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Original Research Paper

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ABNORMAL NEUROGENESIS IN ALZHIEMERS DISEASE

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ABSTRACT

Alzheimer's disease (AD) has become a matter of serious concern as the number of aged individuals is increasing globally. Much progress has occurred in understanding the cognitive deficits in AD since the discovery of this condition. Although neurogenesis has been studied in AD patients, it has been rarely studied in association with cognitive functions in AD. Presently, there is no consensus on the role of impaired neurogenesis in the etiology of cognitive impairments of AD although the findings indicate a strong association in between them. In this review article, we aim at highlighting and elaborating this association. We will begin by reviewing the literature of abnormal neurogenesis in AD. Then we will briefly address the importance of hippocampal neurogenesis in the cognitive functions of adult brain. This will be followed by a review of the studies which have specifically explored the impairments of neurogenesis in association with the severity of cognitive impairments of AD. We will then address the therapeutic implications of these findings. These studies include transgenic animal model studies as well as human studies on AD. We observed that most of the studies showed that cognitive deficits were associated with impairments in hippocampal neurogenesis. However, some studies show that impaired cognition was also found in relation with increased neurogenesis in AD patients. We finally look into the limitations of these studies which inhibit them from becoming ideal models for human AD subjects.

KEYWORDS :

INTRODUCTION

Alzheimer's disease (AD) has become a matter of serious concern as the number of aged individuals is increasing globally. Since the discovery of this condition, much progress has occurred in understanding the cognitive deficits in AD [Goeterd & Spillantini 2006]. At the same time, enormous efforts have been laid in understanding the cellular neuropathology of the same [Selko 2001]. Inspite of all these efforts, specific neropathological underpinnings of these cognitive deficits remain unclear. In the domain of cellular pathologies, impairments of neurogenesis in AD brains have been only recently studied and very few studies have explored this dimension of AD. Recently some important research findings have found a dysfunctional neurogenesis in AD [Oddo 2003; Rodriguez 2008]. In most of these studies, Hippocampus has been commonly implicated as a site of this impaired neurogenesis [Adeosun et al 2014]. Hippocampus has also been almost universally accepted as an important neuropathological substrate for cognitive decline in AD. In normal adult brain, hippocampal neurogenesis is necessary for a proper functioning of several cognitive domains [Leuner et al., 2006; Bruel-Jungerman et al., 2007]. Inspite of this fact, dysfunctional neurogenesis as a possible etiology of the cognitive impairments in AD has rarely been evaluated as most of the studies have focused on neuro degenerative processes rather than neurogenesis in AD. Presently there is no consensus on the role of impaired neurogenesis in cognitive impairments of AD although studies indicate a strong association between them. Another important reason why neurogenesis in AD needs to be studied is that the exact nature of dysfunction of neurogenesis in AD is far from clear, with some studies showing an increase [Chevallier et al. 2005; Lopez-Toledano & Shelanski, 2007] in neurogenesis where as others showing a reduction in AD [Rodriguez 2008]. Our aim in this article is to review the studies which have assessed neurogenesis in AD patients / AD animal models and have seen it in relation to the cognitive dysfunction in such patients. In this article, we will begin by reviewing the literature of abnormal neurogenesis in AD. Then we will briefly address the importance of hippocampal neurogenesis in the cognitive functions of adult brain.

ABNORMAL NEUROGENESIS IN AD

The studies exploring neurogenesis in AD can be divided in to either animal-studies or human studies based on the subject involved in the particular research. Both of these studies have provided us important information regarding the dysfunctions of neurogenesis in AD. In this article we will review both these categories of researches.

Animal studies of neurogenesis in AD

There has been a plethora of animal studies for evaluating the neurogenesis in AD animals. Reviewing all these studies is out of scope of present article. Thus we will highlight some salient features of these studies. The animal model most utilized for researching the neuropathology of Alzheimer's disease is the triple-transgenic 3× Tg-AD mice. This transgenic model harbors mutant genes for APP, presenilin-1, and tau proteins thus making it neuro-pathologically closest to the AD brain. Additionally, this triple transgenic mice model presents with some cognitive deficits similar to AD as well as. Several studies conducted with this model have found that along with the manifestation of cognitive decline, they also had an impairment in hippocampal neurogenesis [Oddo 2003; Rodriguez 2008].

