Clinical Neuropsychiatry (2014) ***11****, 2, 76-85*

IS THERE A ROLE FOR β-AMYLOID IN DEPRESSION?

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Abstract

Objective: Depression may increase the risk of developing Alzheimer's disease (AD). Recent studies have shown modifications in blood beta-Amyloid (Aβ) levels in depressed patients. This literature review examines the potential relationship between Aβ-mediated neurotoxicity and pathophysiology of mood disorders.

Method: A review of the literature was carried out, through Medline databases, focusing on recent studies reporting alterations of plasma and serum Aβ peptides levels in patients suffering from mood disorders.

Results: Different data suggest that patients with mood disorders are at great risk of developing cognitive impairment and dementia. In particular, low plasma levels of Aβ42 peptide and a high Aβ40/Aβ42 ratio have been found in depressed patients. In addition, changes in Aβ protein levels in patients with mood disorders have been associated with the severity of cognitive impairment and correlated positively with the number of episodes and severity of illness course.

Conclusions: Given the intriguing association between change in plasma level of Aβ, depression and cognitive impairment, future studies should focus on the relationship between Aβ peripheral levels, biomarkers of neurodegeneration and development of dementia in patients affected by mood disorders.

Key words: β-amyloid, depression, cognitive impairment, Alzheimer's disease

Declaration of interest: none

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Introduction

Alzheimer's Disease (AD) is the most common cause of dementia in adult life and is associated with the selective damage of brain regions and neural circuits critical for memory and cognition. The pathogenesis of this disease is complex, and involves many molecular, cellular, and physiological pathologies. Typical features of AD are represented by the conformational transition of differently sized small peptides called amyloid-β (Aβ) into soluble oligomers and fibrils, which accumulate to form extracellular plaques and intracellular neurofibrillary tangles. Extracellular plaques are deposits Aβ that are derived via sequential proteolytic cleavages of the β-amyloid precursor protein (APP) (Selkoe 1998). Aβ peptides of 40 (Aβ40) and 42 (Aβ42) aminoacids can be measured in human cerebrospinal fluid (CSF) and their changes represent a blood protein signature to predict development of neurodegeneration in different diseases (Thambisetty and Lovestone 2010). Recent studies on AD patients revealed alterations of Aβ peptides plasma levels with reduced Aβ42 and increased Aβ40/Aβ42 ratio (Van Oijen et al. 2006, Graff-Radford et al. 2007, Xu et al. 2008). A similar alteration was found also in patients suffering from depression (Qiu et al. 2007; Sun et al. 2007, 2008; Kita et al. 2009) suggesting that some forms of depression, especially those occurring in elderly patients, may represent prodromal manifestations of AD, or a subtype of an amyloid-associated mood disorder characterized by cognitive impairment and risk for dementia evolution (Sun et al. 2008).

Much interest has been commonly directed towards the identification of cognitive impairment in mood disorders. In fact, alterations of cognitive functions, such as attention, verbal and non-verbal learning, memory, executive functions (EFs), have been described in patients suffering from mood disorders in both acute and euthymic phases (Wolfe et al. 1987, Waddington et al. 1989; Bulbena and Barrios, 1993, McGrath et al. 1997, Ferrier et al. 1999, Zubieta et al. 2001, Torres et al. 2007). Moreover, the risk for dementia, and generally for cognitive decline, seems to be greater in patients with mood disorders than in the general population (Geerlings et al. 2008, Gualtieri & Johnson, 2008), and has been related to the number of affective episodes, manic polarity or the presence of psychotic symptoms (Kessing et al. 2004, Robinson et al. 2006, Torres et al. 2007). The relationship between mood disorders and cognitive decline has been interpreted as the result of a common neuropathological mechanism, or as the manifestation of a greater vulnerability towards neurodegenerative phenomena (Aznar & Knudsen, 2011).

This review aims to describe some of the neurotoxic actions of Aβ and the potential relationship between Aβ-mediated neurotoxicity and mood disorders.

Submitted March 2014, Accepted May 2014

Method

We reviewed published data searching Medline databases up to January 2014 using the following keywords: "serum beta-amyloid" and "plasma beta-amyloid", each individually matched with "major depression", "depressive disorders", "bipolar disorder" and "psychiatric disorders". We considered all human studies assessing blood Aβ levels in patients with mood disorders.

