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Letter to Editor

The characteristics of astrocyte on Aβ clearance altered in Alzheimer's disease were reversed by anti-inflammatory agent (+)-2-(1-hydroxyl-4-oxocyclohexyl) ethyl caffeate

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Alzheimer's disease (AD) places significant burden on health care budgets around the world while the cost to society is immeasurable. As a consequence of the increase in longevity, the number of Americans living with AD is expected to reach 14 million by mid-century without an urgent medical breakthrough [1].

Deposition of amyloid beta (Aβ) is widely believed to play a key role in the initiation and progression of AD. Indeed, the amyloid cascade hypothesis proposed over 20 years ago still continues to stimulate research in the field [2, 3]. However, conceptual changes have emerged recently highlighting that Aβ exists in equilibrium between deposition and clearance [4]. From a therapeutic perspective, complete elimination of Aβ is not a desired outcome given its various physiological roles [5, 6]. Studies have shown that impaired clearance rather than increased production is the driving force behind Aβ accumulation, and therefore in the initiation of AD [7, 8]. Aβ clearing mechanism(s) have therefore become targets of therapy.

Two of these Aβ clearing mechanisms include break down by enzymes and phagocytosis. Although nearly 20 Aβ degrading enzymes have been identified thus far [4, 9, 10], neprilysin (NEP) is thought to be the most physiologically relevant [11]. Phagocytosis is also an important mechanism of Aβ clearance where microglia and astrocytes play a key role [10]. Evidence shows that astrocytes can phagocytose both monomeric and oligomeric Aβ [12] as well as neurons that contain Aβ [13]. The Aβ degrading enzymes are also expressed by these phagocytic cells making the two processes interlinked.

Normal function of astrocytes is to provide metabolic support to neurons, recycle neurotransmitters, and clear Aβ [8]. However, in AD the phenotypic change in astrocytes to the so called reactive/hypertrophic phenotype results in impaired physiological function [8]. Reactive astrocytes are predominantly engaged in clearing Aβ, resulting in a reduction in the provision of the above mentioned important support functions. It is hypothesised that this change in phenotype contributes to the loss of neuronal function observed in AD [8].

In this context, the recent study by Liu *et al* [14] provides clear evidence that neuro-inflammation, as opposed to prolonged exposure to Aβ, reduces the capacity of astrocytes to clear Aβ. This is supported by previous studies indicating that exposure of astrocytes to Aβ upregulates inflammatory cytokines [15], and that neuroinflammation and oxidative stress can disrupt astrocyte function, including their support

actions [16]. Furthermore, some studies have reported that non-steroidal anti-inflammatory drugs (NSAIDS) can have positive results in the setting of AD [17].

The study by Liu *et al* [14] also provides evidence that (+)-2-(1-hydroxyl-4-oxocyclohexyl) ethyl caffeate (HOEC), with proven anti-inflammatory effects can potentially reverse this effect. The rate of $A\beta_{1-42}$ clearance by astrocytes from wild type (WT) mice was significantly higher than that of AD mice. After 24 h close to 15,000 pg/mL of $A\beta_{1-42}$ was detected in the media of astrocytes from AD mice, while at the same time point there were no detectable levels of $A\beta_{1-42}$ in media from WT astrocytes [14]. The results also indicated that the level of intracellular NEP increases throughout the course of Aβ clearance, with elevated NEP expression in cells from WT animals. However, according to the authors this increase in NEP level did not appear to be statistically significant. The study demonstrated that treatment with lipopolysaccharide (LPS) to activate inflammation leads to a loss of ability by astrocytes to clear exogenous $A\beta_{1-42}$ [14]. While significant levels (~17 ng/mL) of $A\beta_{1-42}$ were detected in the supernatant at 24 h following LPS treatment, levels in the respective control were not detectable. However, pre-treatment of cells for 2 h with the anti-inflammatory agent HOEC prevented LPS-induced loss of capacity to clear Aβ [14]. This was evidenced by the reduction in $A\beta_{1-42}$ levels in the supernatant by nearly 50% (10,000 pg/mL) at 24 h in the presence of HOEC. Furthermore, prior treatment of aged astrocytes from AD mice with HOEC effectively rescued their ability to clear exogenous $A\beta_{1-42}$ [14].

This study by Liu *et al* [14] could be built on in the future and the concepts used to examine the precise mechanism(s) by which HOEC restores astrocyte function. While the authors suggest that HOEC may stimulate phagocytosis, further experimentation is required to exclude the possibility that HOEC may increase the expression or activity of Aβ degrading enzymes such as NEP.

In conclusion, this study provides clear evidence that neuro-inflammation blocks the ability of astrocytes to clear Aβ and HOEC can restore astrocyte function *in vitro* [14]. The results clearly warrant the testing of HOEC in animal models of AD, as well as screening of currently available anti-inflammatory drugs for their effect on astrocyte function. The study supports the notion that early treatment with anti-inflammatory drugs may be a potential approach to restore astrocyte function and therefore to prevent or halt the progression of AD.

Disclosure of conflict of interest

None.

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