Effect of gonadectomy on subsequent development of age-related cognitive impairment in dogs

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Objective—To determine whether gonadectomy predisposes dogs to development of age-related behavioral changes linked to cognitive impairment.

Design—Cohort study.

Animals—29 sexually intact male dogs, 63 spayed female dogs, and 47 castrated male dogs 11 to 14 years old.

Procedure—Information on possible impairments in 4 behavioral categories linked to cognitive impairment (orientation in the home and yard, social interactions, house training, and sleep-wake cycle) was obtained from owners of the dogs by use of a structured telephone interview format. A second interview was performed 12 to 18 months after the initial interview, and differences in responses were evaluated.

Results—Sexually intact male dogs were significantly less likely than neutered dogs to progress from mild impairment (ie, impairment in 1 category) to severe impairment (ie, impairment in ≥ 2 categories) during the time between the first and second interviews. This difference was not attributable to differences in ages of the dogs, duration of follow-up, or the owners' perceptions of the dogs' overall health.

Conclusions and Clinical Relevance—Results suggest that the presence of circulating testosterone in aging sexually intact male dogs may slow the progression of cognitive impairment, at least among dogs that already have signs of mild impairment. Estrogens would be expected to have a similar protective role in sexually intact female dogs; unfortunately, too few sexually intact female dogs were available for inclusion in the study to test this hypothesis. There may be a need to evaluate possible methods for counteracting the effects of loss of sex hormones in gonadectomized dogs. (*J Am Vet Med Assoc* 2001; 219:51–56)

Improved veterinary care and nutrition and safer home environments are allowing dogs to live well into their senior years. Thus, there is increased interest in the behavior and welfare of aging dogs. In addition to age-related changes in the musculoskeletal, cardiovascular, and endocrine systems, caregivers of dogs and their veterinarians have recognized a number of behavioral changes that occur in senior dogs that appear to reflect disturbances of memory and learning.[1] Because memory and learning are integral components of animal cognition,[2,3] the terms cognitive impairment and cognitive dysfunction have been introduced to refer to these behavioral changes in senior dogs.[4-6] The term canine cognitive dysfunction syndrome was recently introduced in association with US Food and Drug Administration approval of selegiline[a] for treatment of this syndrome.[7]

Behavioral changes in senior dogs with cognitive impairment can be classified into 4 general categories[1,8]: disorientation in the home or yard, changes in social interactions with human family members, loss of house training, and changes in the sleep-wake cycle. The first 3 categories comprise behavioral signs that clearly reflect loss of memory and learning. Changes in the sleep-wake cycle would appear to reflect disruptions in the circadian rhythm; however, adaptation of the crepuscular activity pattern of wild canids (active at dusk and dawn) to the diurnal pattern of human family members represents a type of learning, and disruption of the sleep-wake cycle is common in humans with Alzheimer's disease.[9,10]

In a previous study,[1] the prevalence of behavioral impairments in senior dogs was significantly associated with age. Twenty-eight percent of dogs 11 to 12 years old had impairments in 1 or more categories, and 10% had impairments in 2 or more. By contrast, 68% of dogs 15 to 16 years old had impairments in 1 or more categories, and 35% had impairments in 2 or more. A related study[8] of dogs 11 to 14 years old found that over a period of 6 to 18 months, almost all dogs became more impaired or stayed the same. Only 2 of 37 dogs that were initially found to have impairments in a particular category were later found not to have impairments in that category. In addition, 13 of 27 (48%) dogs initially found to have impairments in only 1 category were later found to have impairments in 2 or more categories, whereas only 8 of 73 (11%) dogs that did not initially have any impairments were later found to have impairments in 2 or more categories.

Despite the obvious species-specific differences, behavioral changes in senior dogs appear similar to those in humans with dementia, particularly those with Alzheimer's disease, in which decreased recognition of family members, disorientation in the home or neighborhood, disturbances of the sleep-wake cycle, and, eventually, inappropriate urination or defecation are common.[9,10] As in dogs with cognitive impairment, changes in humans with Alzheimer's disease are progressive.[11-14]

The primary neuropathologic changes in humans with Alzheimer's disease are accumulation of β-amy-

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loid peptide in the frontal cortex and hippocampus and formation of β-amyloid plaques associated with neuronal death.[9,10] The amount of β-amyloid correlates with the severity of dementia in patients with Alzheimer's disease.[15] Aged dogs also accumulate β-amyloid deposits in the hippocampus and frontal cortex, [16-19] and these deposits are similar to the primitive or early-stage plaques seen in the brains of humans with Alzheimer's disease.[20,21] Advanced senile plaques have not been found in dogs, but laboratory research on aging Beagles has shown that the degree of β-amyloid deposition corresponds to the degree of impairment in learning complex tasks.[22,23] Interestingly, selegiline not only improves behavioral signs in dogs with cognitive impairment[7] but also slows the progression of degenerative changes in human patients with Alzheimer's disease.[24]

