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Introduction

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More than 25% of European dogs are considered senior. Nestle Purina Pet Care has a long heritage in understanding the effects of aging in dogs and the health and nutritional implications of growing older. Through improved nutrition and veterinary care and a more structured lifestyle, dogs are living much longer and in better condition.

When dogs age there are physiological changes which result in altered physical and mental abilities. These changes can have a profound effect on the dog’s quality of life as well as the bond between dog and owner. Each year, scientists propose new treatments, pharmacological, nutritional and behavioral which can improve the cognitive changes associated with aging.

Nestle Purina Pet Care is proud to bring together at this symposium some of the world’s leading experts in veterinary behavior, and behavioral physiology as well as our own nutritional expertise to provide you with the most up to date understanding of canine aging, both physical and mental, cognition and new leading edge preventative treatments for cognitive decline.

Christian Iehl
Nutrition and behaviour in senior dogs

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The relationship between nutrition and behaviour is two-fold. First, nutritional factors have a significant effect on behaviour. Second, the nutritional status and health of animals may be affected by their behaviour. The objective of this paper is to illustrate the relationship between nutrition and behaviour in dogs with particular reference to senior animals.

With increasing age, some dogs develop a neurogenerative disease that is characterized by a gradual decline in cognitive function and is commonly referred to as Canine Cognitive Dysfunction Syndrome (CDS) (Milgram et al., 1994). Interest in CDS has rapidly grown as it has been realized that it has many similarities with Alzheimer disease in humans. Clinically, CDS may cause disorientation, altered interactions with people or other animals, alterations in the sleep-wake cycle, changes in activity level and house-soiling, among other signs (Landsberg et al., 2003).

Dietary treatment of CDS has been based on the use of antioxidants and mitochondrial co-factors that may decrease the deleterious effects of free radicals. There is ample evidence suggesting that free radicals play an important role in aging; the brain is particularly susceptible to the effects of free radicals, as it has a high rate of oxidative metabolism, a high content of lipids and a limited ability for regeneration ( Cotman et al., 2002). It has been shown that antioxidants improve the performance of aged rodents (Cotman et al., 2002) and there are several studies showing that an antioxidant-enriched diet improves cognitive performance in senior dogs (e.g. Ikeda-Douglas et al., 2004).

Recent work has shown that long-term supplementation with medium chain triglycerides can improve cognitive function in aged dogs. The underlying mechanism appears to be an increase in the circulating levels of ketones which provide the brain with an alternative energy source.

Apart from the clinical signs mentioned earlier, CDS may cause an increase in anxiety, which is one of the main underlying factors of many behavioural problems in dogs. Nutraceuticals can be useful to reduce anxiety. In particular, tryptic alpha-S1 casein hydrolysate (alpha-casozepine) is a biopeptide from milk that results from the digestion of casein. Alpha-casozepine reduces anxiety in laboratory rodents when administered orally and preliminary results show a similar effect in dogs (Beata et al., 2005). Alpha-casozepine is now marketed as a nutraceutical for use in companion animals that suffer anxiety-related behavioural disorders in some European countries. As it is the case with dietary modifications to treat aggression, the use of alpha-casozepine to reduce anxiety has to be combined with behaviour-modification techniques.

Aging may lead to changes in the hierarchical relationship between dogs living in the same household and this in turn may cause aggression. Also, animals that have impaired senses, physical debilitation or painful conditions may become more aggressive (Bowen and Heath, 2005). Aggressive behaviour in animals is affected by several neurotransmitters and hormones. Among the former, serotonin plays a particularly important role and there is ample evidence that serotonin activity in the central nervous system is negatively correlated with aggression and that increasing serotonin activity reduces aggression in many species, including the domestic dog (Reisner et al., 1996; Edwards and Kravitz, 1997). The effect of serotonin on aggression appears to be particularly important in animals that show impulsive aggression (i.e. a lack of warning signals before the attack) and there is a correlation between low serotonin activity and impulsive behaviour (Reisner et al., 1996).

Serotonin is synthesized in the central nervous system from tryptophan. Availability of tryptophan depends on the content of tryptophan
in the diet as well as on the presence in the diet of other amino acids that compete with tryptophan for transport from the blood to the CNS. Based on this, nutritional management – e.g. giving a low protein diet supplemented with tryptophan – may be useful to reduce some forms of aggression in dogs (Dodman et al., 1996; De Napoli et al., 2000).

Senior dogs may be more susceptible to stress, in particular when they are exposed to novelty. Behavioural stressors have the potential to severely reduce feed intake in animals. Although the mechanisms underlying the effect of stress on feed intake are not completely understood, corticotropine releasing hormone (CRH) – which plays a key role in the stress response – appears to have a significant effect on appetite. It has been shown that intracerebroventricular administration of CRH reduces feed intake in a variety of animals (Materi et al., 2000).

Feeding behaviour is important not only to satisfy nutritional needs but also the so-called “behavioural needs”. Indeed, the possibility to express normal behaviour patterns has positive effects on the health and welfare of animals. Environmental enrichment is widely used in both captive wild animals and domestic animals to improve their welfare. Environmental enrichment techniques for animals in captivity follow one or more of the following guiding principles: (a) increasing control or contingency between animal action and environmental reaction, (b) presenting cognitive challenges such as learning what a trainer is requesting or solving a problem, (c) meeting specific behavioural needs such as need for shelter / hiding or foraging, (d) providing an environment in which exploration is stimulated and rewarded, and (e) stimulating social interaction (Shepherdson, 1998). There is ample evidence showing that environmental enrichment has positive effects on welfare and in most cases it causes a decrease in stress, either in baseline level responses or in responsiveness to acute stressors (Carlstead and Shepherdson, 2000). In aged dogs, environmental enrichment has positive effects on cognitive performance and these are more pronounced when dietary treatment and environmental enrichment are combined (Ikeda-Douglas et al., 2004).

References


Elderly dogs: when to blame the body, when to blame the mind?

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To trick your child into eating his cabbage, you might say, ‘Are you going to eat your cabbage right now or straight away?’ He may well respond by bursting into tears, thereby changing the topic and possibly avoiding having to answer such an impossible question at all. (19)

The question posed in the title is likewise impossible to answer. You cannot understand a dog without taking account of its mind, nor can you assume that its brain works independently of its body. On the contrary, you must view your canine patients as complete entities. Indeed, when treating them, you should assume the role of a generalist and take the entire system into account. This system would also include the owner, since he or she is a critical part of the therapeutic relationship. (11)

This need for a comprehensive approach holds true for all ages. Body and mind obviously influence each other. In older dogs, the influence is even more pronounced. Indeed, most often we are dealing with almost pathological situations. Dysfunction of one part of the body frequently leads to the abnormal or even pathological function of the rest of the body.

When attempting to categorise the origins of aging-related disorders, it is possible to distinguish three types of dysfunction responsible for the behaviour of older animals:

- Motivational and physical dysfunction.
- Hormonal dysfunction.
- Cognitive dysfunction.

Each type of dysfunction amplifies the others, which is why aging is often classified as a pathological process, when it is actually a normal evolutionary process. Aging irreversibly leads to discomfort and to poor responses to changes in the environment. These three characteristics (poor response to change, discomfort and irreversibility) are typical of pathological processes. (10)

Physical and motivational disorders

These are best expressed by phrases such as ‘I can’t do this anymore’, ‘it’s not even worth trying’, ‘I just can’t manage it’, etc.

And yet, it is possible to accept abnormal situations by sheer force of habit.

This principle is similar to and illustrative of the theory of extinction. When an organism ceases to receive, it likewise ceases to demand, and the motivation for productive behaviour is gradually lost.

Aging animals are subject to two types of pressure, that caused by their physical ailments and that caused by their lack of motivation.

Motivation is a reaction by the body to restore its equilibrium. (6) The degree of motivation depends on how strong the imbalance is, whilst the search for a solution is informed by past experience. Thus, when an animal is hungry, its body is no longer in a state
of equilibrium, and foraging mechanisms will be triggered until the sensation of imbalance disappears, i.e., until its hunger has been sated. Likewise, when an animal feels insecure, it gears its behavior toward seeking shelter and restoring its sense of safety. (16)

Aging individuals gradually learn to resign themselves to minor imbalances. As the aging process progresses, the imbalances they tolerate become more and more severe. Powerless to react to ever more serious physical ailments, they grow increasingly resigned. This is one of the mechanisms of pathological inhibition classically observed in depression. (10) (12)

It is thus easy to understand how physical ailments can exacerbate aging. The blunting of the five senses reduces the animal’s sensory awareness and minimizes its responsiveness. (5)

The animal’s reduced ability to respond leads to a process of learning by habituation. In a sense, the animal is almost forcibly immersed and made to operate under the ideal conditions for rapid habituation. What it once saw as a warning sign is now seen as being of little concern. (16)

Take the example of a guard dog. Deteriorating hearing coupled with increasing difficulties to produce a reaction (joint pain, loss of flexibility, etc.) will teach this dog that nothing will happen if it fails to react. Things that years ago would have placed it on maximum alert are now interpreted as an everyday part of its surroundings, requiring no reaction at all.

Conversely, pain will act as a form of punishment for the dog with regard to a variety of reactions, causing new associations to be learned: children equal pain, walks equal discomfort, etc.

**Hormonal disorders**

Although not yet understood with absolute precision, the interactions between hormones and mood are certainly numerous and, in the absence of a more detailed understanding, generally accepted as a reality.

Changes in three hormones are commonly measured in veterinary medicine: thyroid hormones, sex hormones and cortisol.

Behavioral disturbances linked to cortisol.

Aging is often accompanied by a disturbance of the suprarenal secretion of endogenous cortisol. Hypersecretion speeds the aging of neurons, whilst both neurogenesis and synaptogenesis are reduced by excess cortisol. (8)
Conversely, chronic behavioural disorders are often accompanied by disturbances of dopaminergic function. Canine pituitary glands have an anatomofunctional peculiarity. Dogs have a large pars intermedia that only reacts to the secretion of dopamine.

In dogs, aging is accompanied by hyperfunction of the dopaminergic system (anticipation, decreased learning abilities), and this build-up of dopamine secretion leads in turn to a build-up of cortisol secretion. It is not unusual to find animals with a basal cortisol level of approximately 500-700 nmol/l that cannot be considered cases of Cushing’s syndrome in the usual sense of the term. Correcting the dopaminergic flow in these dogs brings about a return to normal circulating cortisol levels.

It is easy to see how anxiety can increase cortisol-related problems, which, in turn, can lead to further anxiety-provoking disturbances. On the plus side, cortisol generally increases certain motivations (hunger and thirst) and reduces problems linked to inflammation.

In healthy individuals, the secretion of cortisol under stress is compensated by the secretion of oxytocin. This mechanism may be less effective in aging animals. [13]

**Thyroid function disorders**

In old dogs, the half-life of circulating thyroid hormones is reduced. In addition to this, several other factors can cause a reduction in the secretion of these hormones. Thus, the collapse in circulating thyroxine levels is compounded by their reduced effectiveness. As a result, periods of functional hypothyroidism are frequently observed in aging dogs. [18]

Overall, these thyroid disorders will affect the sensitivity of the pre- and postsynaptic adrenergic receptors. Whilst there are many noradrenergic pathways, thyroid disorders are undoubtedly most pronounced in the activating pathways of the locus coeruleus. Indeed, an increase in phobic reactions and the inappropriate activation of the locus coeruleus can be observed. [8] The latter leads to demands that cannot be met. Owners describe their dogs as having insatiable needs, claiming ‘He will wake me up at night to spend a penny, but does not pass a drop’ or ‘He wants to cuddle, but cannot stay put in my arms’.

Measured levels of circulating thyroxine are not necessarily very low in these cases. However, the half-life of this hormone in older dogs must be taken into account. Care must be taken when correcting this deficit, as an excess runs the risk of increasing hypertensive disorders.

