67 OXIDATIVE DAMAGE AND PURINE METABOLISM: INVESTIGATION OF HAEMOLYTIC ANAEMIA IN THE BLACK RHINOCEROS

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Objectives To investigate purine and glutathione metabolism in a specific form of haemolytic anaemia with a possible free radical causation.
Design and Methods Red blood cells from a number of mammalian species were examined with labelling techniques and HPLC for differences in purine, carbohydrate, and glutathione metabolism after exposure to oxidising agents.
Results Nucleotide compositions differed markedly between species. Rhinoceros red cells contain levels of ATP which were only 2% of those found in man, despite which there is no major disability in pentose phosphate flux, lactate production, or carbohydrate cycling after exposure to oxidative agents. Red cell tyrosine concentrations, however, were found to be over 20-fold higher than in man.
Conclusion The results suggest the major metabolic changes found in mammalian red cells may be adaptations to environmental variables, but which may be inappropriate in the captive state.

68 POTENT ANTITUMOR ACTIVITY OF THE DIFFERENTIATION-INDUCING AGENT 9-(2-PHOSPHONYLMETHOXYETHYL) ADENINE (PMEA) IN CHORIOCARCINOMA-BEARING RATS

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Objectives Based on the promising *in vitro* differentiation-inducing effect of 9-(2-phosphonylmethoxyethyl)adenine (PMEA) in the rat choriocarcinoma RCHO cell line, we examined the antitumor activity of PMEA in an *in vivo* rat choriocarcinoma model.
Design and Methods An *in vivo* choriocarcinoma model was established by grafting rat choriocarcinoma RCHO cells under the kidney capsule of syngeneic WKA/H rats. During 11 days, the animals received a daily intraperitoneal injection of the test compound, starting on the day before inoculation of the tumor cells.
Results In vitro choriocarcinoma cell differentiation upon exposure of the cells to PMEA at 2 to 50 μM was monitored by morphological changes, induction of alkaline phosphatase, secretion of progesterone and disappearance of a cytotrophoblast-specific surface antigen. Neither macroscopic nor microscopic signs of tumor growth were found in the kidney of rats treated with PMEA at 250 mg/kg/day. In contrast, massive RCHO tumor growth and marked enlargement of the kidney were observed in untreated rats at day 11 after tumor cell grafting. The antitumor effect of PMEA decreased proportionally with lower drug doses. Compared to untreated control rats, only a minor reduction in tumor size was observed at a PMEA dose of 25 mg/kg/day. Methotrexate, which is commonly used for the treatment of choriocarcinoma in humans, completely inhibited tumor growth at a subtoxic dose of 0.8 mg/kg/day in this rat model. No *in vivo* antitumor activity was found for (*R*)-9-(2-phosphonylmethoxypropyl)-adenine ((*R*)-PMPA), a structural analogue of PMEA. This is also in agreement with the much less pronounced *in vitro* differentiation-inducing activity of (*R*)-PMPA, as compared to that of PMEA.
Conclusion PMEA exerts a potent and specific differentiation-inducing effect on rat choriocarcinoma cells *in vitro* and *in vivo*.

69 REGULATION OF DEOXYCTIDINE KINASE BY DEOXYCTIDINE AND DEOXYCTIDINE-5′ TRIPHOSPHATE IN WHOLE CELLS

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Objectives To analyse the importance of dCyd and dCTP on regulation of dCyd analog phosphorylation by dCyd kinase.
Design and Methods Comparative analysis of CEM, Raji, HL-60, and CHO cells with regard to dCyd and dCTP pools and their effect on ara-CTP accumulation during inhibition of ribonucleotide reductase (RR).
Results RR-inhibition depleted dCTP to the greatest extent in CEM cells, but enhanced ara-CTP formation only in Raji, HL-60 and CHO cells. Under control conditions, there was an inverse correlation between the size of the dCyd pool and the cellular capacity to accumulate ara-CTP. When RR was inhibited, cellular dCyd depletion correlated with the enhancement of ara-CTP accumulation. Inhibition or absence of dCMP deaminase expanded the dCyd pool and impaired ara-C phosphorylation.
Conclusion Intracellular depletion of dCyd may reduce the competition of ara-C and dCyd at dCyd kinase and thereby allows enhanced phosphorylation of ara-C.

70 CHANGES OF POLYMORPHONUCLEAR LEUKOCYTES (PMNs) FUNCTIONS UNDER DIETARY NUCLEIC ACID DEFICIENCY AND EFFECT OF ADMINISTRATION OF NUCLEOTIDE AND NUCLEOSIDES MIXTURE SOLUTION IN MICE

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Objectives Dietary nucleic acid deficiency decreases T lymphocytes functions, however, it is not known whether dietary nucleic acid influences on PMNs functions. We evaluated the influence of dietary nucleic acid deficiency and the effect of a nucleotide and nucleosides mixture solution (OG-VI: GMP 30 mM, inosine 30 mM, cytidine 30 mM, uridine 22.5 mM, thymidine 7.4 mM, Otsuka Co., Japan) on PMNs functions.
Design and Methods BALB/C mice were maintained on nucleic acid free diet or standard chow (control: C group) for 7 days. Then nucleic acid free diet colony were randamized into two groups, OG group (0.35 ml/mouse of OG-VI) or NF group (saline) intraperitoneally on the 7th day. Lipopolysaccharide (LPS) uptake, expression of adhesion molecules (Mac-1, LFA-1) and oxidative burst on peripheral blood PMNs were analysed by flow-cytometer. 72-hours survival rate after intraperitoneal administration of LPS (25 mg/kg) was compared.
Results LPS uptake, expression of adhesion molecules and oxidative burst were inhibited in the NF group, and enhansed in the OG group. Survival rate of the NF group was better than that of the C group, and improved more in the OG group.
Conclusions These results suggested that dietary nucleic acid deficiency may aggravate PMNs functions and OG-VI may offer positive responses on PMNs.