Various studies[25-28] have found that postmenopausal women receiving estrogen-replacement therapy had a lower risk of developing Alzheimer's disease, even when variables such as education, ethnicity, socioeconomic status, age at menarche, age at menopause, number of children, and $ApoE_4$ genotype were taken into account. In addition, estrogen treatment of postmenopausal women with Alzheimer's disease enhanced cognition,[29] although whether estrogen enhances cognitive function in older women without dementia is less certain.[30,31]

Clinical studies on the role of testosterone in cognitive function in men are more limited, but recent work suggests that among older men, those with higher testosterone concentrations and lower estradiol concentrations performed better than those with lower testosterone concentrations on tests of cognitive function,[32] and testosterone can enhance verbal fluency in hypogonadal men.[33]

There is research that suggests estrogen potentiates memory and learning in rodents, and ovariectomy results in a decline in learning ability and memory.[34-37] Estradiol appears to enhance memory by interacting with cholinergic systems involved in memory modulation.[38,39] Estrogen maintains the neural circuitry and neural transmitter systems in the hippocampus and frontal cortex,[40-42] and both estrogen[43,44] and testosterone[45] reduce accumulation of the β-amyloid material that comprises the neural plaques associated with cognitive impairment in humans and dogs. Testosterone has also been found to prevent hyperphosphorylation of the neuroprotective protein tau, which is abnormally hyperphosphorylated in human patients with Alzheimer's disease.[46] Cerebral glucose utilization and cerebral blood flow are enhanced by estrogen,[47,48] and estrogen serves to combat oxidative stress.[49-51]

Taken together, this research suggests that the sex hormones may play a role in preventing development of age-related cognitive impairment in dogs. The purpose of the study reported here, therefore, was to determine whether gonadectomy predisposes dogs to development of age-related behavioral changes linked to cognitive impairment. Because in a previous study,[1] only 10% of castrated male and spayed female dogs were found to have severe cognitive impairment (ie, impairment in ≥ 2 behavioral categories), it seemed unlikely that a cross-sectional study would be able to detect significant differences in prevalence of severe impairment between neutered and sexually intact dogs unless an extremely large number of dogs were enrolled in the study. Therefore, the present study was structured to determine whether percentage of senior dogs that progressed from mild cognitive impairment (ie, impairment in only 1 behavioral category) to severe impairment over a period of 6 to 18 months was significantly different between sexually intact and neutered dogs.

Materials and Methods

The study was conducted in parallel with a longitudinal study of the progression of age-related behavioral impairments in dogs.[8] Briefly, information on possible behavioral changes linked to cognitive impairment was obtained from owners of dogs 11 to 14 years old by use of a structured telephone interview format. A second interview was performed 12 to 18 months after the initial interview, and differences in responses were evaluated. Because of the advanced age of the dogs included in the study, some dogs were euthanatized or died of disease before the second interview could be performed. However, the second interview was still performed and the data were used if the dog had lived at least 6 months after the first interview.

Selection of dogs—Records of the University of California, Davis, Veterinary Medical Teaching Hospital were searched to identify dogs 11 to 14 years old. Hospital records for these dogs were screened, and dogs with medical problems that may induce signs similar to cognitive impairment were eliminated. Owners of a random sample of the remaining spayed female and male castrated dogs and of all remaining sexually intact dogs were contacted by telephone to determine whether dogs were still alive, whether the dogs had any medical problems not apparent from the hospital records that may induce signs similar to cognitive impairment, and whether the owners were willing to participate in the study. Owners of all sexually intact male dogs that met the criteria for inclusion were invited to participate, because there were so few records of sexually intact male dogs. Dogs were considered to be sexually intact if they were intact at the time of the first interview or if they had been castrated ≤ 1 year previously. Almost all female dogs were spayed, so sexually intact female dogs were not included in the study.

Interview format and questions—During the initial telephone contact with owners who agreed to participate in the study, an appointment for the first structured telephone interview was made. These owners were sent an information sheet about possible age-related behavioral changes prior to the first interview. Owners were not told they would be called for a second interview. Because clients were sent information about possible behavioral changes prior to the first interview, and there was a 12- to 18-month delay before the second interview, bias associated with sensitization of owners to age-related changes during the second interview should have been minimal. The first and second interviews were conducted by different veterinary behaviorists, but the same structured format was used by both.

