Unequal Neuroprotection Afforded by the Acetylcholinesterase Inhibitors Galantamine, Donepezil, and Rivastigmine in SH-SY5Y Neuroblastoma Cells: Role of Nicotinic Receptors

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ABSTRACT

Donepezil, rivastigmine, and galantamine are three drugs with acetylcholinesterase (AChE)-inhibiting activity that are currently being used to treat patients suffering from Alzheimer’s disease. We have studied the neuroprotective effects of these drugs, in comparison with nicotine, on cell death caused by β-amyloid (Aβ) and okadaic acid, two models that are relevant to Alzheimer’s pathology, in the human neuroblastoma cell line SH-SY5Y. Galantamine and donepezil showed a U-shaped neuroprotective curve against okadaic acid toxicity; maximum protection was achieved at 0.3 μM galantamine and at 1 μM donepezil; at higher concentrations, protection was diminished. Rivastigmine showed a concentration-dependent effect; maximum protection was achieved at 3 μM. When apoptosis was induced by Aβ25–35, galantamine, donepezil, and rivastigmine showed maximum protection at the same concentrations: 0.3, 1, and 3 μM, respectively. Nicotine also afforded protection against Aβ- and okadaic acid-induced toxicity. The neuroprotective effects of galantamine, donepezil, and nicotine were reversed by the α7 nicotinic antagonist methyllycaconitine but not by the α4β2 nicotinic antagonist dihydro-β-erythroidine. The phosphoinositide 3-kinase (PI3K)-Akt blocker 2-(4-morpholinyl)-8-phenyl-1(4H)-benzopyran-4-one hydrochloride (LY294002) reversed the protective effects of galantamine, donepezil, and nicotine but not that of rivastigmine. In contrast, the bcl-2 antagonist ethyl[2-amino-6-bromo-4-(1-cyano-2-ethoxy-2-oxoethyl)]-4H-chromene-3-carboxylate (HA 14-1) reversed the protective effects of the three AChE inhibitors and that of nicotine. Our results show that galantamine, donepezil, and rivastigmine afford neuroprotection through a mechanism that is likely unrelated to AChE inhibition. Such neuroprotection seemed to be linked to α7 nicotinic receptors and the PI3K-Akt pathway in the case of galantamine and donepezil but not for rivastigmine.

Alzheimer’s disease (AD) is a progressive neurodegenerative disease and the most common form of dementia in the elderly population. Clinically, patients with AD show progressive deterioration of all cognitive functions, resulting in their incapacitation. AD is characterized by the presence of two kinds of abnormal protein deposits, amyloid plaques and neurofibrillary tangles (NFTs) in specific areas of the brain, and finally by the atrophy of the affected brain regions, which results from extensive losses of synapses and neurons (Terry et al., 1981, 1991; Price et al., 1991; Arriagada et al., 1992). Amyloid plaques are extracellular deposits containing β-amyloid peptide (Aβ) as the major core deposits. Aβ is a 39- to 43-amino acid peptide fragment derived through proteolysis from an integral membrane protein known as Aβ precursor protein. The basis for the β-amyloid hypothesis arises from various studies showing that Aβ is toxic to neurons; for example, there is increased Aβ release and apoptotic cell death.

ABBREVIATIONS: AD, Alzheimer’s disease; NFT, neurofibrillary tangle; Aβ, amyloid β; nAChR, nicotinic acetylcholine receptor; AChEI, acetylcholinesterase inhibitor; PI3K, phosphoinositide 3-kinase; LY294002, 2-(4-morpholinyl)-8-phenyl-1(4H)-benzopyran-4-one hydrochloride; HA 14-1, ethyl[2-amino-6-bromo-4-(1-cyano-2-ethoxy-2-oxoethyl)]-4H-chromene-3-carboxylate; DMEM, Dulbecco’s modified Eagle’s medium; LDH, lactate dehydrogenase; PI, propidium iodide; PBS, phosphate-buffered solution; PP, protein phosphatase; DHβE, dihydro-β-erythroidine; MLA, methyllycaconitine; AChE, acetylcholinesterase.
death in cells that overexpress Aβ precursor protein (Recuero et al., 2004). A correlation between memory deficits, Aβ elevation, and amyloid plaques on transgenic mice has also been reported (Billings et al., 2005).

