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*Review Article*

# CURRENT ASPECTS OF THE INTERACTIONS BETWEEN DEMENTIA, THE BRAIN RENIN-ANGIOTENSIN SYSTEM AND OXIDATIVE STRESS

Dragomir Serban[1], Emil Anton[1], Roxana Chirita[1], Veronica Bild[1], Alin Ciobica[2,3], Ovidiu Alexinschi[1], Oana Arcan[1,3], Radu Popescu[1], Luminita Paduraru[1,*] and Daniel Timofte[1]

[1] *"Gr. T. Popa" University of Medicine and Pharmacy,* Iasi, Romania

[2] *"Alexandru Ioan Cuza" University,* Iasi, Romania

[3] *Center of Biomedical Research of the Romanian Academy, Iasi Branch,* Iasi, Romania

[*] **Corresponding author:** luminita.paduraru@gmail.com

**Abstract:** There is increased interest in the interactions between vascular disorders and Alzheimer's disease (AD). While initially these interactions were explained by the fact that these are both very common disorders, particularly later in life, recently, the possibility that these deficiencies might actually coexist is increasingly being questioned. This review attempts to present modern aspects and current reports regarding the interactions between AD, the renin-angiotensin system (RAS) and hypertension, while also describing the relevance of antihypertensive drug use acting via the RAS in the treatment and prevention of AD, as well as the importance of oxidative stress, the alteration of the balance between antioxidants and pro-oxidants, in the interaction between AD and the RAS.

**Key words:** dementia; brain renin-angiotensin; oxidative stress.

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Dementia could be defined as the loss of intellectual and behavioral abilities that disturb the capacity to function on a daily basis. Its incidence is approximated to be 5% in 65-year-olds, with an estimated 25 million people worldwide affected by dementia in 2015 and with an overwhelming nearly 5 million new cases diagnosed each year (Ferri et al., 2005). Dementia, which includes Alzheimer's disease (AD), together with other variants of this disorder, such as vascular dementia, dementia with Lewy bodies and frontotemporal dementia, is one of the most important threats to public health in aging people (Cotter et al., 2007).

The causes of AD are considered multifactorial. A number of reports suggest three main risk factors: aging, the accumulation of the abnormal protein amyloid beta in the brain and the deterioration of the cardiovascular system (Webster et al., 2005; Li et al., 2010). While the first two aspects are very well known and discussed, in the last few years there has been an increased interest in the growing body of evidence suggesting an association between vascular risk factors and AD, especially since it also known that the incidence of hypertension correlates with advancing age, with an estimated prevalence of 50% in people older than 70 years (Takeda et al., 2008).

The renin-angiotensin system (RAS), which is known for its fundamental implications in the pathogenesis of hypertension, has become an area of great interest in the management of AD, as this could be a new therapeutic target in this disorder, considering the implications of its various metabolites in the central superior functions and in mediating several important physiological and pathological brain functions (Ciobica et al., 2009; Bild et al., 2013). Regarding RAS metabolites, renin is a protease that cleaves angiotensinogen to produce angiotensin I, which is

then cleaved by the angiotensin converting enzyme (ACE) to produce angiotensin II (Ang II), which is considered the most important and most active of the angiotensins. After that, Ang II is transformed into Angiotensin III, angiotensin IV, as well as a variety of other angiotensinergic fragments, such as angiotensin 1-7 or angiotensin 2-7 (Gard et al., 2008; Li et al., 2010). Ang II binds mainly to the AT1 and AT2 receptors. Important in the context of this mini-review is the fact that lately pharmacotherapy targeting the renin-angiotensin system and mainly Ang II is considered one of the most important means of reducing hypertension and cardiovascular morbidity (Matchar et al., 2008). In this way, hypertension is often treated by the administration of angiotensin-converting enzyme inhibitors (ACEi), angiotensin AT 1 or AT 2 receptor blockers.

Since the RAS is a potential contributor to dementia, the blockade of this system could be important in the aforementioned context. Modern studies are indicating that hypertension could be involved not only in cerebrovascular morbidity and mortality, but also in the pathophysiology of cognitive disorders and dementia (Hanon et al., 2002). However, the relations between cognitive functions and brain RAS have been to the subject of numerous controversies. Ang II has been shown to disrupt learning and memory (Bild et al., 2013), while angiotensin IV and angiotensin 1-7 facilitates memory formation and consolidation (Hellner et al., 2005). In addition, there are conflicting results with regard to the effects of angiotensin II on memory functions, with both positive and negative reports (Braszko et al., 2002).

While classical studies such as the that performed by Kehoe et al. (2009) showed that that elevated blood pressure in mid-life was associated with an elevated risk for later development of AD, there are also reports stating a deleterious effect of the administration of antihypertensive agents on cognitive function in elderly subjects (as cited by Hanon et al., 2002). It seems that most of these different results could depend on the methodology used, the cross-sectional or longitudinal nature of the study, the type of population included and the various methods used for the evaluation of the superior functions (Hanon et al., 2002).

Regarding the mechanisms of these processes, another aspect that is relevant in this context and could also explain some of the aforementioned variable results, are the implications of ACE1 gene polymorphism in the pathogenesis of AD. Thus, it seems that there are significant regional variations in ACE activity and its influence on the neuropathology in AD, which are even more pronounced in women (Kehoe et al., 2003).