In cats, early-stage hyperthyroidism (values of approximately 45-50 nmol/l) can be treated with propranolol at a dose rate of 10 mg/kg.

**Sex hormone disorders**

Apart from the physical problems associated with gonadal dysfunction (prostate pain, ovarian and mammary tumours, etc.), the circulating levels of sex hormones affect all aspects of brain function.

A link between prolactin and anxiety is assumed, but sometimes disputed, and it is still too early to establish the exact role of these hormones. (Beata C: Are T4 or prolactin levels good indicators of the state of anxiety? ECVBM-CA conference, Edinburgh, 2009. In press.)

Oestrogen and testosterone are often responsible for increased irritability.

**Cognitive and mood disorders**

At the membrane and, thus, synaptic level, aging results in a loss of flexibility. Plasma membranes gradually lose their flexibility and responsiveness. Synapses can no longer adapt so easily. NMDA receptors are less easily stimulated and synaptogenesis decreases. [7]

Aging is accompanied by a loss of spatial and temporal awareness, as well as of short-term memory. Clinically, these cognitive disorders are sometimes expressed in strange ways. [10][12] For example, a dog may no longer be able to find its way; it may forget the direction in which a door opens; it may suddenly make friends with a lifelong enemy (for example, the vet), or it may get playful at night. More classically, aging is accompanied by the loss of basic learned skills, such as house-training or the ability to come back when called.

These cognitive disorders rapidly lead to both motivational and mood disorders. Indeed, they cause permanent distress, which can
lead to depression. Mood disorders can also arise as a consequence of pre-existing behavioural problems, such as advanced phobia or chronic anxiety. Finally, synaptic dysfunction can cause abnormal inhibitions, which, in turn, can lead to depressive behaviour. In the French model, this type of pathology is known as ‘involutional depression’.

In any case, cognitive disorders often lead owners to react in less than sympathetic ways. The aging dog often sees its environment become more and more hostile and loses interest in it. Its social relationships deteriorate and it finds fewer and fewer reasons to motivate itself.

Conclusion

When an elderly dog no longer gets up to take its regular turn around the garden, it is clearly a sign of aging. It may be due to a joint disorder or to a learned association between joint pain and the garden. It may be explained by prostate pain. It could be a cognitive disorder resulting from disorientation or a mistaken perception. Or perhaps a hormonal disorder that causes irrational fears due to the animal’s abnormal perceptions in the garden. Alternatively, it could be due to a lack of motivation. Or the dog may have a fever or be suffering from renal failure and, as a result, be seeking to isolate itself. Or perhaps it is the owner’s fault, for no longer bothering to open the door to the garden all the way.

Simply deciding that this symptom is behavioural or physical is wrong on principle. The dog must be treated by a team of specialists with a broad understanding of bone and joint function, endocrinology, behaviour, the owner-dog relationship, the different drug interactions and so on.

Fortunately, these specialists can all be found in the form of a single person: the veterinary surgeon in general practice. Geriatrics is a field best left to generalists, who take a comprehensive view of the animal.

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Elderly dogs: when to blame the body, when to blame the mind?


That dog is smarter than you know: advances in understanding canine learning, memory and cognition

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Canine social and cognitive systems

Hundreds of years of artificial selection have resulted in size, shape and behavior variability in domestic dogs that exceeds that of thousands of years of natural selection on wolves (Sutter et al., 2007). The story of dogs is the story of co-operative work with humans. Dogs share both foraging mode and a virtually identical social system with humans. Dogs also mirror humans in hallmarks of social development (Overall, 1997, 2000). These similarities are the result of co-evolution for co-operative work with humans which has been ongoing for 15,000-150,000 years, depending on varying estimates and the assumptions that go into them (Savolainen et al., 2002). Intense selection for specific suites of behavioral traits (e.g., the development of breeds) occurring in the last 12,000-15,000 years.

This close relationship has influenced both the way humans and dogs communicate with each other, and the types of behavioral problems that dogs may develop. All breeds share characteristics with humans that have rendered dogs so compatible for joint working and social relationships: they have extended and extensive parental care, other family members contribute to the care and social development of offspring, they are socially mature after they are sexually mature, social systems are based in deference, and rules governing it so that signaling is often redundant, and most signaling or affirmation of signaling is non-vocal rather than vocal.

Much of the physical variation in dog breeds is a consequence of overt selection for specific suites of behaviors suites (e.g., coats that are the result of hunting v. retrieving behaviors, and the behavioral patterns that differ with task like herding v. retrieving). The working history and its associated suites of behaviors of extant domestic dogs is reflected both by traditional classifications by various kennel clubs and by clustering analyses that have used genetic information from representative breeds (Parker et al., 2004; Parker and Ostrander, 2005).

Findings with respect to learning, aging and associations with anxiety

There are few canine data on effects of anxiety on learning. Canine aging is known to affect learning and various types of memory (Swanson et al., 2009). There is evidence that treatment with monoamine re-uptake inhibitors speeds learning of specific tasks in dogs (Landsberg, 2005). Similar results have been reported for mice for age-associated impairment in maze learning (Yau et al.; 2002). The mechanisms postulated for these outcomes involve the finding that chronic glucocorticoid excess interferes with learning at the cellular level (Yau et al., 2002). This chronic exposure has also been proposed to affect hippocampal neuronal structure. Viewed in this light chronic cortisol elevation may act as a translational gene regulator - a hormonal response element - in regions of the hippocampus. This finding is relevant for dogs who are either learning jobs or behavior mod: the factor that prohibits most dogs from completing training programs is their fearful / anxious / uncertain response to novel or complex environments.
The basics of learning

Learning is generally defined as the acquisition of information or behavior through exposure and repetition. At the cellular and molecular level learning is defined as cellular and receptor changes that are result of stimulation of neurons and the manufacture of new proteins. It is these new proteins/receptors that then change the way the cell responds when next stimulated. It’s important to remember that no cell/neuron acts on its own: region of the brain, neurochemical tract, and interactions with other cells are critical for determining response.

Reinforcement is key for learning. Reinforcement can either be positive, encouraging repetition of the behavior, or negative, discouraging the repetition of the behavior. Negative reinforcement discourages the behavior because the animal is rewarded with a more favorable experience not just when they cease the undesirable behavior, but as a result of ceasing it. For example, if the dog is held gently with an encircling arm to stop him from jumping at the car before the door is opened, this act is an example of negative reinforcement if as soon as the dog settles, the door is opened and the dog is rewarded with being allowed to jump into the car. It’s important to realize that negative reinforcement is completely different from punishment (now often referred to as ‘positive punishment’) to ensure everyone notes that an aversive/unappealing stimulus/action is applied where no reward structure is in place.

These distinctions and definitions are particularly important when we consider learning at the cellular and molecular level because cellular memory – long-term potentiation (LTP) - can take place in different regions. Fear primarily involves the amygdala, whereas various ‘reward’ systems involve parts of the cortex, the substantia nigra, and miscellaneous parts of the ‘limbic system’ (Davis, 1997). In addition to regional activity, positive reinforcement, negative reinforcement, and punishment primarily use different neurochemical tracts or way-stations. Positive reinforcement uses opiate and dopaminergic systems, punishment involves the flight, freeze, or fight pathways of the noradrenergic sympathetic systems, and negative reinforcement likely involves some complex association of both of these, plus the serotonergic system. It’s important to acknowledge that these neuroanatomical and neurochemical associations are understood poorly, at best, and that generalizations about them are painted in the broadest possible strokes.

Reward Structures

It’s important to understand reward structures and what these mean at the cellular and molecular level for behavior modification. Behaviors are reinforced or learned best if every time they occur they are rewarded. At the cellular level, repeated reinforcement insures better, more numerous, and more efficient connections between neurons (Carter et al., 2002; Wittenberg and Tsien, 2002). Stimulation is induced when a neurochemical in a synapse triggers a receptor to engage it. This stimulation of the receptor engages second messenger systems in the post-synaptic cell, usually cAMP. The result is LTP. By itself, this initial process represents E-LTP or ‘early phase LTP’ and STM (short-term memory). The process is short-lasting, RNA and protein-synthesis-independent, and the result does not persist or become self-potentiating unless the stimulus is consolidated into L-LTP ‘late phase LTP’, which is a more permanent form (Schafe et al., 2001). ELTP can be induced by a single train of stimuli in either the hippocampus or the lateral amygdala.

In contrast, L-LTP and LTM (long-term memory) requires repeated stimulation of cAMP, induction of cAMP response element binding protein (CREB - a nuclear transcription factor), and is long-lasting, protein synthesis dependent, and is RNA transcription dependent (Schafe et al., 2001). When stimulation continues, BDNF enhances neurotransmission and potentiates what is called activity-dependent plasticity at synapses (e.g., learning), particularly in the region of the brain most involved in learning, the hippocampus. This effect can also occur in the lateral amygdala and is one modality postulated to be involved in learned or conditioned contextual fear (Schafe et al., 2001).

This neurobiology is important to consider in the context of reward systems. It explains why continuous reward works best in acquiring a behavior (E-LTP and STM) and why intermittent reward acts best to maintain a learned behavior (L-LTP and LTM). This neurobiology explains why a really excellent reward can help you learn or reinforce a behavior quickly and why a really horrible experience can stimulate the amygdala to encode learned panic or phobia at the molecular level.

Consider neuromolecular biology of scary events. Events that induce panic or phobia all share the trait that those afflicted are unable to escape the stimulus. The amygdala, itself, is an incredibly complex few mm³. Almost all outgoing tracts that control some higher forms of integration of behavior in the cerebral cortex, hypothalamus, brain stem et cetera have their efferents shaped by the location of their origin in the amygdala (Davis, 1997). Additionally, the lateral amygdala is likely the site where memories of conditioned (learned) fear are created through a process involving neuronal plasticity (Schafe et al., 2001). In fact, if one lesions or inactivates the lateral amygdala, it is impossible to either acquire a fear or to express a previously acquired fear (LeDoux et al., 1990).
We now know that the extracellular environment of the amygdala is responsible for the maintenance of memories about fear (Pizzorusso, 2009). Perineuronal nets comprised of chondroitin sulfate proteoglycans (CSPGs) render fears difficult or impossible to ‘erase’ (Gogolla et al., 2009). This ‘resistance’ is not present at birth, so fear is more difficult to learn early in development, and resistance to recovery from fear comes harder once the CSPG landmark is reached. Such findings complicate our understanding of learning but also suggest potential future interventions.

When one considers rewards - or aversive stimuli - which best induce these quick learning experiences, it is important to consider them in terms of their evolutionary value. Evolutionarily tightly coupled rewards - ones that selection has shaped to be of particularly high value - are those directly coupled to survival: food, freedom, elimination, mating. Evolutionarily less tightly coupled rewards - ones on which survival should not hinge - will be of lesser value: praise, play. Similarly, when one considers true aversives that act as positive punishers, fear, uncertainty and pain are often involved. These aversives actually threaten access to behavioral suites coupled to survival [food, freedom, etcetera]. When one considers the molecular biology of learning within the evolutionary context of very pleasurable or very fearful stimuli, it should be clear how behaviors can best be modified.

**Effects of medication on neuronal stimulation, synaptic plasticity, and receptor protein transcription and translation**

Medications commonly used to treat behavioral conditions in dogs and cats are usually antidepressants and anxiolytics that fall into 3 main classes: the benzodiazepines (BZ), the tricyclic antidepressants (TCAs) and the selective serotonin reuptake inhibitors (SSRIs). Currently, medications with a veterinary label are available for treatment of behavioral problems in dogs in the USA: Anipryl® (generic = selegiline) for cognitive dysfunction (Pfizer), Reconcile® (generic = fluoxetine) for separation anxiety and Clomicalm® (generic = clomipramine) for separation anxiety. These medications have labels for other conditions and for cats in some countries outside the USA, and such uses are ‘extra label’ in the USA. Increasingly we see patients treated with serotonin norepinephrine reuptake inhibitors (SNRIs: venlafaxine, duloxetine), serotonin 2A agonist/reuptake inhibitors (SARI: trazadone, nefazodone), and noradrenergic and specific serotonergic antidepressants (NaSSAs: mirtazapine). Less commonly used medications, or those with more restrictive populations likely to benefit include medications that are monoamine oxidase inhibitors (MAOIs: selegiline) and azapirones (buspirone). All of these medications cause their effects through modulation of the neurotransmitters serotonin (5-HT), dopamine (DA), noradrenaline/norepinephrine (NA/NE) and/or gamma amino butyric acid (GABA), and their related metabolites. Accordingly, any medication that shares a metabolic or synthetic pathway with any of these neurotransmitters or medications can affect the amount of any medications available and their utility.

