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The bile acid TUDCA reduces hypothalamic inflammation and food intake in streptozotocin-induced Alzheimer's mice model

Lucas Zangerolamo*, Gabriela M. Soares, Jean F. Vettorazzi, Carina Solon, Daiane F. Engel, Lício A. Velloso, Antonio C. Boschero, Everardo M. Carneiro, Helena C. Barbosa-Sampaio

Abstract

Energy homeostasis can be regulated by peripheral signals acting on the central nervous system, including the hypothalamus. The bile acid TUDCA has neuroprotective functions, reducing the major pathological markers of Alzheimer's diasease (AD) in animal models. However, its role in the hypothalamus of AD brains is still unclear. Here we reported that C57BL/6 mice submitted to intracerebroventricular injection of streptozotocin, experimental model of AD, and treated during 10 days with TUDCA presented reduced hypothalamic inflammation and hypothalamic mRNA levels of the orexigenic markers NPY and AgRP, resulting in decreased food intake and fat depots. Furthermore, this treatment also improved glucose tolerance and insulin sensitivity, as well as mice cognition. Our findings indicate that AD affect the hypothamalus, suggesting that hypothalamic dysfunction are directly involved with metabolic disorders observed in AD, and that the systemic administration of TUDCA attenuates these effects.

Key words:

TUDCA, hypothalamus, Alzheimer's disease

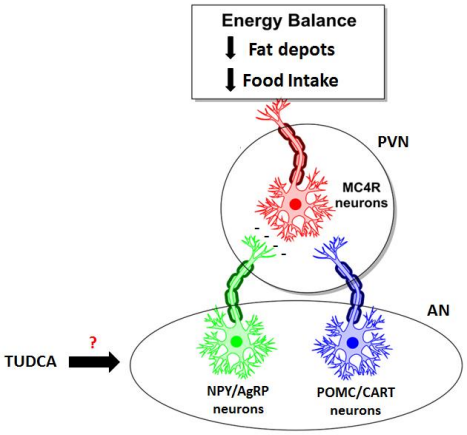
Introduction

Alzheimer's is a neurodegenerative disorder, hallmarked by the deposition of amyloid-β (Aβ) protein and neuroinflammation, mainly in hippocampus, resulting in the process of neuronal death and progressive cognitive decline. The hypothalamus has a crucial role in food behavior and in the interaction between the central nervous system and the periphery. Some studies have shown that Aβ deposits are also found in the hypothalamus of AD brains[1], resulting in inflammation, ER stress and decrease of hypothalamic neuronal population. These pathogenic events are associated in the establishment of peripheral insulin resistance in metabolic disorders, suggesting that hypothalamic dysfunction, that has been largely ignored in the AD field, may have important consequences, predisposing AD patients to develop peripheral metabolic deregulation, as Diabetes. Several strategies have been employed to attenuate the damaging effects of AD, among them, bile acids have been highlighted, inducing important neuroprotective functions. Considering that the bile acid TUDCA reduced Aβ deposits in AD experimental models, we aimed to investigate the effects of TUDCA on hypothalamus, evaluating the energetic homeostasis in streptozotocin-induced Alzheimer's mice model.

Results and Discussion

C57BL/6 mice were submitted to intracerebroventricular injection of streptozotocin (Stz) for induction of AD, which was confirmed by increased amyloid oligomer and proinflammatory cytokines, assessed by Western Blotting, in hippocampus, reduced discrimination index in NORT, a memory test, and increased IBA-1 immunoreactivity in hypothalamus, a marker of microglial activation. The treatment with TUDCA (300 mg/Kg for 10 days) reduced Aβ deposition and gene expression of proinflammatory cytokines in hippocampus, as well as increased NORT index, compared to Stz mice. Moreover, TUDCA treatment reduced IBA-1 immunoreactivity in hypothalamus and the hypothalamic mRNA levels of the orexigenic markers NPY and AgRP, without modulation in mRNA levels of the anorexigenic markers POMC and CART, comparing to Stz group. Mice that received TUDCA also showed improvement in glucose tolerance and insulin sensitivity, reduction in food intake and fat pad depots, although no differences in body weight were observed, comparing to Stz mice.

Image 1. Effects of TUDCA in energy homeostasis (adapted from [2]). The molecular mechanisms by which TUDCA acts have not yet been elucidated.



Conclusions

Our results show that the bile acid TUDCA reduces hypothalamic inflammation, NPY and AgRP mRNA levels and food intake, improving energetic homeostasis in streptozotocin-induced Alzheimer's mice model, suggesting that hypothalamic dysfunction in AD brains impairs peripheral metabolism, and that when TUDCA is administered, these damages are attenuated.

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[2] Rouzer CA. Controlling Energy Balance. **2015**; *VICB Communications*.