Results

β-Amyloid Neurotoxicity

Aβ peptides of 40 or 42 aminoacids are formed after sequential cleavage of the amyloid precursor protein (APP), a transmembrane glycoprotein of undetermined function, by successive action of the β and γ secretases (Zhang 2011). The term soluble Aβ indicates all the forms of Aβ (mainly monomers and oligomers) that remain soluble also after fast centrifugation (Walsh and Selkoe 2007). Different studies have pointed out how the number of senile plaques does not correlate with the severity of AD (Terry et al. 1991, Dickson et al. 1995). On the other hand, soluble Aβ oligomers have been reported to be responsible for Aβ-mediated neurotoxicity (Lambert et al. 1998). Further, in post-mortem studies, Aβ oligomers correlate with the grade of synaptic loss and severity of cognitive decline (Lue et al. 1999, McLean et al. 1999, Wang et al. 1999).

Aβ is a pleiotropic peptide capable of binding to several receptors expressed on different cell membrane sites, including glutamatergic receptors, nicotinic receptors (for a review, see: Palop and Mucke 2010) and the receptor for advanced glycation endproducts (RAGE; Yan et al. 1996). Interestingly, recent data reported that RAGE expressed on endothelial cells mediates transport across the BBB (Deane et al. 2003).

Experiments on neuronal cultures demonstrated that extracellular administration of soluble oligomers may increase cytoplasmatic calcium levels (Demuro et al. 2006). The N-Methyl-D-aspartate glutamatergic receptors (NMDAr) seem to play a central role in Aβ-mediated neurotoxicity (**figure 1**). A direct relationship between levels of synaptic excitatory activity and production of Aβ has been documented (Buckner et al. 2005; Cirrito et al. 2005, 2008). Chronic stimulation of the extrasynaptic NMDAr increases the production rate of Aβ (Bordji et al. 2011) either by modulating α-secretase with consequent inhibition of the non-amyloidogenic pathway through a calcium–mediated mechanism (Lesné et al. 2005), or to increased expression of the more amyloidogenic isoforms of APP (Bordji et al. 2010). In addition, studies on animal models and neuronal cultures showed that memantine, a partial NMDAr antagonist, reduces toxicity (Alley et al. 2010, Ray et al. 2010, Martinez-Corla et al. 2010, Bordji et al. 2010). Aβ oligomers, in turn, modulate the NMDAr activity (Texidò et al. 2011), as they trigger calcium-mediated toxicity and induce neuronal oxidative stress (De Felice et al. 2007). Moreover, Aβ-mediated toxicity seems to be linked to the activation of a kinase with a pro-apoptotic action, namely glycogen synthase kinase 3β (GSK-3β), that phosphorylates the tau protein and leads to its aggregation (Koh et al. 2008, Decker et al. 2010) (**figure 1**). Drugs that are effective in the treatment of bipolar disorder, such as lithium and valproic acid, are known for their inhibitory action against GSK-3β (Chuang et al. 2005, Qing et al. 2008). On the basis of these evidences, it is possible to hypothesize that the increase of the glutamatergic transmission and of NMDAr activation, known to be involved in the pathophysiology of depressive and manic episodes (Kugaya & Sanacora 2005, Yildiz-Yesiloglu & Ankerst 2006, Machado-Vieira et al. 2009), may play a role in the Aβ-mediated neurotoxicity. These data would perhaps explain the cognitive decline related to the severity of the clinical course and the greater risk for developing dementia reported in mood disorders (Kessing et al. 2004, Robinson et al. 2006, Torres et al. 2007, Geerlings et al. 2008, Gualtieri & Johnson 2008).

