IN VIVO EFFECT OF CLIOQUINOL TREATMENT IN A MOUSE MODEL OF ALZHEIMER'S DISEASE

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Abnormal interactions of copper, iron and zinc with amyloid-β (Aβ) peptide leading to oxidative stress occur in brain ageing and neurodegenerative disorders. Clioquinol (CQ) is a chelating antibiotic with a great affinity for copper and zinc ions. This may in turn promote dissolution of Aβ and diminish its toxic properties. CQ treatment may retard the progression of Alzheimer's disease (AD) by inhibiting copper and zinc ions from binding to Aβ and by reducing toxicity mediated by Cu^{2+} and Fe^{3+}. CQ therapy has been reported to significantly slow the rate of cognitive decline in a subset of patients with AD. In this work we used TgCRND8 mice that overexpress a double mutant (Swedish : KM670/671NL and Indiana: V717F) human amyloid precursor protein (APP) and exhibit deposition of Aβ and robust cognitive deficits by the age of 3 months. TgCRND8 mice exhibit AD-like amyloid plaque deposits with a variety of morphologies. Dense-cored deposits are present from an early stage (>80% can be stained with either Congo Red or Thioflavine S).
Eight TgCRND8 and 8 wild type (wt) mice, at 4 months of age, were dosed orally once/day for 5 weeks with CQ (30 mg/kg, 4 mice per group) or vehicle (CMC 0.05%, 4 mice per group). No differences in general health and body weight parameters were observed between CQ- and vehicle-treated Tg and wt animals. Western Blotting and immunohistochemical techniques were used to reveal protein of interest. Antibodies anti-Aβ(1-42) and anti-GFAP were used to detect the amyloid plaque burden, as Aβ-plaque area and numbers, and the astrocytes reaction, respectively, in the hippocampus and motor and piriform cortex. Immunoreactivity of inducible nitric oxide synthase (i-NOS) and nitrotyrosine antibodies was evaluated to reveal nitrosative stress. Cognitive impairments were studied in the Step-Down and Morris Water Maze tasks. CQ treatment showed a significant ($P< 0.05$, one way ANOVA) improvement of learning capabilities in Tg mice in the Step-Down inhibitory paradigm, as compared to CMC-treated Tg mice. A trend towards cognitive improvement was also observed in the Morris water maze search preference. Imaging software analysis of immunohistochemical data demonstrates a slight reduction in both Aβ-plaque area and numbers in the hippocampus of CQ-treated Tg mice, as compared to CMC-treated Tg mice. The effect of CQ on nitrosative stress and astrocytes reaction in 4-month-old TgCRND8 mice is under investigation.
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