RESEARCH ARTICLE

Age Progression of Neuropathological Markers in the Brain of the Chilean Rodent Octodon degus, a Natural Model of Alzheimer’s Disease

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Keywords
Alzheimer’s disease, glial activation, oxidative stress, metabolic sensors, neuronal apoptosis and natural model.

Abstract
Alzheimer’s disease (AD) is the most common neurodegenerative disorder and the leading cause of age-related dementia worldwide. Several models for AD have been developed to provide information regarding the initial changes that lead to degeneration. Transgenic mouse models recapitulate many, but not all, of the features of AD, most likely because of the high complexity of the pathology. In this context, the validation of a wild-type animal model of AD that mimics the neuropathological and behavioral abnormalities is necessary. In previous studies, we have reported that the Chilean rodent Octodon degus could represent a natural model for AD. In the present work, we further describe the age-related neurodegeneration observed in the O. degus brain. We report some histopathological markers associated with the onset progression of AD, such as glial activation, increase in oxidative stress markers, neuronal apoptosis and the expression of the peroxisome proliferative-activated receptor γ coactivator-1α (PGC-1α). With these results, we suggest that the O. degus could represent a new model for AD research and a powerful tool in the search for therapeutic strategies against AD.

INTRODUCTION

Alzheimer’s disease (AD) is the most common form of dementia and affects nearly 10% of individuals over the age of 65 and nearly 50% of individuals over the age of 85. The increased longevity in the population, combined with the high incidence of AD in older adults, will only exacerbate the global impact on public health (13, 80). AD was first described over 100 years ago, but the etiology of AD is still not well understood, which limits the pharmacological treatment of the disease (66, 81). Different cellular and histopathological biomarkers have been described, including amyloid plaques, neurofibrillary tangles (NFTs), increased production of reactive oxygen species (ROS), mitochondrial dysfunction, decreased cerebral glucose consumption and altered autophagy processes (13, 29, 36, 40, 54, 75).

Transgenic mice have been the most useful tool in studying the pathological mechanisms of AD. However, these models do not recapitulate the entire spectrum of lesions present in human AD brains (17, 42, 84). Moreover, the overexpression of human transgenes in a nonphysiological scenario strongly influences the onset of histopathological features and cognitive decline observed in AD (16, 58). The poor reliability of the currently available AD models limits our understanding of AD pathophysiology and compromises the translation of preclinical data into human clinical trials. Thus, the identification and validation of a natural, wild-type AD model that can mimic the pathological hallmarks observed in AD patients would be highly useful to unravel the mechanisms of AD and validate potential therapeutic targets. We have previously suggested that the Chilean rodent O. degus could represent a natural model to study the onset and progression of AD (4, 10, 60). We have described that the O. degus naturally develops extracellular amyloid plaques, NFT, failure in cholinergic transmission and hippocampal disconnection in an age-related manner (5, 8, 34).

In this study, we used the brains of O. degus derived from several different aged (12–72 months) individuals to evaluate the
progression of histopathological markers related to AD progression. We observed significant age-dependent increase in astrocyte activation together with neuroinflammation, microglial markers and several oxidative stress markers, apoptotic signaling in critical brain areas, and alterations in cellular bioenergy regulators, such as peroxisome proliferative-activated receptor γ coactivator-1α (PGC-1α). Taken together these results, we conclude that the spontaneous age-related neurodegeneration reported in O. degus mimics the cellular and molecular events observed during the onset and progression of human AD.

MATERIALS AND METHODS

Animals

O. degus were obtained from a breeding colony at the animal facility of the University of Valparaíso, Chile; the animals were maintained in a controlled room temperature (23 ± 1°C) under a 12:12 h light/dark cycle with water and food ad libitum (4, 5). At the time of behavioral characterization, O. degus of either sex or different ages were evaluated considering 12, 36, 60 and 72 months old. Animals were separated in two groups: young (12, 24 and 36 moths) and old (48, 60 and 72 months). The Ethics and Animal Care and Use Committee of the Pontificial Catholic University of Chile approved all animal work.

