phenomena for the interpretazion of mechanism of chemical radioprotection and radiosensitization and for the development of more active substances. Much of the information concerning the involvement of fast processes in chemical radioprotection and radiosensitization, derives from studies of simple model chemical and cellular systems carried out with fast radiation chemical techniques. Even though the great complexity of"in vivo" systems excludes a unique explanation of chemical radioprotection and radiosensitization in molecular terms only, the contribution of fundamental radiation chemical studies is still of great importance.

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