Cognitive dysfunction and the neurobiology of ageing in cats

With improvements in nutrition and veterinary medicine the life expectancy of pet cats is increasing. Accompanying this growing geriatric population there are increasing numbers of cats with signs of apparent senility. A recent study suggests that 28 per cent of pet cats aged 11 to 14 years develop at least one geriatric onset behavioural problem, and this increases to over 50 per cent for cats of 15 years of age or older. While behavioural changes may result from systemic illness, organic brain disease or true behavioural problems, the possibility of age-related cognitive dysfunction is often overlooked. Studies have revealed a number of changes in the brains of geriatric cats that showed signs of cognitive dysfunction, and potential causes include vascular insufficiency leading to hypoxia, increased free radical damage and the deposition of β-amyloid plaques and/or the modification of other proteins. By recognising the importance of behavioural changes in old cats, investigating them fully for potentially treatable medical conditions, and instigating dietary and environmental modifications to meet their changing needs, we can make the lives of our geriatric cats much more comfortable and rewarding.

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INTRODUCTION

Because of improvements in nutrition and veterinary medicine, there are now more elderly cats than ever before. In the USA over the last 10 years, there has been a 15 per cent increase in the number of cats over 10 years of age (Broussard and others 1995), and in the UK it is estimated that there are currently approximately 2·5 million "senior" cats (Gunn-Moore 2003). As this may account for perhaps 30 per cent of the pet cat population (Venn 1992), effective management of these individuals is becoming an ever more important consideration for small animal veterinary practitioners.

Unfortunately, accompanying this growing geriatric population there are increasing numbers of cats showing signs of altered behaviour and apparent senility (Fig 1). These behavioural changes may result from many different disorders (Box 1) including systemic illness, organic brain disease, true behavioural problems or cognitive dysfunction. Diagnosis involves a full investigation looking for underlying illness (Box 2). Because cognitive dysfunction syndrome (CDS) is an ante-mortem diagnosis of exclusion, this disorder should be considered once any other illness has been ruled out. The most commonly seen behavioural changes in CDS include spatial or temporal disorientation, altered interaction with the family, changes in sleep-wake cycles, house-soiling with inappropriate urination/defecation, changes in activity and/or inappropriate vocalisation (see Box 3).

COGNITIVE DECLINE IN AGEING CATS

Clinical evidence

CDS therefore describes an age-related decline of cognitive abilities, which are characterised by behavioural changes that are not attributable to other medical conditions (Chapman and Voith 1990, Ruehl and others 1995, Landsberg and Araujo 2005: to date, most of the studies have focused on dogs).

Many owners of old cats readily recognise senile behavioural changes in their pets; however, to date, there are very few published reports on this subject. A survey of clients who owned older cats (seven to 11 years of age) revealed that 36 per cent of owners reported behavioural problems in their cats (Landsberg 1998), and the frequency of these behavioural problems increased with age to as high as 88 per cent in cats between 16 and 19 years of age. A more recent study by one of the authors (K. M.) evaluated common behavioural changes in geriatric cats in private practice (Moffat and Landsberg 2003, K. S. Moffat, G. M. Landsberg, E. Head, J. A. Araujo, B. Lindgren, unpublished observations). In this study, cats of 11 years of age or older that were presented for routine medical care (such as vaccines or dental prophylaxis) were screened with a comprehensive medical and behavioural questionnaire.

FIG 1. Elderly Burmese cat (14 years old) showing disorientation and significant elbow arthritis. (Picture courtesy of Marge Chandler.)

Cats with geriatric onset behavioural changes were then assessed by physical examination as well as blood and urine analyses and those found to have systemic illness were excluded from the study. A total of 154 cats between the ages of 11 and 21 years of age were evaluated. The overall percentage of cats displaying geriatric onset behavioural changes was 44 per cent (67/154). Nineteen of these cats had concomitant medical conditions, leaving 36 per cent of the cats (48/135) with behavioural changes not attributed to obvious underlying disease. The older the cat, the more likely they were to demonstrate behavioural changes, with 50 per cent (23/46) of cats 15 years and older showing changes whereas only 28 per cent (25/89) of cats aged 11 to 14 years showed changes (P=0·02). The most common behavioural change seen in the 11 to 14 year old age group was alteration in social interactions with people or other pets. In cats aged 15 years and older the most common signs were alterations in activity, including aimless activity and excess vocalisation.

