TAU PROTEIN IN ANIMAL NEURODEGENERATIVE DISEASES

Dog and cat as spontaneous animal models

Laura Vidal Palencia / Faculty of Veterinary Medicine / Final degree project, June 2020

INTRODUCTION

Rodents are the most used animal models to study Tauopathies, but these neurodegenerative diseases do not occur spontaneously in laboratory mice and rats. Nevertheless, it appears to affect other mammalian species.

OBJECTIVES

- To study the role of Tau protein and human Tauopathies.
- To review the use of dogs and cats as spontaneous animal models to study Tauopathies.

TAU PROTEIN

It is a **microtubule-associated protein** (MAP) in neurons and glial cells.
Binds tubulin and promotes and stabilizes microtubules:

- Maintains axonal transport and neuronal integrity.
- Supports differentiation, polarization, and processes involving cytoskeleton.

TAU REGULATION

- Posttranslational modifications → **Phosphorylation**: Changes tau shape and regulates negatively its activity
- mRNA splicing → **6 isoforms** in the human brain

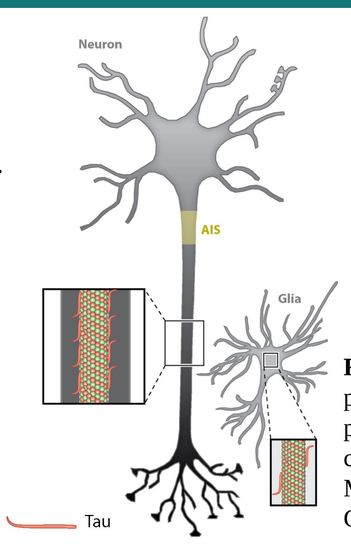

Figure 1. Tau protein in physiological conditions. Modified from Götz et al. (2019).

TAUOPATHIES

Group of heterogeneous neurodegenerative diseases characterized by the deposition of filamentous accumulations of **hyperphosphorylated Tau**.

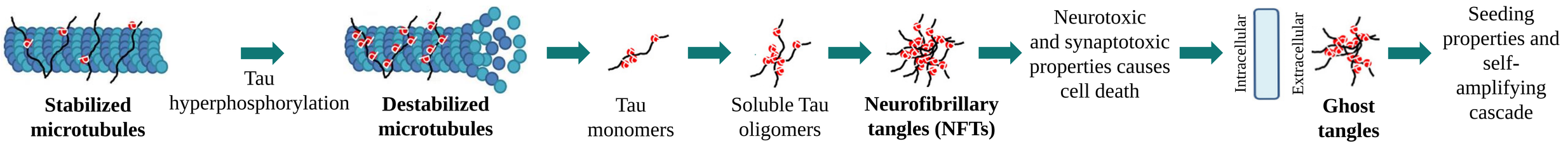

Figure 2. Diagram of Tau pathology. Modified from Barron et al. (2017).

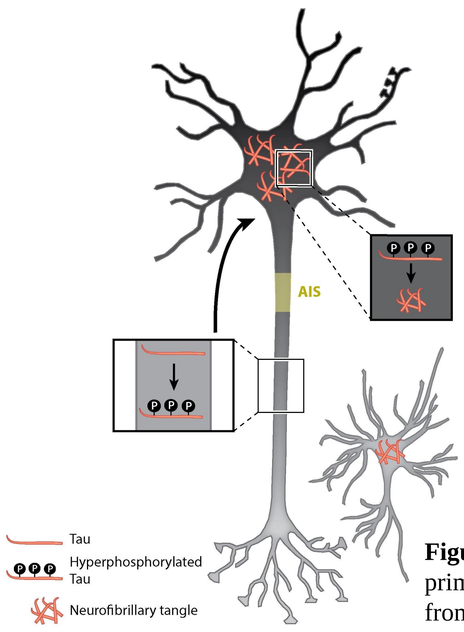

Figure 3. Tau protein in primary tauopathies. Modified from Götz et al. (2019).