The other major lesion in AD is the intracellular deposition of the microtubule binding protein tau in the form of NFTs, which are mainly constituted by hyperphosphorylated tau protein. It has been suggested that the load of this lesion is more closely linked to dementia characteristic of AD than Aβ plaque burden (Terry, 1998). According to the tau/tangle model, the formation of NFTs correlates positively with the disease severity (Tiraboschi et al., 2004). This is due to the observation that structural modifications of tau such as hyperphosphorylation and aggregation interfere with tau function, which is likely to lead to the neuronal dysfunction that causes AD.

The role of cholinergic neurotransmission in memory processing and storage is the basis of the widely accepted “cholinergic hypothesis”. In AD, there is a loss of cholinergic neurons in the basal forebrain and of the cholinergic innervation of the cerebral cortex (Perry et al., 1994). In addition, there is a severe loss of nicotinic acetylcholine receptors (nAChRs) that correlates with the severity of the disease at the time of death (Wilcock et al., 2000). During the past two decades, cholinesterase inhibition has become the most widely studied and effective clinical approach to treat the symptoms of AD (Lahiri and Farlow, 1996; Soreq and Seidman, 2001). Four cholinesterase inhibitors (ChEI)—tacrine, donepezil, rivastigmine, and galantamine—have been approved by the United States Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products (European Union) for treating the symptoms of AD. It has been postulated that the most important therapeutic effect of ChEI for AD patients is to stabilize cognitive function, at least over 6 months of the clinical trial (Giacobini, 2003). Interestingly, although all have ChEI activity, they vary from one another. For example, a recent comparative long-term clinical trial found significant advantages for galantamine in comparison with donepezil, in cognition improvement (Wilcock et al., 2003).

Alternatively, signaling through nAChRs is being increasingly recognized as playing an important role in different processes such as neurite outgrowth, synaptic transmission, control and synthesis of neurotrophic factors, and neuroprotection (Donnelly-Roberts and Brioni, 1998; Belluardo et al., 2000, 2005; Hernandez and Terry, 2005). Recently, several preclinical studies have shown that some of the ChEIs used to treat AD present neuroprotective properties, such as galantamine (Capsoni et al., 2002; Arias et al., 2004; Kihara et al., 2004; Sobrado et al., 2004) and donepezil (Akasofu et al., 2003; Takada et al., 2003). However, these are independent studies that use different cell models and toxic stimuli. Therefore, we thought it would be interesting to study simultaneously, under the same experimental conditions, the potential neuroprotective effects of the main ChEI used in the clinic to treat AD patients in comparison with nicotine in “in vitro” models that could be relevant to the pathogenesis of AD such as Aβ-and hyperphosphorylation-induced toxicity in a human neuroblastoma (SH-SY5Y) cell line. The results of such study are presented here.

Materials and Methods

Materials. Galantamine was a kind gift of Janssen Pharmaceutica (Beerse, Belgium) and rivastigmine of Novartis (Basel, Switzerland); donepezil was purchased from A&A Pharmachem Inc. (Ottawa, ON, Canada). Nicotine, tacrine, okadaic acid, dihydro-β-erythroidine, and methyllycaconitine were purchased from Sigma-Aldrich (Madrid, Spain). LY294002 was from Tocris Cookson Inc. (Bristol, UK). HA 14-1 was from Sigma-Aldrich. Aβ protein was from Calbiochem (Schwalbach, Germany).

Culture of SH-SY5Y Cells. The neuroblastoma cell line SH-SY5Y was a kind gift from Dr. F. Valdivieso from the Centro de Biología Molecular (Madrid, Spain). SH-SY5Y cells, at passages between 3 and 16 after defreezing, were maintained in DMEM containing 15 nonessential amino acids and supplemented with 10% fetal calf serum, 1 µM glutamine, 50 units/ml penicillin, and 50 µg/ml streptomycin (reagents from Invitrogen, Madrid, Spain). Cultures were seeded into flasks containing supplemented medium and maintained at 37°C in 5% CO₂, humidified air. Stock cultures were passaged 1:4 twice weekly. For assays, SH-SY5Y cells were subcultured in 24-well plates at a seeding density of 2 × 10⁵ cells per well or in six-well plates at a seeding density of 5 × 10⁴ cells per well. Cells were treated with the drugs before confluence in DMEM free of serum. These cells, when undifferentiated, express functional nicotinic receptors (Dajas-Bailador et al., 2002).

