DISPUTANDUM

Is Dehydroascorbic Acid an Inhibitor in the Regulation of Cell Division in Plants and Animals?

SZENT-GYÖRGYI[1] has suggested that cell division may be controlled by two antagonistic substances, an inhibitor ('retine') and a promotor ('promine'). He believes that the inhibitor may be an electron acceptor containing a glyoxal grouping, and suggests that the ubiquitous enzyme system glyoxalase may act as a promoter. I wish to suggest that dehydroascorbic acid (DHA) may be an important inhibitor of the type envisaged by SZENT-GYÖRGYI and to show that a substantial body of information is in accord with this idea.

DHA is an electron acceptor, structurally similar to a glyoxal and found, associated with ascorbic acid (AA), in nearly all plant and animal tissues[2]. In accordance with SZENT-GYÖRGYI's theory[1] and in keeping with its chemical properties[3,4], DHA may act as an inhibitor by maintaining essential –SH functions, e.g. those on histones[5] in an oxidized (–S–S–) form. DHA also has a widely dispersed antagonist, reduced glutathione (GSH), which rapidly and irreversibly reduces DHA to AA[6]. In plants, this reduction is catalysed by dehydroascorbic acid reductase[7]. Only recently an equivalent enzyme has been found in animals[8] but GSH readily reduces DHA at a pH above 6.0 without an enzyme[6,7] and it has been suggested that the ability of animal tissue to reduce DHA is almost exclusively due to GSH[9,10]. Thus if DHA acts as an inhibitor, cell division may be promoted by an increase in GSH leading to a shift in the equilibrium (AA $\rightleftharpoons$ DHA) towards the reduced form.

GSH has for many years been indicated as a promoter of cell division[11] and there is extensive evidence in the literature linking growth with an increase in GSH and AA concentrations and a decrease in DHA concentration. STERN[12] has reported that GSH and AA levels increase during microspore mitosis. Similarly in germinating seeds[13,14] and sprouting potato tubers[14], the proportion of DHA falls as AA and GSH concentrations increase and marked increases in AA content are associated with the areas of rapid growth in plants[15]. The auxin, indoleacetic acid, when present in concentrations which promote growth, is reported to have little effect on the total ascorbate but to cause a significant increase in AA and GSH and a corresponding decrease in DHA[16]. At higher concentrations of auxin, when growth is inhibited, the level of DHA increases relative to AA[16].

The antitumour properties of DHA have been reported by several investigators[17,18] and these also support the role of DHA as an important growth inhibitor as do the observations that neoplastic cells are deficient in DHA[19,20] and that AA requirements are abnormally high in cancer patients[21] and during periods of natural growth[22], e.g. in childhood and during pregnancy.

An alternative means of promoting cell division would be by an increase in the rate of catabolism of DHA such that the rate of oxidation of AA would be incapable of maintaining DHA at inhibitory levels. As well as reducing the level of DHA, this would lead to a lowering of AA reserves. The marked depletion of AA observed in man following surgery[23,24], burns[25] and infection[25] may therefore indicate that repair growth is initiated by release of an enzyme or enzymes capable of destroying DHA[26]. SZENT-GYÖRGYI[1], in his scheme, has suggested that liberation of glyoxalase may promote wound healing in this way. Wound healing in plants is also accompanied by a marked decrease in AA[27] and it is significant that in a plant which did not heal no alteration in AA was observed. An analogous effect is found when the growth of dormant potato tubers is stimulated by ethylene chlorohydrin[28]. This treatment causes a slow fall in the level of AA and a rapid fall in DHA and these changes continue until vigorous sprouting occurs.

In the search for an important physiological role for the ubiquitous ascorbate system, the requirement for AA as a reducing agent has overshadowed the electron accepting ability of DHA. AA is a co-factor for a number of hydroxylase enzymes[29]. It reduces and activates these enzymes and in doing so is converted to DHA[30]. The development of collagen from protocollagen involves AA dependent hydroxylation of protein-bound proline and lysine[31] as the rate controlling step[32] and it is tempting to suggest that growth promoters, by maintaining low levels of DHA, may release a 'feed-back' inhibition of collagen development. This would ensure that the forma-

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tion of collagen was controlled by growth promoters and in this way collagen production would be directly related to growth requirements.

