

Octodon Degus: A Strong Attractor for Alzheimer Research

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Article info:

Received: 13 September 2012

First Revision: 2 October 2012

Accepted: 14 October 2012

Key Words:

Animal Model,
 Aging,
 Octodon Degus,
 Alzheimer's Disease.

ABSTRACT

The most popular animal models of Alzheimer's disease (AD) are transgenic mice expressing human genes with known mutations which do not represent the most abundant sporadic form of the disease. An increasing number of genetic, vascular and psychosocial data strongly support that the Octodon degus, a moderate-sized and diurnal precocial rodent, provides a naturalistic model for the study of the early neurodegenerative process associated with sporadic AD. In this minireview we describe and analyze the risk factors that contribute to Alzheimer-like characteristics in the degus, following recent publications, and establish some guidelines for future studies in this model of natural aging associated with the disease. Given the heterogeneity of current data derived from the diverse transgenic animal models of AD, now may be the time for the degus to become a strong attractor for academic research labs and companies involved with AD. This may help to understand the mechanisms responsible for the early neurodegenerative process associated with this devastating disease.

1. Introduction

Advancing age is the major risk factor for Alzheimer's disease (AD), a progressive neurodegenerative disorder characterized by cerebrovascular and neuronal dysfunctions leading to a gradual decline in cognition, daily functioning and behavioural alterations (Zlokovic, 2008). The main neuropathological hallmarks of AD include extracellular senile plaques containing β -amyloid (A β) derived from β -amyloid precursor protein (APP) after sequential cleavage by β -secretase and γ -secretase, and intracellular neurofibrillary tangles caused by abnormally phosphorylated tau protein (Duyckaerts, Delatour, and Potier, 2009).

Research progress over the past two decades, including the elucidation of AD susceptibility and causative genes as well as other proteins involved in the pathogenic process, has profoundly facilitated the develop-

ment of genetically altered mouse models (see <http://www.alzforum.org/res/com/tra> for a listing of currently available models).

The most popular animal models of AD are transgenic mice expressing human genes with mutations known to lead to familial AD. Despite their undoubted value, these transgenic models do not represent the most abundant sporadic form of AD. Although several mammalian species (e.g., bears, cats, dogs, goats, monkeys, sheep) develop Alzheimer's-like pathology with aging, the aged wild-type central Chilean rodent, the Octodon degus (Od) a moderate-size and diurnal precocial rodent, also develops Alzheimer-like pathology (Inestrosa et al., 2005). If this is because of the remarkable close β A sequence homology (97, 5%) between human and Od remains to be shown. Different AD-like phenotypes between transgenic mice models and Octodon degus are compared in Table 1. Moreover, in old age, the laboratory bred Od, expresses cognitive deficits (Ortiz et al.,

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2005), anxiety (Popovic et al., 2009), unstable circadian rhythms of low amplitude (Vivanco et al., 2007), and spontaneous neuropathology in cerebral vessels and significant white matter alterations (van Groen et al., 2011), all of which are also signs seen in AD patients. It has recently been reported that postsynaptic dysfunction is associated with spatial and object recognition memory loss in the Od. This rodent exhibits an age-related accumulation of soluble A β oligomers and tau protein phosphorylation that correlates with cognitive decline in spatial memory (T-maze) and object recognition memory (ORM), as well as synaptic and neural plasticity dysfunction (Ardiles et al., 2012). Their results are consistent with the concept that soluble A β oligomers at prefibrillar stages, specially A β dodecamers (A β *56), can act as toxic ligands at postsynaptic compartments, and suggest that the Od provides a strong and naturalistic model for the study of the early neurodegenerative process associated with sporadic AD. It is also noted that neuronal loss is not present in significant numbers in the Od. Mice and rats do not develop Alzheimer pathology with aging, which is most likely related to the three amino-acid differences between the human and rodent sequence of A β (Guénette and Tanzi, 1999). Aged rats do not show these memory deficits (Rosenzweig and Barnes, 2003; Willig et al., 1987; Lukaszewska and Radulska, 1994) in clear contrast to the Od. This has obvious differences both in APP processing and in A β peptide fibrillization that is produced by the sequential cleavage of APP by the β - and γ -secretase activity (Guénette and Tanzi, 1999; Selkoe and Wolfe, 2007). How-

ever, molecular analysis of the Od APP has indicated that the Od A β presents only one amino-acid substitution with respect to the human sequence (Inestrosa et al., 2005) (Fig. 1).

