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## EFFECTS OF ZIDOVUDINE AND STAVUDINE ON KETONE BODIES AND LIPIDS IN MICE: POSSIBLE ROLE OF $\beta$ -AMINOISOBUTYRIC ACID, A CATABOLITE OF THYMINE

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Recently, we showed that zidovudine and stavudine, but not didanosine, zalcitabine and lamivudine, were able to increase hepatic fatty acid oxidation and ketogenesis in mice after 2 weeks of treatment. The effects of zidovudine and stavudine were reproduced by  $\beta$ -aminoisobutyric acid (BAIBA), a  $\beta$ -amino acid generated during thymine degradation. In the present study, the metabolic effects of zidovudine, stavudine and BAIBA (100 mg/kg/day for all derivatives unless otherwise indicated) were assessed over 6 weeks [T6] in lean and obese ob/ob mice. DEXA was performed at T0, T2 and T6 for mice not submitted to fast during the treatment, or at T2 and T6 for mice fasted for 48 h before measurements. Plasma  $\beta$ -hydroxybutyrate ( $\beta$ -HB) and hepatic and plasma lipids were assessed after a 48-h period of fast at T6. In lean mice, plasma  $\beta$ -HB was increased by zidovudine (36%), stavudine (16 and 49%, respectively, for 13.5 and 100 mg/kg/day) and BAIBA (36%). DEXA performed in the fasted state showed a consistent decrease in body fat mass with BAIBA (31 and 25%, respectively, at T2 and T6). When mice were in the fed state, zidovudine, stavudine and BAIBA decreased the physiological gain of body fat over the T2–T6 period, respectively, by 78, 48 and 75%. Hepatic lipids and triglycerides were decreased by zidovudine and BAIBA. In ob/ob mice, DEXA performed in the fasted state revealed a decrease in body fat mass with zidovudine, stavudine and BAIBA at T2 (8, 14 and 16%, respectively), whereas this effect was less pronounced (stavudine or zidovudine) or absent (BAIBA) at T6. For mice investigated in the fed state, only zidovudine consistently reduced the gain of body fat mass. Finally, zidovudine, stavudine and BAIBA decreased hepatic lipids and triglycerides and plasma cholesterol and phospholipids. Altogether, our results suggest that the effects of zidovudine, stavudine

and BAIBA on body fat depend on the nutritional state and the genetic/metabolic background of the animals. These data also suggest that BAIBA may mediate some of the metabolic effects induced by zidovudine and stavudine. Several of these effects could be related to increased fatty acid oxidation, but other mechanism(s) cannot be ruled out.

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20

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