



Review article

Therapeutic agents for the treatment of cognitive dysfunction syndrome in senior dogs

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Abstract

With increasing age, dogs develop a form of neurodegenerative disease which has many similarities to age related cognitive impairment and Alzheimer's disease in humans. A decline in learning and memory can be demonstrated in dogs beginning as young as 7 years of age using a variety of neuropsychological tests. However, clinical cases of cognitive dysfunction syndrome are seldom identified until the age of 11 years or older. This is likely due to the fact that the owners are relying on clinical observations such as house-soiling, sleep-wake cycles and disorientation, rather than tests of learning and memory. On the other hand, dogs that are trained to more exacting tasks such as guide dogs for the visually impaired, or bomb detection and agility trained dogs might be noticed to have a decline in performance at a much earlier age. Through the use of standardized neuropsychological testing protocols, a number of drugs, natural products and supplement formulations have been developed for use in dogs with cognitive dysfunction and, in some cases clinical trials have validated their efficacy. Furthermore, the testing of products currently licensed and in the pipeline for the treatment of cognitive decline and Alzheimer's in humans, may provide additional therapeutic agents for the treatment of senior dogs, as well as provide insight as to the potential for the efficacy of these compounds in humans. This review will examine those products that are now marketed along with some that might be considered for use in senior dogs with cognitive dysfunction as well as the research that has been used to validate the efficacy (or lack thereof) of these compounds.

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Keywords: Acetylcholinesterase inhibitor; Adrafinil; Alpha-lipoic acid; Antioxidant; Brain aging; Canine b/d®; Cognitive dysfunction syndrome; Discrimination learning; Docosahexaenoic acid; Environmental enrichment; Gingko biloba; L-carnitine; Modafinil; Neurodegenerative; Nicergoline; Phosphatidylserine; Propentofylline; Reversal learning; Selegiline; Scopolamine; Spatial memory

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Abbreviations: CDS, Cognitive dysfunction syndrome; DISHA, acronym for Disorientation, altered Interactions with people and other pets, Sleep-wake cycle alterations, Housesoiling and altered Activity Level; TGTA, Toronto General Test Apparatus; DHA, docosahexaenoic acid; DNMP, delayed-non-matching-to-position-task; DNMS, delayed-non-matching-to-sample task; MAOB, monoamine oxidase B; MCI, mild cognitive impairment; NGF, neurotrophic growth factor; PEA, 2-phenylethylamine; SOD, superoxide dismutase.

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1. Introduction

With increasing age, dogs develop a form of neurodegenerative disease, which has many similarities to age related cognitive impairment and Alzheimer's disease in humans. Neuropsychological testing in the laboratory has led to the development of a number of standardized tests that can clearly demonstrate differences in learning and memory when comparing young dogs to senior dogs as well as different subsets of cognitive impairment within the population of senior dogs. These tests are not only a better objective measure of cognitive impairment than owner assessment but are also more sensitive since they measure learning and memory impairment rather than clinical observations. Using these tests, major advances have been made in the understanding of cognitive impairment in senior pets and in the development of therapeutic agents for the treatment of cognitive dysfunction in senior dogs.

2. Cognitive dysfunction syndrome in dogs; clinical diagnosis

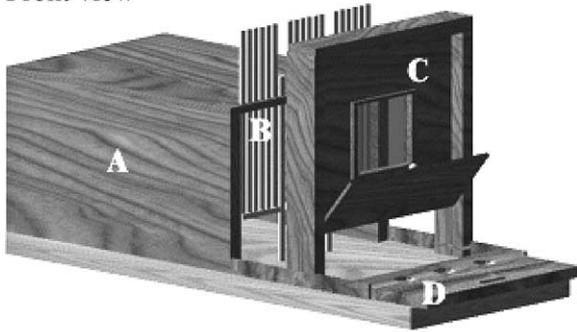
The term Canine Cognitive Dysfunction Syndrome (CDS) is used in the veterinary literature to describe the progressive neurodegenerative disorder of senior dogs that is characterized by a gradual decline in cognitive function (learning, memory, perception, and awareness) (Milgram et al., 1994; Cummings et al., 1996a,b). In one study of 180 dogs with no identifiable health problems, 28% of owners of 11- to 12-year-old dogs reported at least one category consistent with cognitive dysfunction and this rose to 68% for dogs 15 to 16 years of age. Ten percent of owners of the 11- to 12-year-old dogs and 36% of the owners of 15- to 16-year-old dogs reported signs in two or more categories (Nielson et al., 2001). The acronym DISHA has been used clinically to describe these categories: *Disorientation*, altered *Interactions* with people or other pets, *Sleep*–wake cycle alterations, *House-soiling* and altered *Activity* level (Landsberg et al., 2003). However, these categories do not necessarily describe all of the signs that might be associated with cognitive decline in dogs since an increase in anxiety, a decrease in hygiene/self-grooming, altered appetite, a decreased responsiveness to stimuli, and deficits in learning and memory have also been reported (Landsberg and Ruehl, 1997; Landsberg et al., 2003). All such changes in the aging dog are not necessarily due to cognitive dysfunction; a

