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Commentary

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

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The paper in this journal by Tasca and colleagues (Piermartiri et al., 2010) reported on studies in which mice were treated once intracerebroventricularly (icv) with amyloid β-peptide(1–40) along with concomitant oral administration of atorvastatin (10 mg/kg) or isotonic saline for 7 consecutive days. These authors reported that: (1) while no brain cell loss was evident after 9 days following Aβ(1–40), cellular degeneration was pronounced after 16 days following icv injection of this peptide; (2) Atorvastatin-treated mice did not demonstrate brain cell loss 16 days after Aβ(1–40) administration; (3) However, indices of oxidative stress (decreased glutathione (GSH) levels, decreased activity of glutathione peroxidase (GPx) and glutathione reductase (GR)), which were present in brain of Aβ(1–40)-treated mice, were not protected by concomitant atorvastatin treatment; (4) Levels of the glutamate transporters, GLAST and Glt-1, were decreased in brain of Aβ(1–40)-treated mice, and glutamate uptake was decreased. However, concomitant atorvastatin treatment, while reversing the loss of glutamate transporter levels, was unable to prevent the loss of glutamate uptake following Aβ(1–40) treatment; (5) atorvastatin failed to improve spatial learning and memory deficits (Morris water maze) that were induced by icv Aβ(1–40). Specific and general comments related to this paper follow.

Two immediate issues arise in this study: use of Aβ(1–40) vs. Aβ(1–42) and aggregation state of the peptide. Although Aβ(1–40) is neurotoxic when incubated with neuronal cultures, Aβ(1–42) is generally regarded as the more toxic of the two peptides (Sultana and Butterfield, 2009), and it is therefore surprising that the authors did not use this peptide for their studies. We demonstrated that injection of Aβ(1–42) into rat basal forebrain led to oxidative modification of specific hippocampal proteins (Boyd-Kimball et al., 2005). Further, oligomeric Aβ(1–42), rather than the fibrillar 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 fibrillar Aβ(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 significant 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 deficits induced by the administration of $A\beta_{1-40}$ could be related to a non-realworld approach employed, i.e., the co-administration of atorvastatin and $A\beta_{1-40}$. 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 benefits have been reported, and evidently are related to a condition in which patients had already developed the characteristic markers of disease, such as Aβ 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 benefits 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 deficiency in long term potentiation (LTP) was obtained by Clarke et al. who administered atorvastatin for 3 weeks before $A\beta_{1-42}$ 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 different kinds of statins showed that statin users were less likely to have incident dementia or cognitive impairment without dementia (Cramer et al., 2008). Thus, modulating midlife cholesterol and/or statin administration prior to dementia or cognitive impairment without dementia may be more beneficial than treatment approaches in patients with AD. For these reasons, there seems to be wide agreement that, from a clinical point of view, the possible beneficial effect of statin treatment to lower the risk to develop dementia, if sustained by additional studies, will have greater chance of success if administered prior to development of cognitive decline.

Rather, the debate of statin treatment regards the mechanism of action by which statins mediate these potentially beneficial effects. In particular, are these benefits due to the well known ability of statins to lower cholesterol, or to their so called pleiotropic effects (Liao and Laufs, 2005; Wang et al., 2008)?

Regarding the first mechanism of action, statins conceivably could reduce the risk of developing dementia by a concomitant effect on Aβ generation (Hartmann, 2001; Simons et al., 1998) or on its clearance (Shinohara et al., 2010; Tamboli et al., 2010; Whitfield, 2007). A number of *in vitro* and *in vivo* studies have shown that $A\beta_{1-42}$ is a neurotoxic peptide (Drake et al., 2003; Lambert et al., 2001; Oda et al., 1995; Walsh et al., 1999) that leads to oxidative/nitrosative damage in the brain (Butterfield et al., 2010a;2010b; Butterfield and Lauderback, 2002; Calabrese et al., 2007; Calabrese et al., 2006; Mancuso et al., 2007; Markesbery, 1997; Smith et al., 2002), which may be responsible for the clinical aspects of the disease, including memory loss and dementia (Butterfield et al., 2001). Moreover, different studies have highlighted that the effects of a high-fat/high-cholesterol diet on the central nervous system in transgenic mouse model of AD leads to increases Aβ accumulation and accelerates the AD-related pathology observed in this animal model (Refolo et al., 2000; Shie et al., 2002). On the contrary, by reducing cholesterol, the opposite effect was obtained (Petanceska et al., 2002; Refolo et al., 2001). However, although studies in rodents provided evidence about a possible role of statins in the treatment of neurodegenerative disorders, it should be noted that another possible methodological concern in the paper by Piermartiri et al. is that, in response to statin treatment, rodents are able to up-regulate HMG-CoA reductase, the enzyme responsible for the synthesis of cholesterol, with the result that no effect could be observed (Alberts, 1990; Fears et al., 1980; Thelen et al., 2006; Todd and Goa, 1990). For these reasons, in light of the results obtained in clinical trials showing a possible role of statins to lower risk of dementia (Cramer et al., 2008; Pappolla, 2008; Solomon et al., 2009), the use of rodent models to investigate changes in behavior, related to a reduction in cholesterol and maybe Aβ levels, has significant limitations regarding their use as possible translational models to human physiology. Hence, in our laboratory studies in aged dogs, in which HMG-CoA reductase cannot be upregulated following statin treatment, are in progress.