Gliarial activation

To study astrocyte and microglial activation, we used immunocytochemical staining and biochemical analysis with anti-gliarial fibrillary acidic protein (anti-GFAP) (DAKO, Carpinteria, CA, USA) and anti-differentiation molecule 11B (anti-CD11B) antibody (Serotec, Oxford, UK). A free-floating immunocytochemical procedure was performed as previously described. Briefly, the brain sections were pretreated with 0.5% hydrogen peroxide (H₂O₂) for 30 minutes to reduce endogenous peroxidase activity followed by treatment with 3% bovine serum albumin at room temperature for 1 h to prevent nonspecific binding. Hippocampal tissue was homogenized in Radioimmunoprecipitation assay (RIPA) buffer [50 mM, Tris-Cl, pH 7.5, 150 mM NaCl, 1% NP-40, 0.5% sodium deoxycholate and 1% sodium dodecyl sulfate (SDS)] supplemented with a protease inhibitor cocktail (P8340, Sigma-Aldrich, St. Louis, MO, USA) and phosphatase inhibitors (50 mM NaF, 1 mM Na₃VO₄, and 30 μM Na₂P₂O₇) using a Potter homogenizer and then sequentially passed through decreasing caliber syringes from 25G × 5/8” to 28G × 1/2”. Protein samples were centrifuged at 14 000 rpm at 4°C twice for 15 minutes. The protein concentration was determined using the BCA protein assay kit (Pierce, N Meridian Rd, Rockford, IL, USA). Twenty micrograms of hippocampal samples was resolved by 10% SDS-polyacrylamide gel electrophoresis and transferred to a polyvinylidene difluoride membrane followed by incubation with a primary antibody, a secondary anti-goat peroxidase conjugated antibody (Pierce) and ECL development according to the manufacturer’s instructions (ECL, PerkinElmer, Waltham, MA, USA).

Oxidative stress markers

To study the progression of age-related oxidative stress in the brain of O. degus, we used immunofluorescence and immunocytochemical techniques to measure the expression and distribution of two well-described oxidative markers: 4-hydroxynonenal (4-HNE) and nitrotyrosine (N-TYR). 4-HNE is a marker of lipid peroxidation; for these experiments, we used a specific polyclonal antibody (AbD Serotec, Oxford, UK). N-TYR is a marker of the oxidation of proteins generated by an increase in the production of nitric oxide (NO); we used a polyclonal antibody for detection (AbD Serotec, Oxford, UK). Our protocol has previously been described by our laboratory (19, 33, 90).

Interleukin-6 measurement

To study the effects of age on inflammation in the brain of O. degus, we examined the expression and localization of the inflammatory marker interleukin 6 (IL-6) using a specific antibody (Abcam, Cambridge, MA, USA). The protocol was performed as previously described by Ansar et al (3).

Metabolic sensors and autophagy rate

To study the effects of aging on the expression of metabolic sensors in the brain of O. degus, we studied the expression of PGC-1α, AMPK, activated AMPK and the autophagy marker LC3B via immunofluorescence and Western blot. For Western blot analysis, we used an anti-phospho-Thr172-AMPK antibody, an anti-total AMPK antibody (Cell Signalling, Danvers, PA, USA), an anti-LC3B (Cell Signalling) for detection of band I (16 kDa) and lipidate band II (14 kDa). For complementary autophagy studies, we used an anti-p62 antibody (Cell Signalling). Our Western blot protocol was previously described (5). Immunofluorescence was performed with the same antibodies used in the Western blot analysis with the previously described protocol.

Neuronal cell death

Neuronal cell death measured by microscopic analysis with Hoechst staining, which enabled the number of condensed/pyknotic nuclei in the brain slices to be quantified, and the anti-caspase-3 (casp-3)-active antibody for an immunofluorescence assay (Chemicon International, Temecula, CA, USA). Both protocols were carried out as previously described (90).

