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COMMENTARY

Brain neurotoxic amyloid-beta peptides: their potential role in the pathophysiology of depression and as molecular therapeutic targets

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The monoamine hypothesis ascribes an important role to the underactivity of brain monoamines such as 5-HT, noradrenaline and dopamine to the pathophysiology of depression. This view emerged more than 50 years ago and has guided development of most medications currently used for the treatment of this disorder. However, large numbers of depressed individuals treated with currently available antidepressant agents, or even with various combinations, do not respond. Residual symptoms, relapses and recurrences are common while receiving adequate doses of these medications. In a recent issue of the *BJP*, Colaianna *et al.* describe results suggesting that a new neurobiological mechanism with treatment implications should be considered for the development of depression in humans, namely, elevations in potentially neurotoxic brain amyloid-β peptides.

LINKED ARTICLE
To view the paper by Colaianna *et al.* visit http://dx.doi.org/10.1111/j.1476-5381.2010.00669.x

Abbreviations
AD, Alzheimer's disease; APP, amyloid precursor protein; Aβ, amyloid-beta; CRF, corticotrophin-releasing factor; TRD, treatment-resistant depression

The therapeutic limitations of current antidepressant medications are well documented and are highlighted by the results of the recently completed United States NIMH-funded, large-scale STAR*D effectiveness trial that showed a remission rate of only 70% after 12 months with up to four treatment steps (Insel and Wang, 2009). Antidepressant-induced tachyphylaxis is also quite common, and as many as 20% of depressed patients will not respond to any combination of currently available antidepressant medications or electroconvulsive therapy. In their recent report, Colaianna *et al.* (2010) suggested a possible link between increases in soluble brain amyloid-β peptide 42 ($A\beta_{1-42}$) and depression associated with prodromal stages of Alzheimer's disease (AD), as previously proposed by Pomara and Sidtis (2007). This suggestion was based on their findings from an elegant experiment in rats demonstrating that a single intracerebroventricular administration of soluble $A\beta_{1-42}$, which has been implicated to play a major role in AD, induced a depressive state. Also observed were concomitant reductions in the content of 5-HT, in the expression of brain-derived neurotrophic factor, and in nerve growth factor in the prefrontal cortex, a brain region previously implicated in depression. This treatment did not increase level of anxiety or cause any biochemical changes in the striatum or nucleus accumbens, suggesting a possible deleterious effect of $A\beta_{1-42}$ on specific brain circuits linked to depressive behaviour. These findings complement results from other pre-clinical experiments linking cerebral

amyloidosis associated with various animal models of AD, and administration of soluble oligomeric and fibrillary forms of Aβ peptides including $Aβ_{1–40}$ to depressive states and to extensive monoaminergic abnormalities (Gonzalo-Ruiz *et al*., 2003; Filali *et al*., 2009).

However, Colaianna *et al*. (2010) did not consider the potential role of emerging brain Aβ-lowering agents for the treatment of this depression subtype, and future clinical trials should address this question especially because conventional antidepressants have not been found to be effective in depression associated with AD (Pomara and Sidtis, 2007). There is also another important implication from their findings which merits comment and which is central to this commentary, namely, that brain elevations in soluble $Aβ_{1–42}$ and other potentially synaptotoxic Aβ species, which could trigger the emergence of depression, might develop in healthy individuals, independently of underlying AD brain pathology and across all ages. Data derived from pre-clinical experiments indicate that a number of factors including acute and chronic stress, sleep deprivation and brain region-specific hypermetabolic activity, which have been closely linked to depression, can all increase brain levels of soluble Aβ peptides. For example, Kang *et al*. (2007) showed using *in vivo* microdialysis that APP Tg2576 mice isolated for 3 months exhibited an 84% increase in total interstitial fluid Aβ compared with controls, and a 38 and 59% increase in soluble $Aβ_{1–40}$ and $Aβ_{1–42}$ respectively. They also showed that the effect of acute restraint stress on Aβ was mediated by increases in neuronal/synaptic activity in the hippocampus and that the response was mediated by corticotrophin-releasing factor (CRF).

