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Commentary

Atorvastatin and A (1–40): Not as Simple as Cholesterol Reduction in Brain and Relevance to Alzheimer Disease

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TJ 0 -1.3088 TD [(sa)22.3(l)13.6(i)13.6(n)0(e)-213.2(f)0(o)23.3(r)-220(7)-224.7(c)0(o)20(n)0(s)23.9(e)15(cu)22.5(t)15.5(i)
follow.

Two immediate issues arise in this study: use of A (1–40) vs. A (1–42) and aggregation state of the peptide. Although A (1–40) is neurotoxic when incubated with neuronal cultures, A (1–42) is generally regarded as the more toxic of the two peptides (Sultana and Butter eld, 2009), and it is therefore surprising that the authors did not use this peptide for their studies. We demonstrated that injection of A (1–42) into rat basal forebrain led to oxidative modi cation of speci c hippocampal proteins (Boyd-Kimball et al., 2005). Further, oligomeric A (1–42), rather than the brillar form, is regarded as the toxic species (Drake et al., 2003

; Lambert et al., 2001 ; Oda et al., 1995; Walsh et al., 1999). The authors used peptide that had been incubated for 4 days, when a large proportion of brillar A (1–40) would be present. It would have been informative had the authors used oligomeric peptide.

Several cross-sectional or case control epidemiological studies have revealed a tight link between cholesterol-lowering drugs (statins or others) and up to as high as a 70% reduction of risk for the development of AD (Dufouil et al., 2005; Hajjar et al., 2002; Jick et al., 2000; Rockwood et al., 2002; Rodriguez et al., 2002; Wolozin et al., 2000, 2007; Zamrini et al., 2004). However looking at the results of different prospective studies, it seems evident that the involvement of statins in the reduction of the risk to develop dementia is not so obvious. In fact, while some authors suggest there is no signi cant association between statin use and incident dementia or probable AD (Li et al., 2004; Rea et al., 2005; Zandi et al., 2005), others found that in the general population, the use of statins, regardless of lipophilicity, was associated with a lower risk to develop AD compared with persons who had never used cholesterol-lowering drugs (Haag et al., 2009). Most of the conclusions of these above-mentioned studies, may be related to methodological differences, conceivably which may explain why results of cohort investigations differ from those of prior case-control studies. Additional investigation is needed to determine whether and for whom statin use may affect dementia risk. Furthermore, it may be that the causes of these heterogeneous results are linked to the types of statins used, the age group studied, and whether cross-sectional/case control studies or prospective study approaches were applied (Rockwood, 2006; Sparks, 2009). It is of note, that in the study conducted by Piermartiri et al., the inability of atorvastatin to reverse cognitive de cits induced by the administration of A $_{1-40}$ could be related to a non-realworld approach employed, i.e., the co-administration of atorvastatin and A $_{1-40}$. Although this approach potentially could be useful to study some unknown functions of statins, it fails to replicate current clinical practice, due to the fact that, in all clinical trials conducted until now in humans, statin treatment precedes or is consequent to a full-blown state of disease. Regarding the latter case, in preliminary AD clinical trials with simvastatin (Simons et al., 2002) and atorvastatin (Sparks et al., 2005a,b, 2006a,b) modest cognitive bene ts have been reported, and evidently are related to a condition in which patients had already developed the characteristic markers of disease, such as A deposition. In particular, treatment of AD patients with atorvastatin (80 mg/day) with mild to moderate dementia leads to improvements in cognitive performance at 6 months with smaller bene ts after 12 months (Sparks et al., 2005a,b). With regard the use of statins in the prevention of dementia, as Piermartiri et al. refer in their manuscript, the in vivo protective effect induced by atorvastatin

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treatment in rats against de ciency in long term potentiation (LTP) was obtained by Clarke et al. who administered atorvastatin for 3 weeks before A $_{1–42}$ administration (Clarke et al., 2007).

Moreover, recent studies in humans suggest that midlife cholesterol and statin use have a greater impact on the risk to develop AD (Pappolla, 2008; Solomon et al., 2009). A prospective study over 5 years of individuals enrolled when non-demented and using

to levels in mice treated with A (1–40) alone conceivably could be a cellular stress response to the oxidative stress induced by A (1–40) treatment, but as soon as the protein is synthesized and transported to the membrane, it conceivably would become oxidatively dysfunctional following covalent HNE binding, which we previously showed causes changes in the conformation of synaptic proteins (Subramaniam et al., 1997). Similarly, A (1–40)-mediated loss of GSH levels and GR and GPx activities reported by Piermartiri et al. may relate to HNE modi cation of these GSH related enzymes, which causes their dysfunction (Joshi et al., 2010).

The pleiotropic effects of statins are often greater with higher doses. However, despite high statin dose, serious hepatic or musculoskeletal adverse effects are relatively low (0.6% and 1.3%, respectively) (Cannon et al., 2004; LaRosa et al., 2005), although atorvastatin 80-mg is associated with higher rates of elevated hepatic transaminase and simvastatin 80-mg is associated with higher rates of myopathy and rhabdomyolysis (Cannon et al., 2004; LaRosa et al., 2005). Therefore, although high-dose statin therapy appears to provide greater bene ts, it is dif cult to tease out whether the bene ts are really due to lower cholesterol levels or to statin pleiotropy.

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Boyd-Kimball, D., Sultana, R., Poon, H.F., Lynn, B.C., Casamenti, F., Pepeu, G., Klein, J.B., Butter eld, D.A., 2005. Proteomic identi cation of proteins speci cally oxidized by intracerebral injection of amyloid beta-peptide (1 –42) into rat brain: implications