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Nutrition and the aging brain of dogs and cats

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Many nutrients are critical for maintaining brain structure and function, including cognition. A deficiency of some nutrients can lead to compromised brain structure and function, which accelerates brain aging. Additional nutrients may have benefits when provided in quantities greater than those listed in recognized requirements, whereas other nutrients that may be beneficial to cognitive function may not be recognized as essential nutrients. The purpose of the information provided here was to summarize the evidence for beneficial effects of nutrients on brain function and cognition, with an emphasis on the aging brain, and to provide evidence on the dietary management of dogs with cognitive dysfunction syndrome.

Age-related changes in brain structure and metabolism

Aging results in numerous physical, metabolic, and functional changes in the brain that can negatively affect cognition and cause behavioral changes.[1–6] Age-associated changes in the brain include regional atrophy of gray and white matter, increases in ventricular volume, irreversible loss of neurons and synapses, reduced neurogenesis, reduced clearance and subsequent accumulation of abnormal proteins (such as β-amyloid), inflammation, oxidative stress, vascular changes (including cerebral amyloid angiopathy), reduction or deterioration of myelin, diminished cholinergic function, and alterations in gene expression.[7–24]

Energy metabolism in the brain is also altered with age. The brain is a metabolically active organ. In humans, the brain accounts for approximately 20% to 25% of the body's total resting energy metabolism, with most of this energy used to maintain membrane energy potentials necessary for neurotransmission.[25] The primary energy source used by the brain is glucose, although ketones can provide an alternate energy source during periods when food is not consumed.[26] Because of its high metabolic rate, the brain is particularly vulnerable to and intolerant of disruptions in energy metabolism.[27–30] Unfortunately, brain aging is associated with mitochondrial dysfunction and reductions in glucose metabolism.[27,29,31–33] The decline in glucose metabolism in the brain contributes to neurodegenerative diseases and appears to be present well in advance of the onset of measurable cognitive decline.[25] In dogs, overall brain metabolism and regional metabolic reductions as severe as 25% have been detected by 6 years of age.[31] Compromised mitochondrial function reduces energy availability and contributes to increased production of oxygen free radicals and oxidative stress.[32] Oxidative stress is also associated with neurodegenerative diseases and cognitive decline.[20,34,35]

ABBREVIATIONS

DHA	Docosahexaenoic acid
GABA	γ-Aminobutyric acid
MCFA	Medium-chain fatty acid
MCT	Medium-chain triglyceride
PUFA	Polyunsaturated fatty acid
SAMe	S-adenosylmethionine

Age-related cognitive dysfunction in dogs and cats

Cognition is defined as the ability to learn, think, solve problems, remember, and communicate. Cats and dogs can age in a manner wherein age-related changes have minimal impact, or they may develop cognitive decline (comparable to mild cognitive impairment in humans) or more severe cognitive dysfunction syndrome (comparable to dementia and Alzheimer disease in humans). Cognitive dysfunction is associated with more severe physical and physiologic changes in the brain and may manifest clinically as disorientation; altered social interactions and sleep-wake cycles; apparent memory and learning deficits, reduced ability to focus, and inappropriate soiling behavior; reductions in activity and interaction with the pet's environment; repetitive behaviors; and increases in anxiety, including separation anxiety and heightened fear of visual or auditory stimuli and new environments.[36,37]

Even apparently healthy aging animals will have some cognitive impairment as identified by standardized cognitive testing; however, the changes are mild and do not result in altered behaviors or impaired daily function.[37-39] Cognitive impairments have been detected in apparently healthy dogs and cats as early as 6 and 7.7 years of age, respectively.[37] Cognitive decline typically is progressive, although the rate of progression is highly variable.[37,40,41] Investigators of 1 study[42] observed that one-third of 21 cognitively normal senior dogs had progression to mild cognitive impairment and approximately one-fourth of 17 mildly impaired dogs had progression to cognitive dysfunction syndrome within a 24-month period. Investigators of another study,[43] who used a different assessment scale, observed that of 63 aged dogs, approximately 4 in 10 had progression from normal cognition to mild cognitive impairment within 6 months. In the same study,[43] 5 of 7 aged dogs evaluated over a 12- to 14-month period had progressed from normal cognition to mild cognitive impairment during that time, and one-half of the dogs that initially had mild impairment had progressed to moderate impairment.