On the other hand, it is possible that statins might exert cholesterol-independent or *pleiotropic* effects (Liao and Laufs, 2005; Wang et al., 2008) via modulation of some downstream pathways, some of which include: prevention of isoprenoid synthesis and the consequent isoprenylation process that enable proteins to anchor to cell membranes, which is an essential requirement for biological function (Cole and Vassar, 2006; Cordle et al., 2005; Farah et al., 1998; McTaggart, 2006; Wang et al., 2008); ability to modulate immune responses mediated by both the innate and adaptive immune systems (Champagne et al., 2003; Chow, 2009; Lindberg et al., 2005; Pahan et al., 1997); impairment of the remyelination process via inhibition of oligodendrocyte maturation from progenitor cells (Miron et al., 2009) or via myelin formation in mature oligodendrocytes (Klopfleisch et al., 2008).

Thus, it is not surprising that several different molecular pathways are reported to change in response to statins. ApoE expression (mRNA) increases but APOE protein level decreases in response to atorvastatin (30 mg/kg/day) (Petanceska et al., 2003). ABCA1 mRNA increases in the brain in response to simvastatin suggesting brain cholesterol can be modulated by treatment (Thelen et al., 2006). LRP-1, the receptor for ApoE and also involved in the clearance of Aβ across the blood-brain-barrier (BBB) (Owen et al., 2010) also increased in prubocol treated animals (Champagne et al., 2003).

Another intriguing aspect related to the pleiotropic effects induced by statin treatment regards the modulation of oxidative stress-related modifications that occurs in neurodegenerative disorders (Orr, 2008). Statins can inhibit endothelial $O_2^{-}\bullet$ formation by preventing the isoprenylation of p21 Rac, which is critical for the assembly of NADPH oxidase after activation of PKC (Wallerath et al., 2003). In addition, SOD3 activity was more than doubled by simvastatin, and simvastatin treatment also increased the number of functionally active endothelial progenitor cells (Landmesser et al., 2005). Moreover, statins increase the expression of endothelial nitric oxide synthase (eNOS) by inhibition of Rho isoprenylation (Laufs et al., 1998), and statins can also directly activate eNOS via post-translational mechanisms involving activation of the phosphatidylinositol 3-kinase/protein kinase Akt (PI3/Akt) pathway (Kureishi et al., 2000). Indeed, statins showed positive effects against Aβ-induced oxidative stress in mice models of AD (Kurinami et al., 2008; Tong et al., 2009) as well as a reduction in CSF tau protein phosphorylation in humans (Riekse et al., 2006). Conversely, long-term treatment side effects of statins include a decrease in CoQ10 levels resulting in energy metabolism impairment in heart, skeletal muscle, and liver (Bliznakov and Wilkins, 1998). This may cause cardiomyopathy and complicate cardiovascular disease. Supplementation of the diet with CoQ10 can reverse many of the above symptoms (Langsjoen et al., 2005). At the same time, the effect of lipophilic statins can result in elevated tissue oxidative stress through NO reacting with metabolically derived O_2^{-} to form peroxynitrite and other reactive oxidants, which can have negative effects on endothelial cells (Parker et al., 2003).

In the paper by Piermartiri et al., oxidative stress was determined by GSH levels and by TBARS. Both approaches are not appropriate. Rather, to determine the oxidative stress status of cells using glutathione, it is the ratio of GSH to its oxidized form (GSSG) that needs to be determined (Halliwell and Gutteridge, 2007). The lower this ratio the more oxidative stress that is present. Moreover, TBARS, in contrast to what is implied in the Piermartiri et al. paper, is not specific for lipid peroxidation. Rather, oxidized DNA and other moieties can lead to elevated TBARS. Examples of more specific indices of lipid peroxidation are protein-bound 4-hydroxy-2-trans-nonenal (HNE) and isoprostanes, both formed by free radical attack on polyunsaturated fatty acids (such as arachidonic acid), which are rich in brain (Butterfield et al., 2010a,b; Pratico, 2010). Protein-bound HNE and isoprostanes are elevated in AD and MCI brain (Lauderback et al., 2001; Butterfield et al., 2010a,b; Pratico, 2010), and proteomics studies have identified a number of HNE-modified brain proteins in AD and MCI (Perluigi et al., 2009).

The contradiction between atorvastatin-mediated restoration of Glt-1 levels of Aβ(1–40) treated mice, while loss of glutamate uptake was not prevented (Piermartiri et al., 2010) may relate to this point. For example, we demonstrated that Glt-1 was excessively oxidatively modified by covalent binding of HNE in AD brain (Lauderback et al., 2001), and others reported loss of activity of this transporter in AD (Masliah et al., 1996). Moreover, we showed that Aβ(1–42) addition could replicate what was observed in AD (Lauderback et al., 2001). Hence, elevated Glt-1 levels following atorvastatin treatment reported by Piermartini et al. in Aβ(1–40)-treated rodents compared

to levels in mice treated with Aβ(1–40) alone conceivably could be a cellular stress response to the oxidative stress induced by Aβ(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, Aβ(1–40)-mediated loss of GSH levels and GR and GPx activities reported by Piermartiri et al. may relate to HNE modification 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 benefits, it is difficult to tease out whether the benefits are really due to lower cholesterol levels or to statin pleiotropy.

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