Another mechanistic aspect which should be mentioned could be the fact that Ang II could be also involved in the complex processes of neuronal regeneration and tissue repair, since recent findings have shown that Ang II could actually mediate and interfere with these processes, especially considering the increased levels of the AT2-receptor after skin injury or myocardial infarction. It seems that Ang II could have an important role in the repair of peripheral tissues and in wound healing, which could explain some of the controversial results in this area of research described before (Culman et al., 2002).

One more reference study in this area of research is that of Ohrui et al. (2004), which demonstrated a beneficial effect of ACE inhibitor treatment, for more than 10 years, in elderly Japanese patients with hypertension. The positive effects of antihypertensive drugs have been confirmed by complex studies including thousands of patients, as in the case of the Syst-Eur study (Forette et al., 1998) published in Lancet, which included approximately 1200 patients with systolic hypertension and the elderly over 60 years, that demonstrated a significant reduction in the incidence of dementia as a response to antihypertensive treatment. By using basic cognitive testing such as the Mini Mental Status Examination (MMSE), this study demonstrated a 50% reduction in the incidence of dementia after ACE inhibitor treatment.

In the PROGRESS study, also published in Lancet, which involved more than 6000 patients with stroke history, the administration of antihypertensive treatment (e.g. ACE inhibitors) resulted in a

significant reduction in the risk of severe cognitive decline (approx 45%), while in the Scope study the administration of candesartan (Ang II antagonist) on more than 500 patients over the age of 70, resulted in improved quality of life and cognitive function (also tested through the MMSE test) (Hanson et al., 1999).

Similar experimental results were also confirmed by individual studies, such as that of Li et al. (2010), which showed that the use of angiotensin receptor blockers was associated with a significant dose-response reduction in dementia incidence, with the same brain angiotensin receptor blocker candesartan exhibiting the strongest dose-dependent reduction in the incidence of dementia.

These aspects were also confirmed in animal studies, since the administration of ACE inhibitors intraperitoneally in mice could result in a decreased latency time for the mice to avoid an open or an illuminated part of a maze, while the administration of a similar drug such as ramipril (also an ACE inhibitor) facilitates learning and memory in murine when injected directly to the basal forebrain, as cited in Gard et al. (2004).

Another important aspect in the interactions between the RAS and dementia could be amyloid beta deposits, since it was shown that these abnormal protein deposits could be implicated in the loss of cerebral blood flow, which is sometimes an early feature of this disorder (Ruitenberg et al., 2005). Moreover, it seems that some angiotensin receptor blockers could be effective in preventing the vascular damage induced by amyloid beta (Li et al., 2010).

Oxidative stress, which is basically an alteration in the balance between antioxidants and prooxidants (Sies et al., 1997), needs to be considered, particularly in view of the existence of some microcirculation deficits and endothelial dysfunction related to hypertension and excess production of free radicals, which results in increased oxidative stress status. This will further result in cell death (apoptosis), especially at the hippocampus level, which is known for its very important roles in memory storage and AD manifestations (Padurariu et al., 2012; Bild et al., 2013).

In this context we could mention the report of Rozzini et al. (2006), which demonstrated that in patients with mild cognitive impairment (MCI – that is a nosological entity proposed as an intermediate state between normal aging and dementia and seems to represent an early stage of AD) treated with ACE inhibitors, there is a less evident cognitive decline or conversion to AD (Rozzini et al., 2006). This could be also associated to the oxidative stress status, since our group previously demonstrated that a similar decrease in the main enzymatic antioxidant defenses (superoxide dismutase and glutathione peroxidase) and increased production of lipid peroxidation marker appear in the serum of MCI and AD patients when compared to an age-matched control group, suggesting that oxidative damage could be one important aspect in the onset of AD (Padurariu et al., 2010), as well as in most of the neuropsychiatric disorders (Ciobica et al., 2011; Padurariu et al., 2013).

In light of the previous reports on oxidative stress and beta amyloid jointly inducing neuronal death, gliosis and memory impairment in the brain (Lecanu et al., 2006), recent studies have examined the possible connection between RAS and the metabolism of beta amyloid. Interestingly, it seems that ACE inhibition reduces the putative beneficial effect of ACE on amyloid metabolism. The pharmacological inhibition of ACE activity prevents this effect and results in the accumulation of cell-derived beta amyloid (Takeda et al., 2008).

There appears to be solid clinical evidence that Ang II blockers such as ACE blockers or Ang II receptor blockers such as losartan, valsartan, telmisartan and candesartan, are effective in slowing or reversing the cognitive dysfunction associated with dementias and AD. In addition, considering that vascular dysfunction and stroke are associated with cognitive decline, it seems that the combined use of angiotensin receptor blockers and ACE inhibitors might confer superior protection

against cognitive decline by reducing neuronal damage associated with stroke and vascular dysfunction. However, as reviewed by Gard et al. (2004), although the use of ACE inhibitors and Ang II blockers is very promising, it is also very important to keep in mind that the action of these drugs is quite complex, and not necessarily limited to the cardiovascular system, which could result in various alterations and complications.

The early and aggressive management of AD can delay symptom progression and help to maintain the quality of life of both patient and caregiver. For this reason, there is an urgent need for further preclinical and clinical studies of ACE inhibitors and specific angiotensin receptor blockers in AD, because these drugs could confer real cognitive benefits. Additionally, it is becoming increasingly important to clarify the precise mechanisms through which the different components of this system act on the central nervous system and mediate their various effects, including those on cognition. It seems that oxidative stress could play an important role in these protective effects, which could be related to a possible antioxidant action of RAS inhibitors and a reduced formation of reactive oxygen species.

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