variety of medical problems, including other forms of brain pathology (such as brain tumors or infarcts) might contribute to these signs. Therefore, a diagnosis of CDS in dogs is based on identifying the clinical signs and excluding other disease processes that might cause or contribute to these signs.

3. Cognitive dysfunction in dogs: neuropsychological diagnosis

Because of the relationship between owners and their dogs, and the somewhat limited degree to which most pet animals are trained, owner observation and reporting of clinical signs, is the only practical means of detection of cognitive dysfunction. Of course with pets trained to a higher level of performance such as the agility trained, therapy (e.g. guide dogs for the blind) or working dog (e.g. drug or explosive detection), signs of cognitive decline might be more readily detected and at an earlier state of the disease process. On the other hand, a number of laboratory cognitive tasks, including discrimination learning, reversal learning, and spatial memory are used to document a decline in performance in older dogs (Milgram et al., 1994). In these studies, dogs are placed in a testing apparatus, the Toronto General Testing Apparatus (TGTA) and offered a variety of objects that cover food rewards (Fig. 1A and B). Location of the objects are randomized by a computer program and dogs typically are judged to have learned a task if they achieve a score of 90%, or scores of 80% over 2 days and then maintain a score of 70% over the next 3 testing sessions. For discrimination learning and reversal learning two objects of different size, shape and/or color are used. Animals must learn to approach one of the two objects to obtain a food reward in discrimination learning. Once the animal successfully learns which object is correct, they are tested on a reversal learning task in which the reward contingencies are modified; the object that was previously not rewarded is now associated with a food reward. While aged animals are consistently impaired on reversal learning, age does not affect the visual discrimination performance except when dogs are very old (greater than 12 years of age) or if the complexity of the discrimination is increased, such as when objects are more similar (Cotman et al., 2002; Tapp et al., 2003; Milgram et al., 2002a). In the landmark task, where animals are required to respond based on the proximity of a thin block of wood to a rewarded well, there is a significant

Front view



Rear view

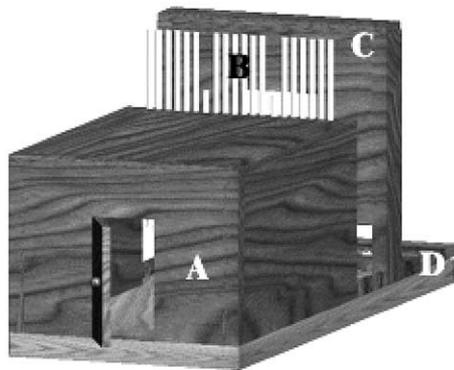


Fig. 1. Toronto General Testing Apparatus (TGTA)—Drawing of test apparatus used in all cognitive testing with dogs courtesy of Joe Costa (previously unpublished). A is the test box where the dogs enter from the door in the rear of the apparatus. B is the front of the test box that consists of stainless steel bars of adjustable heights to provide three openings. C provides a solid screen between the experimenter and animal. These are a one-way mirror and a hinged door, which provides access for a sliding tray to present objects to the animals. D is a plexiglass presentation tray with three food wells, two lateral and one central.

age related deficit in learning. Similarly, aged dogs (8 to 11 years) and old dogs (over 11 years) demonstrate impairment compared to young and middle-aged dogs in size-discrimination learning (Tapp et al., 2003). During reversal learning the food reward is switched to the previously unrewarded object and the dogs must then inhibit their previous learned behavior and respond to the previously unrewarded object. These tasks have proven more difficult to learn for older dogs, which may be linked to deficits in inhibitory control or executive function (Tapp et al., 2003; Adams et al., 2000a).