Image analysis

The stained brain sections photographed using an Olympus BX51 microscope coupled to a Micro-publisher 3.3 RTV camera (QImaging Surrey, BC, Canada). The images were analyzed with ImageJ v.1.40g software (NIH, Bethesda, MD). The selection of the measurement areas was performed by manual threshold adjustment or by direct manual selection of regions of interest (ROIs) in heterogeneous stains. Images of neuron immunofluorescence were captured with a Zeiss LSM 5 Pascal confocal microscope (Jena, Germany). We typically examined a series of 15–20 confocal layers, which represented the fluorescence data from the ROI. The relative intensities of the protein bands were analyzed using ImageJ software. Statistical analysis was performed using GraphPad InStat version 3.00 (GraphPad Software, San Diego, CA, USA).
**Statistical analysis**

Results expressed as the mean ± standard error of the mean. The data were analyzed by one-way analysis of variance followed by Bonferroni’s post hoc test. Asterisks indicate the statistical significance of the observed differences (*P < 0.05; **P < 0.01). The statistical analyses performed using Prism software (GraphPad Software).

**RESULTS**

**Astrocytes and microglia are activated in the brains of aging O. degus**

Increased astrogliosis and microgliosis is an undisputed feature of AD brains with increased Aβ loads (49, 65). Brain sections obtained from O. degus of different ages (12–72 months) were stained with a specific antibody against GFAP in two regions of the brain: the hippocampus and the cortex. Representative micrographs are shown in Figure 1A; detailed images are shown for GFAP in the inset. The graph (Figure 1B) represents the staining intensity in the two regions. Total levels of GFAP in hippocampus were significantly increased in eightfold old animals (60 and 72 months old) compared with the young animals. However, we did not observe an increase in the cortex region (Figure 1B). Total protein levels of GFAP and the microglial marker CD11b were evaluated in the hippocampus and cortex (Figure 1C). The levels of CD11b in the hippocampus increased approximately twofold in the old animals compared with the young animals, whereas no changes were observed in GFAP (Figure 1C). We do not observe an increase in CD11b and GFAP in the cortex region. These results indicate that glial activation is observed in old animals at different brain regions of O. degus, and this trend is similar to the one observed in aging humans and during the progression of AD-like pathology.

**Brains of aging O. degus present high levels of oxidative stress markers**

Oxidative stress is triggered by an imbalance between oxidants and antioxidants in favor of the formation of oxidized compounds and results in damage to membranes, proteins and DNA (6). Extensive and early work demonstrated that oxidative stress plays a role in the onset of AD (7, 20, 43, 89). Tissue oxidative stress markers, including lipid peroxidation, protein oxidation, DNA oxidation, and structurally and functionally damaged mitochondria are major sources of ROS (53, 83). We analyzed two markers of oxidative stress in the brain of O. degus, including an aldehyde product of lipid peroxidation, 4-HNE (Figure 2A,B) and N-TYR, a marker of NO damage (Figure 2C,D). Both markers were analyzed in the brain at different ages. As expected, older O. degus showed increased levels of 4-HNE. 4-HNE was increased over ninefold compared with the young animals in the hippocampal region (Figure 2B). The N-TYR levels were determined using immunohistochemistry. We analyzed the intensity of the signal in the neuronal soma of the young and older animals. We found a fourfold increase of tyrosine nitration in old animals compared with the young animals in the hippocampus (Figure 2D). These data support that the aging in O. degus trigger an increase in the oxidative stress in the hippocampus.

**Brains of O. degus present high levels of IL-6**

Neuroinflammation represents one of several cellular and neurochemical processes that may underlie neurodegeneration (1, 27, 59). As a prototypical cytokine with roles in the control of inflammation, IL-6 is altered in many central nervous system diseases. IL-6 is overexpressed in the brains of AD patients and increase around amyloid plaques and in the cerebrospinal fluid (2, 32).

We measured IL-6 in the hippocampus and cortex of O. degus at different ages using immunofluorescence (Figure 3A) and quantified the results by densitometric analysis (Figure 3B). We found a two- to threefold increase in the levels of IL-6 in the hippocampus and cortex in the older animals compared with the younger animals.