What makes TCAs and SSRIs special and why are they so useful for anxiety and other disorders that affect information processing? The key to the success of these drugs is that they utilize the same second messenger systems and transcription pathways that are used to develop cellular memory or to “learn” something. This pathway involves cAMP, cytosolic response element binding protein (CREB), brain derived neurotrophic factor (BDNF), NMDA receptors, protein tyrosine kinases (PTK) - particularly Src - which regulate activity of NMDA receptors and other ion channels and mediates the induction of LTP (remember, long-term potentiation = synaptic plasticity) in the CA1 region of the hippocampus (Daniel et al., 1998; Salter, 1998; Trotti et al., 1998). See Figure 1 for a schematic representation of how medications can affect genomic responses that produce new proteins.

There are two phases of TCA and SSRI treatment: short-term effects and long-term effects. Short-term effects result in a synaptic increase of the relevant monoamine associated with re-uptake inhibition. The somatodendritic autoreceptor of the pre-synaptic neuron decreases the firing rate of that cell as a thermostatic response. Regardless, there is increased saturation of the post-synaptic receptors resulting in stimulation of the α-adrenergic coupled cAMP system. cAMP leads to an increase in PTK as the first step in the long-term effects. PTK translocates into the nucleus of the postsynaptic cell where it increases CREB, which has been postulated to be the post-receptor target for these drugs. Increases in CREB lead to increases in BDNF and tyrosine kinases (e.g., erk1) which then stimulate mRNA transcription of new receptor proteins. The altered conformation of the postsynaptic receptors renders serotonin stimulation and signal transduction more efficient (Duman, 1998; Duman et al., 1997).

This should sound an awful lot like how learning occurs at the molecular level through LTP - because it is. Simply, TCAs and SSRIs are medications of choice for changing behaviors because they stimulate the neurochemicals involved in anxiety-related pathways, and because the augment the rate at which learning occurs because of the parallel effect on pathways and mechanisms involved in learning.
Figure 1: Schematic of the basic functions of pre- and post-synaptic neuronal function when stimulated by learning and/or medications that affect the same pathways.

Knowledge of the molecular basis for the action of these drugs can aid in choosing treatment protocols. For example, the pre-synaptic somatodendritic autoreceptor is blocked by pindolol (a beta-adrenoreceptor antagonist) so augmentation of TCA and SSRI treatment with pindolol can accelerate treatment onset. Long-term treatment, particularly with the more specific TCAs (e.g., clomipramine) and SSRIs, employs the same pathway used in LTP to alter reception function and structure through transcriptional and translational alterations in receptor protein. This can be thought of as a form of in vivo “gene therapy” that works to augment neurotransmitter levels and production thereby making the neuron and the interactions between neurons more coordinated and efficient. In some patients short-term treatment appears to be sufficient to produce continued “normal” functioning of the neurotransmitter system. That there are some patients who require life-long treatment suggests that the effect of the drugs is reversible in some patients, further illustrating the underlying heterogeneity of the patient population considered to have the same diagnosis.

Regardless, we appear to have seriously underestimated dogs. Changing our worldview to match the expanding data on canine cognitive abilities could revolutionize not just people’s relationships with dogs, but also how we use them for work and research.
How much can dogs learn?

We don’t actually know much dogs can learn, but recent published work from the emergent field of cognitive studies in non-laboratory canines should give us pause. We now know that dogs can take their cues from dogs or humans about hidden objects and communicate this information to other dogs (Cooper et al., 2003; Hare and Tomasello, 1998; Hare et al., 1998, 2002, Topál et al., 1997). Dogs appear to have the ability to “fast map” – to make deductions about object class and name without having learned them directly – and to communicate this ability to humans (Kaminski et al., 2004). ‘Fast mapping’ is the first stage of language acquisition in humans. Recent work shows that dogs make the same classes of cognitive errors in learning as do young children (Tomasello and Kaminski, 2009; Topál et al., 2009). For decades we have used dogs to help those who cannot see and those who require help opening doors, turning on lights, picking up objects and getting dressed or out of bed. Dogs scan the post, luggage, planes, cars, and people for explosives and contraband. Dogs jump from helicopters to rescue the drowning and search disaster sites for both the living and the dead. All of these tasks are deeply cognitive, and while the dogs learn the required responses that we teach them, they also seem to learn and communicate about what they learn as much as we permit them to do so. When gene expression patterns of 2 neuropeptides were compared for dogs, other wild canids and humans, only the domestic dog showed modifications similar to those of humans for mRNA expression patterns in a few hypothalamic genes that have multiple functions (Saetre et al., 2004). All of this strongly suggests that we have barely begun to understand canine learning.

Summary

Because of our shared evolutionary history, what we learn about the behavior of learning from dogs may benefit humans, and vice versa. The key to understanding all learning and cognitive changes – whether they are beneficial or pathological – is to understand how such processes are effected at the molecular level. Once we understand the role that various regions of the brain and learning in those play, it’s a simple step to think of helpful interventions for enhancing learning and, perhaps, cognitive abilities. Meanwhile, we probably owe all our dogs an apology. They are clearly smarter than we thought and have likely been telling us that for a long time.

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Brain energy metabolism and affects of aging: do we become what we eat?

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Dogs as potential models for human cognitive change, and the benefits to dogs from we have learned about humans:

Although rats and mice are more commonly used, the domestic dog may be a better model for complex genetic traits such as those involved behavioral disorders, including brain aging (Sutter and Ostrander, 2004). The dog has several important advantages over rodents as a model for complex behaviors, among which is the shared evolutionary history of dogs and humans emphasized here. In addition, the enthusiasm and close cooperation of dog owners and breeders facilitates an ongoing interest in canine genetics within the dog community, and provides access to needed samples. Finally, breeds were developed through selection for specific types of tasks or work and most extant breeds are less than 150 years old, further reducing heterogeneity (Parker et al., 2004).

Recent advances in canine genomics have potentially facilitated efforts to map genes for complex behaviors (Kirkness et al., 2003; Lindblad-Toh et al., 2005), including some of those potentially involved in information processing and age-related effects on this. The work of Lindblad-Toh and colleagues is remarkable for its demonstration of extensive synteny – basically, exact similarity - between the canine and human genomes, as well as the finding that, despite being more distantly related to humans than rodents are (Springer et al., 2004), the dog shows more nucleotide homology with humans than do rodents. Again, such patterns are likely the result of a co-evolutionary process that still may be ongoing.

Recent data indicate that dogs are significantly more comparable to humans than are chimpanzees and wolves with regard to the complex social cognition involved in understanding long-distance signals that indicate where food is hidden. Dogs are further able to communicate this information to other dogs (Cooper et al., 2003; Hare and Tomasello, 1998; Hare et al., 1998, 2002; Topal et al., 1997). Dogs appear to have the ability to ‘fast map’ – to make deductions about object class and name without having learned them – and to communicate this ability to humans (Kaminski et al., 2004). Also, like humans, dogs suffer from what we recognize as maladaptive anxiety - that which interferes with normal functioning - which was selected against during the co-evolution of dogs and humans (Overall, 2000). Finally, when examining the rates of gene expression mutations in regional brain tissue, the only species studied to date that has comparable rates to those found for humans is the domestic dog (Saetre et al., 2004). Such data, when taken together, strongly suggest that dogs can be excellent models for human brain aging, and that any data that accrue from studies of human brain function may be relevant for understanding canine brain function. Such syntenic patterns open an array of treatment and mechanistic modalities for those interested in brain aging.

Brain aging as a special case - newer challenges and findings

Given the previous evolutionary discussion, no one should doubt that canine brains age, and when they do, many of the dimensions of canine brain aging resemble those seen in humans. While humans are afflicted by numerous tauopathies, each of which may have defining cognitive and/or anatomical dimensions, emphasis in canines has been place on a relatively non-specific diagnosis of canine cognitive dysfunction (CD), sometimes also called cognitive dysfunction syndrome (CDS) (Heath, 2002). In dogs, CD is usually diagnosed because of a history of disorientation, alterations in social/interactive behaviors, changes in locomotor behavior.
and sleep cycles, and what is often called ‘loss of housetraining’. In early-onset cognitive dysfunction, animals may have only slightly altered sleep cycles and appear more anxious. Alterations in social/interactive behaviors may be manifest early in the condition as an increased neediness but change to a form of aloof disengagement in social interactions with all species.

We have chosen to treat such conditions with medications designed to address anxiety, panic and depression (Landsberg, 2005) because of the changes such medications cause at the receptor level. Oxidative damage to receptor systems has been at the core of much research on cascades that become damaged once free-radicals are involved (Roudebush et al., 2005). However, such treatments neglect other aspects that may affect how well learning occurs and how cognition can occur, including those aspects in providing power to the learning process.

Review of what happens in the dog’s brain when it learns something

Behaviors are reinforced or learned best if every time they occur they are rewarded. At the cellular level, repeated reinforcement insures better, more numerous, and more efficient connections between neurons (Carter et al., 2002; Wittenberg and Tsien, 2002). Stimulation is induced when a neurochemical in a synapse triggers a receptor to engage it. This stimulation of the receptor engages second messenger systems in the post-synaptic cell, usually cAMP. The result is cellular memory or long-term potentiation (LTP). By itself, this initial process represents E-LTP or ‘early phase LTP’ and STM (short-term memory). The process is short-lasting, RNA and protein-synthesis-independent, and the result does not persist or become self-potentiating unless the stimulus is consolidated into L-LTP ‘late phase LTP’, which is a more permanent form (Schafe et al., 2001). E-LTP can be induced by a single train of stimuli in either the hippocampus or the lateral amygdala.

In contrast, L-LTP and LTM (long-term memory) requires repeated stimulation of cAMP, induction of cAMP response element binding protein (CREB - a nuclear transcription factor), and is long-lasting, protein synthesis dependent, and is RNA transcription dependent (Schafe et al., 2001). When stimulation continues, BDNF enhances neurotransmission and potentiates what is called activity-dependent plasticity at synapses (e.g., learning), particularly in the region of the brain most involved in learning, the hippocampus. This effect can also occur in the lateral amygdala and is one modality postulated to be involved in learned or conditioned contextual fear (Schafe et al., 2001).

All of these activities require energy to be executed and completed.

What does the brain use for energy

Diet can affect behavior through chemical interactions between amino acids, and by altering brain energy sources, allowing alterations in use of resources. Energy sources for the brain can actually be variable, and lactate, acetate, and pyruvic acid are now considered viable energy sources, in addition to what has traditionally been considered the main energy source, glucose.

Energy sources in the brain

Glucose is considered the common brain energy currency, but it is not stored. The stored form of glucose is glycogen. Glycogen is found mainly in astrocytes, and the amount of glycogen available is affected by glucose concentration and neurotransmitter presence and function (Pellerin et al., 2007). During hypoglycemia glycogen is converted to lactate via pyruvate (glucose → pyruvate → lactate). The lactate is then transferred to adjacent neurons. This conversion and transfer allow the neurons to use a source of aerobic fuel.

Glycolysis can also be anaerobic and is faster at producing energy than is oxidative phosphorylation (Raichle and Minton, 2006). In fact, glycolysis makes pyruvate faster than it can be oxidized, by converting glucose to lactate, ATP is made twice as fast than would be the case were glucose oxidized completely (Raichle and Minton, 2006).

