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Dog close up
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DEMENTIA

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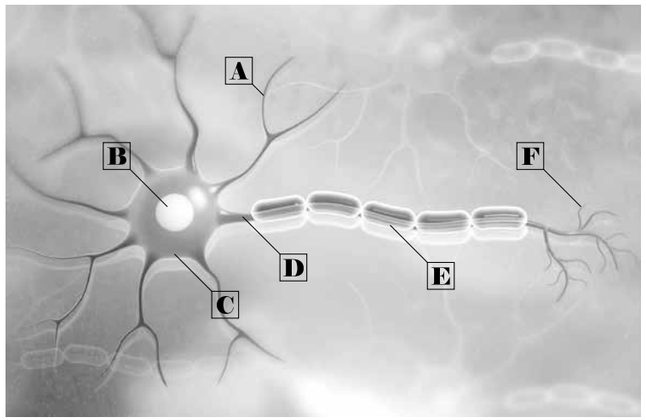
IS DEMENTIA, SPECIFICALLY ALZHEIMER'S DISEASE, A UNIQUELY HUMAN DISORDER?

EXPLORING THE RELEVANCE OF CANINE DEMENTIA TO OUR UNDERSTANDING OF THE DISEASE

Alois Alzheimer, along with Oskar Fischer, first identified the microscopic plaques and other hallmarks of dementia. By the 1960s, CT scans and technology allowed a greater structural understanding, particularly in regard to the formation of proteins in the brain. As a result of scientific progress, our understanding of dementia now allows targeted treatment. Dementia is caused by neurodegeneration, meaning the damage and death of the neurons within the brain. Frontal-temporal dementia contrasts to Lewy body dementia, affecting the frontal lobe and the motor cortex. In addition, many patients with advanced Alzheimer's show, under a CT scan, a widespread deterioration to the hippocampus, which is linked to memory and neurogeneration. Plaques in the brain limit neuron regeneration.

The question of whether animals develop dementia rests on our cognitive and neural differences and is an important one for science and human health; it allows us greater insight into causes and cures. For Paul Bernard, 'dogs and cats may suffer from cognitive dysfunction syndrome, which is similar to dementia or Alzheimer's in humans.' Age causes similar changes – increased anxiety, decreased ability to perform tasks or listen to commands, changes in sleep cycles. Captivity is significant as increasing lifespan allows ageing effects in the brain to occur in domesticated animals.



A
DENDRITES
Receives signals from other cells

B
NUCLEUS
Controls the entire neuron

C
CELL BODY
Keeps the cell functional

D
AXON
Transfers signals to other cells and organs

E
MYELIN SHEATH
Increases the speed of the signal

F
AXON TERMINAL
Forms junctions with other cells

A neuron and its functions
Credit: Rasi Bhadramani / iStock / Getty Images Plus

Toxic aggregates

The main process causing dementia is the build-up of toxic aggregates or proteins. This stops the neurons from transferring information through synapses, pathways and sometimes affects the neuron directly. We know toxic aggregates cause neurodegeneration, but we don't know what causes toxic aggregation in the first place. In addition Prion substances – misfolded proteins – have the ability to transmit their misfolded shape onto normal variants of the same protein. They cause several fatal diseases that can be transmitted in humans and most importantly from animals. The most common of these diseases is known as (CJD) Creutzfeldt-Jakob disease. The symptoms are fairly similar but CJD has an accelerated profile of development.

Amyloid beta and Alzheimer's

Another key peptide is amyloid-beta. The main role of amyloid beta is the creation of neurons. It is also involved in memory and 'message transfer' between neurons. When too much is made or too little cleared amyloid beta builds up and causes plaques, disrupting neurons. As these plaques get larger, they consume and break the dendrites of neurons, interfering with their ability to transmit signals.

The creation of plaques is the key marker of dementia. They clump together to form lump-like structures. The plaques disrupt neuro-transmitters: electrical impulses cannot be carried effectively, causing slow degeneration of brain function. The outcome of plaques is nearly always a death of neurons, memory and function degeneration and in some cases, swelling, bruising and haemorrhage. (Schaun. O, Ho. H, 2016)

The protein tau is also important; it maintains the shape and structure for the neuron's axis. When it starts to degenerate, the 'cytoskeleton' or shape becomes tangled, leading to apoptosis. We know what happens, but we don't know why. One theory links to the way oxygen is metabolised in the brain. Another is that enzymes like kinase work to change the binding and shape of neurons. (Schaun. O, Ho. H, 2016)

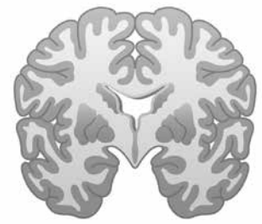
Combined inflammation

The combination of proteins leads to inflammation; it catalyses the speed and the severity of dementia. Recent research into anti-inflammatories used for arthritis suggested a 'lower incidence of Alzheimer's'. Inflammation can cause a range of severe outcomes, including stroke, vision loss and speech impairment; 'something may trigger a conversion from this harmless version of tau into a toxic version – and that's when the trouble begins with a toxic, sticky version.' The aggregates spread from the basal ganglia and other areas, forming deposits in the cells and outside the cells.