**Metabolic sensors in the brains of aging O. degus**

To detect the active form of AMPK in the hippocampus and cortex of young and old O. degus, we conducted both immunofluorescence and Western blot analyses. We observed only a tendency to increase in phosphorylated AMPK in hippocampus in the old animals compared with the young animals by immunofluorescence (Figure 4A,B), whereas no changes were observed in the total levels of active AMPK measured by Western blot in the hippocampus (Figure 4C,D).

We also investigated the LC3-I to LC3-II protein conversion rate and p62 protein levels in the brains of the young and old animals. These proteins are critical in pre-autophagosomal membrane formation and autophagy is deregulated in AD (55, 78). We found that the ratio of LC3-II/LC3-I does not change in the hippocampal tissues of old O. degus. Protein p62 plays an essential role in canonical autophagy by selectively detecting damaged cargo for degradation; it also plays a putative role in the NFTs observed in AD brains (41). Although the levels of p62 have the tendency to increase, we observed that these changes were not significantly different (Figure 4E,F).

**PGC-1α response in the brains of aging O. degus**

PGC-1α is a potent stimulator of mitochondrial biogenesis that enhances the transcription of several key ROS-detoxifying enzymes (glutathione peroxidase-1 and superoxide dismutase 2) (86). Recently, several studies have reported that the amyloid pre-cursor protein (APP) increases PGC-1α expression in the murine brain (69). Thus, we evaluated the levels of PGC-1α using immunofluorescence in the hippocampus and cortex. The levels of PGC-1α were significantly higher (twofold) in the hippocampus of the old animals than young animals (Figure 5A,B).

**Markers of apoptotic neurons in the brains of aging O. degus**

Apoptosis has been associated with several neurodegenerative pathologies (26). We performed nuclear staining using
Figure 1. Levels of glial fibrillary acidic protein (GFAP) and CD11b in the brains of Octodon degus at different ages. A. Representative images of the cortex and hippocampus of young and old O. degus stained with GFAP antibody. Inset shows a magnification of the immunostaining in individual cells. B. Graph shows the quantification of GFAP levels in the brains of O. degus in young and old animals. C. Western blot shows the levels of CD11b and GFAP proteins in the hippocampus. D. Graph shows the quantification of both protein levels. E. Blot shows the levels of CD11b and GFAP in the cortex. F. Graph shows the quantification of both protein levels. Data are presented as the mean ± standard error of the mean. Significant differences were calculated using analysis of variance followed by a post hoc Bonferroni test. Asterisks indicate statistical significance (*P < 0.05; **P < 0.001).
Figure 2. Levels of 4-hydroxynonenal (4-HNE) and nitrotyrosine (N-TYR) in the brains of Octodon degus at different ages. A. Representative images showing immunodetection of 4-HNE in the brains of young and old O. degus. B. Graph showing the quantification of the proteins in the hippocampus and cortex. C and D. Images of N-TYR staining in the sections of cortex and hippocampus of young and old animals, and a graph showing the levels of N-TYR species in the hippocampus and cortex. Data are presented as the mean ± standard error of the mean. Significant differences were calculated using analysis of variance followed by a post hoc Bonferroni test. Asterisks indicate statistical significance (*P < 0.05; ***P < 0.001).
Hoechst and studied the expression of activated casp-3 in the hippocampus and cortex at different ages. The number of condensed nuclei did not change in the cortex of animals of different ages. However, in the hippocampus, we observed a notable increase in apoptotic nuclei, which progressed with age. The increase was four times greater in the older animals compared with the younger animals (Figure 6A,B). Based on this observation, we measured the expression of the apoptotic marker-activated casp-3 as observed in AD and other neurological disorders (9, 71, 72). Activated casp-3 increased in the old animals compared with the young animals particularly in the hippocampus (Figure 6C,D).

