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DNA-binding studies of antimutagenic and repair-stimulating derivative of 1,4-dihydropiridine AV-153 and its structural analogues

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Background. Ability to intercalate between DNA strands with subsequent inhibition of transcription or replication processes determines cytotoxic activity of numerous anticancer drugs. Strikingly intercalating activity was reported also for some flavonoids considered to be antimutagenic agents and genome stabilizers. DNA-repair stimulating drugs appear to be prospective remedies for treatment of complications of diabetes mellitus. Aim of this study was to determine mode of interaction with DNA of antimutagenic and DNA repair stimulating dihydropyridine (DHP) AV-153 and its analogues.

Methods. UV-VIS spectra of the tested compounds were recorded in absence of DNA and presence of increasing amounts of rat liver DNA in 50 mM NaCl and 5 mM Tris HCl at pH 7. Observation of hyperchromic or hypochromic effects produced by DNA indicated interactions of the substance with minor grove of the DNA or intercalation of the substance between the DNA strands. Ability of a drug to compete with ethidium bromide (EBr) intercalation was determined by measuring fluorescence intensity of EBr-DNA complex (λ_{ex} = 335, λ_{em} = 600) in presence of increasing concentrations of the compound.

Results. In a series of water-soluble derivatives of 2,6-dimethyl-1,4-dihydroisonicotinic acid manifested different affinity to DNA determined mainly by groups in positions 3 and 5. Compound AV-153 with ethoxycarbonil groups in positions 3 and 5 evidently interacted with DNA, as addition of the DNA to AV-153 solutions caused pronounced hyperchromic and bathochromic effects on the spectra. Reciprocally addition of the compound to DNA solutions caused hyperchromic effect in DNA spectra. AV-153 competed with EBr for intercalation sites in DNA: 116 □M of the compound caused a two-fold decrease of the fluorescence intensity. Modification of the compound structure: addition of glutamic acid in position-4 as amide of 2,6-dimethyl-3,5-diethoxycarbonyl-1,4-dihydroisonicotinic acid (glutapyrone) or taurine in the same position (tauropirone) abolished ability of the compound to interact with DNA. Compounds with cyano or acetyl groups in positions 3 and 5 (J-3-183 and AV-154 correspondingly) did not interact with DNA. Unsubstituted in position-4 1,4-DHP derivative, carbatone [disodium-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(carbonyloxyacetate)] manifested hypochromic effect in the presence of DNA without any spectral shifts. Addition of DNA caused hyperchromic effects in spectra of tricyclic fused 1,4-DHP derivatives – decahydroacridine-1,8-diones (PP-150-Na and PP-544-NH4).

Conclusions. Thus DNA-intercalating activities of 1,4-DHP are evidently determined by groups in positions 3 and 5. Antimutagenic and DNA repair stimulating substance AV-153 appears to intercalate between the DNA strands. Probably AV-153 opens DNA helix and makes damaged sites more accessible to repair enzymes.

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