Measurement of Lactate Dehydrogenase Activity. Extracellular lactate dehydrogenase (LDH) activity was spectro-photometrically measured using a cytoxicity cell death kit (Roche Diagnostics, Mannheim, Germany) according to the manufacturer's indications. Total LDH activity was defined as the sum of intracellular and extracellular LDH activity; released LDH was defined as the percentage of extracellular compared with total LDH activity.

Nuclear Staining of DNA. For the detection of apoptotic nuclei, cells were incubated with the dye Hoechst 33342 (5 µg/ml; Vybrant apoptosis kit; Invitrogen) for 30 min at 37°C in the dark (Arias et al., 2004). Cells were viewed using a Nikon Diaphot inverted epifluorescence microscope with a 40× objective, using the appropriate filters for an excitation wavelength of 355 nm and an emission wavelength of 465 nm. Cells showing condensed or fragmented nuclei (apoptotic cells) were identified from an average of 300 cells per treatment and cell batch. Each individual experiment was repeated in four different cell batches; therefore, 1500 to 2100 cells were evaluated per treatment. The samples were examined by blinded counting; four samples from different fields were taken from each dish, fields were selected randomly. Data were expressed as percentage of apoptotic cells with respect to the total amount of cells counted.

Measurement of Apoptosis by Flow Cytometry. Apoptosis was determined by flow-cytometry analysis of the cell cycle after DNA staining with propidium iodide (PI; Invitrogen) (Robinson et al., 1997). Cells were grown in six-well plates until they reached 50% confluence (typically after 24–48 h in culture). After treatment, cells that remained attached to plates were harvested in PBS/EDTA (5 mM EDTA in PBS) and collected together with floating (detached) dead cells. Cells were then centrifuged, the supernatant was discarded, and the cell pellet was suspended in 0.5 ml of PBS by pipetting thoroughly to avoid cell clumping. The cell suspension was transferred to 4.5 ml of 70% cold ethanol and kept in this fixative for a minimum of 2 h. Ethanol-fixed cells were centrifuged and washed once with 10 ml of PBS. Finally, the cell pellet was suspended in 1 ml of PI/Triton X-100 staining solution (0.1% Triton X-100 and 20 µg/ml RNase in PBS) and incubated for 15 min at 37°C. Samples were analyzed by flow cytometry (FACSCalibur; BD Biosciences, San Jose, CA). The analysis of the samples included a first selection (gate 1) in which events with appropriate size (forward scatter) and complexity (side scatter) were selected. Then, selected events were analyzed to discard doublets using a PI intensity-width versus PI intensity-area dot plot (gate 2). Finally, events (cells) that were contained in gates 1 and 2 were plotted in a histogram representing the number...
of events (cells) containing a specific PI intensity-area (e.g., specific amount of DNA). Apoptosis was measured as the percentage of cells with a sub-G$_0$/G$_1$ DNA content in the PI intensity-area histogram plot.

Statistical Analysis. Statistically significant differences between groups were determined by an analysis of variance followed by a Newman-Keuls post hoc analysis. The level of statistical significance was taken at $p < 0.05$.

**Results**

Effect of Increasing Concentrations of Galantamine, Donepezil, and Rivastigmine on Cell Death Induced by Okadaic Acid. Okadaic acid is a toxin produced by marine algae that blocks protein phosphatases (PPs) with an inhibitory potency of PP2A > PP1 > PP2B; it induces hyperphosphorylation of tau and NFTs in different “in vivo” (Tian et al., 2004) and “in vitro” (Uberti et al., 1997) models. Thus, it is accepted that okadaic acid-induced toxicity is a good model for the neuronal death occurring in Alzheimer’s disease and that is linked to tau hyperphosphorylation. Under our experimental conditions, 30 nM okadaic acid for 24 h increased cell death measured as LDH released to the extracellular medium, from 7.7 ± 0.25 to 30.9 ± 0.85% ($n = 4$) in SH-SY5Y cells.

In parallel experiments, we evaluated the effects of the ChEIs galantamine, donepezil, and rivastigmine at the concentrations of 0.1, 0.3, 1, and 3 μM on the okadaic acid-induced cell death. The drugs were preincubated for 24 h before and during the toxic stimuli (another 24 h). Galantamine afforded significant protection at 0.1, 0.3, and 1 μM, although maximum protection was observed at 0.3 μM (Fig. 1A). Donepezil afforded maximum protection at 1 μM, although significant protection was also observed at 0.3 and 3 μM (Fig. 1B). Curiously, both galantamine and donepezil presented a U-shaped protective curve. For rivastigmine, protection was milder, but it presented a concentration-response pattern, being significant at 1 and 3 μM (Fig. 1C).