The effects of stress on Aβ extend to wild-type mice (Catania *et al*., 2009). Additionally, chronic glucocorticoid administration results in elevation in brain APP, $Aβ_{1–40}$ and $Aβ_{1–42}$, and APP cleaving enzyme (BACE), or in an increase in the more neurotoxic peptide $Aβ_{1–42}$ compared to $Aβ_{1–40}$ in transgenic AD mice and in non-human primates (Kulstad *et al*., 2005; Dong and Csernansky, 2009). As a large number of depressed individuals are known to have excessive levels of stress hormones including cortisol and CRF, increased interstitial fluid Aβ, especially $Aβ_{1–42}$, may be especially prominent in individuals with these neuroendocrine abnormalities.

Using the same technique and Tg2576 mice described above, Kang *et al*. (2009) showed that soluble Aβ levels in interstitial fluid increased during the awake period compared to the sleep period; Aβ levels were also positively correlated with the time spent awake, but negatively correlated with time spent asleep. The authors ascribed the elevated interstitial fluid Aβ associated with being awake, to greater synaptic activity, which was consistent with results reported by Cirrito *et al*. (2005). They showed that electrical and pharmacologically induced stimulation of the perforant pathway, which increased neuronal and synaptic activity within the hippocampus, resulted in dramatic elevations in hippocampal interstitial fluid Aβ, whereas the opposite was observed with decreased activity. Elevated metabolic activity, which is thought to reflect increased neuronal and synaptic activity and which could result in increased interstitial fluid Aβ levels, has also been documented in several brain regions including the subgenual cingulate region in depression and linked to treatment resistance (Mayberg *et al*., 2005).

Consistent with the previously described observations linking depression to increased soluble Aβ in interstitial fluid, Gudmundsson *et al*. (2007) reported a significantly higher level of CSF $Aβ_{1–42}$ in elderly women with major depressive disorder compared to healthy controls. Interestingly, CSF levels of tau protein, the major component of neurofibrillary tangles which is increased in prodromal AD, were not influenced by depression, whereas levels of neurofilament protein light and CSF/serum albumin ratio possibly indicative of vascular disease were increased (Gudmundsson *et al*., 2007; 2010).

Two studies which employed DSM-IV criteria for the diagnosis of major depressive disorder found elevations in plasma $Aβ_{1–42}$ in non-demented elderly (Pomara *et al*., 2006), and $Aβ_{1–40}$ in young depressives (Kita *et al*., 2009). Kita's group also reported a tendency for elevated $Aβ_{1–42}$ in young depressives, and an increase in the $Aβ_{1–40}/Aβ_{1–42}$ ratio in young and elderly depressives. More importantly, these elevations in Aβ concentrations persisted despite treatment with conventional antidepressants. Sun *et al*. (2007) reported a significant reduction in plasma $Aβ_{1–42}$ and a higher $Aβ_{1–40}/Aβ_{1–42}$ ratio in homebound elderly with depression, which they and others have ascribed to increased brain amyloid deposits associated with prodromal AD. A majority of these patients remained depressed after being treated with conventional antidepressants, and despite having lower plasma $Aβ_{1–42}$ levels and an improved $Aβ_{1–40}/Aβ_{1–42}$ ratio. Unfortunately, this was not a prospective study, and the retrospective analysis did not establish a relationship between clinical improvement and changes in these Aβ indices.

Elevated levels of brain Aβ peptides, especially $Aβ_{1–42}$, have also been reported in acute ischaemic stroke, intracerebral bleeds and traumatic brain injury, which are associated with a high incidence of depression. Thus, future studies should determine if individuals with depression have increased brain

levels of soluble Aβ peptides especially $A\beta_{1-42}$ or other potentially neurotoxic oligomeric and aggregated forms of these peptides and APP fragments, and whether these individuals can be identified using CSF and peripheral Aβ indices or brain PET imaging with specific amyloid ligands. If so, these individuals could potentially benefit from emerging Aβ-lowering strategies, which are presently undergoing clinical trials for the treatment of cerebral amyloidosis associated with AD.

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