The use of lactate in hypoglycemic events can extend axon functions for 20+ minutes (Pellerin et al., 2007). This conversion of astrocyte glycogen to lactate also occurs during periods of intense neural activity, demonstrating the role of astrocytes as bankers of energy-conversion compounds.

Lactate is the preferred energy source for the human brain, after glucose (van Hall et al., 2009), and there is no reason to assume that this may not also be an important pattern in dogs. The majority of lactate used as an energy source is thought to come from glycolic processes because most lactate, itself, is too large a molecular to pass through the blood-brain-barrier. However, blood lactate has been measured in oxidized form and may be a source of some energy for brain tissue (van Hall et al., 2009).
some some astrocytes appear to “prefer” to process glucose glycolytically into lactate (Magistretti, 2009). Lactate can then be converted into pyruvate and enter the tricarboxylic acid (TCA) cycle, providing energy in the form of ATP.

Glucose insufficiency may also be an issue in a number of pathological conditions in which cognition is impaired. Cerebral glucose appears to be reduced by 20-40% in patients with Alzheimer’s disease (Hoyer, 1992), and the hippocampus – the part of the brain involved in associative learning – may be severely sensitive to decreases in glucose. The number of plaques forming in Alzheimer’s disease may be directly proportional to the level of glucose insufficiency (Meier-Ruge et al., 1994). Accordingly, identifying alternate sources of energy may be beneficial.

Ketone bodies have been proposed as one alternate energy source because of their modulating effects on hypoglycemia and because of hydroxybutyrate (β-OHB), an MCT, may provide an alternate substrate in acetyl-CoA generation. β-OHB, in particular, may be useful for protecting hippocampal neurons from toxicity by providing a more usable form of energy (Reger et al., 2004). In a placebo-controlled, double-blind study Reger et al. (2004) found that mildly impaired Alzheimer disease patients who were supplemented with medium chain triglycerides (MCT) showed improvement in a number of pre- versus post-treatment cognitive test measures, and that such improvement correlated with β-OHB increases. It should be noted that this result depended on whether the apolipoprotein E (APOE) genotype: only patients without an APOE-ε4 allele responded to acute elevation of β-OHB.

One of the major foci of age- and illness-related changes is the effect of a cumulative burden of oxidative stress over time. Increased oxidative stress is one of the most common topics examined in brain aging and it appears to affect all major classes of molecules involved in neurotransmission. Development of oxidative stress may not be independent of energy source or use. Interestingly, intermittent fasting has been reported to induce the production of brain-derived neurotrophic factor (BDNF) (Martin et al., 2006) which is associated with neurogenesis and molecular learning and memory, particularly in the hippocampus. Increases in BDNF affect numerous signaling pathways involving tyrosine kinase B (trkB) which may directly or indirectly affect regional brain metabolism and function.

Astrocytes are responsible for de novo synthesis of 2 neurotransmitters: glutamate and D-serine (Dienel and Cruz, 2006). Glutamate, the excitatory neurotransmitter that is responsible for an estimated 85% of synaptic activity, appears to also be essential in metabolic activity of the brain. Glutamate may be responsible for energy regulation by affecting neurovascular exchange (Magistretti, 2009). Glutamate has as its signaling targets the synapse, astrocytes and intraparenchymal capillaries. In normal brain function, glutamate effects its signaling by altering flow of calcium and sodium ions: post-synaptically it modifies the permeability of NMDA receptors to sodium and calcium, and the AMPA receptors to sodium, and presynaptically it affects NMDA receptors and metabotropic receptors via calcium. This interaction is what causes an excitatory post-synaptic potential (EPSP). Glutamate activity is also thought to be involved in pathological conditions where excitatory sensitivity has been implicated (e.g., strokes, impulsively aggressive states, cortical and hippocampal epileptogenic activity). In both normal and pathological conditions, glutamate’s main effect is on excitability and synaptic plasticity.

Glutamate also affects astrocytes which are non-neuronal cells (Magistretti, 2009). Glutamate transporters appear to use the sodium gradient to facilitate glutamate uptake by astrocytes. Recent anatomical studies show that astrocytic processes ensheath intraparenchymal capillaries and synapses, and that many of these processes have receptors and reuptake sites for neurotransmitters. It is these findings that allow glutamate to act as a metabolic intermediary. In short, glutamate stimulates the conversion of glucose into lactate in astrocytes.

Interestingly, many pathways that affect glycolysis for brain energy are also adversely affected at some point oxidative change. Many of these effects may be modulated by anti-oxidant or co-factor treatment, coupled with active behavioral interventions/enrichment. Alphaenolase interconverts 2-phosphoglycerate and phosphoenolpyruvate. Alphaenolase has been shown to be altered in canine models of neurodegenerative disorders and responds to treatment with antioxidants, mitochondrial co-factors (lipoic acid) and behavioral/social/cognitive enrichment (Opip et al., 2009). Decreased oxidation of alphaenolase and GAPDH could improve glycolytic function, with a resultant increase in ATP production. Together, these alterations appear to lead to neuronal recovery and improved cognitive function in the canine model of human brain aging (Opip et al., 2009).
In a study of gene expression in brains of old dogs, the expression of genes involved in neurochemical signaling and synaptic transmission was decreased (Swanson et al., 2009). Particularly affected were levels of growth and transmission factors already discussed, including BDNF and trkB. These factors did not respond to antioxidant diet supplementation. Interestingly, in the same study, compounds like glutathione S-transferase — responders to oxidative stress — were also decreased in geriatric dogs. Such findings show the ultimate interrelatedness of available brain energy, neurotransmission and neuroregulator function and structural changes in aging dogs.

**Structural components of neuronal membranes that may be important for use and transport of energy in the brain**

Arachidonic acid (ARA), docosahexanoic acid (DHA) and eicosahexanoic acid (EHA) are long-chain polyunsaturated fatty acids (PUFAs) that are essential for developing and maintaining the integrity of cells of the brain’s membranes. These PUFAs are related by their synthetic sequence: linoleic acid (18:2 n-6) < ARA (20:4 n-6) < docosapentanoic acid (22:5 n-6). Elongation of alpha-linoleic acid produces eicosapentanoic acid (EPA) (20:5 n-3) < DHA (22:6 n-3) (Bosch et al., 2007).

All of these PUFAs are essential for early brain development. ARA is thought to especially maintain hippocampal cell membrane fluidity and protect cells in the hippocampus from oxidative stress. The hippocampus is one of the main areas involved in long-term potentiation (LTP), a form of molecular learning, and is one of the main regions where associational learning takes place.

DHA may encourage development-stage specific associational learning, although the data are mixed. Supplementation with DHA and EPA affect concentration of these substances in rat brains, and their distribution is not uniform. Diets deficient in alpha-linoleic acid especially cause decreases of DHA in the frontal cortex — the part of the brain responsible for complex learning and integration of information and executive function. In dogs, low concentrations of DHA during gestation and/or lactation depress the retinal sensitivity of puppies, which can have profound and complex behavioral outcomes. The current data support the need for DHA for optimal neurological development in puppies, and there are hints that it may improve both early and long-term cognitive abilities, but the data are scant.

There has been some suggestion that PUFAs are also important in some canine behavioral conditions. In a study of German shepherd dogs with a history of aggressive behavior, aggressive dogs showed a significantly lower concentration of DHA (22:6 n-3) and a higher omega6/omega-3 ratio when compared to unaffected dogs (Re et al., 2008). Plasma concentrations of ARA acid (20:4 n-6) and EPA (20:5 n-3) did not differ. These same animals showed reduced levels of cholesterol compared to control dogs. Similar, non-specific findings regarding cholesterol have been reported for aggressive dogs (Sentürk and Yalçin 2003). It is important to realize that the characterization of ‘aggression’ in these studies is variable, and that such correlations say nothing about cause. Such findings could be the outcome of aberrant neurochemical function. However, one of the main roles PUFAs appears to be maintenance of membrane fluidity and protection from oxidative stress, especially in the part of the brain essential to associational learning, the hippocampus.

Finally, in humans, the brain contains 600 g lipid / kg, with approximately equal amounts of ARA and DHA. It’s been postulated that a dietary intake of 6-12% protein comprised of Rift Valley lake fish and shellfish provided sufficient DHA and ARA that allowed the early hominoid cerebral cortex to grow disproportionately without requiring an increase in body mass (Broadhurst et al., 1998). Any putative effects of these PUFAs on cognitive abilities are likely rooted in this evolutionary history. Interestingly, PUFA levels in brains of young v. geriatric dogs, when measured, have not been shown to be different (Swanson et al., 2009), but effects of varying amounts in different regions of the brain (e.g., the hippocampus, which is key to learning and the frontal cortex, which is involved in learning and essential for executive function or application of that learning) in older animals has not been studied.

**Summary**

Our brains are doubtless shaped by what we eat, and so our dogs’ brains are shaped by what we choose for them to eat. It would surprise no evolutionary biologist that alternative brain energy pathways exist and that they maintain healthy and active brain function and neurotransmission. But the effects of ebb and flow of food on these effects may suggest that our culture — and our dogs’ culture — of constantly available food, rather than constantly available cognitive stimulation, has not adequately considered the extent to which this is a strategy that has not been chosen by the shared dog-human evolutionary history. Exploration of effects of diet on canine cognition and recovery from the dreaded effects of aging could enhance our understanding of the shared development of dogs and humans as inter-dependent species.
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Normal aging of the brain in the dog

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Even in good health, the brain is always aging!
Current research is principally directed at all the mechanisms that can influence longevity, and particularly building up information about aging. However, one should always bear in mind that aging is a normal phenomenon undergone by all organisms during the later stage of their life. It is characterised by the progressive loss of the body’s capacities to adapt to its environment.

It is thus not an illness in itself.
The notion of ‘brain and cognitive reserve’ [1] is now being put forward to underline the importance of the environment, and of the relationship between the spiritual, physical, intellectual and/or recreational activities carried out and the degree of protection against senile degeneration.

In the dog, differences in size make for significant differences in longevity.

<table>
<thead>
<tr>
<th>Dog breed/size</th>
<th>Longevity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small breeds</td>
<td>11.48 +/- 1.85</td>
</tr>
<tr>
<td>Medium breeds</td>
<td>10.90 +/- 1.56</td>
</tr>
<tr>
<td>Large breeds</td>
<td>8.85 +/- 1.94</td>
</tr>
<tr>
<td>Giant breeds</td>
<td>7.46 +/- 1.94</td>
</tr>
<tr>
<td>Cats</td>
<td>11.88 +/- 1.94</td>
</tr>
</tbody>
</table>

Of all the organs affected by aging, there is no doubt that the modifications to the brain give rise to the most dramatic consequences. The ‘classic’ behaviour of the aged dog is linked to changes in function, anatomy, physiology and/or pathology.

The most common mechanisms implicated in cerebral aging can be seen as follows:

- grey and white matter changes - loss of neurons
- vascular changes
- electrical changes
- membrane changes
- endocrine changes
- biochemical changes: amyloid-β deposits
Grey and white matter changes – loss of neurons

It has been accepted for quite some time that cerebral aging goes hand in hand with a loss of neurons, particularly in the cortex. Recent information no longer leads in this direction, but points towards the loss of neurons being correlated with the presence of a pathology rather than the normal course of aging.

As these sections demonstrate, even though it is possible in dogs to show an evolution linked with age, it is also possible to find cases in which the loss is more marked at a younger age (Neurobiology of Aging 19, 1998, 479-85). In human medicine, the reduction in episodic long-term memory appears to be linked to a structural alteration in the white matter [2]. On the other hand, cortical atrophy linked to grey matter, considered to be correlated with aging, is now being questioned. In truly healthy subjects, there is no demonstrable loss. Indeed, this loss may be overestimated because of the difficulty in separating healthy subjects from those as yet asymptomatic at the moment of inclusion [3].

