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Obesity, impaired glucose metabolism and hepatic histopathological damage in 3xTg-AD mice at different stages of disease compared to mice with normal aging†

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Abstract

The crosstalk between obesity, diabetes, steatohepatitis, and dementia creates a controversial scenario also when studied using animal models. In the present work, this crosstalk was investigated in male and female 3xTg-AD mice for Alzheimer's disease (AD) at different ages/stages and compared to sex- and age-matched counterparts with normal aging. The relevance of the genetic background and classical intrinsic factors (AD genotype and sex) were determined using a retrospective analysis of population data and an experimental design. Age/stage of disease was considered a source of stochastic and non-stochastic factors. Data from two different colonies of 3xTg-AD mice with distinct genetic backgrounds were analyzed to verify the functional interplay between the studied factors. Data from asymptomatic/prodromal to early/advanced stages of the disease were screened. Then, all factors' relationships were studied in an experimental design using the same set of animals. The population data unveiled that the genetic background and sex effects were confirmed with regards to the variable body weight, with changes during the disease development and progress. Besides, sexual dimorphism was found as an important factor in glucose metabolism. Statistically significant differences in glucose tolerance and behavioral assessment (exploration, anxiety, and cognition in a two-days open-field paradigm) were found when all the factors were analyzed. In summary, the present study shows that all the studied factors should always be considered when assessing the outcome of the research interventions in the field because they have a distinct functional interplay through the process of normal and AD-pathological aging and from a gender perspective.

Keywords

Obesity; glucose metabolism; liver; dementia; Alzheimer's disease; aging; sex/gender perspective