These data mirror those observed in humans and dogs: in humans, dementia is seen in 1 to 3 per cent of 65 to 70 year olds, and increases to affect approximately 50 per cent of people over 85 years of age (Porter and others 2003). In dogs (n=80), 28 per cent aged 11 to 12 years showed signs of CDS, compared with 68 per cent of those over 15 years of age (Neilson and others 2001). In this context, a 15 year old cat appears to equate to an 85 year old human and perhaps to a 13 to 14 year old dog, although in dogs ageing is particularly breed dependent (Bobik and others 1994).

Unfortunately, studying behavioural changes in pet cats can be problematic. This is because owner evaluations measure global brain dysfunction (overt behavioural changes) and may not detect early or subtle changes in learning or memory abilities. Neuropsychological laboratory-based tests (that are often based on food rewards) directly measure quantitative and objective measurements of cognitive function and are therefore more accurate; however, while they have been developed for the assessment of dogs they have been proven to be very difficult to use in cats.

Box 1. Potential causes of behavioural changes in geriatric cats

- Arthritis (the pain and/or dysfunction of arthritis is often underrecognised in elderly cats)*
- Systemic hypertension (high blood pressure may either be primary or secondary to, for example, hyperthyroidism, renal failure, diabetes mellitus, acromegaly or hyperadrenocorticism)
- Hyperthyroidism
- Chronic renal failure
- Diabetes mellitus
- Urinary tract infection
- Gastrointestinal disease
- Liver disease
- Neurological defects (either sensory or motor deficits)
- Reduced vision or hearing
- Brain tumours (for example, lymphoma, meningioma)
- Infectious disease (for example, FIV, FeLV, toxoplasmosis, FIP or, perhaps, Borna disease)
- Dental or periodontal disease
- Inflammatory disease in general
- Pain in general
- True behavioural problems
- Cognitive dysfunction syndrome

*The importance of arthritis should not be overlooked. Radiographic evidence of degenerative joint disease is present in 70 to 90 per cent of cats over 10 years of age (Hardie and others 2002, Clarke and others 2005). Associated pain and/or dysfunction can result in reduced activity and mobility (Clarke and Bennett 2006), aggression, altered interactions with the family and/or loss of litter box training (Houpt and Beaver 1981). When asked, most owners list the diseases that they see in their older cats in a different order to the list generated by veterinary surgeons. Top of the owner's list is arthritis, and this is followed by kidney failure, deafness, blindness, hyperthyroidism, bronchitis and dental problems (V. Halls, personal communication). Owners can help their arthritic cats by adjusting their house; for example, by moving food and water bowls to lower surfaces, adding ramps to allow easier access to favoured sleeping areas and placing low-sided litter boxes within easy cat reach.

Laboratory-based evidence

Laboratory-based studies provide additional evidence that cats are vulnerable to age-related cognitive decline. It is generally accepted that cognitive and motor performance deteriorates with age, and experiments with cats have indicated that this deterioration typically occurs starting at 10 years of age (Harrison and Buchwald 1982, 1983, Levine and others 1987a). Aged cats also show a decline in visual and auditory ability (Harrison and Buchwald 1982). In addition, they show a heightened sensitivity to changes in their environment, which can result in changes in eating or elimination patterns, and even in aggres-

Box 2. Investigation of behavioural changes in geriatric cats should include the following

- Full history, including the possibility of previous trauma (which may have led to arthritis), any potential exposure to toxins or drugs and any recent environmental changes (in the household, family members, diet, etc.)
- Full physical examination (including assessment of body weight, body condition score, retinal examination and a full neurological examination)
- Assess systemic blood pressure
- Assess haematology and serum biochemistry, including thyroxine levels
- Urine analysis (including specific gravity, dipstick, sediment, urine protein to creatinine ratio and bacterial culture)

Further investigation may include:

