Alzheimer’s disease (AD) is the most common type of dementia in elderly population. With a growing aging population not only in the United States but also in the worldwide, AD constitutes an emergent public health problem. Over decades, the prevailing hypothesis was that neurodegeneration might result from one or two of the specific lesions that characterize AD, e.g., accumulation of amyloid plaques (extracellular deposits of amyloid-beta peptide (Aβ42) and hyperphosphorylation of tau protein. However, molecular mechanisms underlying the pathological lesions in AD are not clarified and the notion that amyloid plaques and phosphorylated tau are pathologic molecules is slowly changing, suggesting that soluble oligomers of Aβ, rather than insoluble in the amyloid plaques, are the most toxic due to the induction of oxidative stress, which has emerged as an important event driving neurodegeneration (Anand et al., 2014). In addition, the Aβ42 contributes to the impaired cholinergic neurotransmission which is a consistent features of AD. The role of cholinergic neurotransmission in memory processing and storage is the basis of the widely accepted cholinergic hypothesis and during the past three decades, acetylcholinesterase inhibition has become the most widely studied and four acetylcholinesterase inhibitors (AChEi), tacrine, donepezil, rivastigmina and galantamine have been approved for treating the symptoms of AD. These drugs provide symptomatic treatment but do not alter the course of the disease.

Galantamine commercialized under the name of Razadyne® is the most recently approved AChEi in many countries for AD patients at mild, moderate, and advanced moderate stages. Lately, its efficacy has also been observed in patients with AD at severe stage. The ability of this drug to cross the blood-brain barrier makes it suitable for AD patients, and unlike other AChEis, galantamine has a weak AChEI effect. Nevertheless, it has a dual mode of action, since it inhibits AChE and modulates allosterically both the nicotinic and muscarinic acetylcholine receptors (AChRs) to potentiate the sensitivity to acetylcholine (ACh); additionally, galantamine and some of its derivatives exert antioxidant activity which has been associated with the presence of enol group and quaternary nitrogen. The antioxidant activity of the molecule disappears after transformation of the enol group (galantamine) into carbonyl group (galanthamine, narvedine). The same effect is observed after transformation of the enol group of galantamine hydrobromide; the presence of quaternary nitrogen is not involved in the radical-scavenging action, but is responsible for the increasing of the strength of the scavenging effect (Tsvetkova et al., 2013). Furthermore, Galantamine modulates non-amyloidogenic processing of amyloid precursor protein and inhibits the aggregation and toxicity of Aβ. In summary, accumulating evidences demonstrate that galantamine exerts neuroprotection against Aβ42-induced cell loss and neurotoxicity; nevertheless, antigenotoxicity studies were still missing to define the contribution of the drug to neuroprotection mechanism through regulation of DNA damage.

Diverse types of DNA damage including DNA double-strand breaks (DSBs), DNA single-strand breaks (SSBs), bulky adducts, abasic sites, crosslinking (interstrand and intrastrand), oxidation of specific bases (8-hydroxydeoxyguanosine), insertions and deletions are associated to neurodegenerative diseases (Figure 1). Consequently, cells deploy a diverse repertoire of mechanisms to maintain genetic integrity; however, with advanced age there is a decreasing at both antioxidant system and capacity of the cell to counteract neurogenic stimulus. Unless repaired in an error-free process, DNA instability can result in mutations and altered cellular behavior (Pearl et al., 2015). The understanding of AD is continually changing; for instance, classical hallmarks of AD, earlier thought to be responsible for the disease development, now rather seem to reflect the damage suffered by neurons over a long time as cellular adaptive strategy to oxidative stress, and although the mechanisms are diverse, neuronal death is the inevitable event in AD (Anand et al., 2014).

The DNA damage responses are essential cellular mechanisms for maintaining the genomic integrity, and its disruption is one of the principal hallmarks of chronic and age-related diseases. Increased production of reactive oxygen species, such as H2O2 and NO• are generated by Aβ which may can impact different molecules such as proteins, lipids, RNA and DNA. Under this condition, the brain of AD patients is submitted to increased oxidative stress, coinciding with depletion of antioxidant defense system. Each cell in the human body receives tens of thousands of DNA lesions per day by a variety of sources; therefore, cells have evolved a multifaceted response to counteract the potentially deleterious effect of DNA damage. The cellular response to DNA damage involves execution of DNA repair and activation of a repertoire of DNA damage signaling (Narciso et al., 2016).