Dogs can also be tested on tasks that test their ability to recall the location of a food reward after a delay of 5 s or more (Delayed Non-Matching to Position or DNMP) or to recall the object under which a food reward was located (Delayed Non-Matching to Sample or DNMS) (Adams et al., 2000a,b; Head et al., 1995). DNMP is a visual spatial memory task in which the food is placed under an object in either the left or right food well. After the animal retrieves the food reward, the object is removed from the animal's sight and the delay is started. After the delay, two identical objects are placed in front of the dog. The dog must learn that the food is under the previously unrewarded location

(Adams et al., 2000a,b). Once the animal learns the rule of the task, increasing the delay tests the dog's memory capacity. The same test can be done with three wells, but old dogs require many more test sessions to learn the task compared to using only two wells (Chan et al., 2002). DNMS is an object recognition memory task in which the food is placed under an object over the center well. After a delay period in which the object is removed from the animal's sight, the original object and a second novel object (the non-match) are offered in a randomized location over the lateral food wells. The dog must learn that the food is under the novel object after a delay of 5 s or longer. Both forms of memory are impaired by age but the object recognition task is more difficult for dogs to acquire. In fact, most aged dogs are unable to learn the object recognition task (Adams et al., 2000b); thus, the spatial task is more useful in characterizing differences between aged dogs. Using the spatial memory tasks, old dogs can be separated into three groups: unimpaired, impaired and severely impaired, which may correspond to human subgroups such as successful aging, mild cognitive impairment (MCI) and dementia (Adams et al., 2000a; Head et al., 2001).

One important question is whether the laboratory methods designed to test learning ability and memory in aging dogs, correlates in any way to clinical behavioral observations. In fact, age related differences are also found in both spontaneous behavior and behavioral reactivity tests (Head et al., 1997; Siwak et al., 2001). The curiosity test allows the dogs to examine and play with a variety of toys to assess an animal's reaction to novel objects or exploratory behavior. In this test, young dogs show significantly more exploration and contact with novel objects than old dogs. Age-impaired dogs, by contrast show higher levels of locomotion and less exploratory behavior during a curiosity test than their age-matched unimpaired peers (Siwak et al., 2001). The curiosity test may be more amenable to clinical use because it requires a 10 min testing session and no special testing apparatus, which makes it a more useful clinical screen for aged animals with cognitive dysfunction. On the other hand, the changes in memory and learning may precede the deficits previously characterized in exploratory behavior.

Collectively, these tests have provided valuable new insights into the diagnosis and treatment of cognitive dysfunction in dogs. For example, the typical age of onset for clinical cases is usually reported at 11 years of age or greater, while laboratory tests have documented cognitive decline from as early as 7 years of age (Landsberg et al., 2003; Milgram et al., 1994). This is similar to neurodegenerative diseases in humans such as Alzheimer's disease where impairments in patients undergoing regular cognitive testing can be detected long before clinical signs appear in the day-to-day environment. Laboratory testing also provides an objective measure for controlled studies that can predict the effect of therapeutic intervention in the treatment of cognitive dysfunction in pet dogs, and a

number of therapeutic agents have now been evaluated and in some cases approved and released for clinical use in pets with cognitive dysfunction.

4. Treatment of cognitive impairment in pet dogs

Owners of dogs exhibiting signs of cognitive impairment may find it increasingly difficult to cope with the changes in their pet's behavior. The human animal bond can be weakened or broken by a pet with behavior problems such as house-soiling or night waking, or by more subtle changes in behavior that gradually turn a close and positive relationship into one that is more distant or even negative. With the relatively short lifespan of pet dogs, most owners will ultimately need to make difficult decisions based on the quality of life of their senior pet, a decision that encompasses their pet's physical health, behavior and treatment options available.

Using neuropsychological tests that have been developed and validated for the assessment of cognitive decline in senior dogs, it is possible to accurately determine whether a particular therapeutic agent is effective at improving learning and memory before entering into larger and far more subjective clinical efficacy trials.