Aβ and neuroplasticity

Neuronal plasticity is a fundamental adaptive process underlying interaction between brain and environment, acquisition of new information and formation of new memories. Several studies showed that neuronal plasticity is altered in mood disorders (Duman 2004) and antidepressants seem to influence both functional and structural neuronal plasticity (Malberg et al. 2000, Castren 2004, Baudry et al. 2011). Several studies on animal models demonstrated a negative effect of the Aβ oligomers on neuronal plasticity that appears long before the induction of cell death and apoptotic phenomena. In fact, soluble oligomers showed an inhibitory effect on synaptic plasticity in different areas of the brain. In particular, human natural oligomers and synthetic oligomeric Ab42 at low concentrations inhibited acutely the long-term potentiation (LTP; Lambert et al. 1998, Chen et al. 2002, Walsh et al. 2002, Zhao et al. 2004, Wang et al. 2004, Walsh et al. 2005), one form of synaptic plasticity that is thought to underlie learning and memory when occurring in critical brain areas, such as the hippocampus and parahippocampal areas (Bliss 1993, Whitlock et al. 2006). Interestingly, extracts rich in soluble Aβ oligomers from the cerebral cortex of AD patients inhibited LTP in the hippocampus, while leading to a reduction of spine density and disruption of learning behaviour (Shankar et al. 2008). Finally, a few reports showed that administration of Aβ at higher concentrations than those inducing pure inhibitory effect on LTP (Origlia et al. 2008, 2009) depressed synaptic transmission and impaired another form of long-term synaptic plasticity, namely long-term depression (LTD), by increasing the synaptic removal of glutamate receptors (Snyder et al. 2005, Tyszkiewicz and Yan, 2005, Hsieh et al. 2006, Parameshwaran et al. 2007, Origlia et al. 2010). All together, the reported results suggest that oligomeric Aβ contributes to the development of synaptic dysfunction and disruption of learning/memory in AD.

Other molecules that are fundamental for brain plasticity is the neurotrophins family. This includes different homologous proteins, such as the brain-derived neurotrophic factor (BDNF), involved in differentiation, survival of peripheral and central neurons and modulation of synaptic plasticity (Poo 2001, Manji et al. 2001, Popoli et al. 2002). It is plausible that Aβ may exhibit a functional interference with BDNF actions. In fact, BDNF stimulates the glutamatergic transmission and LTP expression (Korte et al. 1995, Levine et al. 1998, Lu et al. 2008). In cortical neuron cultures, subtoxic concentrations of Aβ impair the transduction pathways activated by BDNF signalling (Tong et al. 2001). At higher concentrations Aβ can block the phosphorylation of the transcription factor cAMP response element-binding (CREB) (Tong et al. 2004) and its nuclear translocation, inhibiting