Antiapoptotic Effect of Galantamine, Donepezil, Rivastigmine, and Nicotine on $A_β_{25-35}$-Induced Toxicity. We used the toxic fragment of the $A_β$, which corresponds to the fragment 25 to 35, and we determined the fraction of cells suffering apoptosis by analyzing the cell cycle in propidium iodide-stained cells by flow cytometry. Basal apoptotic cell death was 7.04 ± 1.08% and rose to 17.94 ± 2.40% in cells treated for 24 h with 10 μM $A_β_{25-35}$ ($n = 5$). For these studies, we used two concentrations of each compound. Galantamine (0.3 μM) significantly reduced apoptosis to 10.26 ± 1.64% ($p < 0.001; n = 5$), donepezil (1 μM) to 11.43 ± 2.02% ($p < 0.001; n = 5$), rivastigmine (3 μM) to 13.23 ± 1.12% ($p < 0.001; n = 5$), and nicotine (30 μM) to 9.88 ± 2.12% ($p < 0.001; n = 5$) (Fig. 2A). Tacrine at (0.3–3 μM) had no effect. For further studies, we selected those concentrations that afforded maximum protection against okadaic acid and $A_β$-induced toxicity; i.e., 0.3 μM galantamine, 1 μM donepezil, and 3 μM rivastigmine.

The antiapoptotic effect of these drugs was also confirmed by counting the number of apoptotic nuclei in cells stained with the fluorescent dye Hoechst 33342 (Fig. 2B). $A_β_{25-35}$ increased the number of apoptotic nuclei to 22 ± 2 from basal levels of 3 ± 1.5; galantamine (0.3 μM) significantly reduced $A_β_{25-35}$-induced apoptosis to 11 ± 2.3%, donepezil (1 μM) to 9 ± 1.7%, rivastigmine (3 μM) to 13 ± 1.9%, and nicotine (30 μM) to 9 ± 1.3%.

Figure 3 shows microphotographs of SH-SY5Y cells in basal conditions (Fig. 3A) and after 24-h exposure to $A_β_{25-35}$ (10 μM) (Fig. 3B). Note the loss of birefringence of cells treated with $A_β$, the loss of cells, and the decrease of neuritis. Note also that galantamine (0.3 μM), donepezil (1 μM), rivastigmine (3 μM), and nicotine (30 μM) preserved the healthy appearance of the cells (Fig. 3, C–F).

![Fig. 1. Galantamine, donepezil, and rivastigmine offer protection against okadaic acid-induced toxicity in the human neuroblastoma cell line SH-SY5Y. Neuroblastoma cells were treated with increasing concentrations (0.1, 0.3, 1, and 3 μM) of galantamine (A), donepezil (B), or rivastigmine (C) 24 h before and during the 24-h incubation period with the toxic stimuli (30 nM okadaic acid). Cell death was quantified as the fraction of the total cell content of LDH that was released into the incubation medium (LDHe/t), after exposing the cells for 24 h to the okadaic acid treatment. Data are means ± S.E.M. of triplicates of four different cell batches. **, $p < 0.01$ and***, $p < 0.001$ in comparison with okadaic acid-lesioned cells in the absence of drug. ###, $p < 0.001$ comparing basal and okadaic acid-lesioned cells.](https://jpet.aspetjournals.org/article-pdf/10.1124/jpet.117.257372/1348-1993-28610.1124-jpet.117.257372.pdf)
Implication of nAChR in Protective Effects of Different ChEIs and Nicotine. To establish whether the neuroprotective actions of galantamine, donepezil, and rivastigmine were mediated by nAChRs, we used dihydrolipoamide-2-erythroidine (DHβE) to block α4β2 nAChRs and methyllycaconitine (MLA) to block the α7 nAChR. The protective effects of galantamine, donepezil, and nicotine were reversed by MLA (10 nM) but not by DHβE (Fig. 4). For rivastigmine, protection remained unaffected in the presence of either of the nAChR antagonists used. Also, the nonspecific nAChR antagonist mecamylamine reversed the protective effects of galantamine, donepezil, and nicotine against Aβ25-35-induced toxicity (data not shown).