Characterization of cognitive decline and dysfunction in cats lags behind that in dogs, and these conditions appear more challenging to diagnose and may be overlooked in cats.[36,44-46] It is estimated that the prevalence of cognitive dysfunction syndrome in cats between 11 and 14 years of age is 28%, and in cats ≥ 15 years old, it increases to > 50%.[44,45]

Early detection and intervention may provide opportunities to slow the rate of cognitive decline, support the human-animal bond, and address well-being and quality-of-life issues.[36,37,47,48] Cognitive decline and cognitive dysfunction syndrome may be managed by targeting the risk factors for cognitive impairment through medical, environmental, and nutritional interventions. Several dietary modifications, including the use of antioxidants, alternative energy sources, vitamins, and omega-3 fatty acids, can impact brain function or cognition in aged pets.

Ketones and MCTs

Glucose cannot be entirely replaced as an energy source for the brain; however, other energy sources can be used to supplement the energy provided by glucose.[27,49] Two important alternative sources of energy include ketones and MCFAs derived from MCTs.[49,50]

Ketone bodies, including acetoacetate and β-hydroxybutyrate, are derived from oxidation of fatty acids. They are able to cross the blood-brain barrier and mitochondrial membrane and can generate ATP via the tricarboxylic acid (Krebs) cycle and oxidative phosphorylation **(Figure 1)**.[49,51-53] Glucose metabolism of the brain decreases with age, but ketone metabolism of the brain appears to be unaffected by age.[49,50,52,53] Neurons can oxidize ketone bodies at a rate 7 to 9 times the rate for oxidation of glucose, and ketones can provide up to 70% of the brain's energy during prolonged periods when food is not consumed.[49,54,55]

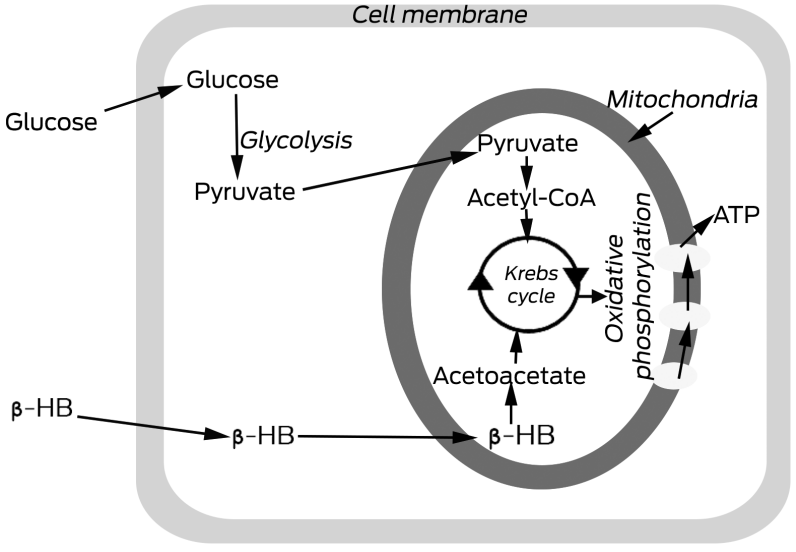

Figure 1—Schematic depiction of the generation of ATP from glucose or ketones. Glucose enters a cell and progresses through glycolysis to form pyruvate, which is converted to acetyl coenzyme A (Acetyl CoA) in the mitochondria and then enters the tricarboxylic acid (Krebs) cycle. The Krebs cycle produces ATP through oxidative phosphorylation. When glycolysis fails or there is a lack of glucose, there is no pyruvate to drive the subsequent energy-producing processes. In contrast, β-hydroxybutyrate (β-HB) diffuses into the mitochondria and is converted to acetoacetate, which can enter the Krebs cycle. The energy ultimately gained from ketones metabolized through the Krebs cycle and oxidative phosphorylation is identical to that produced by glucose metabolized through the Krebs cycle, which allows ketones to bypass a disrupted glycolysis process.

