Octodon degus:

a model for the cognitive impairment associated with Alzheimer's Disease.

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Running title:

O. degus in the study of cognitive impairment

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Abstract

Octodon degus (*O. degus*) is a diurnal rodent that spontaneously develops several physiopathological conditions, analogous in many cases to those experienced by humans. In light of this, *O. degus* has recently been identified as a very valuable animal model for research in several medical fields, especially those concerned with neurodegenerative diseases in which risk is associated with ageing. *O. degus* spontaneously develops β-amyloid deposits analogous to those observed in some cases of Alzheimer's disease (AD). Moreover, these deposits are thought to be the key feature for AD diagnosis, and one of the suggested causes of cell loss and cognitive deficit. This review aims to bring together information to support *O. degus* as a valuable model for the study of cerebral aging.

Keywords: Memory, Mild Cognitive Impairment, Alzheimer disease, *Octodon degus*, Amyloid beta-protein

Introduction

One of the major areas of interest in the field of neuroscience is the study of age-related brain pathologies. Understanding the origin of such pathologies, as well as how they progress through different cellular mechanisms and how this process finally affects cognitive and behavioral processes is essential for developing therapies and intervention strategies. Among the vast variety of brain pathologies, Alzheimer's disease (AD) deserves special attention. Being a neurodegenerative disease, the symptoms do not appear spontaneously, but, unlike in the case of a psychosis or amnesia, gradually. The pathology progresses relentlessly until the symptoms are manifest and the memory function, as well as other cognitive domains such as orientation, problem solving or even changes in personality, become apparent. In most cases, patients are no longer able to take care of themselves and require full-time care [1].

Basic research in Alzheimer's disease

There are currently no approved disease-modifying treatments that are able to halt of slow down the pathology in AD or other common neurodegenerative disease. There are, however, vast ranges of different pharmacological and psychological therapies in development stages that aim to slow down the advance of functional loss. However, it is clear that we need to understand more about the cause of this disease and its natural progression if we are to understand when and how to treat it.

There are several approaches to the study of AD, including those based on cellular models [2-4]. Nonetheless, although these models may be very useful for unraveling the molecular mechanisms that underlie the symptomatology, there is a great gap between the conclusions deduced from them and the clinical outcome that this disease displays. On the other hand, the use of animal species may contribute not only to understanding cellular and pathophysiological

characteristics of Alzheimer's, but also to reproduce the cognitive deficits shown in patients. In our mind, this could seem a more ecological and appropriate approach and one more suited for a better appreciation of the different features of the illness. In this sense, we could say that animal models are good for their capacity to imitate both pathophysiological conditions and behavioral outcome (if any). Therefore, it is fundamental for such models to be able to measure cognitive and behavioral function in an accurately and reliably way.

A number of animal models have been generated in an attempt to reproduce AD pathology. Most of these models have used rodents and there have been some promising advances [5-7]. Several studies have demonstrated that Alzheimer pathology markers are absent in wild-type rodents, making it necessary to generate transgenic animals overexpressing human amyloid precursor protein (β-APP) harboring familial AD mutations [8-10] or to perform intracerebral injections of Aβ aggregates [11,12] to achieve homologous states of the disease.

Despite the wide range of animal models that are currently used in the study of behavioral and physiopathology features of AD [13], rodents are the most utilized. In the last decades, for instance, the number of transgenic models that have been developed has remarkably increased, widening the alternatives and targeting those characteristics that most significantly are identified within this neurodegenerative disease [14]. As the Aβ cascade is the main hypothesis for the AD, the achievement of models that lead to the development of such characteristics is a milestone for the advance in understanding this pathology.

In this sense, following the Aβ hypothesis, transgenic models are mainly derived from different branches that over express three hallmarks identified as regard the AD: APP protein, presenilin 1 and 2, and tau protein [15], aiming to develop the characteristic amyloid accumulation and neurofibrillary tangles (NFTs) [16]. The major advantage of these models is that they succeed in reproducing a similar pathophysiological and behavioral outcome that is observed among AD

patients [17,18]. However, although transgenic models have proved their value for the study of AD, they raise important restrictions.