Pretreatment with the Drugs and Induction of Protein Synthesis Is Required for the Neuroprotective Effect of Galantamine, Donepezil, and Rivastigmine. To determine whether the neuroprotective effect of the different AChEIs needs preincubation before the toxic agent is...
added to the cells, we performed experiments where the protective drugs were coapplied with the toxic agent, or they were preincubated 24 h before addition of the toxic agent. As shown in Fig. 5A, the different AChEIs, as with nicotine, needed a preincubation period to afford neuroprotection; if they were coapplied with the toxic stimuli, protection was not observed.

Protein synthesis seems to be involved in the neuroprotective action of these compounds since cycloheximide, a protein synthesis inhibitor, prevented the neuroprotective action of the different AChEIs used in this study (Fig. 5B). A similar pattern was observed with nicotine.

Implication of the PI3K-Akt Signaling Pathway and bcl-2 on the Neuroprotective Actions of Galantamine, Donepezil, Rivastigmine, and Nicotine. Nicotine’s neuroprotective mechanism has been related to the PI3K-Akt signaling pathway (Kihara et al., 2001). We have therefore used the PI3K antagonist LY294002 to determine whether it can prevent the protective effects of the different AChEIs against Aβ25-35-induced toxicity. The neuroprotective effect of galantamine, donepezil, and nicotine was abolished by LY294002 but not that of rivastigmine (Fig. 6A).

Evidence indicating that the protective actions of all drugs tested in this study (galantamine, donepezil, rivastigmine, and nicotine) are related to up-regulation of bcl-2 is shown in the experiments of Fig. 6B, where HA 14-1, a drug that blocks the antiapoptotic action of bcl-2 (Wang et al., 2000), prevented the protective effect of these drugs. HA 14-1 alone did not significantly modify basal cell death.

Discussion

We have found some analogies but also some differences in the extent of neuroprotection as well as in the mechanism involved, among galantamine, donepezil, rivastigmine, and tacrine. In our model, donepezil afforded maximum protection, followed by galantamine and rivastigmine; tacrine had no cytoprotective effects.

Maximum protection afforded by galantamine, donepezil, and rivastigmine was achieved at the concentrations of 0.3, 1, and 3 μM, respectively. Galantamine and donepezil showed a characteristic U-shaped neuroprotective curve; the loss of protection at high concentrations could be explained as blockade of the nAChR (Schrattenholz et al., 1996; Di Angelanto-
ect et al., 2004); therefore, the survival-signaling cascade cannot be activated. The protective effect of these drugs was obtained at concentrations that differ from their IC50 to block AChE (Table 1). It therefore seems that the neuroprotective effects are not directly related to their capacity to block the enzyme. For example, tacrine, a potent blocker of AChE, did not afford protection. Also, physostigmine, a classical and potent AChE blocker, did not protect rat cortical neurons exposed to glutamate (Takada et al., 2003). During the past years, speculations have been made on the link between the inhibition of AChE and neuroprotection. It seems that inhibition of a peripheral site of AChE may be related to neuroprotection (Dorronsoro et al., 2005); this is likely because of the fact that this peripheral site might be involved in the formation and deposit of β-amyloid in the brain. Considering this hypothesis, perhaps the interaction with the peripheral site correlates better with the neuroprotective effects of these drugs than with its interaction with the active site of the enzyme; however, this still remains to be proven.

Some relationship between nicotinic receptors and neuroprotection seems to be present at least for galantamine and donepezil, whose neuroprotective effects were reversed by MLA, an α7-selective nicotinic receptor blocker, and by mecamylamine, a nonselective nicotinic receptor blocker. These findings agree with recent studies showing an α7 nicotinic receptor-mediated cytoprotective effect of galantamine against thapsigargin-induced cell death in chromaffin cells and SH-SY5Y cells (Arias et al., 2004) and an α7-mediated effect for donepezil against glutamate-elicited toxicity in rat cortical neurons (Takada et al., 2003). In contrast to galantamine and donepezil, the cytoprotective action of rivastigmine did not seem to be linked to nicotinic receptors: neither MLA, dihydro-β-erythroidine, nor mecamylamine reversed its effects.