Ketone production is induced in nonfasting humans through the feeding of a ketogenic diet. These diets, which traditionally are extremely high in fat and low in glucose precursors, protein, and carbohydrates (approx 70:20:10, respectively), promote a shift in metabolism to favor ketone production.[56] Traditional ketogenic diets have been successfully used in the management of refractory epilepsy in humans and are gaining support for use in the management of a growing number of neurologic disorders, including Alzheimer disease.[14,22,37,50,56-58] However, traditional ketogenic diets can induce nutritional deficiencies, and there is often poor compliance to strictly adhere to ketogenic diets because of the severe dietary restrictions.[14,56-59] Furthermore, traditional ketogenic diets are not effective in dogs. Dogs do not achieve high ketone concentrations comparable to those in humans consuming traditional ketogenic diets.[60-63] In 1 study,[a] 9 epileptic dogs were fed a traditional ketogenic diet. Although dogs fed the ketogenic diet had significantly higher se-

rum concentrations of β-hydroxybutyrate, compared with concentrations for a control group, there was no difference in seizure frequency between the control group and the group fed the ketogenic diet.

Dietary MCTs can be part of a feeding strategy that results in the endogenous generation of ketones without requiring a high-fat diet. Dietary MCTs are found naturally in milk fat, coconut oil, and palm kernel oil. The MCT oils are concentrated forms of octanoic and decanoic acids, which generally are derived from coconut or palm kernel oil. However, raw coconut oil and palm kernel oil contain only 7% to 12% of these fatty acids, compared with nearly 100% in purified MCT oils.[64] Natural coconut oil and palm kernel oil also contain longer-chain fatty acids[65] that do not have the same benefits as are seen with octanoic and decanoic acids.

In contrast to long-chain triglycerides, MCTs are rapidly and easily digested without the need for pancreatic lipases or bile acids. The MCTs undergo intraluminal hydrolysis. Most of the MCFAs are absorbed directly through the gastrointestinal wall and are transported via the portal vein to the liver, where they are rapidly oxidized, which results in greater production and release of ketones, compared with results for metabolism of long-chain fatty acids.[66] A small but variable amount of MCFAs may be incorporated into chylomicrons and enter the lymphatics, similar to metabolism of long-chain fatty acids. The longer the fatty acid chain (eg, 12 or 10 carbons vs 8 carbons), the more likely that fatty acid is to be found in lymphatic fluids.[67,68]

The MCT-based ketogenic diets are gaining popularity in human medicine because they provide dietary flexibility (eg, they do not require high amounts of fat) and typically result in better compliance.[56,66] Dietary MCTs can stimulate an increase in circulating concentrations of ketones in dogs without limiting dietary protein and carbohydrate intake.[24,69,70] In an 8-month study[69] of aging dogs without cognitive dysfunction syndrome, feeding an MCT-supplemented diet increased blood β-hydroxybutyrate concentrations and caused enhancements in cognitive function, compared with results for dogs fed a control diet, particularly when the tasks used to test cognitive function of the dogs became more difficult.

It is important to mention that nutritional acetonemia (ketosis) induced by the feeding of traditional or MCT-supplemented ketogenic diets is a physiologic response. In contrast to pathological ketosis, it does not impact blood pH and causes no known adverse effects.[51–53]

In addition to the ketones generated by the metabolism of MCTs, MCFAs can also be used as an energy source by brain cells. Octanoic acid, an 8-carbon MCFA, is preferentially metabolized for energy and can provide up to 20% of the brain's energy needs.[21,66] Both ketones and MCTs (or MCFAs) have cognitive and neuroprotective benefits, including providing an energy source,[27,33,49,50,52,53,55,57,58,66,71] reducing oxidative stress,[57,58,71–74] enhancing mitochondrial function[57,58,71,72,74,75] and mitochondrial biogenesis,[57,58,66,73,74] increasing concentrations of omega-3 PUFAs in the brain,[72,76,77] reducing concentrations of apoptotic and inflammatory markers,[57,58,73,74] reducing concentrations and toxic effects of amyloid-β,[50,66,72,78] increasing concentrations of protective neurotrophic factors,[74] reducing neuronal hyperactivity and seizure activity,[52,53,55,57,58,66,71,73,74] and reducing glutaminergic transmission.[66,74] Most of these actions target the physiologic and metabolic changes that lead to neurodegeneration and cognitive decline or dysfunction, which thus provides numerous opportunities for nutritional intervention to prevent or mitigate age-related cognitive impairment. Recently, it has been suggested that at least some of these benefits are mediated by alterations in the gastrointestinal microbiota.[57,58]