Vascular changes

In humans, vascular risks are linked to possible deterioration of the white matter mentioned above, and hypertension could thus be a significant factor in this process. Increased blood pressure is associated with white matter deterioration in the anterior region [4]. Learning demands vascular perfusion that is both adapted and adaptable in certain regions of the brain. One study compared three groups of rats; normal adult rats, aging rats without cognitive problems and aging rats showing moderate cognitive problems. It was then shown that a relationship could be made between increased basal perfusion of the dorsal part of the hippocampus and these moderate cognitive problems. The reaction to hypercapnia was also significant in the affected animals [5].

A reduction in cerebral perfusion and glucose metabolism in the frontal and temporal cortex is commonly associated with aging [6]. Even though this is only a hypothesis at present, based on a small selection of subjects, it has also been shown that a high level of physical activity reduces the tortuous nature of the cerebral vessels, and augments the number of small vessels. The latter are correlated with improved cerebral perfusion [7].
**Electrical changes**

Failed or inadequate electrical impulses.

In dogs, a slowing of nerve transmission is noted at about 7 years, and it is believed that there is a reduction of 10 to 15% after 10 years [8].

**Membrane changes**

Aging is associated with a loss of plasticity of all membranes, and in particular the neuronal membranes, giving rise to reduced adaptability.

Increased intramembrane cholesterol levels are thought to be responsible for this loss of plasticity. This correlates clinically, for example, with less effective emotional regulation.

Synaptic transmissions activate receptor microdomains, which assemble and migrate into the membrane, and this requires great plasticity.

The increase in cholesterol prevents not only the recruitment of receptors to form these microdomains, but also their dispersion after use. Thus changes may be seen in the emotional reactions of older dogs, their emotional reactions may be exaggerated or at least strongly increased compared with those they habitually expressed throughout their earlier adult life. Above all, they will show problems in settling down again after a stressful episode.

**Endocrine changes**

Many endocrinal changes occur during the aging process and these have direct repercussions on brain function.

Repercussions of thyroid hormone function are heavily debated, but it is commonly agreed that even variations within the commonly agreed range, as well as hypothyroidism and hyperthyroidism, can affect cognitive mental processes in aging subjects [10].

If the actual levels of T4 vary very little, its metabolic availability diminishes greatly, and it is therefore possible to observe classic symptoms of hypothyroidism within normal levels.

But the thyroid hormones are not the only hormones implicated. Glucocorticoids in the brain are also responsible for repercussions on emotion and/or cognitive functions [11].

Changes in the level of melatonin, levelling out variations in circadian rhythm, are also involved in modifications associated with mood, emotional regulation and cognition in aging subjects [11].

**Biochemical changes**

These are without doubt the most significant changes, and the bulk of research has been directed towards these modifications because a link has been established between these biochemical changes and degenerative diseases such as Alzheimer’s disease.

The dog is not a human being, and does not show the same changes. Nonetheless, amyloid-β deposits have also been described in the dog, and of particular interest, a correlation has been shown between amyloid load and cognitive deficit.

There are many differences compared to humans. The short form of peptide, amyloid-β peptide (1-40) is not found, only the long form amyloid-β peptide (1-42). There is no neurofibrillary degeneration and no true senile plaques. On the other hand, there are diffuse, cloud-like and vascular deposits.

Age is the major correlation factor for the cognitive deficit in the study cited in the reference list, but there is also a strong correlation between the amyloid load and cognitive deficit.

**Conclusion**

Aging leads to numerous changes either directly or indirectly affecting the brain. There can be no question of reducing the process of cerebral aging to a single factor as all the studies have shown that aging involves a combination of several factors which are responsible for the cognitive and/or emotional changes associated with aging [13].
References


Dietary Supplementation with Medium Chain Triglycerides Has Long-Lasting Cognitive Enhancing Effects in Senior Dogs

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Introduction
Dog cognitive function, like that of other mammals, becomes impaired over the course of aging [1, 2]. Decline in energy metabolism is a common feature of aging in animals, and is one of several processes that are closely associated with age-dependent cognitive decline. Rapoport et al. [3] found that brain glucose metabolism was reduced by up to 30% between 3 and 12 months of age in rats. London et al. [4] reported that brain glucose metabolism in dogs was significantly reduced at 6 y when compared to one year old dogs. Further changes occurred later in life, but in a manner that varied between brain structures. Age-associated reduction in cerebral glucose metabolism is a common feature in aging, and the process involved may be progressive, starting around the middle age. Metabolic decline contributes to cognitive decline associated with aging. One possible means of counteracting deficits in cerebral glucose metabolism is by nutritional supplementation. Henderson [5] has proposed that dietary supplementation with medium-chain triglycerides (or MCTs) can be used to increase brain levels of metabolites which serve as alternative energy sources. MCTs are converted to beta-hydroxybutyrate and acetacetate in the liver and, to a lesser extent, by astrocytes in the brain. These metabolites could then be used by neurons as an alternative energy source to alleviate the deficit in glucose metabolism. To partially test this MCT supplementation hypothesis, Reger et al. [6] provided an MCT supplement to patients with Alzheimer’s disease and reported an improvement in cognitive function in a subset of subjects that were negative for the apolipoprotein E ε4 allele. They also found that cognitive improvement correlated positively with serum levels of beta-hydroxybutyrate.

This paper details the results of a study recently completed by Nestle Purina which evaluated the efficacy of MCT supplementation on the cognitive function of healthy senior dogs.

Animals, Diets and Blood β-hydroxybutyrate levels
Animals. Twenty-four Beagle dogs (10 males and 14 females) ranging in age between 7.5-11.6 y old, with at least 6 months of previous cognitive test experience were used in the present study. All dogs were provided with environmental enrichment consisting of toys, beds and the opportunity to play outside alone or with other dogs on a daily basis. Housing temperature and humidity were held relatively constant by automated temperature control and continuous ventilation.

Diets. The control diet was a commercial super premium-type product for adult dogs (Nestle Purina products: ~ 32% protein, 19% fat, 3% fiber). The test diet was formulated by adding 5.5% MCTs. Both diets were isocaloric and contained the same levels of protein, fat and carbohydrates. The dogs were fed once daily and provided free access to water. The study lasted 8 months.
Blood β-hydroxybutyrate levels. Dogs fed the diet containing MCTs had significantly higher blood β-hydroxybutyrate levels in non-fasting conditions at 4 and 8 months after initiation of the diet regime which indicated that the MCTs from the diet were being absorbed and circulated throughout the body and presumably to the brain to be used as an alternative energy source. Table 1.

<table>
<thead>
<tr>
<th>Serum β-hydroxybutyrate (μmol/L)</th>
<th>Time</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>day 0</td>
<td>120 days</td>
<td>240 days</td>
</tr>
<tr>
<td>Control - fed dogs</td>
<td>24.25±3.73</td>
<td>29.83±14.17</td>
<td>30.67±14.77</td>
</tr>
<tr>
<td>MCT - fed dogs</td>
<td>25.08±3.73</td>
<td>123.83±14.17</td>
<td>110.17±14.77</td>
</tr>
</tbody>
</table>

Table 1. Effects of MCT diet addition on blood β-hydroxybutyrate at 3 sampling points

**Cognitive tasks**

Three cognitive tests (landmark test, egocentric test and variable oddity test) were used to evaluate the effect of MCTs on cognitive function in the senior dogs. Each test was performed sequentially and chosen to evaluate specific functions of the brain which have previously been identified to be sensitive to changes with increasing age. The three cognitive tests were developed to assess learning ability, visuospatial function and attention. Baseline cognitive assessment evaluated the performance of the dogs on each of the three cognitive tests. Each dog was ranked and the ranking used to place subjects into two cognitively equivalent groups. Figure 1.

In the first test protocol, learning ability, memory and visuospatial function was assessed using a landmark discrimination learning protocol. These tasks are intended to assess allocentric spatial ability or the dogs’ ability to use external ‘landmarks’ to localize objects in space. Previous work (7) has found that performance with the landmark protocol is sensitive to age.

The landmark discrimination protocol included three separate tasks: landmark - 0cm, landmark -1 cm, and landmark-2 cm (8). This protocol started with the subjects being trained to approach one of two objects based on their proximity to an external landmark (land-0). Figure 2. The subjects were tested on successively more difficult versions of the same general problem. Each time the dogs were able to successfully discern that the food reward was associated with the landmark, object containing the food reward was moved 1 cm away from the chosen landmark. Dogs were then re-tested to see if they were still able to associate the landmark with
a food reward. In this and subsequent tasks, food inaccessible to dogs was placed in the bottom of the object associated with non-reward in order to prevent the dogs from responding based on olfactory cues. Dogs were able to obtain food reward if they displaced the correct cover closest to the defined landmark. The test objects were placed 25 cm from the dog to allow for a brief inspection interval, enabling the dogs to see the spatial arrangement on the tray. The tray was then presented to the dog, and the dog was allowed to respond within 60 seconds. In this and all subsequent levels of the landmark test, the dogs were required to respond to the object closest to the landmark to obtain food reward.

Dogs fed MCTs had significantly improved performance on the landmark 1 cm and 2 cm tests (p < 0.05) with marginal significance on landmark-0cm test (p<0.10). Figure 3. Landmark-0cm tests are relatively easy for dogs to learn and involve memory and simple discrimination skills. Landmark- 1 and 2 cm tests are more difficult tasks for dogs because these tests require the dog to utilize allocentric spatial discrimination (orientation of objects in the environment) and memory skills. MCTs seem to help preserve the senior dogs’ ability to orient between objects in space. Significant improvements were observed within one month of initiation of MCT feeding. The relevancy of this to the dog owner is that MCTs improved complex learning ability, trainability, and cognitive performance of senior dogs.

Dietary supplementation with medium chain triglycerides

Figure 2. Landmark discrimination test. Dogs were asked to indicate the object closest to a designated landmark.

Figure 3a. Dogs’ number of errors on Land-0cm and Land-1cm test

Figure 3b. Dogs’ number of errors on Land-2cm test
The second test protocol focused on egocentric spatial ability or the dogs’ ability to orient objects in their environment in relation to the position of their own body (9). The protocol first examined the ability of the dog to selectively respond to an object based on proximity of the object to its left or right side and second, to reverse its original response.

The egocentric protocol had three phases, a preference phase, an acquisition phase and a reversal learning phase. The preference phase consisted of presenting the dog with 2 identical objects both of which covered food and provided a reward on each trial. Figure 4.

![Figure 4. Egocentric test. Dogs were tested to determine their preferred side.](image)

The side chosen most frequently was designated the dog’s preferred side, and assigned to be the positive side for the initial acquisition phase of testing. Thus, if the dog chose the object to its left most frequently, then the dogs’ left side was designated its preferred side. For the acquisition (original learning) phase, dogs were shown the same objects from the preference phase but presented in 2 of 3 positions—left, center or right. Dogs were rewarded for choosing the object closest to their previously determined preferred side. Figure 5.

![Figure 5. Egocentric test. Dogs were asked to indicate object closest to their preferred side during the acquisition phase](image)

All dogs were given two reversal tests (reversal 1 and reversal 2). The reversal phase was initiated following completion of initial learning and was identical to that followed during the acquisition phase except that the rewarded position was switched to the opposite side. Thus, if the object closest to a dog’s left was rewarded in acquisition testing, the object closest to its right was rewarded in reversal 1 testing. After dogs passed reversal 1 testing, they were then tested on reversal 2 testing, which was identical to reversal 1 testing, except that the rewarded position was switched to the originally preferred side.
Egocentric acquisition of task learning depends on spatial memory (ability to remember the orientation of things in the environment) and is easy for dogs, whereas egocentric reversal learning is more difficult and relies on executive function (ability to change strategies or adapt) and concept learning skills. Though there were numerical differences in the simple egocentric acquisition test, and the reversal-1 test, there were no significant differences between senior dogs fed control diets or diets with MCTs (p > 0.05). Figure 6. However, there was a significant improvement in the reversal-2 test for MCT-fed dogs (p < 0.05). Figure 6. These data suggest that MCTs are overall helpful in preserving the senior dogs’ ability to remember spatial relationships but are especially useful for preserving more complex skills such as adaptation (requiring executive function) and concept learning. Senior dogs that retain these cognitive functions should be better able to cope with variations in day to day life and adapt to changes like new people or places.