4.1. Selegiline

The first therapeutic agent approved for use in dogs based on results of both neuropsychological testing (including reversal and spatial memory) as well as clinical trials is selegiline (Milgram et al., 1993, 1995; Ruehl et al., 1995; Campbell et al., 2001). Selegiline is a selective and irreversible inhibitor of monoamine oxidase B (MAOB) in the dog (Milgram et al., 1993; Gerlach et al., 1994). Although the mechanisms by which selegiline produces clinical improvement in dogs with CDS are not clearly understood, enhancement of dopamine and perhaps other catecholamines in the cortex and hippocampus is presumed to be an important factor (Knoll, 1998). Selegiline increases 2-phenylethylamine (PEA) in the dog brain (Milgram et al., 1993), which is a neuromodulator that enhances dopamine and catecholamine function and may itself enhance cognitive function (Paterson et al., 1990). Catecholamine enhancement may lead to improved neuronal impulse transmission. Selegiline may also contribute to a decrease in free radical load in the brain by directly scavenging free radicals and enhancing scavenging enzymes such as catalase and superoxide dismutase (SOD), the latter of which is increased in dogs on selegiline therapy (Carillo et al., 1994). In addition, because MAOB is inhibited, fewer toxic free radicals may be produced. Selegiline may also have neuroprotective effects on dopaminergic, noradrenergic, and cholinergic neurons (Heinonen and Lammintausta, 1991). For CDS, selegiline is dosed at 0.5–1 mg/kg each morning and, if there is not significant improvement in 30

days, the dose can be adjusted up to the next tablet size for another month. Toxicity has been reported on rare occasions in humans when selegiline is used concurrently with antidepressants, ephedrine, narcotics, phenylpropanolamine, or other MAO inhibitors.

4.2. Dietary therapy

A new canine therapeutic diet (Prescription diet[®] Canine b/d[®], Hills Pet Nutrition, Topeka, KS) is now available through veterinarians for the treatment of cognitive dysfunction in senior dogs. The diet's efficacy was assessed using neuropsychological testing procedures for more than 2 years, as well as in clinical trials. The strategy was to supplement the diet with a broad spectrum of antioxidants and mitochondrial co-factors that might improve antioxidant defenses, as well as decrease production, increase clearance, and reduce the toxic effects of free radicals. Antioxidants may help to delay age related cognitive decline in humans and improve the performance of aged rodents (Cotman et al., 2002; Jama et al., 1996; Sano et al., 1997; Joseph et al., 1998, 1999; Halliwell, 1994). Many of the antioxidants in this diet may also have anti-inflammatory properties (Fryer, 1998; McGahon et al., 1999).

The brain may be particularly susceptible to the effects of free radicals because it has a high rate of oxidative metabolism, high lipid content, and limited ability for regeneration (Cotman et al., 2002; Ikeda-Douglas et al., 2004). Widespread oxidative damages, extensive production of free radicals, and lowered vitamin E levels have all been identified in the brains of dogs with dementia (Skoumalova et al., 2003; Shigenaga et al., 1994; Head et al., 2002).

The diet is supplemented with vitamins E and C, and other antioxidants including beta carotene, selenium, DL-alpha-lipoic acid and a number of flavonoids and carotenoids from fruits and vegetables such as spinach flakes, tomato pomace, grape pomace, carrot granules, and citrus pulp. The addition of L-carnitine and DL-alpha-lipoic was also intended to enhance mitochondrial function (McGahon et al., 1999; Hagen et al., 1998, 2002; Hager et al., 2001; Packer et al., 1997). The level of omega-3 fatty acids has also been increased to promote cell membrane health as well as a possible anti-inflammatory effect (Youdim, 2000; Lands et al., 1990). Vitamins E and C help to neutralize free radicals and prevent damage to cells and cell membranes (Fryer, 1998; Mayes, 2000; Packer, 1994; Kamal-Eldin and Applqvist, 1996; Joseph et al., 1998). A variety of studies in other species have shown that high intakes of fruits and vegetables might also decrease the risk for age related cognitive decline through their antioxidant and anti-inflammatory properties (Joseph et al., 1999; Youdim et al., 2000; Martin et al., 2000; Halliwell, 1994).

The supplemented diet was found to improve performance on a number of cognitive tasks. When compared to a

non-supplemented diet, improved performance was seen beginning as early as to 2 to 8 weeks after the onset of therapy on a landmark discrimination test (Milgram et al., 2002a), and continuing through 6 months on an oddity discrimination learning task. The oddity discrimination task is a paradigm in which the dogs are required to find the location of the food reward under sets of three objects of increasingly greater similarity (Milgram et al., 2002b; Cotman et al., 2002). In a 60 day double blind clinical trial of 142 dogs, there was a significantly greater improvement in cognitive signs in the group on the fortified diet (Prescription diet[®] Canine b/d[®]) than in the control group (Dodd et al., 2003). Another recent study also found that cognitive performance on the landmark task could be improved by the antioxidant diet in aged beagles, and that blood concentration of vitamin E was positively correlated with improved performance (Ikeda-Douglas et al., 2004).