In the first place, to our view, the most important limitation these models present is the need for genetic and/or pharmacological manipulation to reach the inherent pathophysiological state of Alzheimer's. For instance, it is known that AD patients show a significant neuron loss [19], and this feature has to be implanted in the mouse because even transgenic models show no such loss without manipulation [20]. Another important similarity between human and rodent pathology that these models lack of, is the anatomical distribution of the senile plaques and NFT accumulation [17]. In humans, neuronal death derived from these two properties has been primarily located in the prefrontal and parietal cortices (mainly hippocampus) [16]. However, this allocation has not been achieved with the different models available. Taking this into account, the availability of a model that may cover these limitations would be undoubtedly appreciated.

In recent years, a rodent endogenous to Chile, the *Octodon degus* (*O. degus*) has gained prominence as a valued model for many different diseases, including those related with neurodegeneration, since this animal may develop naturally several symptoms that can be linked to a similar number of pathological conditions (Figure 1). Because of its particular diurnal cycle, it has frequently been used in circadian studies [21,22]. It is also a highly social rodent, which explains its role in social and neuroaffective research [23,24]. However, over the last few years, the participation of degus in the study of neurodegeneration has suggested that this area of research is the most promising application of this model. This diurnal cavimorph rodent lives up to 7 years average in captivity [25], making it *per se* an interesting model for use in longitudinal studies, including those related in the neuropsychobiology of ageing, and AD.

Octodon-Human Aβ aggregates similarities

Among the different hypotheses raised to explain the origin and evolution of AD, the most widely held is that which stresses the importance of cholinergic neurodegeneration and the appearance of two principal markers: the NFTs formed through the dysfunctional hyperphosphorylation of tau protein, and the deposition of Aβ aggregates, which are thought to be the trigger for neuronal death [26]. However, the relationship between these two elements is not clear, although several hypotheses have attempted to link them [26,27].

A few years ago, Inestrosa and collaborators demonstrated that *O. degus* naturally develop characteristic histopathological hallmarks typical to those found in AD patients [28]. The discovery showed that this rodent, in its natural environment, might produce plaques in different brain areas [29], including hippocampus and frontal cortex, both of which are severely affected in AD patients [16]. Moreover, immunohistochemical and genetic analyses performed on the *O. degus* revealed a high degree of similarity between human deposits and the Aβ precursor protein (Aβ-PP). Also, RT-PCR analysis showed the *O. degus* and human Aβ peptide sequence to be 97.5% homologous [28]. This animal presents only one amino acid substitution with respect the human, which presents an advantage to other models (rats, for example, present in their Aβ sequence three amino acid substitution) (Figure 2). In this sense, differently to transgenic animals, there is no need to overexpress this human APP to generate significant levels of amyloid protein, which will help to avoid the overexpression of APP. This is an important question, since it has been postulated as to why there is a limited neuronal loss in the APP transgenic models, and is one of the main advantages of the *O. degus* as a model in preclinical research in AD.

Nevertheless, as promising as this animal might be, it still needs to satisfy certain requirements before it can be used as an appropriate model. In this sense, it is worth mentioning that the histopathological changes occurring in *O. degus* brains are only observed in aged animals [28,29], and have never been detected in young animals so far. Similar comments may be made

regarding tau, which suggests that amyloid and tau deposition are age-dependent, as they are in AD patients [30,31] and in some of the more successful transgenic mice studied to date [10].

Another interesting analogy concerns the cholinergic system. The cerebral cortex of some human and non-human primates contains acetylcholine (AChE)-rich pyramidal neurons, which have been seen to decline in numbers during the progression of AD, a decrease claimed to be partly responsible for the memory deficits in Alzheimer patients [15,19]. *O. degus* apparently shares the same AChE-rich neurons that are found in the cerebral cortex of adult humans. Moreover, the high degree of homology (97.5%) between the human and *O. degus* in Aβ sequence and the Tau structure, possibly triggered by the Aβ found in these animals, suggest that both play a major role in the appearance of AD markers in this rodent, including the presence of extra- and intracellular amyloid deposits and NFTs [10,28,31].