B vitamins

Certain B vitamins, especially thiamine (B_1), pyridoxine (B_6), folate (B_9), and cobalamin (B_{12}), are important for neurodevelopment and cognitive function.[79–84] Deficiencies in B vitamins can lead to a high blood concentration of homocysteine,[82–84] which is a risk factor for brain atrophy, cognitive impairment, and dementia in humans.[79,82,84–86] Long-term provision of B vitamins reduces homocysteine concentrations, oxidative stress, and brain atrophy and improves memory and cognition, compared with results for a placebo.[83,87] However, use of B vitamins to slow brain atrophy and cognitive decline provides benefits only in human subjects with high blood concentrations of omega-3 PUFAs.[75]

The B vitamins are thought to serve roles in dogs and cats that are similar to their roles in humans. However, deficiencies of the B vitamins are uncommon in dogs and cats. The authors are not aware of any studies that found a benefit of increasing the amount of B vitamins beyond the amount typically provided in nutritionally balanced pet foods. However, studies of dogs[88] and cats[89] revealed cognitive benefits for animals fed a diet supplemented with a blend of B vitamins, omega-3 fatty acids, antioxidants, and other nutrients. Because of the design of the studies, it could not be determined whether the B vitamins specifically contributed to the benefits.

Omega-3 fatty acids

The omega-3 PUFAs, in particular DHA, play critical neuroprotective and anti-inflammatory roles in the brain.[85,88,90–92] Neural tissues are rich in DHA, but aging is accompanied by a reduction in DHA content in the brain, which favors neurodegeneration.[93,94] Increased intake of long-chain omega-3 PUFAs protects against cognitive decline or improves cognitive function in mice[93] and humans.[94,95] Interventional studies[96,97] conducted to investigate the impact of dietary supplementation with omega-3 PUFAs on cognition in humans have yielded equivocal results because of

the study design, dosage, and duration of the study; however, cognitive benefits were typically reported for the use of higher doses and longer durations. The benefits of omega-3 PUFAs in humans may depend on the B vitamin status.[84]

Studies on the effects of omega-3 PUFAS in dogs and cats are sparse. Investigators of 1 study[98] evaluated a marine alga, *Schizochytrium* sp, as a source of DHA fed to aged Beagles. Over the 25-week study,[98] some benefits were observed for visual and variable contrast discrimination learning tests, but there were no enhancements for memory tests. A cocktail of nutrients that included B vitamins and omega-3 PUFAs from fish oil was evaluated in dogs[88] and cats.[89] The nutrient blends tested in each of those studies resulted in improvements in cognitive function, compared with results for the control groups, but the specific contribution of omega-3 PUFAs to the benefits could not be determined.

Arginine

The amino acid L-arginine serves several roles, including an antioxidant function. It is metabolized in neurons and other cells to form citrulline, which results in the formation of nitric oxide.[88,99] Nitric oxide serves as a regulator in a number of physiologic functions, including vascular tone and blood flow, immune responses, neural communication, and expression of antioxidant enzymes. The high metabolic activity of the brain during cognitive tasks results in the use of more oxygen; thus, cognitive activity requires an increase in blood flow, which is primarily mediated by nitric oxide.[85]

As previously mentioned, L-arginine is metabolized to citrulline. Citrulline derived from L-arginine is a precursor to compounds that support neurogenesis and is also a precursor to the neurotransmitter GABA.[99] In addition, L-arginine is also metabolized to form agmatine, a neuromodulator involved in learning and memory processing.[99] Agmatine also plays a role in regulating the production of nitric oxide and is thought to provide neuroprotection via multiple mechanisms.[99-101]

To the authors' knowledge, no studies have revealed benefits to dogs or cats of increasing the dietary L-arginine content beyond the amount typically provided in nutritionally balanced pet foods. However, studies of dogs[88] and cats[89] fed a diet supplemented with L-arginine at amounts above the proposed daily requirement in addition to fatty acids, antioxidants, and other nutrients revealed cognitive benefits for animals fed the supplemented diet. However, the degree to which L-arginine or its metabolites specifically contributed to the benefits could not be determined.