Dogs were considered to have an impairment in any particular behavioral category if they were exhibiting ≥ 2 specific signs related to an impairment in that category and had not been exhibiting those signs earlier in their lives (ie, at 5 to 8 years of age). Dogs were considered to have an impairment in orientation in the home or yard if they had ≥ 2 of the follow-

ing or similar signs: staring into space, getting lost in the house or yard, getting stuck in corners, and standing at the wrong door or at the wrong side of the door to go out or in. Dogs were considered to have an impairment in social interactions if they had ≥ 2 of the following signs: a decrease in how frequently the dog would greet its owners, a decrease in how frequently the dog would solicit attention from its owners, and a definite increase or decrease in how frequently the dog would follow its owners around the house. Dogs were considered to have an impairment in house training if they started to urinate or defecate in the house without any apparent medical or other behavioral explanation (eg, urinary incontinence or separation anxiety), and there was decreased signaling to go out, decreased use of a doggy door, or some other change reflecting a decrease in learned housetraining behavior (eg, urinating or defecating in the house just after coming in from outdoors). Dogs were considered to have an impairment in the sleep-wake cycle if they had ≥ 2 of the following signs: waking up the owner at night by some activity such as pacing or vocalizing, sleeping noticeably less at night, and sleeping noticeably more during the day. In addition, dogs were considered to have impairment in a particular category only if the associated signs had been observed more than once a week for at least the previous month.

Efforts were made to avoid leading the owners to expect that there was a correct answer to any of the questions. Before questions about specific signs associated with each behavioral category were asked, owners were given an opportunity to provide their own open-ended comments to a general question related to that category. During the second interview, in addition to questions regarding signs of cognitive impairment, owners were asked whether their dogs had any evidence of visual or auditory impairments, arthritis, or dental problems. These abnormalities did not necessarily have to have been diagnosed by a veterinarian.

Data analysis—A cross-sectional analysis was conducted only on dogs 13 to 15 years old at the time of the second interview to compare percentages of spayed female, castrated male, and sexually intact male dogs with impairments in each of the 4 behavioral categories as well as percentages of dogs with impairments in 1 category, ≥ 1 category, and ≥ 2 categories. In a previous study,[1] a significant age by sex interaction was not detected for dogs with impairments in any category. Therefore, data for dogs of all ages (13 to 15 years) were combined, and for some analyses, percentages of neutered dogs of both sexes with impairments were compared with percentage of sexually intact male dogs.

The longitudinal analysis was performed comparing the percentages of 11- to 14-year-old spayed female, castrated male, and sexually intact male dogs that progressed from having no impairments at the time of the first interview to having impairments in 1 category at the time of the second interview. Similarly, percentages of dogs that progressed from having no impairments at the time of the first interview to having impairments in ≥ 2 categories at the time of the second interview were compared among groups, as were percentages of dogs that progressed from having impairments in 1 category at the time of the first interview to having impairments in ≥ 2 categories at the time of the second interview. Percentages of dogs positive for 0 or 1 sign associated with a particular behavioral category at the time of the first interview that had impairments in that category (ie, positive for ≥ 2 signs) at the time of the second interview were also determined.

The Fisher exact test or the Pearson χ^2 statistic was used for all analyses. Values of $P < 0.05$ were considered significant. Because it was hypothesized that behavioral signs of cognitive impairment would not progress as quickly in sexually intact male dogs as in spayed female and castrated male dogs, some tests were performed as 1-tailed tests.

Results

Prevalence of cognitive impairments among groups—The cross-sectional analysis included 20 sexually intact male dogs, 33 castrated male dogs, and 41 spayed female dogs. For each of the 4 behavioral categories, percentages of spayed female, castrated male, and sexually intact male dogs with impairment in that category at the time of the second interview were not significantly different (**Fig 1**). However, the *P* value for impairment in house training ($P = 0.056$) was close to the cutoff for significance, and when spayed female and castrated male dogs were combined, the percentage of neutered dogs with an impairment in house training at the time of the second interview was significantly ($P = 0.029$) higher than the percentage of sexually intact male dogs with an impairment in that category. Percentages of dogs with impairments in 1 category, percentages of dogs with impairments in ≥ 1 category, and percentages of dogs with impairments in ≥ 2 categories at the time of the second interview were not significantly different among groups.