4.3. *Environmental enrichment and previous cognitive experience*

In addition to the effects of the fortified diet, the multi-year longitudinal study also examined the effects of environmental enrichment (exercise, novel toys and continued testing) in comparison to a group of dogs that had no such enrichment. After following these dogs for over 2 years, the control group (no enrichment, no supplemented diet) showed a dramatic decline in cognitive function, while those in either the enriched diet or the environmental enrichment group alone continue to do better than control on discrimination and reversal tasks. However, the combined effect of the enriched diet plus the enriched environment provided the greatest improvement (Milgram et al., 2002b, 2004a,b). In the second study, aged beagles with previous cognitive experience were compared to naïve dogs. Previous cognitive experience had a positive impact on performance, which was further improved with the antioxidant-fortified diet (Ikeda-Douglas et al., 2004).

4.4. *Drugs for enhancing cerebral perfusion and/or alertness in aged dogs*

Drugs that putatively enhance cerebral vascular circulation may also have the potential to improve the signs of cognitive decline since cerebral perfusion may decrease with age in the dog (Peremans et al., 2002). Nicergoline is an alpha-1 and alpha-2 adrenergic antagonist that is available in the United Kingdom for the treatment of aging-related behavior disorders in dogs. It may increase cerebral blood flow, enhance neuronal transmission, and have a neuroprotective effect. It may also increase dopamine and noradrenaline turnover and inhibit platelet aggregation. Propentofylline is licensed for the treatment of dullness and lethargy in old dogs in a number of European countries. It is purported to inhibit platelet aggregation and thrombus formation, make the red cell more pliable and increase

blood flow. Testing of both of these drugs in clinical trials has been limited and neither was subjected to neuropsychological testing prior to their approval.

Drugs that may enhance the noradrenergic system such as adrafinil and modafinil, might be useful in older dogs to improve alertness and help maintain normal sleep–wake cycles (by increasing daytime exploration and activity). The noradrenergic system helps to maintain alertness, wakefulness, attention, memory and learning, and neuroprotection. With age, alterations in the noradrenergic system may contribute to declining cognitive function, decreased alertness, mood alterations as well as neurodegenerative diseases. In laboratory studies on discrimination learning in dogs, adrafinil has been shown to have cognitive enhancing potential, possibly due to increased vigilance (Milgram et al., 2000). In open field testing in dogs, adrafinil caused increased locomotion without producing stereotypical activity at a dose of 20 mg per kg and higher (Siwak et al., 2000a). However, further testing is needed since doses that improve learning may lead to memory impairment (Siwak et al., 2000a). This highlights the importance of using tests that measure various cognitive components when determining the efficacy of a putative treatment. Another implication of this finding is that various therapeutic classes or drugs may be better suited to a particular age-related symptom than another.

One recent study has compared changes in activity produced by adrafinil, nicergoline and propentofylline. While adrafinil led to a significant increase in locomotion, there was no effect of nicergoline or propentofylline (Siwak et al., 2000b).

4.5. *The effects of systemic disease and obesity on health and behavior*

Disease processes can cause physical signs and behavioral changes that affect quality of life as well as longevity. Medical conditions ranging from endocrinopathies to organ failure can also have varying effects on cognition and may lead to further accumulation and decreased clearance of free radicals. Treatment and control of underlying medical problems may improve quality of life, cognition, and even longevity. In fact, the most significant effects on health and life span might best be achieved through weight control in dogs (Kealy et al., 2002).

4.6. *Complimentary therapy*

A wide variety of complimentary therapies including nutraceuticals, herbal extracts and vitamins have been advocated for use in pets to help calm, reduce anxiety and induce sleep. Some of these include melatonin, valerian root, Bach's flower remedies, and DAP[®] (Veterinary Products Laboratories, Phoenix, AZ), a synthetic pheromone modeled upon those secreted from the sebaceous glands of the intermammary chains of the lactating bitch.