- Where appropriate, serological testing for FeLV, FIV, toxoplasmosis or FIP
- Thoracic, abdominal or skeletal radiography, abdominal ultrasound examination, electrocardiography, echocardiography, intestinal endoscopy/exploratory laparotomy and biopsy collection, as indicated from initial findings
- Head CT or MRI

sion (Houpt and Beaver 1981). Other age-linked behavioural deficits include reduced classical conditioning and disturbances in patterns of habituation in tests of locomotor activity and auditory reactivity (Harrison and Buchwald 1983, Levine and others 1987b) (Box 4). The nature of these changes is suggestive of caudate dysfunction because impairments in habituation are seen in cats that have had the caudate area of their brain experimentally damaged (Villablanca and others 1978).

NEUROBIOLOGICAL MECHANISMS UNDERLYING BRAIN AGEING

The pathophysiology of feline brain ageing still requires considerable study: it may involve a number of different mechanisms occurring either singularly or in combination.

Vascular insufficiency leading to hypoxia

Although atherosclerosis, cerebral ischaemia and cerebral haemorrhage are less common in cats and dogs than in humans, numerous vascular and perivascasular changes can be seen; these include a decrease in cerebral vascular blood flow, microhaemorrhages or infarcts of the periventricular vessels and arteriosclerosis of the non-lipid variety (consisting of fibrosis of the vessels walls, endothelial proliferation, mineralisation, and β-amyloid [Aβ] deposition) (reviewed in Dimakopoulos and Mayer 2002, Landsberg and Araujo 2005). In addition, the brain of elderly cats may be subject to compromised blood flow and hypoxia because of decreased cardiac output, systemic hypertension, anaemia, altered blood viscosity or platelet hypercoagulability, all of which occur commonly in this species. Because neurons have a continuous high demand for oxygen, they are particularly at risk of hypoxic damage, regardless of its underlying cause.

Box 3. Behavioural changes that can be seen in geriatric cats and may be associated with cognitive dysfunction syndrome

- Spatial disorientation or confusion, for example, getting trapped in corners or forgetting the location of the litter box (house-soiling is the most common reason for referral of old cats to behaviouralists)
- Altered social relationships either with their owners or other pets in the household, for example, increased attention seeking or aggression
- Altered behavioural responses, for example, increased irritability or anxiety, or decreased response to stimuli
- Changes in sleep-wake patterns
- Inappropriate vocalisation, for example, loud crying at night
- Altered learning and memory, such as forgetting commands or breaking house training
- Changes in activity, for example, aimless wandering or pacing, or reduced activity
- Altered interest in food, either increased or, more typically, decreased
- Decreased grooming
- Temporal disorientation, for example, forgetting that they have just been fed (Houpt and Beaver 1981, Landsberg and Ruehl 1997, Houpt 2001, Landsberg and others 2003)

Reactive oxygen species

During normal cellular metabolism a small amount of the oxygen that is used by mitochondria for energy production is converted to reactive oxygen species (that is, free radicals, such as hydrogen peroxide, superoxide and nitric oxide). As mitochondria age, they become less efficient, producing less energy and more free radicals (Shigenaga and others 1994). Normally, these free radicals are removed by the body's natural antioxidant defences, including enzymes (such as superoxide dismutase [SOD], catalase and glutathione peroxidase) and free radical scavengers (such as vitamins A, C and E). However, the balance between production and detoxification can be upset by disease, stress and advancing age, so that an excess of free radicals can react with DNA, lipids and proteins, leading to cellular damage, dysfunction and mutation. The brain is particularly susceptible because it has a high demand for oxygen (because of its high metabolic rate), high lipid content and limited repair mechanisms (reviewed in Landsberg and Araujo 2005, Roudebush and others 2005).