The final test to assess attention and concept learning was a variable oddity test during which dogs were asked to identify the odd item out of a group of similar items. (10) The task involved an acquisition and distractor phase. The first phase, or acquisition phase, required the senior dogs to learn to selectively respond to one particular object out of a choice of two in order to obtain a food reward. In the distractor phase, each trial consisted of presenting to the dogs one, two, three, or four objects, including the object that they had been trained to respond to during the acquisition phase. All distractors had non-accessible food in them to prevent dogs from making decisions based on olfactory cues. Alternative objects served only as distractors, and the number of distractors varied from 0 to 3. Figure 7. The correct object was always the one associated with reward in the initial two-choice discrimination problem. On each test session, the subjects received 3 trials with 0 distractors, 3 with 1, 3 with 2 and 3 with 3. Both accuracy and speed of responding were used as dependent measures that were indicative of attention dependent processes. Concept learning was assessed through the dogs’ ability to accurately indicate the previously trained object in the face of multiple distractors.

Figure 6. Dogs’ number of errors on egocentric acquisition, reversal-1 and reversal 2 tasks

\* p < 0.05

Dietary supplementation with medium chain triglycerides
In the acquisition phase of the attention task, the MCT group committed fewer errors than controls, but the differences were not significant (p > 0.05). The control-fed dogs performed more poorly than the MCT-fed dogs when there were 2 or 3 distractors. Figure 8. Performance was similar when the groups were only presented with 1 distractor. These results indicated that more distractors led to poorer performance, which is consistent with the concept that the task provides a measure of selective attention. Although the groups did not differ in initial learning, differences did occur during the distractor phase suggesting that MCT supplementation improved the dogs’ ability to focus their attention on the previously trained object. Improved attention span could result in the senior dog having more interest in its environment and potentially more interactivity with family members. Preserving concept learning skills through MCT addition to the diet could help maintain flexibility of senior dogs’ thinking processes.

Collectively the cognitive assessment data showed that performance of the MCT supplemented group was superior to that of controls on the land-1 cm and land-2 cm tasks, the egocentric learning and reversal task, and the variable object components of the attention protocol. By contrast, smaller and statistically insignificant group differences were noted in the land-0 cm task, the egocentric discrimination learning task, and the object discrimination phase of the attention task. A primary difference between the tasks that showed significant treatment effects and those that did not is task difficulty: the more difficult tasks were the ones that showed the
more significant effects. Previous research has shown a similar link between task difficulty and a cognitive modifying intervention like enrichment [11].

Loss of polyunsaturated fatty acids involved in maintaining neural structure is another consequence of aging [12]. Beyond serving as an alternative energy source for the brain, the cognitive-enhancing effects of MCT’s may relate to brain distribution and concentration of polyunsaturated fatty acids [13], that are involved in maintaining neural structure and known to decrease during aging [12].

Up to 50% of European dogs are over the age of 7. The physical signs of aging are apparent and easier for owners to recognize, and subsequently seek treatment from the veterinarian. Changes in brain physiology and metabolism however, are more subtle but certainly real. The clinical symptoms associated with those changes occur well after there have been significant physiological changes which make “turning back the clock” very difficult. At this point, there is no way to reverse the physical changes to the brain tissue like increased ventricle size, loss of brain mass or amyloid plaque deposition. However, based on this study, it is possible to improve energy delivery to the aging brain and thereby improve its cognitive function.

βHB levels increased in the blood of senior dogs fed diets containing MCTs resulting in key improvements in cognitive function like memory, executive function and attention.

Senior dogs fed MCTs had improved memory and learning ability. London [4] reported changes in brain glucose metabolism, specifically of the frontal cortex and hippocampus as dogs aged. Milgram [14] indicated that dogs have more difficulty learning new skills as they age. Based on the results of this study, dogs over 7 fed diets containing MCTs had improved memory, trainability and learning capacity. This can be important for owners of dogs over 7 who still want to engage in new activities requiring these cognitive skills.

The ability of senior dogs to cope with day to day life can be taxed, particularly if there are physical limitations later in life like joint disease. However, better cognitive adaptability and ability to change strategy for example, deciding to exit the house via the door with the least number of steps to the garden, could help improve quality of life as dogs’ age. Dogs fed diets containing MCTs had improved executive function (ability to change strategy) as well as improved concept learning skills.

The dogs in this study fed the diet with MCTs had improved attention. It is possible that dogs with improved attention will engage in their environment more, leading to more brain stimulation from interactions within their environment. It is well known in human cognition that people who actively exercise their mind appear to maintain cognitive function later in life.

In summary, healthy senior dogs who lead enriched lives fed a complete and balanced diet with MCTs had significantly improved cognitive function. The proposed mechanism is that MCTs are metabolized into βHB which is a highly efficient alternative energy source for the glucose-deprived aging brain cells. A series of cognitive evaluations indicated that dogs fed MCTs had improved attention, memory, learning capacity and ability to adapt (an executive function process). Though this study was intended to address slowing the inevitable cognitive decline of health aging dogs, it is possible that a diet supplemented with MCTs will have positive effects on dogs with mild to moderate canine cognitive disorder as well. Further studies would be required to confirm this hypothesis.

References

Dietary supplementation with medium chain triglycerides


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Canine Cognitive Dysfunction: definition, causes and current treatments

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Introduction
Ageing is an inevitable process and veterinary surgeons cannot offer any miracle solution to this problem. However, with increasing knowledge about the ageing process and the ways in which it can be affected by diet, lifestyle and medication, they can offer the means of increasing the quality of life for the ageing pet population.

A changing population
Within the field of human medicine the importance of maximising the quality of life for people in their senior years has been recognised for a long time. In contrast the importance of geriatric care within the field of veterinary medicine has been a relatively recent concept, which has been fostered by the significant increase in the geriatric pet population. Advances in veterinary care in terms of better nutrition and better disease prevention and identification, has resulted in an ageing population and dogs that live into their late teens are no longer considered to be out of the ordinary. This change in demographics has led to a changing emphasis in veterinary care and providing a full support service for the geriatric animals within the practice is rapidly becoming a priority.

The need for geriatric clinics
The effect of the ageing process on the major body systems is well documented and understood and geriatric clinics are an accepted way for general veterinary practices to ensure regular health checks for senior patients in order to aid in the early detection of organ failure. Clients are encouraged to act on the principle that early intervention in age related medical conditions will increase the success of treatment and offer the best prognosis in terms of an extension of good quality life for their pet. However age does not only take its toll on the circulatory, renal and hepatic systems and changes in the central nervous system which are associated with the ageing process, are also an important consideration for the geriatric pet. Changes in neurotransmitter levels, alterations in membrane permeability and increased production of free radicals can all lead to the onset of age related behavioural changes and those pets that exhibit these symptoms are suffering from a medical condition, which requires appropriate veterinary attention.

Why are so many cases of canine dementia left undiagnosed?
Canine dementia is a medical condition but in most cases there is a lack of recognisable clinical symptoms and the signs that lead to accurate diagnosis are almost entirely behavioural. Without the appropriate line of questioning in the consulting room many of these cases will go undetected. There are four main categories of presenting signs for canine dementia namely disorientation, changes in social and environmental interaction, changes in sleep/wake cycle and breakdown in housetraining. On their own each of these categories could be indicative of organic disease or of a purely behavioural condition but when signs are present from each of these categories, and most importantly from the first two, a diagnosis of canine dementia needs to be considered.
The human dimension

Clients are often reluctant to tell their veterinary practice that their old dog is behaving in an odd manner as they are frightened that they will be advised to euthanase their companion. In many cases owners see the signs as an inevitable effect of growing old and the belief that nothing can be done to change them will drive considerable changes in their own lifestyle in order to accommodate their pet’s peculiar ways. Alterations in sleep/wake cycles often take the largest toll on the humans in the household but owners will put up with broken nights and significant sleep deprivation rather than approach their veterinary practice and run the risk of being persuaded to put their pet to sleep. Breakdown in house training may put an enormous strain on the pet owner relationship and many owners feel guilty about their negative feelings toward their dog and chastise themselves for not being patient with their ageing companion. “After all”, many owners will say, “old age comes to us all and I would hate to think that my family would want to put me to sleep just because I had a few accidents”. Quality of life is a difficult concept and it is important to remember that the criteria by which owners judge the quality of their pet’s life may be very different from those that veterinary practices would employ. For the client, the relationship between themselves and their pet is central and behaviour is one of the major indicators of the strength of that relationship as well as one of the most significant sources of strain upon it. While changes in sleep patterns and breakdowns in house training may be seen by owners as an inconvenience that has to be endured, changes in social interaction and signs of disorientation are often interpreted as indicators of distress. Owners find it upsetting to see their dog looking confused and when their pet fails to respond to previously known commands or startles when they enter the room as if he does not recognise them the effect on the pet-owner relationship can be devastating. These owners are left feeling guilty on every side, first of all they feel guilty because their pet is no longer enjoying life and they see euthanasia as their only option and then they feel guilty for even considering euthanasia when their pet appears to be in such good physical health. After all human society frowns upon the concept of euthanasia and the only way of justifying it in a veterinary context is as a means of stopping physical suffering. Putting to sleep due to changes in behaviour is seen by many owners as a convenience and this only adds to the guilt.

As the ageing process takes its toll on a dog’s heart and brain some changes in behaviour and personality are almost inevitable and it is important to be able to differentiate between cases where the animal is simply slowing down out of necessity and those where the animal is finding it increasingly hard to function at a social level. In some cases behavioural changes in old dogs will noticeably resemble the symptoms of Alzheimer’s disease in people. Lack of connection between behaviour and context is a classic sign of dementia and many owners have reported that their dog seems like a stranger in its own home. In cases of canine cognitive dysfunction post mortem have shown similar neuropathological lesions to those seen in people with Alzheimer’s disease and dementia and there is no doubt that this condition is part of mainstream medicine.

Slow down or true dementia?

Asking the right questions

Noticing the signs of dementia early on is crucial and there is a much better prognosis in terms of the level of improvement and the extension of good quality life if treatment is instituted in the early stages of this disease. However, it is this early stage that often goes unnoticed and the most effective way of increasing the detection rate for this condition is to include a behavioural questionnaire in routine geriatric clinics. Asking specific questions about the dog’s social behaviour both at home and on walks, as well as seeking information about sleep patterns and toileting habits will enable the veterinary practice to identify cases of dementia early and institute treatment as quickly as possible.

Disorientation

Dogs suffering from dementia will show a delay in the recognition of people, places and objects and in some cases there may be no recognition at all. Obviously when dogs fail to recognise their owners this is likely to be noticed quite quickly but failure to respond to people who call regularly at the house or to those that are met while out on daily exercise may go unnoticed for quite some time. Asking specific questions about the way in which the dog greets people at home and on walks can help to identify these changes. Old dogs will often wander aimlessly around the house and it may be obvious that they are disoriented and confused but in other cases asking questions about the dog’s reaction to previously familiar objects such as household furniture and trees and bushes in the garden can help to pinpoint the symptoms of dementia. These dogs will often bark at these objects as if they have never seen them before and they may show reaf fear. Failure to recognise the home driveway on the return from a walk or a tendency to sit at internal doors when asking to go out into the garden can also be symptoms of disorientation and unexplained staring is also a potential indicator of dementia.
Changes in social and environmental interaction

One of the most obvious signs of a lack of connection between context and behaviour is seen in the interactions that senile dogs have with the people and other dogs that they come into contact with. One of the most distressing examples of this is an alteration in the social interaction between the dog and its owners and a decrease in the enthusiasm of greeting behaviour. Together with a decrease in the time spent engaging in play and in affectionate interaction this can signal the onset of dementia changes. There is often a change in the consistency and speed with which these dogs respond to commands and owners often mistake this change for stubborn behaviour. When considering interactions with other dogs it is not uncommon to see an increase in confrontational reactions in other dogs who appear to be threatened by the bizarre behaviour of the senile individual. Dogs suffering from dementia may also become more irritable themselves and owners may be aware of an increase in aggression from their dog together with a general decrease in the desire to interact and play with other dogs on walks.

