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Effect of Nucleosides on Mitochondrial Functions in HepG2 Cells. L. Cui,[1] R.F. Schinazi,[2] G. Gosselin,[3] J.-L. Imbach,[3] C.K. Chu, [4] R.F. Rando,[5] and J.-P. Sommadossi.[1]University of Alabama, Birmingham, AL 35294, USA;[1] VA Medical Center/Emory University, Decatur, GA 30033, USA;[2] University of Montpellier II, 34095 Montpellier, France;[3] University of Georgia, Athens, GA 30602;[4] Triplex Pharmaceutical Corporation, The Woodlands, TX 77380, USA.[5]

Investigations by our group on the cellular and molecular events involved in 1-(2-deoxy-2-fluoro-1-ß-D-arabinofuranosyl)-5-iodouracil[FIAU] -induced hepatotoxicity using a human hepatoma HepG2 cell line have demonstrated that FIAU and its *in vivo* metabolite 1-(2-deoxy-2-fluoro-1-ß-D-arabinofuranosyl)-5-thymine[FMAU] incorporate into mitochondrial[mt]DNA of cells and lead to a marked mt dysfunction as evidenced by disturbance in cellular energy metabolism and detection of micro- and macrovesicular steatosis. (*J. Clin. Invest.* 1995 In Press). In the present study, we have studied other nucleosides with a ß-D and a ß-L configuration, which represent potential candidates for treatment of hepatitis B infection. Compounds were incubated with cells for 4 to 14 days at concentration between 0.1µM and 10µM and effects on mtDNA content, lactic acid production, lipid vesicle formation and mt morphology were evaluated. No effect on lactic acid production was detected in cells treated with ß-L-2',3'-dideoxy-3'-thiacytidine[3TC] and ß-L-2',3'-dideoxy-5-fluoro-3'-thiacytidine[ß-L-FTC], while a dose-dependent increase on lactic acid production was observed in cells exposed to ß-D-2',3'-dideoxy-5-fluorocytidine[ß-D-FddC], ß-L-2',3'-dideoxy-5-fluorocytidine[ß-L-FddC],ß-L-2-hydroxymethyl-5-(5-fluorocytosin-1-yl)-1,3-dioxolane[ß-L-FDOC] and T-70080 (an analogue of FIAU with similar sugar moiety). Cells treated with 3TC, ß-L-FddC and ß-D-diaminopurine dioxolane [ß-D-DAPD] did not show morphological changes compared to control. Formation of micro- and macro-lipid vesicles and loss of cristae in mitochondria were detected in cells treated with ß-D-FddC and T-70080. Cells treated with ß-L-FDOC led to lipid vesicles formation but no change on mt morphology. Inhibition on mtDNA content was demonstrated with ß-D-FddC and T-70080, whereas 3TC, ß-L-FTC and ß-L-FddC had no effect and ß-L-FDOC and ß-D-DAPD are being evaluated. In summary, 3TC, ß-L-FTC and ß-D-DAPD had no effect on mitochondrial functions in HepG2 cells. No correlation was observed among the investigated mt functions suggesting that these effects may be indirect and/or different mechanisms may be involved when toxicity by a specific nucleoside is observed.