Attenuation of neuroinflammation by ciproxifan, a histamine H3 antagonist in transgenic mouse models of Alzheimer's disease

In Alzheimer's disease (AD), neuroinflammation mainly occurs at the site of Aβ deposition. Apart from the direct toxic effect of Aβ to the neuronal cells, Aβ itself promotes neuroinflammation by activating microglia and astrocytes. Ciproxifan, A histamine H_3 receptor antagonist has been reported to enhance the release of neurotransmitters which play an important role in cognition (1). However, the role of ciproxifan on Aβ associated neuroinflammation has not been well documented.

Nine-month aged male B6.129-Tg (APPSw)40Btla/J mice (2) were administered repeatedly at 2 doses 1 (Tg-Cip 1 mg/kg, i.p.) and 3 mg/kg (Tg-Cip 1 mg/kg, i.p.) of ciproxifan for fifteen consecutive days. The same strain of the control group received intraperitoneal injection of normal saline (Tg-Con). A group of age matched male C57BL/6J was used as the wild type control (WT-Con). At the end of the treatment, brain tissues were collected to measure cyclooxygenase (COX) and pro-inflammatory cytokines, while plasma were collected to measure TGF-1β (anti-inflammatory cytokine) using ELISA kits. The data was analysed using two-way ANOVA followed by Tukey-Kramer multiple comparison test.

The significant elevation ($P< 0.001$) of COX-1, COX-2, IL-1α, IL-1β and IL-6 levels and reduction ($P< 0.001$) of TGF-1β level in the transgenic control group as compared to the wild type control confirm the occurrence of neuroinflammation in the transgenic model. The treatment of ciproxifan reduced both COX-1 and COX-2 activities, decreased the level of pro-inflammatory cytokines IL-1α, IL-1β and IL-6 and increased the level of anti-inflammatory cytokine TGF-1β as compared to transgenic control (Table 1).

Table 1 Effect of ciproxifan on neuroinflammation in transgenic mouse model of AD.

	WT-Con	**Tg-Co**	**Tg-Cip 1 mg/kg**	**Tg-Cip 3 mg/kg**
COX-1 activity (nmol/min/ml)	2.32 ± 0.08	4.28 ± 0.16$^{\#}$	4.08 ± 0.12	2.09 ± 0.23***
COX-2 Activity (nmol/min/ml)	2.97 ± 0.14	4.46 ± 0.15$^{\#}$	4.30 ± 0.07	2.50 ± 0.33***
IL-1α (pg/ml)	4.12 ± 0.25	8.16 ± 0.47$^{\#}$	7.77 ± 0.23	6.06 ± 0.35**
IL-1β (pg/ml)	11.92 ± 0.85	39.10 ± 0.51$^{\#}$	30.64 ± 1.29***	27.79 ± 1.74***
IL-6 (pg/ml)	2.67 ± 0.12	5.15 ± 0.26$^{\#}$	3.91 ± 0.21**	2.90 ± 0.24***
TNF-β1 (pg/ml)	194.21 ± 11.72	75.65 ± 7.97$^{\#}$	154.75 ± 3.06***	164.33 ± 7.47***

The results were expressed as mean ± SEM (n=6)
$^{\#}$ $P< 0.001$ vs WT-Con group ; $^{**}P< 0.01$, $^{***}P<0.001$ vs Tg-Con group

The significant reduction of both cyclooxygenase and pro-inflammatory cytokines (IL-1α, IL-1β and IL-6 levels) as well as elevation of an anti-inflammatory cytokine TNF-β1 level mediated by ciproxifan may signify the potential mechanism it exerts the beneficial effects against neurodegenerative diseases such as AD.

(1). Vohora and Bhowmik (2012). *Front Syst Neurosci* **6**: 72.

(2). Ryman *et al*. (2008). Neurobiol Aging **29**: 1190-1198.