

That Dog Is Smarter Than You Know: Advances in Understanding Canine Learning, Memory, and Cognition

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Tests of canine cognition are now receiving much deserved attention. Not only are dogs excellent models for human anxiety-related conditions and those involving brain aging, but how dogs learn and problem solve are interesting stand-alone topics. A number of factors can affect learning at the molecular level including stress or distress, factors that affect olfaction, effects of breed and nutritional factors including that may affect available brain energy. This review provides an overview of how these factors may affect baseline learning and brain aging.

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Keywords: canine cognition, nutraceutical, learning, PUFA, MCT, diet

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.¹ The story of dogs is the story of cooperative 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.^{2,3} These similarities are the result of coevolution for cooperative work with humans, which has been ongoing for 15,000 to 150,000 years, depending on varying estimates and the assumptions that go into them.⁴ Intense selection for specific suites of behavioral traits (e.g., the development of breeds) has occurred in the last 12,000 to 15,000 years.⁵

The singular close working relationship shared by dogs and humans has influenced 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 nonvocal 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 vs. retrieving behaviors, and the behavioral patterns that differ with tasks like herding vs. retrieving). The working history and its associated suites of behaviors of extant domestic dogs are reflected both by traditional classifications by various kennel clubs and by clustering analyses that have used genetic information from representative breeds.^{6,7}

Recent data indicate that dogs are comparable with humans 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.⁸⁻¹² 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.¹³ Also, like humans, dogs suffer from what we recognize as maladaptive anxiety, that which interferes with normal functioning, which was selected against during the coevolution of dogs and humans.³ Finally, when examining the rates of gene expression mutations in regional brain tissue, the only species studied to date that has comparable rates with those found for humans is the domestic dog.¹⁴ Such data, when taken together, strongly suggest that dogs can be excellent models for many aspects of human social behavior, cognition, and pathological behavioral conditions, including those involving anxiety and brain aging. One advantage of these parallel findings is 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 studying any canine behavioral conditions.

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.¹⁵ There is evidence that treatment with monoamine

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1527-3369/06/0604-0171\00/0

doi:10.1053/j.tcam.2011.01.001

reuptake inhibitors speeds learning of specific tasks in dogs.¹⁶ Similar results have been reported for mice for age-associated impairment in maze learning.¹⁷ The mechanisms postulated for these outcomes involve the finding that chronic glucocorticoid excess interferes with learning at the cellular level.¹⁷ 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 that are either learning jobs or behavior modification: the factor that prohibits most dogs from completing training programs is their fearful or anxious or uncertain response to novel or complex environments. Obviously, these data suggest that training environments should be as humane as possible and rely neither on aversives nor fear. Task learning can be enhanced when stress and distress are mitigated. In addition to changing the way we behave with dogs, we may ultimately be able to modify some training errors through diet. New supplements and diets may suggest interventional or treatment modalities that could redress the neurochemical effects of stress on learning at the molecular level.

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 the 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 is 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. It is important to realize that negative reinforcement is completely different from punishment, 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.”¹⁸ 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 norepinephrine sympathetic systems, and negative reinforcement likely involves some com-

plex association of both of these, plus the serotonergic system. It is 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 is critical 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 ensures better, more numerous, and more efficient connections between neurons.^{19,20} 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 postsynaptic cell, usually cyclic adenosine monophosphate (cAMP). The result is LTP. By itself, this initial process represents early-phase LTP (E-LTP) and short-term memory (STM). 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 late-phase LTP (L-LTP), which is a more permanent form.²¹ E-LTP can be induced by a single train of stimuli in either the hippocampus or the lateral amygdala.