DISCUSSION

Research on neurodegenerative disorders as well as other pathologies was limited by the reliability of available disease models. In several cases disease models are based on the introduction and/or expression of foreign genes in a specific organism, such as the transgenic models of AD. Even though these models are widely used, the rate of success of new therapeutic intervention strategies or therapeutic alternatives derived from the models is quite poor (12, 23, 38, 42, 46). AD and other neurodegenerative disorders are highly complex pathologies, with several critical factors that interact during the establishment and progression of the disease. Unfortunately, none of the current models are able to mimic the full range of alterations that occur during AD (66). A natural model of AD could provide a powerful tool to understand the complexity of AD neuropathology. Previously, Inestrosa et al (34) demonstrated that the Aβ peptide shares the same amino acid sequence in humans and O. degus, with only one amino acid difference (34). Subsequently, we demonstrated neural plasticity impairments prior to the appearance of amyloid and tau deposition (5). van Groen et al (82) have demonstrated that Aβ deposits in the blood vessel...
Figure 4. AMPK and autophagy markers, two associated metabolic elements, in the brains of Octodon degus. A and B. Representative images of cortical and hippocampal sections immunostained to detect pThr172-AMPK in young and old animals. The graph shows the levels of active AMPK in both areas. C and D. Blots show the phosphorylated and total AMPK in the hippocampus. The graph shows the levels of phosphorylated AMPK in young and old animals. E and F. Autophagy markers were studied in the hippocampus of young and old animals. The graph shows the ratio of LC3-II/LC3-I and p62 protein in young and old animals. Data are represented as the mean ± standard error of the mean. Significant differences were calculated using analysis of variance followed by a post hoc Bonferroni test.
walls precede the deposits of Aβ and tau in the hippocampus of 3-year-old animals (82).

In the present work, we used a comprehensive approach to identify several age-related neurocytopathological alterations related to the onset and progression of AD. Moreover, our findings demonstrate that the brains of aged O. degus exhibit a wide range of differential biomarkers related to aging and human AD neuropathology. Our findings provide further support to hypothesis that O. degus represents a natural wild-type rodent model of AD (8, 34, 42).

We observed age-related glial cell activation. In young animals, we identified normal expression of the astrocyte marker GFAP and the microglial marker CD11b. However, in old subjects, both markers were increased. The activation of astrocytes and microglia has been described in several models of neurodegenerative disease and has been postulated to represent a common alteration in AD in response to neuronal damage (37, 56). Neuronal damage in AD induced by Aβ aggregates (amyloid fibrils and Aβ oligomers) could be an important triggering factor for the activation of glial cells, which is an important step in the pathology of the disease. The activation of glial cells is a well-recognized trigger of an inflammatory response in the progression to brain damage (31, 44, 56, 73, 74). A direct relationship between glial and microglia activation is mediated by systematic inflammation and IL cross talk. The activation of glial cells induces the production of IL-6 by blood cells, including T-cell and monocytes. In brain tissue, IL-6 stimulates several process related to protection against brain injury, including tissue remodeling, reduction of oxidative stress and inhibition of apoptosis induced by an increase in intracellular Ca²⁺ (21, 39, 57). However, the molecular mechanisms responsible for the effects of IL-6 remain unclear. In the O. degus model, we observed an increase in the levels of IL-6 in old animals. This increase could represent a response against the oxidative stress and massive neuronal death observed in the final stages of the animal’s life. The relative importance of the inflammatory process in age-related AD in O. degus deserves further studies.

Glial activation and inflammatory processes are present in several neurodegenerative diseases, including AD. Both processes