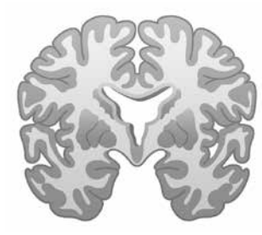
'DOGS AND CATS MAY SUFFER FROM COGNITIVE DYSFUNCTION SYNDROME, WHICH IS SIMILAR TO DEMENTIA OR ALZHEIMER'S IN HUMANS.'

BRAIN CROSS SECTIONS SHOWING THE PROGRESSION OF ALZHEIMER'S DISEASE

Healthy brain



Mild Alzheimer's disease



Severe Alzheimer's disease

Tau and amyloid beta proteins in this manner atrophy the brain. As damage to the neurons accumulates, due to plaques, tangles and inflammation, short-term memory is one of the first signs of dementia, then loss of motor skills and speech impairment. Long-term memory is next to go, with disorientation being late-stage.

Dementia in dogs

There is a difference between the neuron deterioration of canines compared to that of humans. However, when broken down into the biological and chemical formations in the brain that cause these symptoms of dementia (cognitive dysfunction), canines and humans may have a lot in common. For instance, impaired memory function and learning ability are common symptoms. Decline is more rapid, according to the Canine Dementia Scale (CADES), due to shorter life expectancy. Certain cells like AD Glial cells are just as important in the role of support of neurons within the brain in canines as they are in humans.

How breed affects symptoms of cognitive dysfunction

Amyloid beta plaques and senile plaques are found in canines, and both proteins destroy neurons, as in humans. Older dogs commonly develop canine cognitive dysfunction, a disease similar to Alzheimer's disease in many aspects. (Mihevc, P. S., Majdič, G. (2019) 60% of older dogs show symptoms of cognitive dysfunction.

The differences in time for these insoluble aggregates to build up, such as the amyloid proteins and taus mean that many dogs die before any real build-up causes decline of the brain. Larger dogs have a shorter lifespan than smaller dogs, making smaller dogs more apt for study in terms of cognitive decline; they have more time to develop these insoluble aggregates. Therefore, breed can have an indirect effect on the symptoms in canines.

Role of protein aggregates in neurodegenerative diseases in canines

Amyloid beta plaques are found in neurons in canines. This is unusual for amyloid beta plaques as they are normally extracellular hallmarks rather than intracellular. Similarly, amyloid beta plaques were found in cells (intracellular) in humans. This is an unusual similarity. 'In dogs, formation and maturation of Aβ deposits was observed by immunostaining throughout the canine cortical grey matter layers in a four-stage distribution, which is also characteristic for human AD, and this, according to some studies, correlates with the severity of cognitive deficit in the dog (Bosch et al., 2012) and varies as a function of age and size (weight) in companion dogs' (Mihevc, P. S., Majdič, G. (2019) This supports the idea that the difference in size of dog affects the symptoms of dementia and how quickly the symptoms arise. These symptoms correlate with the development of amyloid beta plaques in canines.

Immunostaining of canines and humans

The study of immunostaining is 'used to detect the distribution and localization of specific proteins within individual cells or tissues using immunostaining, defined as the use of specific antibodies to detect a single target protein.' (Maity, B., Sheff, D., Fisher, R. (2013) This can be specifically used to look at amyloid beta proteins and neurofibrillary tangles (NFTs). This can give photo evidence of the build-up of these proteins, and their association with the symptoms of dementia. 'Immunostaining is used in cell biology to study differential protein expression, localization and distribution at the tissue, cellular, and subcellular level.' By using this we can compare the protein build-up in canines and humans, and so demonstrate the similarities and differences hereby allowing us to show that AD and dementia are not uniquely human and can be seen in other animals. (Maity, B., Sheff, D., Fisher, R. (2013)

'Neprilysin (NEP) mRNA, coding for a pivotal Aβ-degrading protein, was poorly expressed in the prefrontal cortex of aged dogs with CCD (Canudas et al., 2014), similar to human AD brain, where areas with higher Aβ aggregation express lower levels of NEP' (Reilly, 2001). This means that the mRNA (messenger Ribonucleic acid) present, which codes for the proteins to break down the amyloid beta plaques, was not expressed well within the brains of dogs with CCD. There was also the same picture within humans showing another similarity.