In contrast, L-LTP and long-term memory (LTM) require repeated stimulation of cAMP and induction of cAMP response element-binding protein (CREB—a nuclear transcription factor), are long-lasting, protein synthesis dependent, and are RNA transcription dependent.²¹ When stimulation continues, brain-derived neurotrophic factor (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.²¹

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 cubic millimeters. Almost all outgoing tracts that control some higher forms of integration of behavior in the cerebral cortex, hypothalamus, brain stem, and so forth, have their efferents shaped by the location of their origin in the amygdala.¹⁸ Additionally, the lateral amygdala is likely the site where memories of conditioned (learned) fear are created through a process involving neuronal plasticity.²¹ 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.²²

We now know that the extracellular environment of the amygdala is responsible for the maintenance of memories about fear.²³ Perineuronal nets comprised of chondroitin sulfate proteoglycans render fears difficult or impossible to erase.²⁴ 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 chondroitin sulfate proteoglycans 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. 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, 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 United States: Anipryl (selegiline; Pfizer) for cognitive dysfunction, Reconcile (fluoxetine; Novartis) for separation anxiety and Clomicalm (clomipramine; Novartis) for separation anxiety. These medications have labels for other conditions and for cats in some countries outside the United States, and such uses are “extra label” in the United States. Increasingly, we see patients treated with serotonin norepinephrine reuptake inhibitors (venlafaxine, duloxetine), serotonin 2A agonist/reuptake inhibitors (trazadone, nefazodone), and noradrenergic and specific serotonergic antidepressants (mirtazapine). Less commonly used medications, or those with more restrictive populations likely to benefit include medications that are monoamine oxidase inhibitors (selegiline) and azapirones (buspirone). All of these medications cause their effects through modulation of the neurotransmitters’ serotonin (5-HT), dopamine, noradrenaline/norepinephrine, and/or gamma amino butyric acid, 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 use the same second messenger systems and transcription pathways that are used to develop cellular memory or to “learn” something. This pathway involves cAMP, CREB, BDNF, NMDA receptors, protein tyrosine kinases (PTK)— particularly Src— which regulate activity of NMDA receptors and other ion channels and mediate the induction of LTP (remember, long-term potentiation = synaptic plasticity) in the CA1 region of the hippocampus.²⁵⁻²⁷ See Figure 1 for a schematic representation of how medications can affect genomic responses that produce new proteins.

There are 2 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 reuptake inhibition. The somatodendritic autoreceptor of the presynaptic neuron decreases the firing rate of that cell as a homeostatic response. Regardless, there is increased saturation of the postsynaptic receptors resulting in stimulation of the β -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 postreceptor target for these drugs. Increases in CREB lead to increases in BDNF and tyrosine kinases (e.g., tyrosine kinase B [trkB]), which then stimulate messenger RNA transcription of new receptor proteins. The altered conformation of the postsynaptic receptors renders serotonin stimulation and signal transduction more efficient.^{28,29}

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 they augment the rate at which learning occurs because of the parallel effect on pathways and mechanisms involved in learning.

Knowledge of the molecular basis for the action of these drugs can aid in choosing treatment protocols. For example, the presynaptic 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, uses the same pathway used in LTP to alter receptor function and structure through transcriptional and translational alterations in receptor protein. This can be thought of as a form of *in vivo* “gene therapy,” which 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.

