

POSTER PRESENTATION

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Corynoxine isomers decrease levels of amyloid- β peptide and amyloid- β precursor protein by promoting autophagy and lysosome biogenesis

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Background

One of the key histopathological features of Alzheimer's disease (AD) is the formation of neuritic plaques characterized by accumulation of amyloid β -peptide (A β) derived from amyloid precursor protein (APP). Impairment of the autophagy-lysosomal degradation pathway has been associated with AD. Recently we have identified a novel natural autophagy inducer, corynoxine B (Cory-B), a major oxindole alkaloid from the Chinese medicinal plant *Uncaria rhynchophylla* (Miq.) Jacks (Gouteng in Chinese). In this study, we have also established that corynoxine (Cory) and its isomer of Cory-B, not only increases basal level of autophagy but also increases the lysosomal activity in neuronal cell lines. Interestingly Cory but not Cory-B showed the enhanced lysosomal activities.

Materials and methods

N2a cell stably expressing Swedish APP (N2aSwedAPP) cells were treated with Cory or Cory-B at different dosage and time-course. Elisa was performed to measure the total A β in the supernatant of cell culture. Double immunostaining on N2aSwedAPP cells were performed using by carboxy terminal fragment (CTF) of APP (CT15) and LC-3 antibodies. Tg2567 mice at the age of 8 months, randomly distributed into Cory-B-treated Tg2567 group (Cory-B group) or Tg2567 group, and age matched non-Tg mice (C57BL/6, NT group) were assigned as aging control. Mice were intraperitoneally administered Cory-B (20 mg/kg/d) or vehicle (0.9% saline) once daily except weekends for 2 months. Cell and brain lysates were prepared for Western blot assay.

Results

We observed a dose-dependent significant decrease in A β in cells incubated with Cory or Cory-B for 24h. Next we found that Cory- or Cory-B mediated decreases in A β are due to changes in its precursor protein APP, by measuring the level of full-length APP and APP-CTFs in cell lysates from N2a-sSwedAPP. Simultaneously, we also found that Cory and Cory B dose-dependently increased levels of LC3-II, an autophagy specific marker in N2aSwedAPP cells. Furthermore we found that Cory- or Cory-B induced LC3-II was enhanced by lysosome inhibitor chloroquine (CQ) and slightly decreased by autophagy inhibitor 3-methyladenine. We have confirmed this finding in immunocytochemistry of N2aSwedAPP cells with CT15 and LC3 antibody. Further, we found that only Cory but not Cory-B dose dependently increased the mature Cathepsin D. Cory treatment simultaneously increased Lamp-1 and decreased APP staining. Importantly, Cory dose-dependently induced the nuclear translocation of Transcription Factor EB (TFEB). In cell signaling studies, we found that Cory but not Cory-B time dependently decreased mTORC-1 activity via p70SK and GSK pathway. Two months of Cory-B treatment significantly decreased FI-APP and APP-CTF in Tg2567 ($p < 0.05$). Cory-B treatment did not influence the levels of FI-APP in NT mice.

Conclusions

Our data reveal that corynoxine isomers reduce A β through an increase of the degradation of APP and its CTF by activation of the autophagy/lysosomal pathway.

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