Problems with phosphorylated tau in canines

Tau NFTs were identified in canine brains very occasionally. 'Increased phosphorylation of TAU was observed at some amino acid sites in canine brain,' (Mihevc, P. S., Majdič, G. (2019). These tangles were uncommon as they are normally seen in human AD.

Furthermore, in canines 'cytoplasmic deposits of phosphorylated TAU' (pTAU) have been detected only in the prefrontal cortex. This pTAU was observed more and more in synaptosomes of demented dogs. (Mihevc, P. S., Majdič, G. (2019). Synaptosomes are a part of brain tissue which contains a synapse; it is prepared by homogenisation then followed by fractionation. This is dependent on the size and the density of the tissue (Weiler. I, J. 2009). This study led to the conclusion that CCD might be caused by the weakening of the synaptic function. This was different as it was not caused by the neurofibrillary tangles, but was caused by the pTAU building up.

Age correlation with tau build-up

In one study, the brains of 20 'old' dogs were studied, ranging from eight to 18 years. They were compared to 10 young dogs through immunostaining of the brain. They routinely did this staining using special staining techniques 'and immunohistochemical techniques to detect glial fibrillary acid protein, neurofilaments, ubiquitin, and beta-amyloid' (Borras, D., Ferrer, I., Pumarola, M. (1999) Scientists found clear differences in 'lipofuscin, polyglucosan bodies' and amyloid beta plaques seen in humans. Polyglucosan is large sugar-based molecules that are normally broken down, but if there is a deficiency of 'glycogen-branching enzyme' then it is not broken down fast enough, so it can build up in tissue and sometimes in nerve tissue. This has an effect on the canine brain. Similar studies showed this in humans but not to the same extent.

Scientific concluding opinions

There is a dissimilarity between canine tau protein sequence and humans. Secondly, the lifespan of dogs might be too short to develop NFTs, as Aß deposition precedes NFT's formation. Thirdly, although the amyloid protein sequence is highly conserved between species, its N-terminal part is not, which might influence tau phosphorylation and its subsequent aggregation into NFTs. (Mihevc, P. S., Majdič, G. (2019). These points suggest that canines do not develop full AD. However, the similarities are significant enough for canines to be said to develop AD and dementia. We do not know the triggers for the build-up of insoluble aggregates in either canines or humans.

In light of this, examining canines as a species for testing may provide a better understanding of AD than mice or rodents. It could be argued that canines develop a form of AD. Dementia and AD are not uniquely human disorders; symptoms and formation of proteins are seen to a considerable extent and there is an overlap within the range of difference. To put it concisely, dogs can be used as a natural animal model for the study of normal ageing and human neurodegenerative diseases. T

SELECTED BIBLIOGRAPHY

Bale, C., (2017). A tale of two proteins. Available at: https://medium.com/parkinsons-uk/a-tale-of-two-proteins-d76293f7f764 [accessed on 3rd January 2020]

Borras, D., Ferrer, I., Pumarola, M., (1999). Age-related Changes in the Brain of the Dog. Available at: https://journals.sagepub.com/doi/pdf/10.1354/vp.36-3-202 [accessed 4th January 2020]

Dolman, L., MacLeod, P., (1981). Advances in Cellular Neurobiology. Available at: https://www.sciencedirect.com/topics/medicine-and-dentistry/lipofuscin [accessed on 19th December 2019]

Hardy, J., Higgins, G., (1992). Alzheimer's disease: the amyloid cascade hypothesis. Available at https://www.ncbi.nlm.nih.gov/pubmed/1566067 [accessed on 3rd December 2019]

Mihevc, P. S., Majdič, G., (2019). Canine Cognitive Dysfunction and Alzheimer's Disease – Two Facets of the Same Disease? Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6582309/ [accessed on 2nd January 2020]

Noble, W., Hanger, D., Lovestone, S., (2013). The Importance of Tau Phosphorylation for Neurodegenerative Diseases. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3696910/#!po=0.500000 [accessed on 9th January 2020]

Sodhi, N., Jaggi, A., Singh, N., (2014). Animal models of dementia and cognitive dysfunction. Available at: https://www.sciencedirect.com/science/article/abs/pii/S0024320514005165 [accessed on 25th December 2019]

Walker, L., Dhenain, M., Head, E., Hof, P., Lemere, C., Nelson, P., (2016). Is Alzheimer's Disease a Uniquely Human Disorder? Available at: https://www.alzforum.org/webinars/alzheimers-disease-uniquely-human-disorder [accessed on 28th January 2020]