185 THE MECHANISM OF DEOXYGUANOSINE MEDIATED TOXICITY IN PROLIFERATING HUMAN PERIPHERAL BLOOD T LYMPHOCYTES

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We previously showed that deoxyguanosine (dGuo) is toxic not only to purine nucleoside phosphorylase (PNP) deficient T cells but also to normal peripheral blood T and B lymphocytes activated in vitro with appropriate mitogens or antigens. The dGuo-mediated toxicity of proliferating T and B lymphocytes is accompanied by intracellular accumulation of guanine ribonucleotides like GDP and GTP. DeoxyGuo does not affect the expression of interleukin-2 (Il-2) receptors on T cells activated with mitogens. The latter finding indicates that the process of T cell activation up to the appearance of Il-2 receptors is insensitive to dGuo despite ongoing accumulation of GTP. However, addition of Il-2 to T lymphocytes activated with mitogens in the presence of dGuo and expressing Il-2 receptors does not induce T cell proliferation. Binding studies using radiolabelled Il-2 showed that neither the number of high affinity receptors nor that of low affinity receptors is significantly affected by dGuo. We therefore hypothesize that the effect of dGuo and hence of GTP is at the level of signal transduction following the interaction of Il-2 with the Il-2 receptor.

186 3'-AZIDO-3'-DEOXYTHYMIDINE (AZT) AND ACYCLOVIR (ACV): ANTIVIRAL NUCLEOSIDE ANALOGS WITH UNUSUAL CELL MEMBRANE PERMEATION PROPERTIES.

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AZT and ACV are nucleoside analogs which are clinically useful in the treatment of infections caused by the human immunodeficiency virus and by herpes viruses, respectively. Since both agents must enter cells in order to exert their antiviral activity, the mechanism of their cell membrane permeation has been investigated. Unlike most nucleoside-like compounds, AZT was found to permeate human erythrocytes and lymphocytes chiefly by nonfacilitated diffusion and not via the nucleoside transport system (J. Biol. Chem. 262, 5748-5754 (1987)). In subsequent studies it was found that 2',3'-dideoxythymidine (ddThd) also entered human erythrocytes chiefly by nonfacilitated diffusion, thus indicating that the unusual cell membrane permeation behavior of AZT is due largely to elimination of the 3'-hydroxyl moiety of thymidine. However, the rate of nonfacilitated diffusion of AZT into these cells was 2- to 3-fold greater than that of ddThd, indicating that the increased lipophilicity conferred on AZT by its 3'-azido moiety enhances its penetration of cell membranes. Although often referred to as an "acyclic nucleoside," ACV has been found to permeate the human erythrocyte membrane solely via the same purine nucleobase carrier which transports adenine, guanine and hypoxanthine and not via the nucleoside carrier. Elucidation of the unusual transport properties of these two antiviral drugs may contribute to our understanding of their human pharmacokinetics and disposition.

187 DEFICIENCY OF AMP DEAMINASE IN HUMAN ERYTHROCYTES.

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The deficiency was first found by Ogasawara et al /BBRC 1984, 122, 1344 - 1349, Hum.Genet. 1987, 75, 15 - 18/ to occur in Japan, Seoul and Taipei as one heterozygote in about 30 of the population. In order to find the frequency of the defect in the european area, 410 blood samples have been collected from the blood donors in the county blood center in Gdańsk /Poland/. The mean AMP deaminase activity in the erythrocytes was found to be 8.3 µmole ammonia/min per g hemoglobin, which is about 30% less than found in Japan but exactly the same which was found in U.S.A. by Campbell et al. /Clin.Chim Acta 1977, 79, 379 - 385/. Among the 410 individuals investigated 26 displayed half or less of the mean erythrocyte AMP deaminase activity. This could mean that the frequency of the mutant gene is one heterozygote in about 16 of the population in Poland. One case of a complete deficiency of the erythrocyte AMP deaminase activity was found in the family member of one of the heterozygotes. All the deficient subjects appeared to be perfectly healthy, there were no evidence of either anaemia or hemolysis.