The apparent importance of AA in other areas associated with growth, e.g. in the formation of mucopolysaccharide[33], the maintenance of ribosome orientation[34] and in the removal of histone from inducible chromatin[35], would also ensure that unrestrained growth did not accompany 'ascorbate' deficiency. Thus scurvy is mainly characterized by the lack or faulty development of structural substances and the inability of cells to differentiate although an increase in nuclei, respiration and enzyme activity[36] have also been observed during the development of scurvy.

The reason for the high concentration of AA in the adrenal glands has not been established but it has been suggested that it may play a primary part in the control of steroidogenesis through the adrenal hydroxylase system[37]. Stress in animals leads to the hydroxylation of adrenal steroids and secretion of these and DHA from the adrenal glands[37]. The increase in the level of circulating DHA is in agreement with the reduction in the mitotic rate associated with stress and would also explain the diurnal mitotic rhythm found in a number of animal tissues[38]. Thus during sleep stimulation of the adrenal glands is less, the level of DHA falls and the mitotic rate increases.

The above examples of existing evidence support the hypothesis that DHA is an important inhibitor of cell growth and division and suggest that many aspects of the extensive literature on 'ascorbate' may be rationalized on this basis.

Résumé. L'acide dehydroascorbique peut agir comme un inhibiteur de la croissance et de la division des cellules, suivant une théorie générale proposée par SZENT-GYÖRGYI[1]. Des exemples tirés d'autres témoignages soutiennent ce point de vue.

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STUDIORUM PROGRESSUS

Radiation Induced Avoidance Behavior Transfer by Brain Extracts of Mice

Since 1951 we have been studying the effects of X-radiation on brain tissue of mammals[1]. In recent years our interest has been concerned with cellular effects, as well as radiation induced behavioral changes. That the effects of radiation are not confined to their direct effects on cells nor to the immediate period of exposure to the radiation has long been known by students of experimental radiology. Hiroshima and Nagasaki are prime examples, also this axiom was re-emphasized through the study of HOLSTEN et al.[2] on plant cells and especially their growth media, while their results for *Drosophila melanogaster* were less definitive.

A considerable literature has accumulated in recent years concerning the effect of ionizing radiation on behaviour, especially on the radiation-induced behaviour involved in conditioned avoidance of a distinctive taste substance (saccharine sodium)[3,4]. The sweet solutions are offered simultaneously to the mice with plain tap water before, during, or after the animals are exposed to radiation. A concentration of 0.1% by weight of saccharine has been found adequate to establish taste preference of this solution to that of tap water, and the conditioned stimulus is thus established.

In this report we are extending our past studies[5-8] concerning the direct and indirect effects of X-radiation on conditioned avoidance behaviour. The work of many laboratories, including our own, has established that mice prefer saccharine sodium solution to plain water. However, when the saccharine solution is offered just before the animals are exposed to ionizing radiations, post-irradiation avoidance is induced. The physiological mechanism of saccharine avoidance behaviour has not yet become clear. Still unanswered are the questions: is the effect caused by pathological changes in the irradiated animals, or are changes induced in the taste perception mechanism? Is it strictly a prolonged disturbance of some of such mechanisms or is an impairment of memory function involved? Furthermore, what is the duration of these effects, and how are the basic cell biological mechanisms altered?

Most memory transfer studies date back to 1960 when MCCONNELL[9,10] found that untrained flatworms would learn more quickly when injected with ribonucleic acid from trained flatworms. Several other scientists have postulated that transfer of knowledge might be accomplished by feeding an animal which has learned some particular task to untrained animals or by grinding up the brain of one animal and injecting it into another.

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