Aβ deposition and/or tau hyperphosphorylation

While there are a number of theories suggesting how these proteins may be associated with neurological degeneration, it is currently believed that the extracellular accumulation of Aβ into senile plaques (SP) may initiate inflammatory changes and neurotoxicity which ultimately results in tau hyperphosphorylation (tau is an intraneuronal microtubule-associated protein that in its unphosphorylated form is involved in forming the cytoskeleton of neurons), neurofibillary tangle (NFT) formation and further neurological dysfunction (Hardy and Higgins 1992, Dickson and others 1995; reviewed in Selkoe 1997, Mattson 2004, Hardy 2006). In addition to accumulating as SP, Aβ also accumulates around the meninges and blood vessels, eventually resulting in cerebral amyloid angiopathy (CAA) (Selkoe and others 1987, Selkoe 1997). However,

while these changes may be associated with Alzheimer's disease (AD) they are not specific to it. In humans, SP and CAA are also seen in the brains of many elderly people who did not have clinical signs of dementia (Selkoe and others 1987), and similar but less pronounced SP and CAA have been seen in the brains of other aged mammals, including dogs, sheep, goats, bears and wolverines (Head and others 2001). In addition, hyperphosphorylated tau is not only associated with age-related neurodegeneration, it is also present during normal early postnatal development (Riederer and others 2001), and arises in response to degenerative events such as ischaemia or seizures (Burkhart and others 1998, Blumcke and others 1999).

EVIDENCE OF NEUROPATHOLOGY RELATED TO AGE IN CATS

Compared with dogs the relationship between neuropathology and age-related behavioural dysfunction has not been well explored in cats. In general, compared with younger mammals, the brains of older mammals (for example, dogs and humans) show a number of anatomical and physiological changes. These include a reduction in overall brain mass (including atrophy of cerebral cortex and basal ganglia); a reduction in the number of neurons; generalised gliosis; degeneration of white matter; demyelination; neuroaxonal degeneration; increases in ventricular size; meningeal fibrosis and/or calcification; vascular and perivascasular changes; increasing amounts of lipofuscin, apoptotic bodies and Aβ; and tau hyperphosphorylation. Functional changes include depletion of catecholamine neurotransmitters (noradrenaline, serotonin and dopamine), a decline in the cholinergic system, an increase in monoamine oxidase B (MAOB) activity and a reduction of endogenous antioxidants (reviewed in Dimakopoulos and Mayer 2002, Landsberg and Araujo 2005, Roudebush and others 2005). While the brains of older cats show many of these changes (see below) it is not yet clear which of the changes may be directly associated with cognitive dysfunction.

Cerebellar changes with age

Consistent with motor dysfunction observed in ageing cats, there is a loss of neurons in the cerebellum of old animals (12 to 13 years of age; n=4) as compared with younger animals (2 to 3 years of age; n=4) (Zhang and others 2006). The thickness of the molecular layer of the cerebellum decreases while the granular layer increases, and there is a significant increase in astrogliosis along with hypertrophy of neurons. In addition, Purkinje cells in aged cats show less immunoreactivity for a protein marker of neurofilaments suggesting a decrease in the number of dendrites in these neurons.

Caudate nucleus changes with age

The caudate nucleus is affected in many age-associated neurodegenerative diseases, including AD and Parkinson's disease. The caudate nucleus of young cats (1 to 3 years of age; n=5) was compared with aged cats (≥10 years of age; n=6) and a number of age-related changes in the morphology and number of neurons was observed (Levine and others 1986). Ultrastructural studies confirmed a loss in the density of synapses in the caudate neuropil (Levine and others 1988) and electrophysiological studies of caudate neurons in aged cats suggest synaptic impairments consistent with these morphological changes (Levine and others 1987b). The functional implications of dysfunction in the caudate nucleus of aged cats may involve impairments in motor function or in the cat's ability to habituate to repeated stimuli (Levine and others 1978, 1982, Villablanca and others 1978).

