Further Studies on Cytostatic Activity of Alkoxymethyl Purine and Pyrimidine Acyclonucleosides

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The influence of 14 acyclonucleosides[1], derivatives of adenine, guanine, uracil and thymine on the phosphorylation of dAdo, dGuo, dCyd and dThd occurring in the cytosol of growing amelanotic melanoma transplanted to Syrian hamsters, as well as on inhibition of tumor growth were studied. From among the studied ACNs eight were tested earlier (Modrzejewska *et al.*, 1996, The influence of alkoxymethyl purine and pyrimidine acyclonucleosides on growth inhibition of Kirkman-Robbins hepatoma and possible mechanism of their cytostatic activity, Z. Naturforsch. **51c**, 75–80); from among the newly synthesized ACNs, 1,3-*N,N*-diallyloxymethylthymine (AMT2), 1-*N*-allyloxymethyl-5,6-tetramethyleneuracil (AMUTM), and tested previously 1-*N*-allyloxymethylthymine (AMT1), administered i.p. in a dose of 0.2 mmol /kg body weight reduce the tumor mass from 0.98 g to 0.64 g ± 0.11 g (i.e. 35% ± 12%). 48 hours after i.p. administration of the mentioned ACNs in the same dose a reduction of tumor mass is accompanied by the inhibition of dAMP, dGMP and dTMP synthesis. AMT1 inhibits dThd phosphorylation from 6.2 to 4.22; AMT2 suppresses dAdo, dGuo and dThd phosphorylation by, correspondingly, from 2.8 to 1.7, from 10.8 to 7.5 and from 6.2 to 4.2; AMUTM depresses dAMP synthesis from 2.8 to 1.6 (all data: μmol of 2'dNMP formed per mg of protein per min. × 10^{-4}). None of the 14 studied acyclonucleosides influences dCMP synthesis. *In vivo*, after hydration of allyloxymethyl group to hydroxypropoxymethyl residue (having -CH_2OH group), AMT1, AMT2 and AMUTM undergo phosphorylation to corresponding triphosphates. Phosphorylated ACNs are not incorporated into tumor DNA, however they inhibit dAdo, dGuo and dThd incorporation into DNA. It is concluded that ACN triphosphates are not substrates for DNA polymerase but, competing with dATP dGTP and dTTP, inhibit incorporation of these 2'dNTP into DNA and, in consequence, reduce tumor growth, which is presumed to be the main mechanism of cytostatic activity of the studied ACNs.