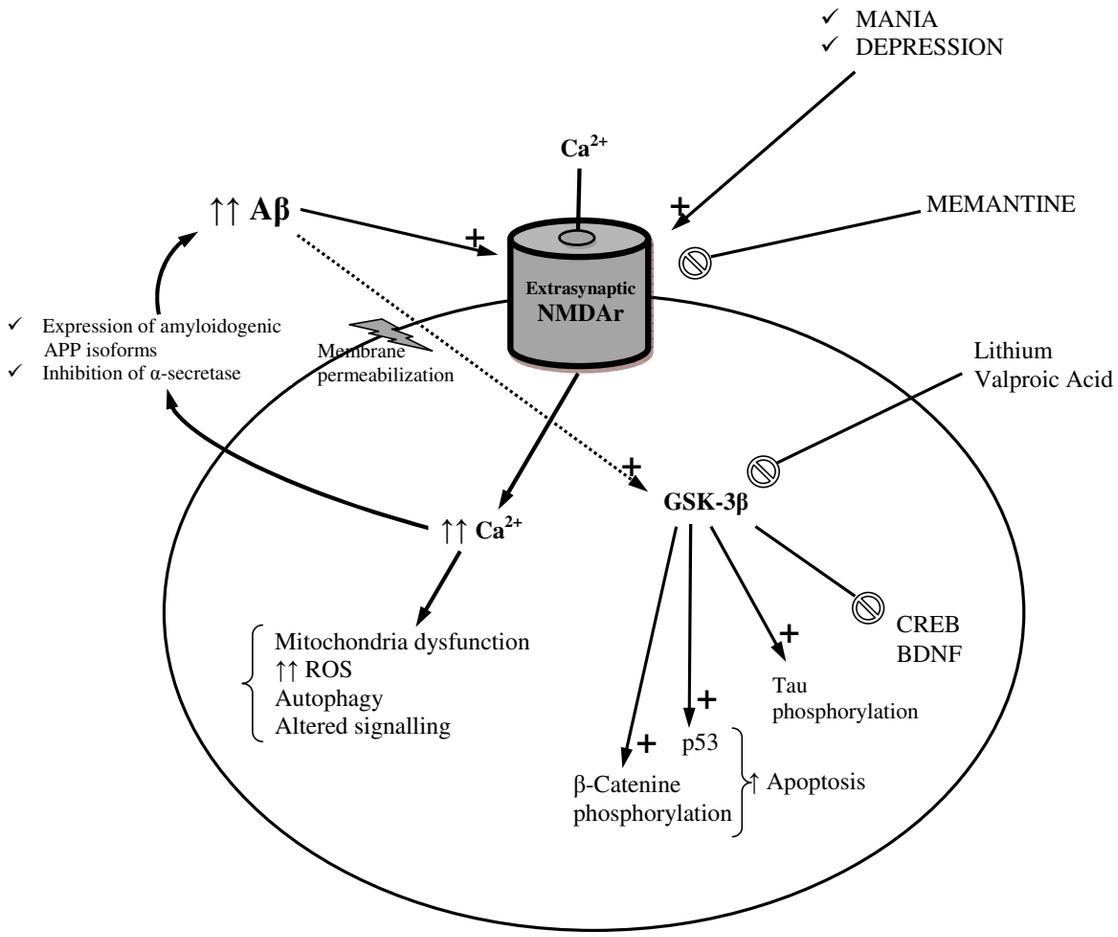

Figure 1. *The central role of extrasynaptic NMDAr in Aβ neurotoxicity and in the hypothetical relationship between mood disorders and Aβ production. On the right side the protective actions of mood stabilizers and memantine are shown. (Aβ: β-amyloid; APP: β-amyloid precursor protein BDNF: brain derived neurotrophic factor; CREB: cAMP response element-binding; GSK-3β: glycogen synthase kinase 3β; NMDAr: N-Methyl-D-aspartate receptor; ROS: reactive oxygen species)*

the synthesis of BDNF (Arvanitis et al. 2007, Arancio & Chao 2007). Interestingly, neurotrophins and APP share a common regulatory mechanism mediated by the proteolytic enzyme γ- secretase that, on one hand, induces cleavage of the APP and forms the neurotoxic Aβ peptides, and, on the other, promotes the function of neutrophin proapoptotic receptor p75 (Arancio & Chao 2007). In vivo studies demonstrated that pre-treatment with BDNF can protect the hippocampus, in particular of somatostatin secreting cells, from cellular damage and neuronal loss induced by intracerebral administration of Aβ peptides (Arancibia et al. 2008).

Another recent study showed that a single intracerebroventricular (i.c.v.) injection of soluble Aβ in the rat induces a significant reduction of BDNF and of its mRNA in the prefrontal cortex (Colaianna et al. 2010). Aβ-treated rats showed a significant reduction in exploration of the environment and a motivational deficit. Moreover, a marked increase in time of immobility was noted in the forced swimming test, a behavioural paradigm for depression (Colaianna et al. 2010). The same authors described a marked reduction of 5-hydroxytryptamine (5-HT) and dopamine (DA) levels in the prefrontal cortex of Aβ-treated rats. This finding was in agreement with previous data in rats showing that the direct intracerebral Aβ injection provoked a significant reduction of the density of 5-HT and norepinephrine neurons in the pons and mesencephalon (Gonzalo-Ruiz et al. 2003). Similarly, the infusion of soluble Aβ led to a reduction of DA levels in the prefrontal cortex (Trabace et al. 2007) and in nucleus accumbens of rats (NAc, Preda et al. 2008).

Given the central role of monoaminergic transmission impairment at a prefrontal level in depression (for review, see: Krishnan & Nestler 2008) and taking into account the role of BDNF as a possible marker of depression (Duman 2004; Sen et al. 2008; Piccinni et al. 2008, 2009; Dell'Osso et al. 2010), the negative effect of Aβ on monoaminergic transmission and the functional antagonism BDNF-Aβ, might suggest a potential involvement of Aβ in the pathophysiology of mood disorders.