Changes in sleep/wake cycles

Alterations in sleep/wake cycle are common in cases of canine dementia but unless the dog is disrupting the owner’s sleep this aspect may easily go unnoticed. When the dog is whining or barking at night most owners will rapidly respond by taking their pet out into the garden on the assumption that it needs to relieve itself but dogs suffering from dementia will rarely need to eliminate on these occasions. In some cases they may respond to being outside by toileting but once back in the house they will be very slow to settle and will soon recommence barking and whining. Pacing is another common feature in these cases and owners often comment that their dog shows signs of agitation and restlessness at their usual bedtime and paces and vocalises when they make preparations to go to bed. Waking in the middle of the night is another classic symptom of dementia and since these dogs are also disorientated and confused they will often seek out their owners when they wake. If the dog is housed downstairs during the night this may cause the dog to scratch at doors and this symptom can commonly lead to confusion with separation anxiety. During the day the sleep/wake cycle is also affected and dogs suffering from dementia will sleep for longer in the day but once again this symptom may easily be overlooked and considered to be a normal change in a dog of advancing years.

Loss of previously conditioned behaviours

The most common example of this aspect of dementia is a loss of previously reliable house training. However there are numerous other examples of conditioned behaviours which can be lost as a result of this condition. Learned verbal commands such as sit or stay may no longer register with the patient and this may be misinterpreted as an increase in stubborn behaviour or a decrease in obedience. When there is a break down in house training it can occur for two reasons. Firstly the disorientation associated with dementia can lead to a situation where dogs sit at internal doors when they want to go out into the garden and owners can easily disregard this signal until it is too late. Staring at the hinged side of the door rather than the handle side has also been noted by owners and in these cases they often observe the peculiar behaviour but do not recognise it as a signal for needing access to outdoors. Another factor in the house training problems associated with old age behavioural changes is a failure to maintain associations with suitable latrine substrates and in many cases there is a history of a progressive break down in associations leading to elimination in a wide range of unsuitable locations. These dogs often start by not always toileting on grass as they have done in the past and making mistakes on the patio, on the flowerbeds and eventually on the carpeted floors in the house. In many cases the onset of this problem behaviour is gradual and it is only when the dog is toileting in a number of locations that the owners realise that these are not one off accidents.

Medical differentials

In all of the categories of behavioural symptoms for canine dementia there are a number of medical differentials. Sensory deficits need to be considered when signs of disorientation, changes in social interaction and changes in sleep/wake cycles are encountered since a dog that is not fully aware of its surrounding through a lack of sensory input can easily present with signs which resemble those seen in dementia. Cardiovascular and neurological disorders will also need to be ruled out and the influence of pain on activity levels, social interaction and sleep patterns should be investigated. Disorders of the gastrointestinal and urinary tracts will need to be investigated in cases where a break down in house training is the major presenting sign and metabolic diseases and endocrine disorders which result in polyuria and polydipsia will form part of the list of differential diagnoses. These clinical considerations highlight the need for a medical approach to these cases and a combination of clinical examination and additional tests, such as blood samples, will enable the veterinary surgeon to determine the dog’s physical state of health. Only once this has been done can the behavioural investigation continue and treatment for canine dementia be considered.
Medication for canine dementia

Although primarily behavioural in presentation there can be no doubt that canine dementia is a medical condition and when deciding on medication to treat these cases it is important to consider the changes that are occurring within the body systems, including the central nervous system. Old age behavioural changes can often result from a compromising of the cerebral blood flow and medication with the appropriate drugs, such as nicergoline and propentofylline can vastly improve this situation and give increased energy and vigour to dogs that are beginning to slow down. However, dogs that are suffering from canine dementia are not just slowing down and in these cases it is important to choose a medication that can tackle all of the processes which are responsible for the condition.

In addition to compromise of the circulation these animals are showing a depletion of brain dopamine levels and an increase in the presence of free radicals leading to cell injury and brain pathology. Dealing with these changes is best approached by administration of the drug Selegiline hydrochloride which has three important actions in cases of canine dementia. It enhances brain dopamine concentrations and metabolism, it decreases substances in the brain which are responsible for neural cell damage, and it protects nerve cells, decreases cell death, and promotes synthesis of nerve growth factors. It is administered as a once daily dose at a rate of 0.5 mg/kg and in cases of dementia the dog will usually require long term medication. It can take up to six weeks for Selegiline to take effect but in dementia cases improvement is often noted by the owner within 3 weeks. It is recommended that all dogs are given pre-treatment biochemistry and haematology screens and that these blood profiles are repeated at six monthly intervals during treatment. Side effects are minimal but some owners do report transient self correcting episodes of vomiting and diarrhoea during the first week of treatment.

Nutritional support for canine cognitive dysfunction

From a nutritional perspective the importance of antioxidant rich diets has been well documented and a number of published papers have shown that nutritional supplementation can produce a significant difference in relation to improvement in signs of disorientation, changes in interaction and house soiling behaviour. Antioxidants are believed to prevent the development of the age-related neuropathology, which is implicated in cases of canine cognitive dysfunction. In addition antioxidants are believed to promote recovery in neurons that are exhibiting signs of neuropathology and therefore nutritional manipulation is believed to offer another option in the management of this condition. A range of antioxidants and free radical scavengers have been shown to be effective including N-acetyl cysteine, which is a primary precursor to glutathione, alpha lipoic acid, acetyl-l carnitine, vitamins C and E, L-carnitine and Co-enzyme Q10. Essential fatty acids DHA and EPA are also beneficial. Another nutritional supplement which has been shown to be an effective component in the nutritional approach to canine cognitive dysfunction management is phosphatidylserine, which is a natural phospholipid. Its’ main physiological effect is to enhance and maintain the cell activities based on the functionality of the plasma membrane. Clinical studies have demonstrated the role of phosphatidylserine in cognitive function of human patients and in experimental animals administration of phosphatidylserine rapidly induced dose-dependent improvements during learning and memory tests.

Providing behavioural support for a medical condition

Although canine dementia is undoubtedly a medical condition there is a strong behavioural component and behavioural therapy is needed as a support for the pharmacological treatment. One of the consequences of age-related behavioural disorders is the loss of learned responses. As a result the dog may lose its ability to perform simple tasks or respond to previously known commands. Teaching dogs with dementia needs patience and understanding and the use of simple unambiguous commands and clear reward signals is essential. Ideally rewards should be things that the pet particularly values and this will be dependent on the breed and will also vary from individual to individual. For example some dogs will value games, others petting and others food. The use of a clicker, which has been previously associated with reward in a simple introduction process, gives the pet a clear unambiguous signal that will help to reinforce success. Patients will often need to be house trained and in many cases owners also need to reintroduce some of the basic obedience commands. It is important that the owner begin this re training as early as possible in order to avoid the establishment of unsuitable behaviours through inappropriate learning.

The aim of behavioural therapy in dementia cases is to give structure and predictability to the environment, in a way, which helps the dog to understand what is expected. Dementia results in a lack of association between action and context and therefore it is important to ensure that all commands are consistent and that the dog is given as many clear signals of success as possible. Visual signals can be very useful, provided the dog is not showing any sensory deficits of course, and marking exit doors can be beneficial for those dogs showing signs of disorientation leading to house soiling problems.
Dementia patients often show difficulty in concentrating and the owner should be encouraged to introduce games that will provide mental stimulation and increase social interaction with their pet. Ideally, play and exercise sessions should be of short duration, involve simple tasks, which are repeated frequently and culminate in a positive reward for the pet. For example, several short exercise outings each day will be preferable to one long one since this will stimulate the pet’s interest in the environment and provide increased opportunities for interaction between the pet and its owner.

The effect of treating canine dementia on the pet-owner relationship

The onset of old age is an inevitable fact of life and for many dogs their transition into the ranks of the geriatrics is smooth. However, this is not always the case and when signs of disorientation and confusion begin, many owners find it hard to recognise their faithful family friend. The changes in social interaction can make canine dementia a distressing condition for the owner and when dealing with these cases it is important to remember the human element. Detecting the symptoms of this condition at the earliest opportunity will enable these dogs to receive appropriate veterinary care and maximise the benefits of therapy in terms of increased quality and duration of life. Practices can vastly improve their service to geriatrics by incorporating a programme for the early detection of canine dementia into their geriatric clinics.

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Introduction

In nature individuals live until they are able to cope with the challenges of the wild, for example, finding shelter and food. However, the final point of death is preceded by a long process during which physical and mental capabilities start to deteriorate slowly. Researchers find it generally hard to mark the start of this process. The separation of being “medium aged adult” and “old” is a complicated issue. For example, in humans, people older than the mean life span have been often considered as being old. Importantly, mean age of humans varies across different geographic ranges and socioeconomic groups, and this means that people over 55 years could be considered as being old in some African countries, but in this sense one must live at least for 75-80 years to be counted as old in Japan. Since the world average life expectancy is now around 65 years, this is age is regarded world-wide as separating the elderly from the middle aged.

There is however another issue that puts the study of aging in the forefront of research. In parallel with the rapid growth of the human population both the number and ratio of elderly is on increase. It seems very likely that this novel phenomenon which seems to be exceptional when considering animal species in general has contributed to intensive research in biology and medical sciences, which does not only aims at understanding the mechanisms of aging but also the ultimate evolutionary and ecological causal factors that influence the aging in animals and humans. Recently many researchers have suggested that our best friends, with whom we have shared much of our personal history, may parallel our story of aging, and thus dogs may provide an important animal model (Patronek et al 1997).

Aging in nature: Do wolves die young?

Apart from humans, data for aging are difficult to find. This is especially true for populations living in the wild, because individual deaths from natural causes go usually unnoticed. Moreover different measures are used for characterising aging in animals for comparative purposes. One may determine the mean age of a population, and referring to a certain percentage of animals over some value as being old. Further, life expectancy is defined as how long an individual may live under its specific situation. Longevity refers either to the mean age at death or to an exceptional individual, which died at the oldest age ever recorded for that species.

The comparison of wolves (Canis lupus L.) living in the wild with pet dogs (Canis familiaris, L.) may give some hints about the problems in comparative research on aging. Mech and others (1998) captured 120 wolves in Denali for radio tracking, and the estimated age of this population was about 3.3 years. Although, this may be not the best way to determine the mean age but other data from wolves killed by hunters provide a similar value. Clearly, the mean age of a population depends on how puppies are represented in the data. So, if one only considers wolves older than 2 years (sexually mature wolves) then the mean age of this adult population is about 4.4 years. However, all this does not reflect on the life expectancy in wolves. According to Mech (1998) and other sources in the wild some individuals may live for 13.5-16 years that is often taken as a good estimate for longevity in wolves. Note that wolves of this age were not found in large samples of captured and killed wolves reported in the literature.
For example, only 3% of the wolves in Mech’s sample were older than 8 years, and less than 10% or wolves was older than 6 years. This means that life expectancy in wild wolves varies probably between 4.4 and 8 years depending of the specific conditions of the habitat which is about the third of the longevity reported for captive wolves (approx. 20 years).