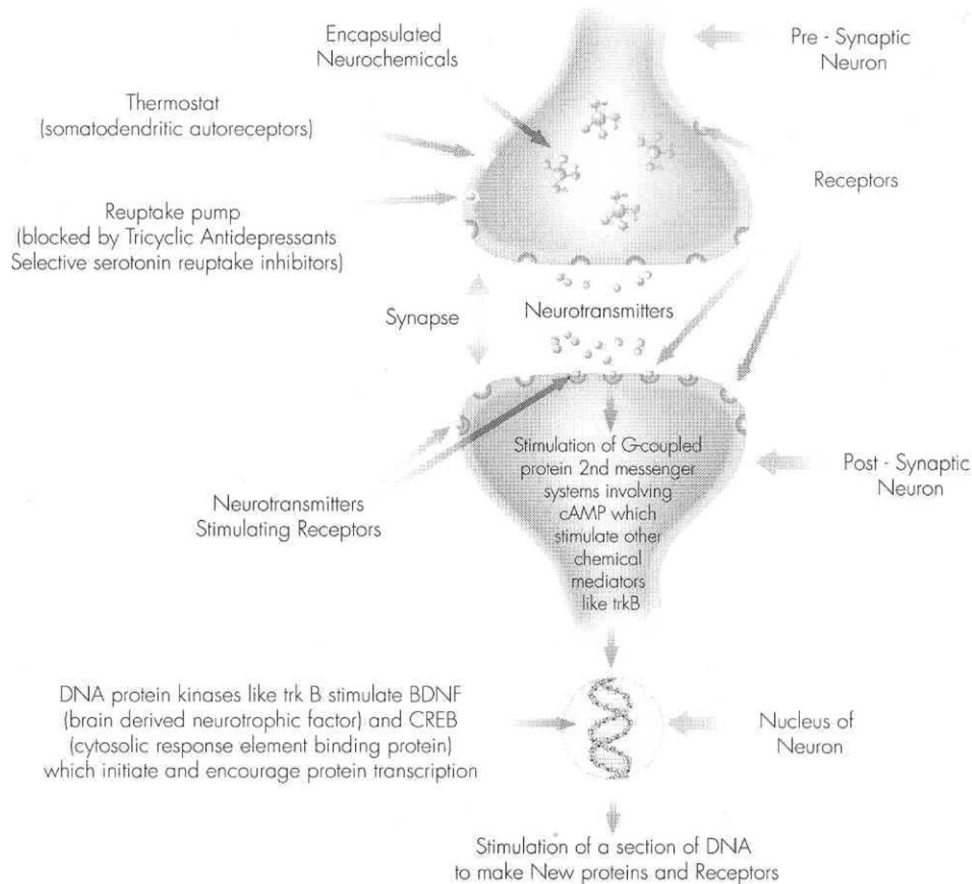


Fig. 1. Schematic of the basic functions of presynaptic and postsynaptic neuronal function when stimulated by learning and/or medications that affect the same pathways. The stimulation of second messenger systems as a result of neurotransmission ultimately produces increases in BDNF and CREB, which are responsible for new protein formation as one mechanism by which molecular memory is produced. Note that many psychotropic medications affect this process, as may diet.

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 do not actually know much dogs can learn, but recent published work from the emergent field of cognitive studies in nonlaboratory canines should give us pause. Most of this work has focused on the ability of dogs to understand and respond to visual cues given by humans and/or dogs that are successful in the studies' tasks in situations in which humans would be able to understand and respond to the cue. In other words, this is an anthropocentric approach to studying canine cognition: we study signals that humans find important, interpret clearly, and can measure in other species. The companion ethological studies indicating which visual signals are most commonly used by dogs, in which contexts these are used, and what these and other cues mean to dogs have yet to be done. When asking how cognitive are dogs we may also wish to remember that olfaction plays a role in learning and

is also governed by the same neurobiological rules that govern learning that occurs with other signaling modalities. Few studies have focused on the conjoined roles of olfaction and memory/information processing, but given that nasal biopsies have shown that amyloid accumulates in canine olfactory neurons with age olfactory³⁰ and given that olfactory function and extent of cognitive impairment may be linked, such foci should provide rich studies in the future. Additionally, dogs who are overly reactive to noise may possess molecular polymorphisms that affect the way they process information.³¹ If these patterns hold true in larger studies, we will have to consider questions about how dogs learn as part of a more complex heuristic construct that will require us to understand canine hearing and vocalization in some depth and to investigate roles for environmental noise on canine neurobiological development.