Recurrent mood illness and risk for cognitive decline

Impairment in attention, working memory, executive functions (EFs), including cognitive inhibition, problem- and task-planning were largely reported in major depression (for review, see: Marazziti et al. 2010). Moreover, attention, memory and verbal/

non-verbal learning impairments can be found both in the depressive and the manic phases of bipolar disorder (Wolfe et al. 1987, Gruzelier et al. 1988, Waddington et al. 1989, Bulbena and Berrios 1993, McGrath et al. 1997, Martinez-Aran et al. 2004a). However, in the past decade, a growing bulk of evidence has been accumulated to suggest that patients suffering from recurrent mood illness may present cognitive disturbances not only during acute episodes. In a meta-analysis, there were reported broad domains of cognitive dysfunction in attention/processing speed, episodic memory, and executive functions of medium to large effect sizes in well-documented euthymic patients with bipolar disorder (Torres et al. 2007). They did not find evidence of an effect of medication dose, but could not rule out effects of the presence of sub-threshold symptoms. They did not examine relationships to the number of episodes or duration of illness, however (Torres et al. 2007). Cognitive impairment in bipolar subjects in remission correlates with the presence of psychotic symptoms or with the duration of the illness, number of episodes (in particular of manic episodes) and number of hospitalizations (McKay et al. 1995, Zubieta et al. 2001, Martinez-Aran et al. 2004b, Robinson et al. 2006, Bora et al. 2007, Glahn et al. 2007, Selva et al. 2007, Martinez-Aran et al. 2008, Osher et al. 2011).

There are fewer number of studies on cognition in relationship to the number of prior episodes in the recurrent unipolar patients. Unipolar patients with a greater number of past depressive episodes showed a reduction in a measure of empathy (perspective taking) (Cusi et al. 2011). In addition, delayed recall deficits were observed to be related with the number of prior depressions and cumulative length of depressive disorder (Gorwood et al. 2008).

Moreover, depression has been shown to be a risk factor for baseline normal cognition or mild cognitive impairment (MCI) progressing to a full-blown diagnosis of AD (Boyle et al. 2010, Cui et al. 2007, Kim et al. 2010, Kohler et al. 2010, Rosenberg et al. 2010, Singh-Manoux et al. 2010). Comparing patients affected by mood disorders and age-matched healthy controls, an acceleration in cognitive decline was found in patients over 65 years old (Gualtieri and Johnson 2008). The Rotterdam Scan Study (Geerlings et al. 2008), a perspective study on the general population, showed that patients with a history of depression had almost twice as much risk of developing AD. The risk is even greater if a group with early-onset depression is considered (onset < 60 years). A recent study on a large sample of more than thirteen thousand people demonstrated that depressive symptoms in midlife or in late life are associated with an increased risk of developing dementia. The authors hypothesized that recurrent depression may be etiologically associated with increased risk for both vascular and Alzheimer's dementia (Barnes et al. 2012).

Two perspective studies (Kessing et al. 1999, Kessing and Nillson 2003) showed that the presence of recurrent depression or bipolar disorder determines a greater risk for dementia, as compared with the general population and to patients with neurosis, osteoarthritis or diabetes. Moreover, the risk for dementia increases with the number of episodes, both in depressive and bipolar disorders (Geerlings et al. 2008, Kessing and Andersen 2004). Two recent studies in the US also support these findings: they found that even the occurrence of two prior depressions increases the risk of dementia (Dotson et al. 2010, Saczynski et al. 2010). Moreover, there is some evidence that treatments for mood illness are associated with a reduction of dementia rate. Kessing et al. (2008, 2011) in two observational cohort studies on patients treated in psychiatric healthcare settings demonstrated that long-term treatment with either tricyclic antidepressants or lithium are associated with a reduced rate of dementia.

Also retrospective studies carried out on AD patients suggest that a history of depression may be associated with an increased risk to develop late-onset AD (Jorm et al. 1991, Steffens et al. 1997, Green et al. 2003). In addition, demented patients who experienced depressive episodes manifest more severe anatomo-pathological signs compared to patients with no history of depression, as emerges from post-mortem analysis of plaque number and distribution in the hippocampus (Rapp et al. 2006).

Plasma Aβ in patients with cognitive impairment

In AD, there is a progressive deposit of amyloid, particularly of Aβ42 that is the main constituent of the senile plaques (Selkoe 2006). The peptide Aβ40, on the other hand, is more implicated in cerebral amyloid angiopathy (Zhang-Nunes et al. 2006), and its increased plasma levels have been associated with microvascular cerebral pathology, hyper-intensity of white matter and lacunar infarcts (van Dijk et al. 2004, Gurol et al. 2006). All these conditions correlate with cognitive decline in the elderly population (Longstreth et al. 1996), the risk for dementia (Vermeer et al. 2003) and depressive symptoms (de Groot et al. 2000).