2. AD Risk-Factors Acting During Octodon Degus Aging

Based on epidemiological studies, genetic studies, neuroimaging methods and neuropathology research, three basic etiological hypotheses of the development of AD have been formulated: genetic, vascular and psychosocial (Povova J et al., 2012). It is also known that high blood pressure, serum cholesterol concentrations, and impaired glucose regulation are among the factors which are most associated with increased vascular risk of AD. Cerebral amyloid angiopathy precedes brain parenchyma A β pathology in the old Od (van Groen et al., 2011). The observed changes in the brain blood vessels may have been caused by hypertension, another risk factor for the development of AD (Helzner et al., 2009; van Groen et al., 2011). Several studies have shown that a cholesterol-fed rabbit model of AD displays as many as fourteen different pathological markers of AD including amyloid- β accumulation, thioflavin-S staining, blood brain barrier breach, microglia activation, cerebrovasculature changes, and alterations in learning and memory (Sparks, 2008; Deci et al., 2012). A significant increase in ventricular volume is one of the hallmarks of AD. Cholesterol-fed rabbits also show a significant increase in ventricular volume following 10 weeks on

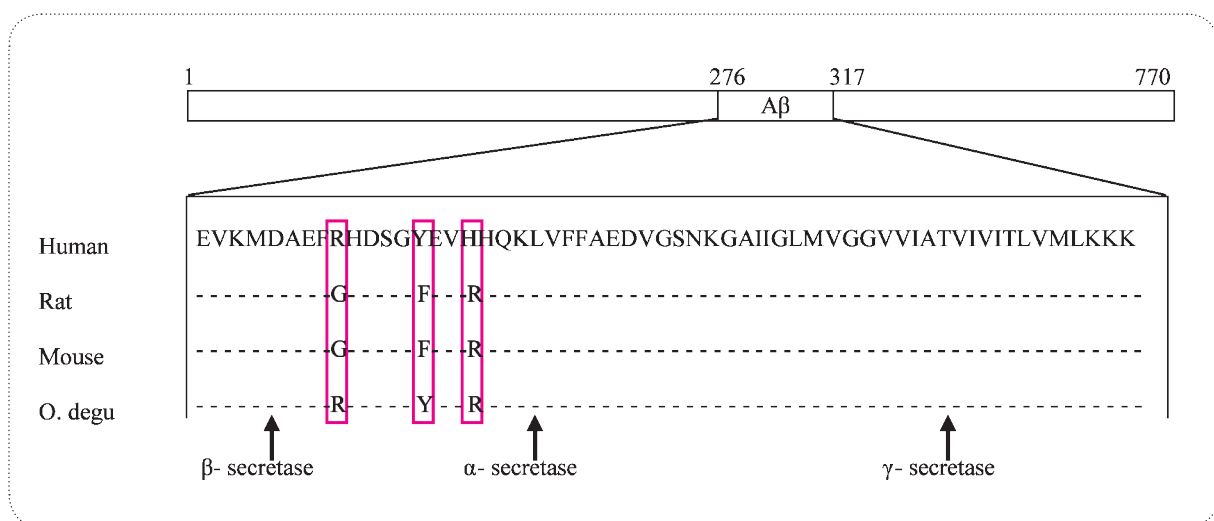


Figure 1. Sequence alignment of A β from vertebrate species. Sequence alignment of A β and flanking sequences from the human, rat, mouse and octodon degus. Amino acid homology of deduced OdA β sequence with human, rat and mouse A β sequences. The degu A β presents only one amino acid substitution with respect to the human sequence (Arg13 His, respectively; Inestrosa et al., 2005).

Table 1. Neuropathological features comparison between the main transgenic mouse models of Alzheimer disease and Octodon degus.