Branched-chain amino acids

Branched-chain amino acids may improve hippocampal function and brain networks associated with sleep and wakefulness.[102,103] Through their role in de novo synthesis of glutamate, branched-chain amino acids play an intrinsic role in maintaining glutamate and GABA stores in the brain.[102] Feeding diets supplemented with branched-chain amino acids (40% valine, 35% leucine, and 25% isoleucine) before and during exercise improves cognitive performance in human athletes.[104] In a preliminary study,[104] senior dogs that were provided a similar branched-chain amino acid product before (but not during) agility trials made fewer total errors during subsequent trials, which suggested a cognitive benefit.

L-carnitine

One of the functions of L-carnitine is to facilitate transfer of long-chain fatty acids into the mitochondria for β-oxidation, and L-carnitine can enhance mitochondrial function in cardiac and other tissues.[105,106] In the brain of adult humans, fatty acids are preferentially incorporated into structural lipids, rather than being oxidized, which potentially limits the value of L-carnitine's transfer facilitation in adults.[107] However, L-carnitine also functions as an antioxidant. In rodents subjected to increased amounts of oxidative stress, L-carnitine reduced oxidative injury, enhanced recovery from oxidative stress, and aided cognitive function after recovery.[106] Cognitive function improved in aging dogs fed a combination of the mitochondrial cofactors L-carnitine (or its metabolite, acetyl-L-carnitine) and α-lipoic acid, but it did not improve when the components were fed separately.[105,108,109]

Antioxidants

Oxidative stress is caused by an imbalance between pro-oxidative enzymes (eg, NADPH oxidase, xanthine oxidase, or enzymes in the mitochondrial respiratory chain) and antioxidative enzymes (eg, superoxide dismutase or catalase) and nutrients (eg, vitamins E and C). Antioxidants bind to, prevent the formation of, or capture free electrons (free radicals) on reactive oxygen species.[16] The body produces numerous compounds and enzymes that function as antioxidants[16,110]; however, endogenous antioxidant capacity decreases with age, which results in oxidative stress. Because of its extremely high metabolic rate and relatively low amount of endogenous antioxidants, the brain is particularly susceptible to oxidative stress.[34]

Brain mitochondrial function becomes less efficient during aging, which results in increases in the production of free radicals and increases in oxidative stress that can accelerate brain aging and neurodegeneration.[41] Increased amounts of oxidative stress are correlated with the severity of behavioral changes associated with cognitive dysfunction syndrome.[111] Dietary supplementation with antioxidants can enhance cognitive function and slow cognitive decline in several species, including rats[100] and dogs.[112-114]

Combinations of nutrients

As mentioned previously, combinations of nutrients provided benefits that were not appar-

ent for single nutrients. An increasing body of evidence suggests that combinations of nutrients provide more promising results than the use of single nutrients.[87]

Numerous studies have been conducted to evaluate the effects of antioxidants in combination with a number of additional nutrients. Combinations of antioxidants and mitochondrial cofactors enhance cognitive function in dogs.[16,112,114,115]

Aged dogs fed a diet containing vitamin E, vitamin C, mitochondrial cofactors α-lipoic acid and L-carnitine, and a mixture of fruits and vegetables made fewer errors on cognitive tests, compared with results for dogs fed a control diet.[16,113,114,116] The improvements were substantially enhanced when the diet was coupled with environmental enrichment, which indicated a complementary and synergistic effect of environmental enrichment and antioxidants.[2,108,114,116–119] A subsequent clinical investigation[114,120] of the effects of antioxidants combined with environmental enrichment revealed improvements in age-related behavioral changes in pet dogs as well as improvements in mitochondrial function. Results of an investigation of the effects of α-lipoic acid and acetyl-L-carnitine suggested that these individual components may have improved long-term memory but did not affect other cognitive measures.[105,119]

Aged dogs[88] and cats[89] fed a combination of fish oil, antioxidants, arginine, and B vitamins had significantly better cognitive function, compared with aged cats and dogs fed a control diet. Dogs with cognitive dysfunction syndrome that were fed a diet with the same combination of fish oil, antioxidants, arginine, and B vitamins but that also contained MCTs had significant improvements in aberrant behaviors associated with cognitive dysfunction syndrome beginning within 30 days after the onset of the dietary intervention.[121]

A 1-year trial of pet dogs fed a diet supplemented with antioxidants, omega-3 fatty acids, phosphatidylserine, and tryptophan failed to detect an impact on cognition.[6] Authors of the study[6] suggested that the lack of effect may have been attributable to the simplicity of the test used for evaluation. This argument is consistent with findings of another study[88] in which investigators found that enrichment benefits were best observed when more complicated cognitive tests were used.