Some of the complimentary products have also been purported to be useful in improving or preventing cognitive decline and many have now been incorporated into supplements for senior pets. In addition to herbal ingredients, these products contain a mix of vitamins and nutraceuticals, including phospholipids, fatty acids, antioxidants and mitochondrial co-factors that might, in theory be complimentary or synergistic in their actions. Although anecdotal improvement with some of these products has been reported, there has not yet any published data from either cognitive studies or controlled clinical trials to validate their efficacy. Senilife™ (Innovet Italia S.r.l., Milano) contains a combination of phosphatidylserine, Ginkgo biloba, pyridoxine, and Vitamin E. Geriactive® (Centaur Pharmacy, Guelph) is a supplement for senior pets containing Ginkgo, Ginseng, Bilberry and Alpha-lipoic acid. Proneurozone™ (Animal Health Options, Golden, CO) contains vitamin E, many of the B vitamins, Folic Acid, *N*-acetylcysteine, alpha-lipoic acid, fruit and herbal extracts such as grape seed, rosemary, sage, bilberry, choline, lecithin and fatty acids. Senior Moment® (Nutramax Laboratories, Englewood, MD), a human supplement for the treatment of cognitive dysfunction contains phosphatidylserine and DHA.

As discussed previously vitamin E, flavonoids and carotenoids may be useful as antioxidants or for their anti-inflammatory properties in the treatment of cognitive decline. B-vitamins (thiamine, riboflavin, niacin B6 and B12) may also have antioxidant properties and neuro-protective effects, as well as the ability to normalize neurotransmitter levels. Phosphatidylserine is a phospholipid that constitutes a major building block of the cell membrane. In humans with cognitive decline, it has been reported to improve scores for activity, social interactions, memory and learning. (Crook et al., 1991, 1992). Since neurons are highly dependent on their plasma membranes, phosphatidylserine may facilitate membrane-dependant neuronal processes such as signal transduction, release of secretory vesicles and maintenance of the internal environment. Phosphatidylserine may also help maintain neurotransmitter levels and normalize the density of neurotropic growth factor (NGF) receptors and increases NGF synthesis and release. DHA is an omega 3 fatty acid, required for maintenance of normal brain cell function. A deficiency in the elderly may contribute to cognitive decline (Lim et al., 2003; Kalmijn et al., 1997; Horrocks and Yeo, 1999). DHA has anti-inflammatory properties and lowers amyloid levels and plaque formation in a murine model of Alzheimer's disease (Horrocks and Yeo, 1999; Lim et al., 2003). Preliminary studies in the dog using a combination of DHA and cerebral phospholipids showed a trend towards improvement in memory capacity and a significant improvement in quality of life (Studzinski, in preparation). There is some evidence that Ginkgo biloba may improve memory loss, fatigue, anxiety, and depression in the elderly as well as delay the progression of Alzheimer's in humans, perhaps as

an MAO inhibitor, as a free radical scavenger or by enhancing blood flow (Lebars et al., 1997; Maitra et al., 1995).

4.7. Other treatment considerations

Since alterations in neurotransmitters or their receptor sites can lead to behavioral changes such as increased irritability, decreased responsiveness to stimuli, fear, agitation, altered sleep-wake cycles (and depression in humans) antidepressants and anxiolytics such as benzodiazepines, gabapentin or valproic acid might also be considered for some older pets (Nebes et al., 1999; Butters et al., 2000). The only such drug licensed for use in dogs is clomipramine (Clomicalm®, Novartis Animal Health, Greensborough, North Carolina), although other antidepressants such as amitriptyline, fluoxetine, and paroxetine, and anxiolytics such as the benzodiazepines and buspirone are also used in clinical cases. However, since the elderly are particularly susceptible to the effects of drugs with anticholinergic effects which include clomipramine, amitriptyline and paroxetine, it would be prudent when selecting this class of drugs for older pets, to consider those with less anticholinergic effects (perhaps fluoxetine) and those that are less sedating (e.g. buspirone). A recent study found that senior dogs showed a greater sensitivity to the memory impairment effects of an anticholinergic drug (scopolamine) than younger animals (Araujo et al., 2004).