Mouse model	Gene (mutation) fAD	Intraneuronal A β	Parenchymal A β plaques	Hyperphosphorylated Tau	NFT	Neuronal - loss	Synaptic dysfunction	CAA	AD- like signs	Primary reference
PDAPP	APP (V717F)	-	Yes	Yes	No	No	Yes	-	< 2 years	Games et al. 1995
Tg2576	APP (K670N/M671L)	Yes	Yes	-	No	No	No	-	< 2 years	Hsiao et al. 1996
TgCRND8	APP (K670N/M671L,V717F)	-	Yes	-	No	No	-	-	< 2 years	Chishti et al. 2001
APP/PS1	APP (K670N/M671L), PS1 (M146L)	-	Yes	-	-	-	-	-	< 2 years	Holcomb et al.1998
APP23	APP (K670N/M671L)	-	Yes	Yes	No	Little	Yes	Yes	< 2 years	Sturchler-Pier-rat et al. 1997
Tg-SwDI	APP (E693Q, D694N)	-	Yes	-	-	-	-	Yes	< 2 years	Davis et al. 2004
APPDutch	APP (E693Q)	-	Little	-	-	-	-	Yes	< 2 years	Herzig et al. 2004
AP-PDutch/PS1	APP (E693Q), PS1 (G384A)	-	Yes	-	-	-	-	Little	< 2 years	Herzig et al. 2004
hAPP-Arc	APP (E693G, K670N/M671L, V717F)	-	Yes	-	-	-	-	Little	< 2 years	Cheng et al. 2004
Tg-ArcSwe	APP (E693G, K670N/M671L)	Yes	Yes	-	-	-	-	Yes	< 2 years	Lord et al. 2006, Knobloch et al. 2007
APPArc	APP (E693G)	-	Yes	-	-	-	-	Yes	< 2 years	Rönnbäck et al. 2011
TAPP	APP (K670N/M671L), Tau (P301L)	-	Yes	-	Yes	-	-	-	< 2 years	Lewis et al. 2001
3xTg-AD	APP (K670N/M671L), Tau (P301L), PS1(M146V)	Yes	Yes	Yes	Yes	-	No	-	< 2 years	Oddo et al. 2003
APPSL/PS1	APP (K670N/M671L,V717I), PS1 (M146L)	Yes	Yes	-	-	Yes	Yes	-	< 2 years	Wirhth et al. 2002
APP/PS1KI	PS1 (M233T/L235P)	Yes	Yes	-	-	Yes	Yes	-	< 2 years	Casas et al. 2004
5xFAD	APP (K670N/M671L, I716V, V717I), PS1 (M146L/L286V)	Yes	Yes	-	-	Yes	Yes	-	< 2 years	Oakley et al. 2006
Octodon degus	SAD	Yes	Yes	Yes	Yes		Yes	Yes	\geq 3 years	Inestrosa et al.2005

fAD = familial AD; sAD = sporadic AD; NFT = Neurofibrillary tangles; CAA = cerebral amyloid angiopathy;

Dash (-) = not reported. (modified from Schaeffer et al. 2011).

a diet of 2% cholesterol (Deci et al., 2012). It is still unknown if the Od naturally develops an increase in the ventricular size during aging. Previous data showed that the Od has a human-like lipoprotein metabolism and develops extensive atherosclerosis with cholesterol feeding in the presence of hyperglycemia (Homan et al., 2010). In fact, when fed a high cholesterol diet, the LDL fraction is enriched disproportionately, such that approximately 60% of cholesterol is carried in the

LDL fraction, which more closely resembles the human lipoprotein profile (Tannock and King, 2010). Diabetes is also one of the risk factors for AD development (Sims-Robinson et al., 2010; Cheng et al., 2012). Interestingly, the wild Od is hyperglycemic and develops features suggestive of diabetic complications (Tannock and King, 2010), therefore breeding animals will need to receive an appropriate diet.

One challenge for social-affective neuroscience programs is to identify simple and yet valid animal models for studying the expression of basic social emotions and their role during different developmental windows, from infancy to adulthood (Colonnello et al., 2011). The Od is a very social animal with a broad array of communication methods (Edwards, 2009). Social animals are susceptible to high infection levels by contact-transmitted parasites due to increased nonspecific interaction. It has been shown that viral infections such as herpes play a role in the development of AD (Honjo, van Reekum, and Verhoeff, 2009; Itzhaki and Wozniak, 2008; Robinson, Dobson, and Lyons, 2004), and the wild Od is also often infected with Herpes-like viruses (Spear, Caple, and Sutherland, 1984) and with *Trypanosoma* (Galuppo et al., 2009).