Cholinergic system changes with age

Cholinergic system dysfunction and neuron loss in the locus coereleus occur in AD (Muir 1997) and virtually all approved pharmacological treatments for AD involve anticholinesterases (which increase the availability of acetylcholine to neurons). Zhang and others (2005) examined this area of the brain in young (2 to 3 years old; n=4) and aged cats (15 to 18 years; n=4) using an antibody against choline acetyltransferase (ChAT) to identify cholinergic neurons, their size, number and total dendritic length. There was a striking reduction in the size but not number of ChAT-positive neurons and the average dendritic length of ChAT-positive neurons was reduced in aged cats. Ultrastructurally, the mitochondria of the cholinergic neurons appeared abnormal in aged cats, large vacuoles were observed, and there was an accumulation of liposfuscin. In dendrites, the cytoplasm appeared to contain fewer microfilaments, and vacuoles and myelin bodies were observed. In addition, axonal degeneration and myelin disruption were seen in some cases. These abnormalities in the cholinergic neurons in this area of the brain may result in functional consequences associated with disruption in the sleep-wake cycle (Chase 1983).

β-Amyloid

Aβ pathology has been observed in the brain of many aged mammals (Head and others 2001, 2005). (This amyloid is not the same as that found in other organs such as liver, kidney or pancreas.) Aβ pathology is thought to be critically involved in brain ageing in humans, and with the development of AD where the hallmarks of disease are the presence of SP and NFT (see below) (Selkoe 1996, 1997, Mattson 2004). In dogs, the pattern of Aβ accumulation parallels that seen in humans, being age related and having a direct correlation between the extent and location of Aβ deposition and the extent and nature of cognitive dysfunction (Cummings and others 1996a, Kuroki and others 1997, Satou and others 1997, Head and others 1998, 2000, 2001, Head 2001; reviewed in Head and Zicker 2004, Roudebush and others 2005). Intriguingly, while all dogs naturally accumulate diffuse SP and CAA with age (generally beginning in middle age), some breeds appear to develop them earlier than others (with the same breeds developing earlier signs of CDS) (Bobik and others 1994, Head and others 2000; reviewed in Head and others 2001).

A number of studies have investigated Aβ deposition in cats. As with all species, visualising Aβ in the cat brain is dependent on the staining technique used. For example, SP are not detected with silver staining even in very old cats

(>17 years old) (Braak and others 1994). In contrast, more sensitive immunohistochemical techniques can reliably identify SP, although they are only found in cats over 10 years of age (Cummings and others 1996a, Nakamura and others 1996, Brellou and others 2005, Gunn-Moore and others 2006).

Interestingly, the SP of cats (Fig 2) appear to be even more diffuse than those seen in dogs, and quite unlike the well-developed and circumscribed SP that are typical of humans. Aβ is a long-lived peptide species, and once deposited in the extracellular space can become spontaneously isomerised and undergo a conformational change that can lead to further aggregation. Isomerised Aβ has been observed in the aged canine and human brain (Satou and other 1997, Fonseca and others 1999) but is not seen in the aged cat brain. In a recent study, one of the authors (E. H.) showed that antibodies specific for $A\beta_{1-42}$ and $A\beta_{17-24}$, but not for $A\beta_{1-16}$ or $A\beta_{1-40}$, labelled diffuse SP in cat brain (Head and others 2005). A lack of $A\beta_{1-40}$-positive SP suggests that the more soluble $A\beta_{1-40}$ species, which is typically deposited after $A\beta_{1-42}$ may not accumulate in the brain of the ageing cat (Cummings and others 1996b, Wisniewski and others 1996) – although it has been seen within their cerebral blood vessels when they are exhibiting signs of CAA (Nakamura and others 1996). This implies that if and when $A\beta_{1-40}$ is deposited in the extracellular space in the cat brain, it is rapidly turned over (Hyman and others 1993), and indicates that plaque accumulation in the aged cat brain more closely parallels the type of pathology detected in non-demented elderly humans than patients with AD (Iwatsubo and others 1994, Head and others 2005).

In cats, the association between Aβ deposition and CDS remains to be clarified. In Cummings and others (1996b), the brains from three aged cats that had exhibited abnormal behaviour such as wandering, confusion and inappropriate vocalisation were found to contain diffuse SP. In addition, another study (n=19 cats) showed that more cats with signs of behavioural and/or neurological disorders are found to have SP than those cats without clinical signs (Gunn-Moore and others 2006). However, there was variability among the cases and in a separate study looking at five cats with well-documented CDS, the severity of the behavioural changes did not appear to correlate particularly well with the extent of the Aβ formation (Head and others 2005).