It is well established that cholinergic function in the brain is associated with memory impairment in both animal species and humans (Bartus, 2000). Therefore, a major focus of drug therapy for Alzheimer's disease in humans is the use of drugs that enhance cholinergic transmission. Drugs that act to augment cholinergic transmission might therefore also have applications for clinical use in dogs with cognitive decline. In dogs, disruption of cholinergic transmission has been demonstrated to impair working memory, but not discrimination, which parallels the decline seen in canine and human cognitive aging (Araujo et al., 2004; Bartus, 2000). Furthermore, aged dogs demonstrate greater sensitivity to cholinergic disruption than young dogs, which further suggests a decline in cholinergic tone with aging (Araujo et al., 2002). Two cholinergic agonists, citicholine and carbacholine improve performance in operant conditioning tasks in dogs. (Bruhwiler et al., 1998; Shapovalova, 1999), which suggests that cholinergic enhancement, may improve signs associated with CDS. Early work on the use of a novel acetylcholinesterase inhibitor phenserine has shown promise in the improvement of complex discrimination learning, spatial memory performance, and in reversing scopolamine-induced working memory deficits (Studzinski, personal communication).

Based on the similarities in beta-amyloid peptides and regional brain distribution between dogs and humans with cognitive dysfunction, as well as the correlation between the amount of beta-amyloid and the degree of cognitive

dysfunction, it is also possible that drugs in development to block the production and deposition of beta-amyloid may also prove to be beneficial to dogs (Cummings et al., 1996; Colle et al., 2000).

Other treatment strategies may include anti-inflammatory drugs (such as ibuprofen or perhaps carprofen), the NMDA receptor antagonist memantine, and hormone replacement therapy (Breitner, 1996; Flynn and Theesen, 1999; Resnick and Maki, 2001). Estrogen may have an anti-inflammatory effect as well as antioxidative effects and may lead to an increase in cerebral blood flow. In dogs, estrogen treated females made significantly fewer errors in a size-reversal learning task than estrogen treated males or placebo-treated males and females. However, estrogen-treated aged females made more errors in spatial memory tasks than estrogen treated-males and controls (Tapp et al., 2001). In a recent study of a small group of dogs, intact aging male dogs showed less evidence of cognitive impairment than neutered dogs (Hart, 2001). Recent studies in humans may support testosterone as being neuroprotective against Alzheimer's. If supplementation is considered with testosterone or estrogen, they should be given at physiologic levels since high levels can be toxic.

5. Clinical guidelines for senior pets

A number of therapeutic agents are now licensed for the treatment of cognitive dysfunction in dogs. When one considers the possible antioxidant and neuroprotective effects afforded by many of these products, they might prove to be even more useful as a means of slowing the progression of the disease than simply a symptomatic treatment. It seems prudent therefore, to advise pet owners to begin treatment with these drugs and supplements at the earliest possible signs of cognitive impairment. However, since laboratory findings can detect impairments in memory and learning well before the onset of clinical signs, and until such time as these tests might become available to client owned pet dogs, consideration might also be given to beginning treatment for senior dogs prior to the onset of clinical signs.

Owners of senior pets should work closely with their veterinarians to report any behavioral changes as soon as they arise, so that appropriate diagnostic testing can be initiated to determine the cause of these signs. In addition to cognitive dysfunction, these behavioral changes may be the first sign of a wide range of disease processes from metabolic and endocrine disease to painful conditions such as arthritis or dental disease (Landsberg and Ruehl, 1997; Landsberg et al., 2003). Early detection allows for early intervention, which for most problems is the best way to resolve or at least slow the progression of disease and to improve quality of life and perhaps even longevity. Another important component of clinical therapy is to insure an adequate level of behavioral enrichment for senior pets in

the form of: training, play, exercise and novel toys (use it or lose it). Keeping up a regular, predictable daily routine may help to reduce anxiety, maintain temporal orientation, and keep the dog active during daytime hours so that it sleeps consistently through the night. Making gradual rather than sudden changes to the pets household or routine can also help the senior pet better adapt. As sensory acuity, sensory processing and cognitive function decline, adding new odor, tactile, and sound cues might help the pet better navigate its environment and maintain some degree of environmental familiarity and comfort. Pets might better maintain their orientation by identifying rooms, pathways, and sleeping areas with audible cues such as a TV, radio or CDs (when hearing is not significantly impaired), odor cues such as scented candles or room fresheners and tactile cues such as mats or area rugs.

6. Conclusion

Neuropsychological testing in the laboratory has clearly demonstrated differences in learning and memory between young dogs and senior dogs. These tests have proven to be an effective means of objectively testing therapeutic agents, many of which are now licensed for use in client owned senior dogs. Therefore, the canine laboratory model for assessment of brain aging has proven valuable in both comparative studies for human Alzheimer's as well in understanding the diagnosis and treatment of brain aging in senior pet dogs.

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