Nutraceuticals

Nutraceuticals are nutrients and other compounds, usually provided as oral products, that confer medical or health benefits.[122] Many nutraceuticals have purported cognitive benefits.

S-adenosylmethionine is a universal methyl group donor that is believed to play important roles in membrane fluidity, receptor function, and neurotransmitter turnover as well as promotion of endogenous antioxidant capacity.[123] Reduced amounts of SAMe and DNA methylation have been associated with aging as well as a number of neuropsychiatric disorders in humans,[124,125] and dietary supplementation with SAMe may partially mitigate these clinical effects.[124] A meta-analysis of human studies yielded preliminary support for the cognitive benefits of SAMe, although further studies were recommended.[123] Provision of SAMe to aged Beagles and cats without cognitive dysfunction syndrome significantly improved executive function (including goal-oriented behavior, decision-making, and problem solving) but not memory.[126] In dogs with age-related cognitive decline, provision of SAMe improved activity and awareness and decreased the mental impairment score in a double-blinded, placebo-controlled trial.[127]

Apoaequorin, a calcium-binding protein that originates from jellyfish, is believed to improve age-associated intracellular calcium dysregulation that can lead to neurodegeneration and neuronal cell death.[b] Human subjects who received the nutraceutical had significant improvement in cognitive tasks, compared with results for those who received a placebo in a double-blinded study.[b] Apoaequorin improved the performance of aged Beagles for learning and attention tasks, but not memory tasks, and dogs that received 10 mg of apoaequorin performed better on those same tasks than dogs that received selegiline.[128]

Other substances with putative benefits for cognitive impairment and dysfunction include cysteine and methionine (endogenous antioxidant production), inositol (neurotransmitter cofactor), phosphatidylserine (membrane quality), choline (acetylcholine precursor), avocado oil (antioxidant and preserves mitochondrial function), nicotinamide riboside (nicotinamide adenine dinucleotide precursor and mitochondrial homeostasis), *N*-acetylcysteine (antioxidant), and *Gingko biloba* (monamine oxidase inhibitor that can increase serotonin and dopamine concentrations).[36,129,130] Polyphenols (eg, resveratrol, curcumin, and flavonoids) are believed to decrease oxidative stress and enhance mitochondrial homeostasis, and they have received attention for their purported cognitive and health benefits.[86,122,131] A supplement-type product that contained melatonin and astaxanthin (a marine algae–derived antioxidant) improved selective attention and motor learning in dogs, but it did not improve working memory.[c] Aged Beagles fed a combination of turmeric, green tea extract, *N*-acetylcysteine, α-lipoic acid, and black pepper extract made fewer errors on an attention task, but no significant differences for other cognitive tests were detected.[35,132]

Many nutraceutical products currently available to veterinarians and pet owners include a combination of several ingredients, including antioxidants, minerals, and vitamins. Use of a combination nutraceutical[d] significantly improved a number of cognitive dysfunction syndrome–associated signs in aged dogs in a multicenter, double-blinded, placebo-controlled clinical trial[133]; however, the dogs relapsed once administration of the nutraceutical was discontinued.

Use of another combination nutraceutical[e] improved short-term memory and significantly improved behavioral signs in a small sample of dogs with cognitive dysfunction syndrome.[134] Administration of a choline-based combination nutraceutical[f] lessened confusion and improved appetite in aged cats.[36]

A number of nutraceuticals can decrease anxious behaviors in dogs and cats, although few studies have been conducted to specifically evaluate their effects in aging pets. α-Casozepine, which is derived from bovine milk casein, is similar in structure to the inhibitory neurotransmitter GABA and exerts benzodiazepine-like anxiolysis without sedative effects.[135–137] Use of an α-casozepine nutraceutical[g] resulted in improvements in some fearful behaviors of cats.[136] However, 3 of the 4 aged (≥ 10 years old) cats in that study[136] were assigned to the placebo group, and the 1 aged cat in the treatment group had no improvement. Administration of the same nutraceutical resulted in anxiolysis comparable to that seen after the administration of selegiline to adult dogs.[135] However, the oldest dog in that study[135] was only 6.5 years old. Other nutraceuticals with reported anxiolytic benefits, but that have not been specifically investigated to determine their effects on cognition and behavior in aged pets, include L-theanine, a tea plant–origin amino acid that reduces excitatory neurotransmission by competing for binding on glutamate receptors, and melatonin, which binds GABA receptors and has purported benefits for disturbances in sleep-wake cycles, fear, and anxiety but that lacks scientific support for its use in pets.[137]