The situation is quite different in pet dog populations. Using data from Egunvall et al (1999) one can estimate the average age of an (insured) dog population living with humans as being around 4.7 years old. This value is about one and half years larger than that for wolves (3.3 years), in addition, approximately 17% of the dog population is over 8 years old. (Note that, because dogs older than 10 years could not be insured, this is reflects a significant underestimation.) If one considers a more comparative measure, like taking into account the percentage of animals which live longer than twice the mean age of the population (approximately 6 years in wolves and 9 years in dogs) then this value is 7% for wolves and over 10% for dogs. Importantly, longevity data do not seem to reflect any difference between these two species, because the dogs do not live longer in families then wolves in captivity.

Thus domestication does not seem to have affected fundamentally the biology of aging in dogs which is in contrast what we find, for example, comparing humans and chimpanzees. The main differences are displayed by a changed population structure in which older age groups are overrepresented in dogs in comparison to the wolf. Whereas old 3% of wolves survive over 8 years in the wild, approximately one in four pet dogs pass that age. This is, however, only true if we consider the dog population as a whole, and disregard the effect of local population differences. There are no data for feral dogs and the population structure of dingoes seems to be similar to that of wolves (Corbett, 1995). Thus the discrepancy is valid only for “pet” dogs living in close association with humans.

In summary extant wolves die indeed too young compared to present day pet dogs, but this could be the result of humans who have displaced them and hunted them everywhere on the northern hemisphere for many thousand years (Miklósi 2007). Before the arrival of humans wolves were the top predators without other competitors, and abundant prey may have provided better chances for survival and pushed upward both the mean age and the expected life span in this species.

2. Aging as a phase in life history

For many years aging has been viewed as an unavoidable consequence of the wearing out of the body. The more time an individual spends alive (the longer it lives) the larger the chance is that the environmental events exert a negative effect: Wounds, parasites and physical impacts increase the possibilities of system-level failures. Similarly, larger number of cell divisions increases the chance of somatic mutations which could be the cause for malfunctions at the cellular level. One could contrast aging with development as the two processes take opposite directions. The later increases the complexity of the body whilst aging leads to decrement of complexity. Development is often seen as a processes shaped by evolution, consequently programmed partly in the genes in the form of activation of genetic cascades. Aging, however, is portrayed as a chaotic process running freely and unaffected by selective forces. More recently, biological thinking has changed this view and aging is also looked at through evolutionary “spectacles”.

Generally, it is assumed that some traits which are under selection will directly or indirectly influence the aging process, especially through setting expected life span or longevity. Modern evolutionary treatment of life history in animals suggests that age (as any other phenotypic) character should be under selection. More importantly however, the environment of a species will determine how it can maximise fitness, and generally there is a trade off between allocating energy to reproduction and to self-support. For example, increased offspring mortality may push the organism toward investing more energy in his own survival, and delay reproduction to older age, and as consequence longevity increases. The well-known observation that larger species live longer, fits well with this assumption because larger animals tend also to reproduce later at life. Thus selection for a larger body (for whatever reason) seems to have a positive impact on longevity. This has been shown to be the case for both mammals and birds both at the level of the species (e.g. birds: Forslund and Part, 1995; mammals: Williams, 1966) but also at the level of populations (e.g. for squirrels: Descamps et al 2006). Moreover, there are experimental demonstrations that selection for earlier age of first reproduction may also shorten life span.

Other ideas reflect more directly on genetic mechanisms. For example, Medawar (1946) hypothesised that harmful mutations accumulate in a population because many of them affect only matured animals and most of these die from other causes before natural selection could have an effect on them. The contribution of this process in life span can be tested by assuming that inbreeding shortens life by the larger number of homozygous deleterious mutations. Laboratory models of fruit fly populations seem to support such an effect (Hughes et al 2002).

In 1957 Williams suggested that pleiotropic effects of some genes may also contribute to aging. Accordingly, genes that exert a
beneficial effect in the young could be disadvantageous in adults. Some evidence supporting the plausibility of this theory comes from genetic studies on a small nematode. The mutation of a specific gene (Age-1) caused doubling of life span in these creatures but although these animals seemed to be as healthy as wild type individuals, they could only survive only if food supply was abundant (Jenkins et al. 2004). Research showed also that this and other mutations changed the way how affected animals metabolise sugars, and further decreased fertility seemed to be also a cost to be paid for longer life span.

In summary recent genetic research both from an evolutionary and molecular perspective has provided clear evidence that aging is not a simple by product of life but is an outcome of complex multi-level processes which are affected by the evolution and ecology of the species. Very likely many processes act in parallel and some of them are synergic whilst others have opposing effects on longevity. Thus the causal chain of aging can only be understood if the relative contribution of these factors is separated at the level of species under study.

3. Considering the role of genetic and anthropogenic factors in aging dogs

From the foregoing overview it should be clear that no single genetic or environmental effect can account in a simple way of aging in dogs. Moreover it is to be expected that even if dogs (as a species) may not differ from wolves with regard to pattern of aging (see above) both genetic (domestication) and environmental (living as pets) effects may have significantly changed the role played by some underlying biological processes. In other words, dogs may live for similar duration as wolves but this may come about by the contribution of different processes. It follows that if we want to influence the life span of dogs in a positive way, we may have to make use of other processes that we would need to take into account in the case of wolves.

There are many signs that during domestication dogs were selected for being more productive by reproducing earlier. This may have come about by increased survival of the young, abundant food, and selection for a smaller body size. The direct correlations among these traits could be debated but the above discussion on wild animals clearly suggests that either of these phenotypic traits should select for evolution of a shorter life span in dogs in comparison to wolves.

There is however an interesting observation that seems to be specific for dogs, and which is in conflict with what has been described for mammals at the species level: Smaller dogs live longer (Patronek et al. 1997)! There are two different lines of arguments which could help in explaining this finding. In the case of small breeds decreased body size allowed for reaching the adult size with similar growth rate during a shorter time period (Hawthrone et al. 2004). Thus this direction of selection may actually lead to an increase in longevity when compared to that of wolves. Accordingly, in the small breeds the opposing effect of domestication (reduction of life span) and optimal (shorter) growth for the anthropogenic environment (longer life span) may have cancelled each other, and these dogs expect the same during of life as wolves.

In contrast, larger breeds (especially those that approach or even surpass the mean body size of wolves) may have emerged after a secondary selection for increased adult body size. These dogs may grow relatively rapidly for an extended time reaching final adult body size around 40-60 weeks of age (Hawthrone et al. 2004). Thus in large breeds domestication resulting in a shorter life span and less advantageous metabolism to support growth for a bigger size have an additive effect in shortening the life of these dogs. This might explain why these breeds have a short life expectancy and their longevity is much shorter in comparison to extant wolves despite living in captivity where life expectancy is expected to be better.

Importantly, inbreeding, which is present in many breeds, may also compromise longevity in dogs. This effect is independent from the above explained genetic causes but could be as severe. The effect of inbreeding depression has been reported for wolf populations close to extinction (e.g. Mexican wolf: Fredrickson et al. 2007) and very likely occurs also in dog breeds.

Note that the above processes take place in a human environment which is generally thought of affecting longevity of dogs in a positive way. Without denying that modern veterinary care, including protection from viral and bacterial infection increase expected life span in dogs, and appropriate diet may also add to this effect, human environment exposes dogs also to toxic substances (Calderón-Garcidueñas et al. 2003, 2008). Here again we find a contradictory situation despite overall efforts to improve welfare of the aged dog population.

Proximal effects on aging

Genetic differences among dog breeds are translated in differences in physiology, and naturally, breeds have different metabolic activity, preferred way of processing food, store energy etc. All this is also reflected in variations in the levels of neurotransmitters and
hormones (see Overall’s paper for details). In a complex net of interactions breed specific physiology affects the aging process but more research is needed. For example, it is often cited that cortisol levels are enhanced in old dogs which facilitates aging of neurons (see Muller’s paper for details). However, in a recent study in male German shepherd police dogs we did not find such a difference between adult and old dogs. Nevertheless older dogs reacted with a much increased elevation of cortisol to stressful challenges (Horvath et al 2007). Thus increased cortisol levels in the aged may not be necessarily the consequence of some organic failure but may indicate that the same environment is perceived as more stressful for dogs passing a certain age.

Neutering in dogs seems to be also a potential source affecting the aging process. Studies both on human and laboratory animal suggest that the decreasing level of circulating sex hormones may facilitate aging processes in both females and males. There are several indications that supplementation with oestradiol or testosterone in females and males, respectively, decreases the chances of certain body conditions and illnesses. In neutered dogs low levels of these hormones over extended duration (or for the entire life) could affect adversely aging (Hart 2001).

It is generally assumed that both physical and mental exercise improves the well-being later in life. Sensory stimulation, as well as, challenges, which keep the body and mind “fit”, makes the organism more resistant to the deteriorating processes of aging. Behaviourally enriched laboratory beagles performed better in cognitive learning and memory tasks than control animals (Milgram et al 2006). Although more research is needed here, a substantial part of the pet dog population is clearly under-stimulated, that is, they lack species-specific bodily and mental stimulation during juvenile and adult life, which worsen the effect of aging in these animals. Such research should not only inform dog owners but also identify the most efficient ways of improving the quality of life in pet dogs.

In recent years there has been an increased awareness in the composition of the diet for dogs. Although any effect of the diet on the life expectancy of dogs should be viewed in a perspective outlined above, some nutritional components could play a vital role in postponing the harming effects of aging. For example, recent results show that medium chain triglycerides improve cognitive performance at later ages in beagles. This effect is thought to come about by providing an alternative source of energy (beta-hydroxybutyrate) instead of glucose for the nerve cells in the brain (see Pan et al’ study). Similar results have also been obtained in humans.

Finally, some form of social interaction between humans and their pets can also affect life quality negatively. In recent years obesity became a major factor in influencing life quality of both humans and dogs. In both species increased energy input was paralleled with reduced physical activity. In this sense many pets are actually dependent on their owners because if the owner does not live an active life (taking regular walks, meeting friends etc), which is often accompanied with unhealthy eating habits, then this also restricts the dogs chances to stay healthy. It is not uncommon to find that obese people have obese dogs. Both humans and dogs are prone to eat in a social setting and humans have also a preference for active food sharing. Such social facilitation plays an important role in the development of obesity with clear negative effects on aging.

Summary – Food for thoughts!
1. Determining the limits of dog-human analogy in aging
Many interesting parallels in the life history of humans and dogs make comparative aging research very promising. Mammalian homology ensures that biological processes of aging are similar in both species. Sharing the same environment dogs and humans are also facing similar risks. Moreover dogs are among the few animals that “are allowed” to age and die without being physically harmed by predators or conspecifics. Thus the understanding of aging in dogs could be mutually fruitful by improving life quality both in dogs and humans. It is, however, equally important to understand the depth and limits of the similarities. Laboratory models of dog aging might be supplemented by studying dogs living with humans, and because evolution might have acted differently on aging processes in dogs and humans, some differences in the underlying mechanisms should also be expected. For example, even in a very optimal case the life expectancy of some breeds should not be expected to increase because of biological constrains mentioned above.

2. Does the diet select the dog or the dog selects the diet?
Domestication and specific breeding practices may have selected dogs for a narrow path of adaptability to food. This process could have been facilitated by a preference for designing “perfect” dog foods which does not challenge the metabolic system of the dogs for increased efficacy. The variability in food sources is a natural phenomenon for a scavenging predator, and a metabolic system that is practiced to deal with such challenges may be more robust and adapt better to aging.
3. Make the dog fit for being old

Aging is a natural process which goes ahead independently from our understanding of the ultimate and proximate biological causes. Owners need to be made aware that the well-being of their dog during its old age depends to a large degree on them. The better the quality of life when young the better quality of life can be expected in the old age. Dogs, which receive early and regular physical and mental stimulation, a carefully adjusted diet are very likely to experience a much more enjoyable old age. Owners may be reminded to keep in mind the “4-Ps”: Prepare early for your dogs getting old by providing regular stimulations. Prevent early aging by appropriate diet, and protect old animals by adjusting the environment to their needs.

References


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Notes