Octodon degus, what does it offer?

We have already mentioned the histological advantages that this model presents for AD research. However, without a cognitive counterpart, assessment of this model is not complete. As mentioned above, one of the key features of an animal model for AD should be its ability to mimic the cognitive and behavioral response in the different domains affected by this illness.

It has been recently demonstrated that the age-progressive accumulation of Aβ oligomers and phosphorylated tau proteins in *O. degus* from 12 to 36 months, negatively correlated with their performance in spatial and object recognition memory measured by two different behavioral paradigms: the Object Recognition Memory task and a spatial T-Maze. In this work, Ardiles et al. demonstrate that memory performance declines in an age-dependent manner, as aged animals committed less correct choices in the arms of the T-Maze and the time spent exploring the novel objects was significantly reduced in the object recognition task. Interestingly, the synaptic

strength in the old *O. degus* was reduced compared with the young ones, and the postsynaptic transmission was also impaired [32].

As memory impairment is the first manifestation of AD symptoms and the most prominent of observable consequences, one of the requirements that *O. degus* should fulfill is that it should discriminate in different cognitive tests different memory deficits classically impaired in AD. Moreover, this should be achieved in response to the different challenges that are used to induce cognitive impairment, one of the most widespread of which is sleep deprivation.

Sleep deprivation (SD) has been widely documented as one of the challenges that most effectively induce transient cognitive impairment [33-36] in animals [37-39] and humans 40. SD has also been studied in the *O. degus* [41] (Figure 3). This condition affects the formation, expression and retrieval of memories [35,36], and produces a deficient consolidation in both procedural and declarative memories [33,42]. Evaluating memory impairment caused by this challenge in the *O. degus* is especially interesting, given their phase inversion capacity [22]. Sleep-wake deregulation is commonly seen in AD [43,44], and is displayed as agitation, disrupted sleep or breathing difficulties [43]. Sleep studies performed on *O. degus* have demonstrated that, despite being diurnal, this animal is able to switch from diurnal to nocturnal phase behavior in a few days [45]. Together with all the AD-like hallmarks displayed by this rodent, this chronobiological characteristic adds value to the *O. degus* as an attractive model of the cognitive decline and behavioral outcome observed in age-related neurodegenerative diseases, and also confirms SD as an appropriate methodological choice. With this method, researchers would be able to induce transitory memory deficits in both young and old animals to further compare the impact of such procedure and the effect of aging and histopathological hallmarks formation on the behavioral outcome.

The most noteworthy feature of AD is memory loss, but it is not the only one. Besides the well-known deficit in problem solving [46,47] and spatial orientation [47,48], patients with Alzheimer's also

present a wide range of psychological affectations such as stress [49] and anxiety [50,51], as well as different systemic impairments [52]. In this sense, it has been demonstrated that the *O. degus* may develop atherosclerosis, a pathological states frequently concomitant with AD [53]. It has been demonstrated that this rodent is able to develop an atherosclerosis condition directly derived from a rich-cholesterol diet, together with a lipoprotein metabolism similar to humans, being [54]. This, combined with the presence of hyperglycemia strongly correlates with the appearence of a type-2 diabetes [55]. Interesntingly, aged *O. degus* also share with humans these pathological conditions [54].

Despite the fact that many studies have shared inconsistent results concerning age-related changes in anxiety in different rodent models [56,57], there is evidence of a significant age-related effect in *O. degus* (young and old adults) in the open field test and dark-and-light test, two widely validated procedures to assess anxiety in rodent models [58]. Popovic and collaborators explored the relationship between age and anxiety and demonstrated that, the older group spent less time in the center of the open field, compared with the young adult group [59], and that the latter group were more willing to spend more time in the light than the older ones [59], suggesting that anxiety may increase with age in these animals.