Recent evidence suggests that circadian dysregulation may act to exacerbate AD pathology (Bedrosian and Nelson, 2012). The decline in melatonin production in aged individuals has been suggested as one of the primary contributing factors for the development of age-associated neurodegenerative diseases (Srinivasan et al., 2005). Melatonin, the principal hormonal output of the circadian system, is dysregulated in AD, and this may be important because melatonin is protective in cells exposed to toxic A β . In fact, because of its powerful antioxidant properties (Tan et al., 2000), melatonin has been proposed as a potential therapeutic agent in diseases in which oxidative stress is thought to be a major pathogenic factor. In this regard, oxidative damage is thought to be a significant contributing factor in the pathogenesis of AD. Most of the small laboratory animals are nocturnal and regulate melatonin synthesis by mechanisms that diverge from those of humans. However, the Od may provide an ideal model system for laboratory investigation of mechanisms of melatonin synthesis and secretion in diurnal mammals (Lee et al., 2009).

All these risk-factors acting during Od aging would likely lead to an increase in the chances of developing AD-like symptoms in these wild animals.

3. An Array of Research Possibilities in *Octodon Degus*

The amyloid theory suggests that deposits of A β 42 are the key event of this disease and that they precede clinical signs by several years (Hardy and Selkoe, 2002; Jack et al., 2010; Selkoe, 2011). This peptide can be removed by capillaries, enzymatically degraded, or eliminated into cerebrospinal fluid (CSF) (Tanzi, Moir,

and Wagner, 2004). The discovery of pathogenic mutations in the following three genes, encoding APP and the γ -secretase-complex components presenilin-1 and presenilin-2, in patients with autosomal dominant, early-onset familial AD, provided incontestable evidence that aberrant APP processing can be sufficient to trigger the pathological cascade leading to AD (Sleegers et al., 2010). However, the majority of late-onset AD patients (>99%) do not have a mutation that causes an increase in APP processing (Tanzi and Bertram, 2005) and, therefore, increases in A β production have not been found in late-onset AD. The pathological accumulation of A β in the far more common late-onset AD is more likely to be the result of defects in the clearance of A β (Mawuenyega et al., 2010). Clearance of A β from the brain occurs via active transport at the blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCSFB). In this way, it might be possible to open up, by using the Od, a spectrum of possibilities to investigate the mechanisms of the brain barriers involved in the clearance of A β during the early neurodegenerative process associated with sporadic AD. In their work, Ardiles et al. (2012), suggest that the decline in synaptic plasticity may be associated with an increase in A β peptides before the increase in tau phosphorylation and, because this process occurs naturally in the Od, it represents a unique opportunity to examine physiological mechanisms. Since the postsynaptic compartments are more susceptible to the effects of A β peptides, as shown by the reduction of PSD-95 and glutamate receptors in the aged Od (Ardiles et al., 2012), an array of research possibilities is open to new drugs and therapies for the initial phases of AD. The promise of effective therapy has created a great need for biomarkers able to detect AD in the prodementia phase, because drugs will probably only be effective if neurodegeneration is not too advanced. In this regard, Od research also opens up new possibilities for CSF and plasma biomarkers, but it will be necessary to develop, from the methodological point of view, biological tools and reagents (antibodies, nucleotide sequences, etc) for these and other studies.

4. Discussion

An accumulation of recent evidence strongly support that the Od provides a naturalistic model for the study of the early neurodegenerative processes associated with sporadic AD. Given the heterogeneity of current data derived from the diverse transgenic animal models of AD, now may be the time for the Od to take its place as a strong attractor for academic research labs and companies involved with AD. This may help to understand

the mechanisms responsible for the neurodegenerative process associated with this devastating disease.

Acknowledgments

This work was supported by the Canary Islands Government and by the FIS grant PI 10/00283.

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