Tau pathology

Tau pathology occurs during the development of NFT, which are formed initially by the intracellular accumulation of the abnormally hyperphosphorylated form of tau (reviewed in Selkoe 1997, Mattson 2004). NFT classically occurs in AD (Trojanowski and others 1993). To our knowledge, no evidence for NFT formation has been reported in the aged cat brain (Braak and others 1994, Nakamura and others 1996, Kuroki and others 1997) even though cats express multiple tau isoforms similar to humans (Janke and others 1999). However, while NFT has not been seen in cat brains, immunostaining for hyperphosphorylated tau has been demonstrated, occurring concurrently within the neurons of some of the cats showing SP development, and providing evidence of possible pre-tangle formation in older cats (Fig 3) (Head and others 2005, Gunn-Moore and other 2006). As yet, an association between tau hyperphosphorylated and CDS cannot be determined as too few cats have been found to be positive for this altered protein.

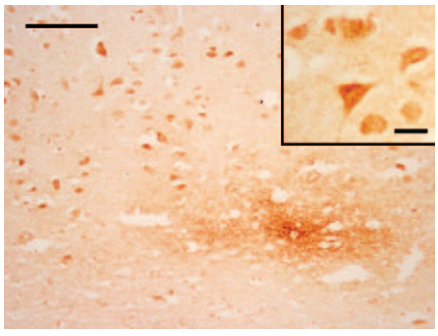

FIG 2. Cat brain, frontal cortex, from a 10 year old cat showing chronic progressive neurological signs, with ataxia. Intense staining of neurons and diffuse granular focus of extracellular β-amyloid deposits within the neuropil of the deep cortex. Immunostain, 4G8. Bar, 100 μm. Inset: higher magnification of neurons, where the stain is punctate and intracellular. Bar, 25 μm. (Picture reprinted with permission; Gunn-Moore and others 2006.)

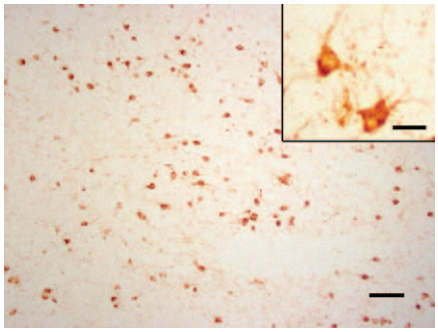

FIG 3. Cat brain, anterior cerebrum, from a 11 year old cat showing signs of chronic neurological disorder. AT8-immunoreactivity in neurons. Immunostain, antibody to hyperphosphorylated tau protein (AT8). Bar, 100 μm. Inset: higher magnification of neurons, where the stain is punctate and intracellular. Inset bar, 25 μm. (Picture reprinted with permission; Gunn-Moore and others 2006.)

SUMMARY OF NEUROPATHOLOGY

In humans and dogs, genetics, diet and lifestyle choices have all been found to influence the prevalence and pattern of neuropathological changes (particularly SP formation) and the nature of cognitive dysfunction. However, these relationships have still to be determined in cats, and the association between Aβ deposition, tau pathology and CDS requires considerably more investigation. Further studies are needed to confirm, for example, whether changes only relate to progressive age, and/or to the presence of particular disease processes. In addition, the extent of the changes needs to be correlated with the clinical signs of CDS, and it remains to be seen whether particular breeds of cat may be predisposed. Thus, while there are many similarities between CDS in cats and dogs and AD in humans, there are also a number of subtle differences.

TREATMENT OPTIONS FOR CDS

Although there are no published studies relating to the treatment of cats with CDS, it is possible to consider potential treatment options by extrapolation from studies of humans with AD and dogs with CDS. Potential interventions therefore

include dietary modification, environmental management and drug therapies (reviewed in Landsberg 2006).