Another AD-like symptom that is apparent in the *O. degus* is related to their social life. It is known that in many cases of AD, patients tend to develop social problems mainly for two reasons: because of the dementia associated with the disorder 60 and the stress causes to caregivers [61,62]. *O. degus* is generally described as a very social rodent with a highly complex social behavior [23,24]. However, as in AD, this animal is also subjected to problematic interactions with other members of its colony when stressful events occur [63]. In this sense, Poeggel and colleagues reported severe behavioral deficits and neural alterations in the frontal cortex [64], which has also shown to be affected in AD patients [62,65].

It is also common to find patients that have difficulty in manipulating complex objects, or performing fine motor movements [66,67]. To date, the range of possibilities to test this particular deficit is scarce, and is mainly confined to non-human primates. However, to the best of our knowledge there is no literature covering manipulative and fine motor problems in rodents. Thus, it is worth mentioning that *O. degus* is the only rodent to date which has been demonstrated to be sensitive to training in object manipulation towards obtaining a reward [68]. The authors of this work were able to train 5 animals to retrieve a food reward located in a platform that could only be reached using one of the different tools to which they were given access. Animals learned the task with the same efficiency as shown by non-human primates in similar conditions [69], demonstrating an increasingly understanding of tool usage, not only regarding the physical properties of the tool, but also its functional attributes [68].

Further directions

We have reviewed a range of studies performed with the *O. degus*, a diurnal rodent native to Chile. The main interest in this animal in the field of cognition is that it has recently been proposed as a putative model for AD, principally because it presents two of the major histopathological markers for this disorder (β-Amyloid plaques and neurofibrillary tangles containing hyperphosphorylated tau). Several reports have also suggested that cognitive impairment in *O. degus* may be compared with that observed in humans. Therefore, this animal could represent one of the most promising models for the study of cognitive impairment associated with AD impairment. Whilst investigation with *O. degus* in the field of cognitive sciences is still in its early stages, we believe that the degus provides an excellent opportunity for exploring the mechanisms underlying late developmental changes in the nervous system, and therefore, the behavioral and cognitive outcomes resulting from such changes.

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Figure 1. **Characteristics of *O. degus***. Brief description of several characteristics that naturally develop in the *O. degus* making it useful as an animal model in several fields. Numbers in brackets are for the correspondent reference in the bibliography.

Figure 2. **Amino acid Aβ sequence**. Differences and similarities between mice/rat, human and *O. degus* amino acid Aβ sequence. Differently from the mice/rat, the *O. degus* is only one amino acid different from the human sequence [28,29].

Figure 3. **Procedural scheme of the sleep deprivation induced by gentle handling.** Adapted to the normal diurnal activity of the *O. degus*, sleep deprivation challenge starts at 7 p.m. in a 12/12-hour light and dark cycle. Gentle handling is a non-stressful way of preventing the animal from sleeping. After the procedure, the behavioral test takes place [41].

Figure 1

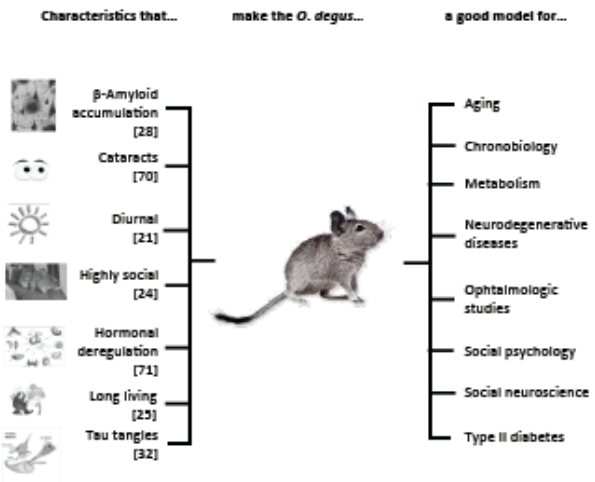

Figure 2

Figure 3