Another interesting difference rests in the intracellular messenger pathways involved in the neuroprotective effects of the three agents. Activation of the PI3K-Akt pathway via α7 nAChRs and increase in bcl-2 expression have been described as the neuroprotective cascade for nicotine (Kihara et al., 2001); this cascade also seems to be targeted by galan-
tamine and donepezil. Thus, galantamine induced the expression of the antiapoptotic protein bcl-2, corroborating a previous observation of our laboratory in bovine chromaffin cells and SH-SY5Y neuroblastoma cells (Arias et al., 2004). It has been documented that the induction of bcl-2, for example in stably transfected PC12 cells, leads to enhanced cell resistance to toxic stimuli (Dispersyn et al., 1999). The cytoprotective effects of bcl-2 may be due to its ability to modify the cell's Ca\(^{2+}\) homeostasis, particularly by reducing the depletion of Ca\(^{2+}\) from its endoplasmic reticulum store (Pinton et al., 2000, 2001). Regardless of the ultimate mechanism, what seems clear is that the induction of bcl-2 expression by galantamine is linked to the PI3K-Akt pathway; thus, interruption of this pathway with the selective inhibitor LY294002 reversed the neuroprotective effects of galantamine. This agrees with a recent observation that galantamine induced phosphorylation of Akt at the time that it offered neuroprotection in rat cortical neurons (Kihara et al., 2004).

The neuroprotective mechanism of donepezil seems to be similar to that of galantamine. Neuroprotection afforded by donepezil was also prevented by MLA, HA 14-1, and LY294002, indicating that \(\alpha_7\) nAChRs, activation of the PI3K-Akt pathway, and overexpression of bcl-2 are implicated in its neuroprotective mechanism. This was not the case for rivastigmine; although it was capable of inducing the antiapoptotic protein Bcl-2, like galantamine and donepezil, its protective effect was not reversed by nicotinic antagonists or the blocker of the PI3K-Akt.

There are several recent studies showing the neuroprotective actions of different AChEIs, although the results are controversial. Thus, in rat cortical neurons subjected to glutamate neurotoxicity, galantamine and donepezil afforded neuroprotection (Takada et al., 2003); this agrees with our results. However, these authors found that tacrine had neuroprotective effects, although we did not find this neuroprotection. In contrast, donepezil afforded neuroprotection in rat cortical neurons exposed to oxygen and glucose deprivation, whereas galantamine did not (Akasofu et al., 2003). However, in a recent study from our group we have found that galantamine exhibited clear neuroprotective effects in rat hippocampal slices subjected to glucose and oxygen deprivation.

**Table 1**

IC\(_{50}\) values to block AChase and BuChase in nanomolar (taken from Greig et al., 2003)

<table>
<thead>
<tr>
<th>Drug</th>
<th>AChase</th>
<th>BuChase</th>
<th>Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrine</td>
<td>190 ± 40</td>
<td>47 ± 10</td>
<td>4 × BuChE</td>
</tr>
<tr>
<td>Donepezil</td>
<td>22 ± 38</td>
<td>4150 ± 1700</td>
<td>188 × AChE</td>
</tr>
<tr>
<td>Galantamine</td>
<td>800 ± 60</td>
<td>7300 ± 830</td>
<td>9 × AChE</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>4150 ± 160</td>
<td>37 ± 5</td>
<td>122 × BuChE</td>
</tr>
</tbody>
</table>

BuChE, butyrylcholinesterase; AChase, acetylcholinesterase.
tion (Sobrado et al., 2004). The different cell types and/or cytotoxic models used in each study may explain the distinct results found in the various studies.

Differences in the extent of neuroprotection and/or in the mechanism involved may have clinical relevance. However, very few and not conclusive comparative clinical trials have been performed with the different AChEIs currently used to treat Alzheimer’s disease. The study by Aguilia et al. (2004) is the first to compare the effects of donepezil, rivastigmine, and galantamine on the Mini-Mental State Examination, Alzheimer’s Disease Assessment Scale–cognitive subscale, Instrumental Activities of Daily Living, and Activities of Daily Living; however, limitations of the study included its small population size, its open-label design, and the fact that patients were randomized only after the introduction of galantamine. The results of this study showed no statistical significant differences between the three drugs at 3 months, although numerical trends were observed that suggested the effect of rivastigmine > donepezil > galantamine. There is a long-term clinical study published, but it compares galantamine and donepezil but not rivastigmine in patients suffering from AD; this study showed significant advantages for the treatment response to galantamine, versus donepezil, on cognition, measured by response rates on the MMSE and ADAS-cog (Wilcock et al., 2003). Therefore, there is still little information on the comparative effects of these drugs in AD patients.

In conclusion, the results of this study show that all the AChEIs currently used in the clinic for AD can provide different degrees of neuroprotection in cytotoxic models that can be relevant to AD pathology.

References


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