Dietary modification and environmental management

Diets enriched with antioxidants and other supportive compounds (for example, vitamin E, β-carotene and essential fatty acids) are believed to reduce oxidative damage, so reducing Aβ production and improving cognitive function. In humans, studies have shown that high intakes of fruits, vegetables, vitamins E and/or C, folate and/or B_{12} may improve cognition (although excessive intakes of antioxidants can have a pro-oxidant effect). In addition, alpha-lipoic acid and *l*-carnitine enhance mitochondrial function, and omega-3 fatty acids promote cell membrane health and have, in humans, been found to be beneficial in the treatment of dementia. In general, combinations of these compounds are believed to work best.

There have been a number of studies investigating the potential benefit of various supplements in dogs with CDS (Ikeda-Douglas and others 2004; reviewed in Head and Zicker 2004, Roudebush and others 2005, Landsberg 2006). For example, a study of dogs over six years of age, when given a supplement containing omega-3 fish oils, vitamins E and C, L-carnitine, alpha-lipoic acid, coenzyme Q, phosphotidylserine and selenium (this supplement is sold in the UK as Aktivait® from VetPlus) over a two-month period resulted in significant improvements in signs of disorientation, social interaction and house-soiling (Heath and others 2007). Unfortunately, a different formula is needed for cats as alpha lipoic acid is toxic in this species (Hill and others 2004) so products containing it should not be given. While the new feline-safe version of Aktivait is now on the market, trials in cats still need to determine its efficacy, as they have for the other supplements that have also recently become available, such as Feli-Age® from VetriScience.

Environmental enrichment can lead to an increase in neuronal growth factors, the growth and survival of neurons and an increase in cognitive function. The combination of environmental stimulation (for example, toys, company, interaction and food-hunting games) and a diet enriched with antioxidants is believed to have a synergistic action in improving cognitive function. In aged dogs, a four-year study on the use of an antioxidant-enriched diet (for example, vitamins E and C, selenium, fruit and vegetable extract [β-carotene, other carotenoids, flavinoids]), mitochondrial cofactors (*dl*-lipoic acid and *l*-carnitine) and essential fatty acids (omega-3 fatty acids) (Hill's b/d®), plus environmental enrichment (for example, toys, kennel mate, walks and cognitive experience testing), revealed rapid (two to eight weeks into treatment) and significant improvements in learning and memory. Interestingly, while there was no reversal of existing pathology, the antioxidants appeared to prevent the deposition of more Aβ, while the environmental enrichment did not (Milgram and others 2004, 2005).

While a similar study showing improvement of CDS in cats in response to dietary supplementation is not yet available, a five-year study feeding healthy old cats (seven to 17 years old; n=90) a diet (Nestlé Purina Pro Plan Age 7+®) supplemented with antioxidants (vitamin E and β-carotene), essential fatty acids (omega-3 and -6 fatty acids) and dried whole chicory root (which contains the prebiotic inulin to modify intestinal flora) resulted in the supplemented cats living significantly longer than the unsupplemented ones (Cupp and others 2006). Other similarly supplemented diets will soon be on the market (for example, Hill's Science Plan Feline Mature Adult 7+®).

Unfortunately, once cats develop significant clinical signs of CDS, instigating environmental change can actually have a negative effect. This is because affected cats often become very stressed and cope poorly with change; whether in their environment, their daily routine, their diet or the members of the household with which they live. The cat's response to this stress is to show more obvious signs of CDS (for example, anorexia, hiding and/or upset of toileting habits) (Houpt and Beaver 1981). For these cats, where possible, change should be kept to a minimum, and when it cannot be avoided it should be made slowly and with much reassurance. Some cats may become so demented and cope so poorly with change that they may benefit from having their area of access reduced in size (for example, to a single room containing everything they need); this small area can then be kept safe and constant. Environmental application of synthetic feline appeasement pheromone (Feliway®; Ceva) can also help in reducing feline anxiety.

Potential drug therapies

There are a growing number of possible drug options for AD. These include various cholinesterase inhibitors (to increase the availability of acetyl choline at the neuronal synapses), selegiline (to manipulate the monoaminergic system), antioxidants (for example, vitamin E) and non-steroidal anti-inflammatory drugs (to reduce neuronal damage). While there are no drugs licensed for the treatment of CDS in cats, selegiline, propentofylline and nicergoline have all been used in this species with varying degrees of success (see below) (Landsberg and others 2003, Landsberg and Araujo 2005, Studzinski and others 2005, Landsberg 2006). Anecdotally, other drugs that have been used to treat particular signs of CDS in cats include anxiolytic drugs, such as buspirone and benzodiazepines (although hepatotoxicity is a particular risk with the latter), or antidepressants (that lack anticholinergic effects) such as fluoxetine.