Levels of Aβ42 in the cerebrospinal fluid (CSF) are significantly reduced in patients with AD and in those with MCI (Schroeder et al. 1997, Andreasen et al. 2001). So far, the study of plasmatic levels of Aβ has produced conflicting results. However, most of them have shown a reduction of Aβ42, an increase of Aβ40 and of the Aβ40/Aβ42 ratio in patients with overt AD and subjects at risk for AD and MCI (Graff-Radford et al. 2007, Xu et al. 2008, Van Oijen et al. 2006). A large community study on subjects with a mean age of 60 years, who were subsequently re-evaluated after 10 years, showed that both the initial Aβ40/Aβ42 ratio and its increase during the period of observation correlated positively with global cognitive decline (Okereke et al. 2009). Similarly, in a six-year follow up on subjects aged between 60-76 years, lower plasma levels of Aβ42 at baseline were associated with ongoing cognitive decline. In addition, a further reduction of Aβ42 levels was observed in those subjects who showed cognitive worsening during the follow up (Seppala et al. 2010). Furthermore, a community 9-year follow up study on 997 elderly non-demented subjects showed an association between a high Aβ40/Aβ42 ratio and subsequent cognitive decline that was more evident in those subjects with low cognitive reserve (low education and school attendance), and in carriers of apolipoprotein E e4 allele (associated with increased risk for AD) (Yaffe et al. 2011). However, in other studies, increased plasma levels of Aβ42 were also described in subjects who subsequently developed AD (Mayeux et al. 1999, Blasko et al. 2010).

It is worth noting that cognitive decline and reduction of peripheral levels of Aβ42 may be also found several years before the diagnosis of dementia and the formation of senile plaques (Graff-Radford et al. 2007). It has been argued that the peripheral reduction may be due to the deposition and concentration of Aβ42 in the brain (Graff-Radford et al. 2007). A recent study compared production and clearance of Aβ40 and

42 between AD patients and healthy control subjects, reporting matching cerebral production rates in the two groups and lower clearance rates in AD patients (Mawuenyega et al. 2010). In addition, different preclinical data showed impairment in the clearance operated by the blood-brain barrier as an early event in the process of Aβ-mediated neurotoxicity (Deane et al. 2009).

In fact, the concentration of the Aβ peptides in the brain is regulated not only by their synthesis from APP, but also by their crossing through the blood-brain barrier (BBB), which is mediated by active transports. The receptor for advanced glycation endproducts (RAGE) mainly regulates the entry of the Aβ soluble peptides through the BBB (Deane et al. 2003), while the LRP-1 (protein-1 relative to the receptor of the low-density lipoproteins) regulates their exit from the brain (Shibata et al. 2000, Deane et al. 2004, Deane and Zlokovic 2004). The expression of RAGE in the endothelium of cerebral vessels is increased in AD mouse models and AD patients (Deane et al. 2003, Yan et al. 1996, Donahue et al. 2006, Miles et al. 2008), while the expression of LRP-1 is reduced (Shibata et al. 2000, Deane et al. 2004, Donahue et al. 2006). These changes would contribute to an increase of Aβ in the brain, to its consequent oligomerization and, thus, to higher levels of the amyloid neurotoxic form (Kayed et al. 2003, Walsh et al. 2005, Lesne et al. 2006).

Plasma Aβ in depressed patients

As already mentioned, depression represents a risk factor for the development of AD (Devanand et al. 1996, Wilson et al. 2002, Ownby et al. 2006, Barnes et al. 2012), and a depressive symptomatology can often be found at the onset of or during dementia. These depressive symptoms are not attributable only to an emotional reaction, but they could rather be a consequence of neurobiological changes in specific brain areas (Andersen et al. 2005).