Other transgenic animal models for AD have also been studied. One of them is the transgenic mice expressing the mutant amyloid precursor protein (APP). The neuropathological findings of these studies have also been similar to the triple transgenic model as mentioned above, demonstrating decreased neurogenesis either in the Dentate Gyrus (DG) or in both the DG and the subventricular zone (SVZ) [Feng et al. 2001; Haughey et al. 2002b; Wen et al. 2002; Wang et al. 2004; Donovan et al. 2006; Wolf et al. 2006].

However, in another study of APPSwe, Ind mutant transgenic mouse, ***enhanced*** neurogenesis was observed which was linked to the presence of oligomeric Aβ (Jin et al. 2004a; Chevallier et al. 2005; Lopez-Toledano & Shelanski, 2007). A unique finding was that a transgenic model of mice expressing various mutated presenilins showed both enhanced as well as decreased neurogenesis (Chevallier et al. 2005). Increased neurogenesis was also reported in the SVZ of young APP/ presenilin 1 (PS1) mice (these animals expressed mutant APP and PS1). Similarly, an increase in neurogenesis was observed following in vivo and in vitro exposure to Aβ 1–42 (Sotthibundhu et al. 2009).

An important contribution of these animal studies has been that they have been able to unravel various physiological variables associated with the of the decline in neurogenesis such as age, location of decline and gender related variations. For example, age-dependent decline in the rate of neurogenesis was depicted in the hippocampal DG of 3xTg-AD mice (Kuhn et al. 1997; Abrous et al. 2005) where the rate of neurogenesis started to decrease from the age of 6 months (over 50% reduction when compared with early ages such as 2 months) and decreased further at later ages which affected females more than males (Rodrıguez et al. 2008). Especially

when compared to controls, this age-dependent decrease in neurogenesis, was much more prominent in the 3xTg-AD mice. At the age of 9 to 12 months, both genders retained very little capacity of forming new cells within the GCL whereas in non-Tg control animals the neurogenic levels that accounted approximately for a 20–35% of the young age levels were still preserved. A significant decrease in neurogenesis has also observed in the SVZ during normal aging. [Rodrı´guez et al. 2009]. The 3xTg-AD when compared with normal animals presented a further 40% decrease in neurogenesis, that appeared as early as the age of 3 months, and sustained through later ages [Rodrı´guez et al. 2009]. Studies in the 3xTg-AD model also demonstrated that female mice were affected earlier than males (4 vs. 9 months old) [Rodrı´guez et al. 2008]. These findings are not only in line with the recently reported sexual dimorphism observed in cognitive performances [Clinton et al. 2007], but also reinforce the well-known fact that AD affects women earlier and with more severity than men [Baum, 2005; Webber et al. 2005]. Several lines of evidences suggest that this difference, even with a potential disruption mechanism, might be exacerbated by the circulating levels of estrogens [Manly et al. 2000; Baum, 2005; Webber et al. 2005] as a result of the endocrine status [Galea et al. 2006].

These results are in agreement with the majority of data obtained from other studies conducted on APP mutant animals (Feng et al. 2001; Haughey et al. 2002b;Wen et al. 2002;Wang et al. 2004; Donovan et al. 2006; Wolf et al. 2006). Some studies have also addressed this phenomena of neurogenesis at cellular level. For example, Hamilton et al (2010) recently found that in both neurogenic niches of the brain, which are the hippocampal dentate gyrus and forebrain subventricular zones, 3xTg mice had decreased numbers of (i) proliferating cells, (ii) early lineage neural progenitors, and (iii) neuroblasts at middle age (11months old) and old age (18months old). These reductions correlated with major decrements in the addition of new neurons to the respective target areas, the dentate granule cell layer and olfactory bulb. In both these neurogenic niches, a fair number of newly generated cells could be detected with different proliferation markers, such as BrdU, Ki67, PCNA and HH3 (Abrous et al. 2005; Rodrı´guez et al. 2008, 2009). These novel generated cells depicted the specific characteristics of proliferating cells. For example, these cells weremainly localized in the inferior part of the GCL as well as demonstrated typical morphology such as irregularity of shape and smaller size. Sometimes they tended to appear close together and / or form clusters (Abrous et al. 2005; Rodrı´guez et al. 2008, 2009), which rarely co-localize with glial fibrillary acidic protein (Rodrı´guez et al. 2008, 2009).