Selegiline (*l*-deprenyl; Selgian® in the UK, Anipryl® in the USA; Pfizer) is licensed to treat dogs with CDS in the USA. It is a selective and irreversible MAOB inhibitor, which leads to an increase in 2-phenylethylamine and enhances the effects of dopamine. While its exact mechanism of action is still unclear, it may also have an antioxidant effect by increasing the effect of SOD. There have been a number of studies on its use in geriatric dogs, with up to 80 per cent of the dogs ($n \geq 600$ in different studies) showing improvement after being medicated for longer than a month. Improvements are typically seen in disorientation, sleep-wake cycles and interaction with the family, but are less marked in the most severely affected cases, and the disease continues to progress in all cases (Ruehl and others

1995, Campbell and others 2001). While selegiline is not approved for use in cats with CDS, anecdotally evidence is supportive, as was a small open trial (Landsberg 2006), and the American Association of Feline Practitioners has supported its use for this disorder (suggested dose 0·25 to 1·0 mg/kg orally every 24 hours; dog dose 0·5 to 1·0 mg/kg orally every 24 hours).

Propentofylline (Vivitonin®; Intervet) is licensed for the treatment of CDS in dogs in Europe. It is a xanthine derivative that is purported to increase blood supply to the brain, particularly the cerebral tissues, without increasing oxygen demand. It is also supposed to inhibit platelet aggregation, thrombus formation, inflammation and excessive activation of microglia, and decrease the formation of free radicals, cytokines and abnormal amyloid precursor proteins (Parkinson and others 1994). While studies show some benefit in dogs with CDS, increasing general demeanour, alertness and willingness to exercise (Siwak and others 2000), there is only weak evidence that it slows the progression of AD in people. Anecdotally, it has been used to treat cats with CDS (suggested dose 12·5 mg/cat orally every 24 hours; dog dose 3 to 5 mg/kg orally every 8 to 12 hours).

Nicergoline (Fitergol®; Merial) is licensed to treat CDS in dogs in Europe. It is an ergoline derivative that acts as an α1 and α2 adrenergic agonist. It increases cerebral blood flow, has a neuroprotective effect on neurons, and inhibits platelet aggregation. It may also act as a scavenger of free radicals and even increases appetite (Siwak and others 2000). Anecdotally, it has been used to treat cats with CDS (suggested dose quarter of a 5 mg every 24 hours: dog dose 0·25 to 0·5 mg/kg orally every 24 hours).

Glossary

Cerebral amyloid angiopathy	The accumulation of Aβ around meninges and blood vessels
Caudate area of the brain	Nucleus located within the basal ganglia in the brain. The caudate, originally thought to be primarily involved with control of voluntary movement, is now known to be an important part of the brain's learning and memory system
Caudate dysfunction	Occurs when the caudate area of the brain is not functioning correctly, and can result in alterations in movement, learning and memory
Cognitive dysfunction syndrome	Describes an age-related decline of cognitive abilities; it is characterised by behavioural changes that are not attributable to other medical conditions
Classical conditioning	Also termed Pavlovian conditioning is a type of associative learning in which a response is elicited by a neutral stimulus which has previously been repeatedly presented in conjunction with the stimulus that originally elicited the response
Cognition	The operation of the mind by which we become aware of objects of thought or perception; it includes all aspects of perceiving, thinking and remembering
Habituation	The gradual adaptation to a stimulus or to the environment
Locus coereleus	An area on the floor of the fourth ventricle of the brain; it is involved in vigilance and autonomic activity
Neurofibillary tangles	Made from hyperphosphorylated tau protein (tau is a intraneuronal microtubule-associated protein that in its unphosphorylated form is involved in forming the cytoskeleton of neurons)
Senile plaques	Made from the extracellular accumulation of Aβ

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