Probably because of the procedure invasiveness, there is a lack of CSF studies assessing Aβ levels in depressed patients. Few and contrasting reports are available. Hock et al. (1998) assessed CSF Aβ levels in AD patients and compared them to age-matched depressed patients. They found similar CSF Aβ levels in AD and depression hypothesizing the existence of common pathophysiological mechanisms. Following studies on elderly non-demented women reported higher levels of CSF Aβ42 levels in those who were depressed (Gudmusson et al. 2007, 2010). On the contrary, Pomara et al. (2012) found significantly lower CSF Aβ42 in cognitively intact elderly depressed patients with respect to those of healthy volunteers, suggesting that the reduction in CSF levels of Aβ42 may be related to increased brain Aβ plaques or decreased soluble Aβ production in elderly individuals with major depression. Depression scores were not associated with reduced CSF Aβ42 levels in a recent study on 183 elderly subjects with and without AD (Kramberger et al. 2012). The different design of such studies could justify the heterogeneity of results.

The first study on the concentration of Aβ in the blood of depressed patients was that of Pomara et al. (2006) that reported higher plasma levels of Aβ42 and Aβ42/40 ratio in a sample of geriatric patients with late onset depression (after 60 years), compared with control subjects. These authors did not highlight any correlations between levels of Aβ and the cognitive functions, as assessed by MMSE (Mini Mental State Examination), nor between Aβ and indexes of platelet activation. However, they found an association between higher levels of Aβ42/40 and a greater severity of the morphological changes, such as hyper-intensity of white matter revealed by MRI. Nevertheless, the results of this study have not been confirmed. Three other studies performed on depressed geriatric patients, in comparison with control subjects, described lower plasmatic levels of Aβ42, matching levels of Aβ40 in the two groups and a higher Aβ40/42 ratio (Qiu et al. 2007; Sun et al. 2007, 2008). In particular, Qiu et al. (2007) measured lower plasma levels of Aβ42 in depressed elderly subjects without cardiovascular disease, compared to control subjects, reporting an inverse correlation between plasmatic Aβ42 and the severity of depression. The concentration of plasma Aβ42 among the depressed subjects of the last cited studies was comparable with Pomara's depressed cases, and so the different results could be caused by the different age of controls: Pomara's depressed patients were indeed older than controls and plasma Aβ was reported to increase with age (Fukumoto et al. 2003, Mayeux et al. 2003).

Sun et al. (2007) also showed that the levels of Aβ42 did not seem to be influenced by the use of antidepressants, that was however associated with lower values of the Aβ40 peptide. Nevertheless, the so-called "amyloid-associated depression", identified by a higher Aβ40/42 ratio, was shown to correlate with a more severe deficit of memory, as well as of visuo-spatial skills and EFs (Sun et al. 2008). Therefore, according to them, it should be considered a clinically distinct subtype of depression that may precede AD. Another longitudinal 9-year follow up study on 988 community-dwelling elders demonstrated an association between high plasma Aβ40/Aβ42 ratio and increased risk for incident depression over time among those patients with one or more apolipoprotein E e4 allele (Metti et al. 2012). The authors hypothesized the existence of a synergistic relationship between apolipoprotein E e4 allele, Aβ40/Aβ42 ratio and depression similar to that found with dementia (Yaffe et al. 2011).

Kita et al. (2009) measured serum levels of the Aβ peptides in elderly and young depressed patients, and showed a significantly higher Aβ40/42 ratio, compared with the two age-paired control groups. This is an important observation, as it demonstrates how young subjects may also display similar pathological modifications to those found in early stage-AD and how an early-onset depression may be associated with a greater risk for AD. This last observation was replicated in the study by Baba et al. (2012) on a sample of 193 depressed patients compared with 413 healthy controls. Therefore, the modification of Aβ peptides peripheral levels observed in depression may reflect Aβ-mediated neuronal damage which, in turn, could contribute to the increased risk of cognitive deterioration in patients suffering from mood disorders. In a recent study on bipolar depressed patients a significant negative correlation was found between Aβ42 plasma levels and the duration of the illness, while a positive correlation was detected between the Aβ40/Aβ42 ratio and the number of affective episodes (Piccinni et al. 2012).

Conclusions

Changes in Aβ protein levels in patients with mood disorders have been found to be associated with an increased risk for dementia and developing AD and to correlate positively with the number of episodes and

severity of illness course. Another important question is whether plasmatic Aβ peptides may represent a good and reliable bio-marker of neurodegeneration and cognitive deterioration in depressed patients, especially in those with high illness recurrence. Given the preclinical evidence of the neurotoxic and potentially depressing action of the soluble oligomers of Aβ, further research is fundamental to understand the role of Aβ in the pathophysiology of mood disorders.

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