We now know that dogs can take their cues from dogs or humans about hidden objects and communicate this information to other dogs.⁸⁻¹² 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.¹³ 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.^{32,33} Furthermore, dogs may use the visual referential signals that humans do when exchanging information with humans.³⁴

A number of studies have begun to focus on differences in performance, problem solving, and cognitive capabilities across canid species.³⁴⁻³⁷ It is important that we interpret the studies to date with the limitations of the studies and their foci in mind. Although dogs were originally selected on the basis of their behaviors—and specific tasks gave rise to breeds—most dogs are no longer “worked.” This means that there is a large amount of divergence in populations of any breed that can be reflected in both their behavior and genetics.³⁸ We should not expect dogs, even within a self-labeled “breed,” to be homogeneous with respect to behavioral capabilities, even if those results are not dependent on the rearing and learning environments, simply because dogs selected for work and those selected to not work may look the same but may not be the same. Studies within one culture have shown that at some level dogs’ responses to basic cognitive tests do not vary by breed or age³⁹; however, they may vary by culture. Pet dogs in one culture may have been developed under a different set of expectations than those in another culture. Specific expectations about performance (e.g., whether the dog is capable of being a trained detection dog or a service dog) are, themselves, also affected by culture. This means that source, culture, trainability/capability of the parents (for dogs bred to be working dogs), early experience, and in utero and early brain development may all be sources of variation that may need to be considered when the story of cognition in domestic dogs is finally written.

Maintaining Our Dogs’ Abilities to Learn

Our current understanding of canine cognition is incomplete. Even when there has been some control over the population of dogs studied, our understanding of what can affect cognitive development at any age is fairly rudimentary.

Nutritional Factors That May Play a Role in Brain Function Are Associated with Learning

One approach has been to examine nutritional factors that may play a structural or regulatory role in brain function. Arachidonic acid (ARA), docosahexanoic acid (DHA), and eicosahexanoic acid (EHA) are long-chain polyunsaturated fatty acids (PUFAs) that are known to be 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).⁴⁰

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 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 ALA 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 omega-6/omega-3 ratio when compared with unaffected dogs.⁴¹ 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 with control dogs. Similar, nonspecific findings regarding cholesterol have been reported for aggressive dogs.⁴² 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 of PUFA 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 of lipid/kg, with approximately equal amounts of ARA and DHA. It has been postulated that a dietary intake of 6% to 12% protein comprised of Rift Valley lake fish and shellfish provided sufficient DHA and ARA, which allowed the early hominoid cerebral cortex to grow disproportionately without requiring an increase in body mass.⁴³ Any putative effects of these PUFAs on cognitive abilities are likely routed in this evolutionary history. Interestingly, PUFA levels in brains of young versus geriatric dogs, when measured, have not been shown to be different,¹⁵ 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.

Cognitive Changes and Their Molecular Correlates in Aging Dogs

Another approach has focused on examining cognitive and molecular brain changes in aging dogs. 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 BDNF,⁴⁴ which is associated with neurogenesis and molecular learning and memory, particularly in the hippocampus. Increases in BDNF affect numerous signaling pathways involving 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.⁴⁵ 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.⁴⁶ 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: postsynaptically, 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 postsynaptic potential. 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 that are nonneuronal cells. 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 by oxidative change. Many of these effects may be modulated by antioxidant or cofactor treatment, coupled with active behavioral interventions/enrichment. Alpha-enolase interconverts 2-phosphoglycerate and phosphoenolpyruvate. Alpha-enolase has been shown to be altered in canine models of neurodegenerative disorders and responds to treatment with antioxidants, mitochondrial cofactors (lipoic acid), and behavioral/social/cognitive enrichment.⁴⁷ Decreased oxidation of alpha-enolase 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.

In a study of gene expression in brains of old dogs, the expression of genes involved in neurochemical signaling and synaptic transmission was decreased.¹⁵ 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.

Amyloid Like humans, when dog neurons begin to suffer from oxidative assaults, amyloid deposition may occur. Dogs develop plaques comprised of β -amyloid that are like those seen in humans. When amyloid deposition is sufficiently extensive, it physically disrupts communication between neurons, worsening the processes discussed above.

Shifts in Oxygen and Energy Availability for 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 by neurotransmitter presence and function. During hypoglycemia, glycogen is converted to lactate via pyruvate (glucose \blacktriangleright pyruvate \blacktriangleright lactate). The lactate is then transferred to adjacent neurons. This conversion and transfer allow the neurons to use a source of aerobic fuel.