We recently assess the effects of galantamine on the cell toxicity and DNA strand breaks induced by Aβ42 using a set of biomarkers such as clonogenic assay (a cell biology technique for studying the effectiveness of specific agents on the survival and proliferation of cells), cytoskeleton block micronucleus cytome (a comprehensive system for measuring DNA damage, cytostasis and cytotoxicity) and comet assay (a sensitive technique for the DNA damage detection at the level of the individual eukaryotic cell) in SH-SY5Y human neuroblastoma cell line as in vitro model in neurotoxicity research. Consistent with previous studies, we reported that Aβ42 (10 µM) for 24 hours decreased cell proliferation by inducing cell death by necrosis rather than apoptosis. Additionally, Aβ42 treatment had a stronger impact on genomic stability events compared to untreated control. In contrast, Galantamine post-treatments (0.1, 1.0 and 10 µM) significantly improved the rate of cell survival and exerted a high antigenotoxic activity by reducing Aβ42-induced DNA damage. Interestingly, the effects of galantamine here reported are at a range of concentrations including blood concentration found in human after oral administration. Overall, our study provided the first experimental evidence indicating that Galantamine also contributes to the neuroprotection mechanisms through regulation of DNA damage in addition to AChEi activity (Castillo et al., 2016). However, there are many questions about DNA damage and cholinergic impairment in the AD brain that should be answered, including which specific mechanisms are involved in cellular changes associated with AD pathogenesis and progression; and which specific enzymes are involved in cellular changes associated with DNA damage.

The lack of a detailed picture of genome repair in the brain could be attributed to the fact that damage repair in the human brain genome can only be studied in postmortem samples, making it difficult to examine these processes individually in specific type cells. Nevertheless,
SH-SY5Y cells are classical model in neuroscience to understand some events associated with neurodegeneration and neuroprotection. In recent studies, there is still no effective treatment for AD and no new therapeutic drugs have been approved since 2003. However, several putative drugs have been thoroughly investigated in preclinical studies, but many of them have failed to produce promising results in the clinical scenario. We speculate that lack of effectiveness might be associated with the fact that these drugs do not take into account the genetic instability as potential mechanism in AD pathogenesis. Galantamine is a natural alkaloid, isolated from bulbs and aerial parts of plant from Amaryllidaceae family. Numerous studies have shown that bioactive compound belongs to a variety of phytochemical groups such as phenolics, pigments, allysulfides, glucosinolates, tannins, flavonoids and phytotheres are effective phyto-antigenotoxins in addition to their antioxidant, antimutagenic, anticancerogenic, antioestrogenic, and antiinflammatory properties which might be beneficial in preventing diseases by improving genomic stability. In previous studies, Amaryllidaceae alkaloids such as galantamine, Lycorine, Homolycorine and Hemantamine have been shown by exerting a high antioxidant activity and AChEi activity (Lopez et al., 2002; Stellaibello et al., 2017). Based on these findings and coinciding with antigenotoxic capacity of Galantamine, it is possible that the modulation of DNA damage exerted by Amaryllidaceae alkaloids may represent an important biological property in addition to AChEi activity. We anticipate results obtained in our laboratory, which showed AChEi and antigenotoxic activities of crude extract from a plant belonging to Amaryllidaceae family against Aβ₁₋₄₂ induced cytotoxicity and genotoxicity in SH-SY5Y cells when evaluated through a set of genotoxic and cytotoxic biomarkers. The results showed that Aβ₁₋₄₂ significantly inhibited cell viability through necrosis rather than apoptosis and increased the DNA damage and exerted mitochondrial morphological alterations; however, treatments with the extract led to a significant recovery of cell survival, deceased necrotic cell death and also exerted antigenotoxic effects; additionally, the extract showed an inhibitory activity of AChE (submitted paper). Overall, the modulation of neurodegeneration by agents with antigenotoxic properties might emerge as a new avenue for the development of interventions that may improve the neural defense response against neurodegeneration.

This research was supported by the Brazilian funding agencies: CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico), CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior)-No: 5614112 and Student Agreement Program for post graduation – PEC-PG.

Willian O. Castillo*, Andres Felipe Aristizabal-Pachon
Department of Biology, University of Cauca, Popayan, Colombia
(Castillo WO)
Department of Genetics, Ribeirão Preto Medical School, University of São Paulo – USP, Brazil (Aristizabal-Pachon AF)

*Correspondence to: Willian O. Castillo, Ph.D., wocastillo@unicauca.edu.co.
Accepted: 2017-06-05
orcid: 0000-0001-9138-1248 (Willian O. Castillo)
doi: 10.4103/1673-5374.208572

How to cite this article: Castillo WO, Aristizabal-Pachon AF (2017) Galantamine protects against beta amyloid peptide-induced DNA damage in a model for Alzheimer’s disease. Neural Regen Res 12(6):916-917.

Open access statement: This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

Contributor agreement: A statement of “Publishing Agreement” has been signed by an authorized author on behalf of all authors prior to publication.

Plagiarism check: This paper has been checked twice with duplication-checking software iThenticate.

Peer review: A double-blind and stringent peer review process has been performed to ensure the integrity, quality and significance of this paper.

References


917

NEURAL REGENERATION RESEARCH
June 2017, Volume 12, Issue 6
www.nrronline.org