PRIMARY TAUOPATHY

Tau inclusions are the predominant pathology

Hyperphosphorylated Tau accumulates in neurons and glia

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NFTs

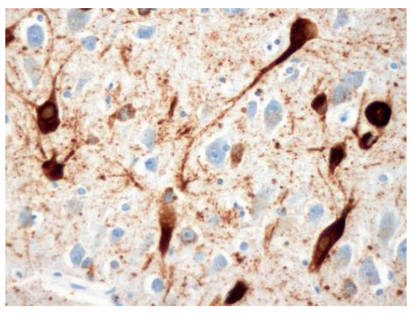

Figure 4. Immunohistochemistry labelling NFTs, which are often flame-shaped. Modified from Götz et al. (2019).

SECONDARY TAUOPATHY

Tau inclusions with another neuropathological hallmark

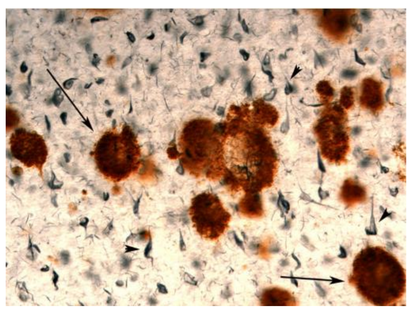

Figure 5. Immunohistochemistry showing plaques of βA (arrows) and NFTs (arrowheads). Modified from Youssef et al. (2016)

Alzheimer's disease
Extracellular plaques of β-amyloid (βA)
+
Intracellular NFTs

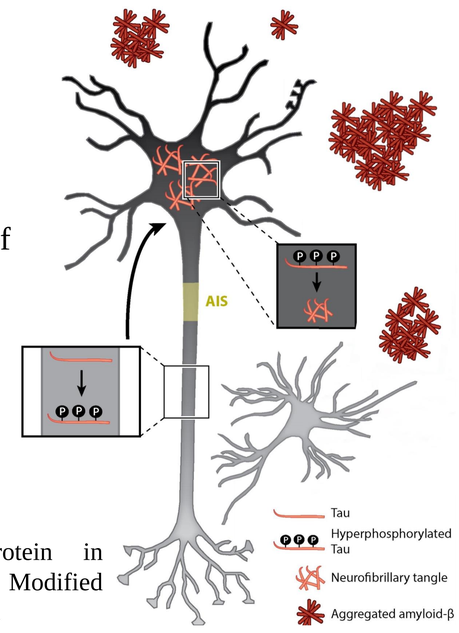

Figure 6. Tau protein in Alzheimer's disease. Modified from Götz et al. (2019).

DOG SPONTANEOUS MODEL

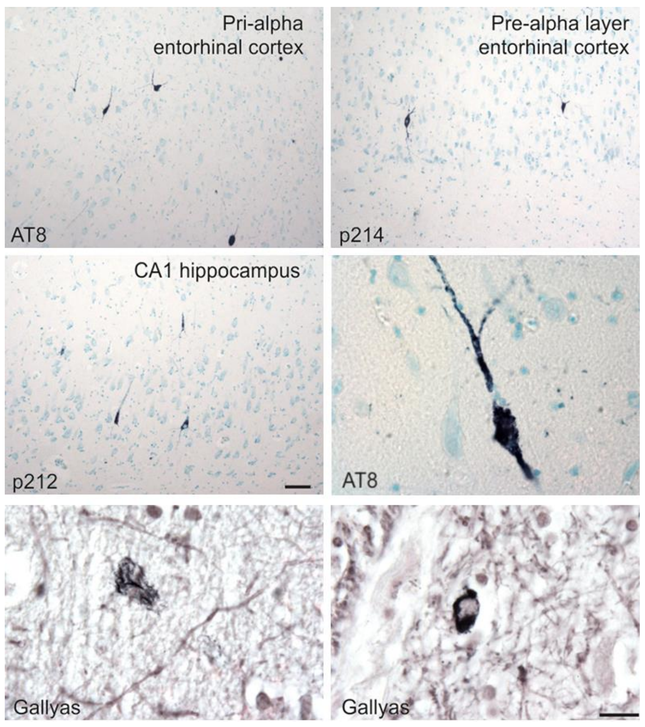

Figure 7. Immunohistochemistry showing Tau neurofibrillary inclusions in an aged demented dog. Modified from Smolek et al. (2016).