Dietary supplementation with tryptophan has been investigated to determine its anxiolytic benefits; tryptophan is a precursor for the neurotransmitter serotonin.[137,138] Diets supplemented with tryptophan or a combination of tryptophan, beet pulp, salmon oil, soy, lecithin, and green tea increase plasma tryptophan concentrations in dogs but do not cause detectable changes in behavior[139]; however, dogs in that study may not have been sufficiently anxious to enable detection of noticeable changes. Because other amino acids compete with tryptophan for transport molecules, the ratio of tryptophan to other dietary amino acids may mediate the effects of dietary supplementation with tryptophan.[137,140]

A diet combining α-casozepine and tryptophan improves some anxiety-related behaviors in adult dogs, but a placebo effect cannot be ruled out.[138] Results of a study[141] on a similar diet fed to cats suggest that the diet has anxiolytic effects, but it is recommended that more research be conducted to determine those effects.

Caloric restriction and cognition

There is evidence to suggest that caloric restriction without malnutrition has neuroprotective effects, including reduction of oxidative stress, increased production of brain-derived neurotrophic factor, improvements in mitochondrial function and metabolic efficiency, reduction in apoptosis, and improvements in glucose metabolism of the brain.[74,85] However, to the authors' knowledge, cognitive effects of caloric restriction in dogs and cats have not been assessed. Dogs with long-term calorie restriction had enhanced systemic glucose metabolism during aging, but its impact on cognitive function was not evaluated.[142] Caloric restriction is a common characteristic of traditional ketogenic diets,[75] but studies[69,70,72,76,121] have not investigated the effects of caloric restriction in combination with an MCT-based ketogenic diet.

The gut-brain axis and cognition

The gastrointestinal microbiota affects brain function and behavior, and the brain, in turn, influences the microbiota through top-down and bottom-up bidirectional intercommunication.[143] Although the mechanisms involved in the gut-brain axis have not been fully elucidated, known mechanisms include microbiota-stimulated release of gastrointestinal peptides and hormones, microbiota-induced cytokine and chemokine release, activation of the immune system, and bidirectional communication via the vagus nerve.[144,145]

A clear association exists between the microbiota and anxiety, and there is growing support for a role of the microbiota in age-related cognitive decline.[145] Tryptophan metabolism plays a central role in microbiota-host interactions. The gastrointestinal microbiota regulates the availability of tryptophan for conversion to serotonin,[146] which introduces complexity to the investigation of dietary supplementation with tryptophan to manage anxiety. Certain gastrointestinal bacteria, including *Bifidobacterium longum*, are associated with anxiolytic effects. Dietary supplementation with a strain of *B longum* reduced cortisol concentrations, heart rate, and several anxious behaviors in dogs.[147] The existence of complex and robust interactions, even interdependence, of the gastrointestinal microbiome and brain has complicated investigations of nutritional interventions in health and disease, but those interactions also provide ample opportunity to influence brain health through nutrition.

Clinical summary

Aging results in changes in brain metabolism, and many risk factors associated with the underlying pathological processes have been identified. Nutritional interventions targeted to address underlying risk factors provide opportunities to slow cognitive decline, mitigate the behavioral signs of cognitive dysfunction, and improve quality of life for senior pets. Although cognitive decline and cognitive dysfunction may occur as pets age, neither should be accepted as simply a consequence of aging. On the basis of the changes that occur in the aging brain and the risk factors associated with accelerated brain aging and neurodegeneration, it is apparent that nutritional support complements appropriate medical treatment and provides opportunities to mitigate behavioral changes seen as a result of neurodegeneration.

Acknowledgments

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Footnotes

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e. Senilife, Ceva Animal Health, Lenexa, Kan.
f. Cholodin, MVP Laboratories Inc, Omaha, Neb.
g. Zylkene, Vetoquinol, Fort Worth, Tex.

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