

Lipoatrophy and ubiquitous mtDNA depletion in mice following long-term stavudine treatment.

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ABSTRACT

Background: Mitochondrial DNA (mtDNA) depletion has been proposed as an important factor leading to peripheral lipoatrophy in HIV-patients receiving antiretroviral therapy. The extent to which mtDNA depletion occurs in other organs and tissue in humans has not been evaluated and animal models for lipoatrophy have not been established so far. We aimed to investigate the effect of NRTI mono treatment on the mtDNA content of various organs and tissues in a murine model as well as to establish a murine model of lipodystrophy.

Methods: Groups of C57BL/6 mice were treated with d4T, AZT or vehicle (5-20 mice per group) for up to 15 weeks with daily human doses adjusted for murine body surface area. In order to better parallel the pharmacokinetics in humans, drugs were administered via oral gavage. MtDNA content was determined by Real-Time PCR in liver, muscle, heart, brain, and fat tissue. Adiponectin and leptin were measured by ELISA in the serum.

Results: Over a time period of 15 weeks mice receiving pharmacological doses d4T or AZT gained less weight (d4T $3.5 \pm 0.3g$, AZT $4.1 \pm 0.4g$) as compared to control animals ($8.6 \pm 0.5g$) while no differences in food and water intake were detected. Post mortem examination revealed that mice on AZT treatment but particularly animals receiving d4T had less of both peripheral as well as central fat. Similarly, d4T treated animals had lower serum adiponectin levels as compared to control mice ($5.245 \pm 0.222 \mu g/ml$ vs. $6.105 \pm 0.2061 \mu g/ml$; $p < 0.05$) and lower serum leptin concentrations ($4.450 \pm 1.451 ng/ml$ vs. $12.44 \pm 3.338 ng/ml$). Neither d4T nor AZT had an effect on glucose levels during GTT. Analysis of mtDNA content revealed depletion of mtDNA in organs including the brain (*20%) and fat tissue (27%) but the most profound and significant depletions were evident in muscle (-56%), liver (-64%), and heart (-45%).

Conclusion: This is the first study to show fat loss and hypoadiponectinemia in mice after treatment with thymidine-analogues. d4T and AZT can cause fat wasting, without causing insulin resistance in mice. Long-term treatment of mice with d4T led to mtDNA depletion that was not restricted to fat tissue. These data indicate that mtDNA depletion is an unspecific event during treatment with thymidine-analogues. If indeed mtDNA depletion is a major contributor to mitochondrial dysfunction, potential long-term toxicities in various organs need to be considered.

INTRODUCTION

Mitochondrial DNA (mtDNA) depletion has been proposed as an important factor leading to peripheral lipoatrophy in HIV-patients receiving antiretroviral therapy. The extent to which mtDNA depletion occurs in other organs and tissue in humans has not been evaluated and animal models for lipoatrophy have not been established so far.

OBJECTIVE

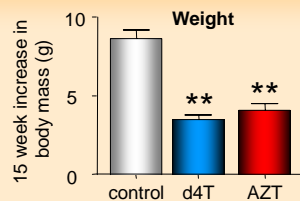
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METHODS

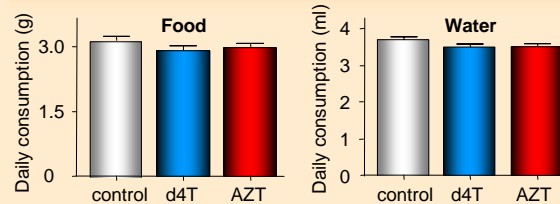
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RESULTS

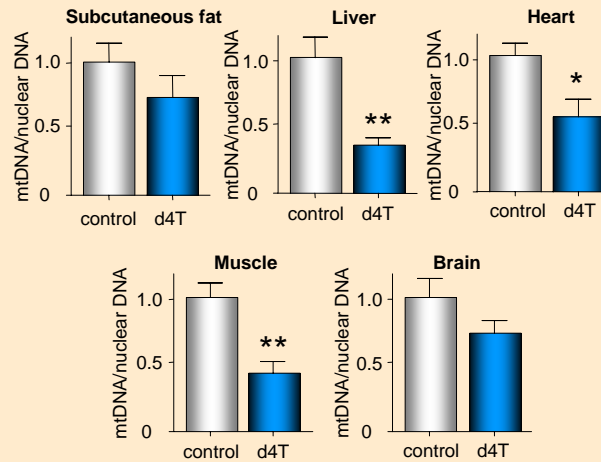
NRTI induce weight loss in C57BL/6 mice



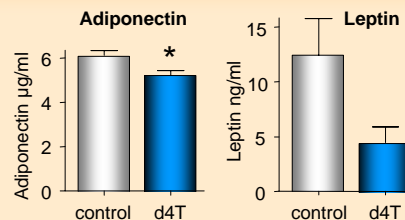
NRTIs do not affect the daily water and food consumption



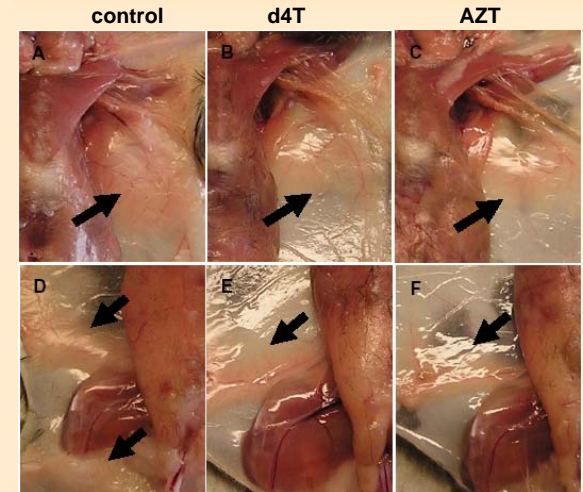
Effect of d4T on mtDNA content of various mouse organs and tissues



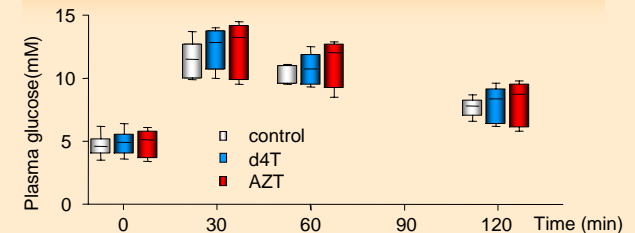
Effect of a d4T on plasma leptin and adiponectin levels in C57BL/6 mice



NRTIs induced fat atrophy in C57BL/6 mice



NRTIs do not affect glucose tolerance



CONCLUSION

- This is the first study to show fat loss and hypoadiponectinemia in mice after treatment with thymidine-analogues.
- d4T and AZT can cause fat wasting, without causing insulin resistance in mice.
- Long-term treatment of mice with d4T led to mtDNA depletion that was not restricted to fat tissue.