✓ NFTs are not a common characteristic of the aged dog brain.

COGNITIVE DYSFUNCTION SYNDROME

Neurodegenerative process related to the ageing of dogs and cats.

✓ Background for studying the **factors that influence ageing** (genetic, comorbidities, environment, nutrition…) and increasing life expectancy.

✓ **Behavioural changes** (disorientation, house soiling…).

✓ **Neuropathological changes** (cortical atrophy, βA plaques…).
- Hyperphosphorylated Tau in neurons and glial cells of hippocampus, entorhinal cortex and cerebral cortex.

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Spontaneous model for human Tauopathies
&
Development of new veterinary diagnostic procedures and treatments

Table 1. Comparison of Tau pathology. The formation of NFTs differs between species, what could be associated with the life span of the animal and the sequence and isoforms of Tau.

Species	Life span (years)	Tau			Neuronal loss
		Sequence vs human	Isoforms	NFTs	
Human	80	-	6 (3R + 4R)	Yes	Yes
Mouse	2	88%	3 (4R)	No	No
Dog	15	92%	4 (3R + 4R)	Few	Yes
Cat	15	93%	5 (3R + 4R)	Substantial	Yes

CAT SPONTANEOUS MODEL

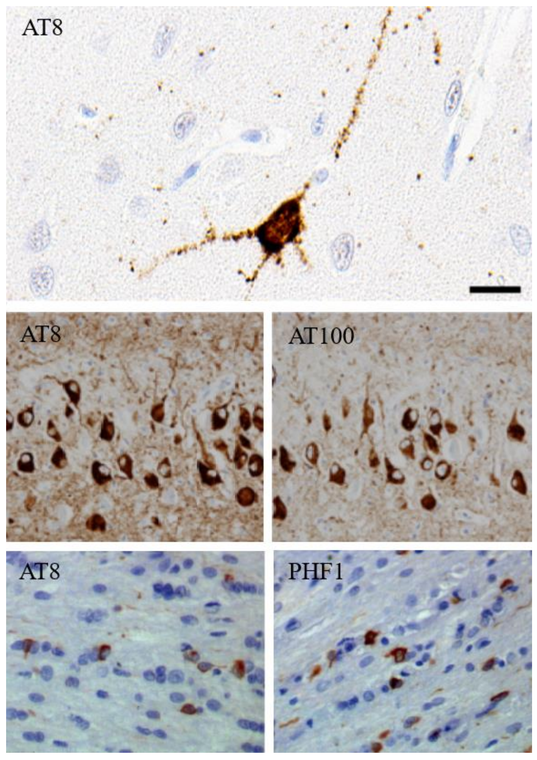

Figure 8. Immunohistochemistry showing NFTs and Tau inclusions in aged cats brains. Modified from Chambers et al. (2015) and Poncelet et al. (2019).

✓ The formation of NFTs follows the same staging and spatial distribution as human Tauopathies.

CONCLUSIONS

✓ Elderly dogs and cats develop tau inclusions with cognitive deficits, so both could be **valuable animal models of Tauopathies**. However, there are limitations…
- Not replication of all aspects of human Tauopathies → **Intermediate model** between humans and other models.
- Late onset of disease in comparison with rodent models → Companion animals as a **preclinical model.**
- Disparity between antibodies and protocols → **Technical protocols** need to be refined.

✓ Additional research is needed to clarify the differences between human and animal Tauopathies.

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