The use of lactate in hypoglycemic events can extend axon functions for 20+ minutes—a very long time for a neuron. Astrocytic glycogen is also converted to lactate during periods of intense neural activity, demonstrating the role of astrocytes as bankers of energy-conversion compounds. The majority of lactate used as an energy source is thought to come from glycogenic 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.

Ketone bodies and fatty acids have also been proposed as alternate energy sources because of their modulating effects on hypoglycemia. β -hydroxybutyrate (β -OHB), in particular, may be useful for protecting hippocampal neurons from toxicity. In a placebo-controlled, double-blind study in humans, mildly impaired Alzheimer disease patients who were supplemented with medium-chain triglycerides (MCT) showed improvement in a number of pretreatment versus posttreatment cognitive test measures, and such improvement correlated with β -OHB increases.⁴⁸ It should be noted that this result depended on whether the apolipoprotein E (APOE) genotype: only patients without an APOE-epsilon4 allele responded to acute elevation of β -OHB.

The role for adequate provisioning of brain energy is not separate from that of protecting against β -amyloid lesions. In a study of 8 beagles (4 control, 4 treatment) 9 to 11 years of age, supplementation with MCT at a dosage of 2 g/kg/d

resulted in improved mitochondrial function, which was most pronounced in the parietal lobe.⁴⁹ Steady state levels of amyloid precursor protein also decreased in the parietal lobe after short-term supplementation, leading to the conclusion that short-term MCT supplementation can improve brain energy metabolism and also decrease amyloid precursor protein levels in old dogs. A companion study using the brains of the same dogs investigated effects of MCT supplementation on n-3 PUFA levels in the parietal lobe. The dogs in the dietary enrichment treatment experienced a significant increase in brain phospholipid and total lipid concentrations in the parietal cortex.⁵⁰ Pan and coworkers⁵¹ tied these neurochemical findings to potential cognitive correlates. In a study using a 5.5% supplement of MCT for laboratory dogs tested with a battery of cognitive tests, 8 months of supplementation produced better performance in most of the test protocols, with more difficult tasks showing a greater effect of supplementation than easier tasks.

Evidence is mounting that ketogenic diets, in general, may have promising effects for a number of neurodegenerative conditions.⁵²⁻⁵⁵ The focus of most research has been on the effects that ketone bodies, fatty acids, and/or limited glucose could play in seizure control. However, the effects of chronic ketosis on the tricarboxylic acid cycle that results in increases in gamma amino butyric acid synthesis may have a role for enhancing learning by decreasing reactivity. Coupled with the putative effect of a ketogenic diet to increase norepinephrine in the hippocampus, such diets may help regulate or re-regulate and protect molecular and neurochemical pathways involved in learning. Ketogenic diets have also been shown to limit reactive oxygen species generation, directly, in addition to that associated with increased energy production in brain tissue discussed earlier. Finally, ketogenic diets may favorably affect gene regulation, including enhancing the regulation of some genes associated with mitochondrial biogenesis.⁵²

As we become more sophisticated in our understanding of how and how much dogs can learn, we may wish to consider whether such interventions can and should be used in targeted populations including those of dogs who are chronically stressed (shelter dogs), those who may have had compromised in utero and early development, whether or not due to or magnified by diet (puppy mill dogs), those where reactive oxygen species and other neurocytotoxic challenges may be present (illness, ongoing distress), and in situations where any enhancement of regulation of neurotransmitter function may be useful (true behavioral pathologies, especially if recognized early). The ancestral diet of the domestic dog is considerably more ketogenic than most of those commercially available today, a correlate that may help us to think about how dogs think and problem solve and the factors that may affect these processes.

Conclusion

Because of our shared evolutionary history, what we learn about the behavior of learning from dogs may benefit hu-

mans, 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, and how such mechanisms affect the behavioral manifestations we can observe and measure. Once we understand the role that various regions of the brain and learning in those regions play, it is a simple step to think of helpful interventions for enhancing learning and, perhaps, cognitive abilities.

Meanwhile, we probably owe all 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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