Experimental studies of neurogenesis in various AD animal models, however, have also resulted in contradictory findings. For example, in contradiction to the findings mentioned earlier, recent studies, performed on the $APP_{Sw,\ Ind}$ (Swiss/Indian mutation) PDGF-APP mutant and on FAD post-mortem human material [Jin et al 2004; Jin et al 2004 b] reported an increase of neurogenesis. It has to be noted, though, that this study analysed only immature newly generated neurons without providing definitive probes of further development and/or progress into mature cells. Similarly, Yu et al [2009] found that compared with age-matched wild-type controls, 9-month-old transgenic mice with memory impairment and numerous brain Aβ deposits showed increased numbers of proliferating hippocampal cells.

Inspite of so many studies reporting dysfunctional neurogenesis in AD, the exact mechanism by which neurogenesis is affected in AD has not been completely understood. Recent evidences from the APP and in the 3xTg-AD models indicate that it is not a single but instead several potential systems which are involved in its pathogenesis (Crews & Masliah, 2010; Crews et al. 2010; Hamilton et al. 2010). Several potential mechanisms have been speculated: (i) *Abnormal activation of the p35 cyclin-dependent kinase-5 (CDK5)*, becoming hyperactive with the disease progression due to β accumulation and plaque formation. Several studies using different methodologies have observed that abnormal activity of CDK5 has been associated with several physiological alterations in NPCs, including impairing or even arresting the neuroblast migration and triggering aberrations in synaptic plasticity (Ohshima et al. 1996; Chae et al. 1997; Fischer et al. 2005; Johansson et al. 2005; Hirota et al. 2007; Jessberger et al. 2008; Lagace et al. 2008; Crews & Masliah, 2010). (ii) *Altered metabolism in NPCs* as indicated by the abnormally high levels of lipid droplet accumulation in the SVZ, which is known to have direct association with the genetic risk factor, ApoE4 (Hamilton et al. 2010) and(iii) *Parallel abnormal Tau hyperphosphorylation* in the SVZ striatal as well as in DG hilar neurons, which could result in impairment of the maturation and network connectivity of newly formed cells (Kippin et al. 2005; Tozuka et al. 200).

Post-mortem and other human studies of neurogenesis in AD

Parallel to the animal studies mentioned in previous sections, some effort has also been laid to various human studies regarding neurogenesis in AD. However, these studies are too few as compared to transgenic animal studies. Ziabreva et al (2006) observed that there was a significant ninefold decrease of progenitor cells (as labeled by Musashi 1) in the SVZ of patients with AD, but an increase in GFAP-negative astrocyte-like cells with progenitor characteristics. Ziabreva and colleagues (2006) analysed the post mortem brain tissues of patients with pre-mortem clinical diagnosis of of AD which revealed a reduction in progenitor cells in the SVZ (Ziabreva et al. 2006). On the other hand, Jin et al (2004b) observed an increase in progenitor cells in the DG (BDNF levels were found to be decreased in brain and cerebrospinal fluid of patients with AD [Peng et al 2005]. The major source of growth factor production secreted into the cerebrospinal fluid and therefore available to nourish NSCs. in the SVZ are the epithelial cells of the choroid plexus made up of modified ependymal cells, and it has therefore been hypothesized that aging and thinning of the choroid plexus epithelium concurrent with a declining growth factor secretion may be an underlying cause of neurodegenerative diseases, including AD [Redzic 2005; Stopa 2001; Emerich 2005; Emerich 2004].

Similar to animal studies, contradictory findings have been observed in the post mortem human studies. Jin et al (2004b) for example, found that in comparison to controls, the brains of Alzheimer's diseae patients showed significantly more expression of doublecortin, polysialylated nerve cell adhesion molecule, neurogenic differentiation factor and TUC-4. Of specific interest were the localizations of the expression of doublecortin and TUC-4 which were to the neurons in the neuroproliferative (subgranular) zone of the dentate gyrus, the gralune cell layer (considered as the physiological destination of these neuroproliferative neurons), and the CA1 region of Ammon's horn, which is the principal site of hippocampal pathology in AD.

CONCLUSION

Both animal and human studies have shown that the there is abnormal neurogenesis in Alzheimers disease. However, this seems to be location specific in the brain. Where as the dentate gyri and hippocampal areas show increased neurogenesis, other areas like supraventricular zone show decreased neurogenesis. This differential neurogenesis in different areas represents an unknown pathology which needs to be explored further.

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