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Uridine supplementation with Mitocnol antagonizes antiretroviral nucleoside analogue-induced mitochondrial peripheral and cerebral neuropathy in vivo

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Purpose of the study

Peripheral neuropathy and CNS neurodegeneration may be a toxic effect of some antiretroviral nucleoside analogues on mitochondria. We investigated if this neuropathology may be antagonized by uridine supplementation in vivo.

Methods

BalbC mice (7 weeks of age) were fed with zalcitabine (13 mg/kg/d) or zidovudine (100 mg/kg/d) with or without Mitocnol (340 mg/kg/d) a dietary supplement with high uridine bioavailability for 9 weeks. Hippocampus and ischiadic nerve ultrastructure and mitochondrial functions were assessed.

Summary of results

Zalcitabine and to a lower extent zidovudine induced a significant peripheral and cerebral neuropathy with disrupted mitochondrial architecture, depleted mitochondrial DNA (mtDNA), and reduced levels of cytochrome C-oxidase activity (COX) and mtDNA-encoded cytochrome C subunit I (COX I). Mitocnol had no side-effects but attenuated or fully normalized all pathology of the peripheral and central nervous system (Table 1).

Conclusion

Zidovudine and zalcitabine induce a mitochondrial peripheral and cerebral neuropathology, both of which are antagonized by Mitocnol.

Table 1:

	Control	Mitocnol	Zidovudine (100 mg/kg/d)	Zidovudine (100 mg/kg/d) + Mitocnol	Zalcitabine (13 mg/kg/d)	Zalcitabine (13 mg/kg/d) + Mitocnol
Ischiadic nerve						
mtDNA copies ‡	374 ± 49	372 ± 38	290 ± 65*	346 ± 35†	237 ± 61**	335 ± 48*†
Hippocampus						
mtDNA copies ‡	211 ± 51	219 ± 80	104 ± 32**	145 ± 21*†	151 ± 30*	181 ± 53*
COX activity @	11 ± 3	9 ± 3	4 ± 2**	6 ± 2**†	5 ± 2**	8 ± 3*†
COX/SDH-ratio %	100 ± 9	107 ± 9	48 ± 19**	90 ± 18††	50 ± 15**	92 ± 20††
Citrate activity @	1152 ± 201	1086 ± 179	1124 ± 275	1265 ± 314	1791 ± 33*	1361 ± 173*†
COX II/COX IV-ratio %	100 ± 5	122 ± 26	57 ± 25**	89 ± 22†	45 ± 20**	94 ± 20††

*, $p < 0.05$ vs. controls; † vs. no Mitocnol. **, $p < 0.001$ vs. control; †† vs. no Mitocnol; %, of control; ‡, copies/nucleus; @, μmoles/min/g protein.