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**Figure 5.** Peroxisome proliferative-activated receptor γ coactivator-1α (PGC-1α) increased in the brains of Octodon degus. A and B. Representative images of PGC-1α immunoreactivity in young and old O. degus. The graph shows the quantification in the cortex and hippocampus. Data are represented as the mean ± standard error of the mean. Significant differences were calculated using analysis of variance followed by a post hoc Bonferroni test. Asterisks indicate statistical significance (*P < 0.05).
Figure 6. Apoptosis markers in the brains of Octodon degus. A and B. Representative images of Hoechst staining in the young and old O. degus. The graph shows the quantification of condensed nuclei in the cortex and hippocampus. B and D. Images show active caspase-3 immunodetection in the hippocampus and cortex of the young and older O. degus. The graph shows that the levels of active caspase-3 in the hippocampus and cortex are in young and old animals. Data represented as the mean ± standard error of the mean. Significant differences were calculated using analysis of variance followed by a post hoc Bonferroni test. Asterisks indicate statistical significance (*P < 0.05; **P < 0.001).
have also been correlated with oxidative stress (30, 45, 51). In the same line, the administration of an anti-oxidant, such as vitamin E, or an anti-inflammatory drug, such as indomethacin, causes an additive anti-amyloidogenic effect in some mouse models of AD (87). In our model, we observed an increase in the expression of two markers of oxidative stress: 4-HNE and N-TYR. 4-HNE is a marker of lipid peroxidation. N-TYR is a product of tyrosine nitration mediated by reactive nitrogen species, such as peroxynitrite anion and nitrogen dioxide, which are markers of inflammation and NO production (77). The increase in both markers was primarily observed in the hippocampus, which is similar to the changes described in AD pathology (47, 48, 85). In fact, the damage induced by oxidative stress in the hippocampus has been suggested as critical to the failure of cognitive performance in AD patients (62, 64, 79, 89). Moreover, we also observed increased levels of additional cell death markers, such as activated casp-3, which is typically considered the terminal step in the biochemical cascade that leads to apoptosis, which has been for a long time a clear trend in AD (35, 50, 67, 70). The role of casp-3 activation in AD has been recently emphasized in vitro in Aβ-challenged neurons and the brains of individuals with AD (76).

Oxidative stress affects several processes in the brain, including DNA homeostasis, protein oxidation and mitochondrial dysfunction. Several groups have described that mitochondrial failure is a critical step in the progression of AD because of its fundamental role in neuronal metabolism (24, 83, 89). Altered cell metabolism and energy imbalances represent additional variables that explain some reported biochemical changes in AD (22, 36). In the clinic, diabetes and some cardiometabolic disorders have been correlated with an increased risk of dementia and AD development because
of an altered energy balance (52, 68). Some authors have even defined AD as a “diabetic brain” primarily because of a molecular link between diabetes and AD, which includes brain resistance to insulin (11, 14, 15, 18) and results in the deregulation of memory processes. This “cognitive–metabolic syndrome” might include altered cellular energy sensors, such as AMPK and PGC-1α (25). PGC-1α has been associated with the mitochondrial health status and has been proposed to play a major role in the modulation of mitochondrial fusion–fission events, which provide protection against β-derived oxidative damage (69, 91). An altered expression of the active form of AMPK (pThr172-AMPK) has been observed in AD transgenic mice models, such as the APPswt-PSEN1dE9 (28, 63). We evaluated these markers in the brains of O. degus and found increased expression only in the case of PGC-1α, which suggests a compensatory mechanism to overcome β-induced damage and prevent neuronal metabolic stress (22).

A general hypothesis is that the augmentation of autophagy flux capacity could represent a potential mechanism of the clearance of tau intracellular deposits (61). LC3 is involved in membrane recruitment, and p62 is involved in auto-phagosomal elongation (41). In our model, both markers (mainlyp62) exhibited similar increases, which replicates the pathology in other animal models of AD (APP/PS1) and in the human post-mortem brain (88). We were not able to find changes in LC3 and p62 markers suggesting a difference with the pathology in other models (88). In conclusion, we measured several tissue biomarkers in O. degus of different ages that have been described as characteristic of AD, including the classic hallmarks and emerging markers for inflammation (gliosis and microgliosis), oxidative stress (4-HNE and N-TYR), neuronal death and the metabolic stress marker PGC-1α. A summary of the observed changes is in Figure 7. We present evidence for a high correlation between the pathological changes that occur during the aging process in O. degus and the changes described in human AD. Taken together, the previously reported evidence and the research presented here provide a strong platform to consider O. degus as a reliable “natural” model to investigate the pathobiology of AD. The potential uses of this model are wide: it could increase our knowledge regarding aging and neurodegeneration, enable the development of more efficient staging, and provide novel therapies to slow down or ameliorate AD progression.

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