Progression of signs of cognitive impairment—This analysis involved 29 sexually intact male dogs, 47 castrated male dogs, and 63 spayed female dogs. Twenty of the 29 (69%) sexually intact male dogs, 29 of the 47 (62%) castrated male dogs, and 34 of the 63 (54%) spayed female dogs were still alive at the time of the second interview. The remaining 56 dogs had died or been euthanatized prior to the second interview, but all 56 had survived at least 6 months after the first interview. Mean follow-up time for all 139 dogs in the study (ie, mean time from the first to the second interview or mean time from the first interview to time of death) was 15.3 months (SD, 2.6 months). Mean age at which spayed female dogs had been spayed was 2.8 years (SD, 0.1); mean age at which castrated male dogs had been castrated was 4.8 years (SD, 1.2). At the time of the first interview (ie, when dogs were 11 to 14 years old), 41 of the 63 (65%) spayed female dogs did not have impairments in any of the behavioral categories, 18 (29%) had impairments in 1 category, and 4 (6%) had impairments in ≥ 2 categories. Thirty-two of the 47 (68%) castrated male dogs did not have impairments in

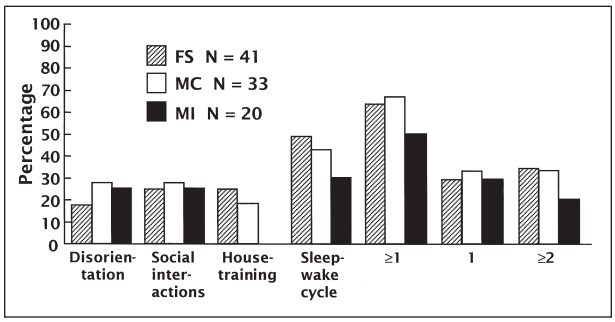

Figure 1—Percentages of dogs between 13 and 15 years old that had impairments in each of 4 behavioral categories associated with cognitive function and that had impairments in 1 category, ≥ 1 category, or ≥ 2 categories. FS = Spayed female. MC = Castrated male. MI = Sexually intact male.

any of the behavioral categories, 9 (19%) had impairments in 1 category, and 6 (13%) had impairments in ≥ 2 categories. Nineteen of the 29 (66%) sexually intact male dogs did not have impairments in any of the behavioral categories, 6 (21%) had impairments in 1 category, and 4 (13%) had impairments in ≥ 2 categories.

For all groups, between 27 and 41% of dogs that did not have any impairments at the time of the first interview had impairments in ≥ 1 category at the time of the second interview, and approximately 10% had impairments in ≥ 2 categories. Analysis of the percentages of dogs progressing from impairments in 0 categories at the time of the first interview to impairments in 1 category at the time of the second interview and of dogs progressing from impairments in 0 categories at the time of the first interview to impairments in ≥ 2 categories at the time of the second interview did not reveal any significant differences among groups (**Fig 2**; $P = 0.124$ to 1.00).

Of the 18 spayed female dogs with impairments in 1 category at the time of the first interview, 9 (50%) had impairments in ≥ 2 categories at time of the second interview. Of the 9 castrated male dogs with impairments in 1 category at the time of the first interview, 4 (44%) had impairments in ≥ 2 categories at time of the second interview (1 of these castrated males improved to no impairments on the second interview). By contrast, none of the 6 sexually intact male dogs with impairments in 1 category at the time of the first interview had impairments in ≥ 2 categories at time of the second interview (Fig 2). Percentages of dogs progressing from impairments in 1 category at the time of the first interview to impairments in ≥ 2 categories at the time of the second interview were not significantly different between spayed female and castrated male dogs ($P = 0.512$). Numbers of dogs were too small to allow comparisons between sexually intact male dogs and castrated male dogs or spayed female dogs. However, when castrated male and spayed female dogs were combined, the percentage of sexually intact male dogs that progressed from impairments in 1 category at the time of the first interview to impairments in ≥ 2 categories at the time of the second interview was significantly less (1-tailed Fisher exact test, $P = 0.035$; 2-tailed Pearson χ^2 statistic, $P = 0.03$) than the percentage of neutered dogs that progressed.

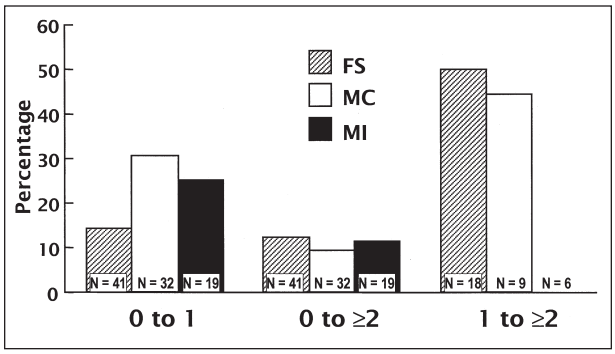

Figure 2—Percentages of dogs 11 to 14 years old that progressed, over a period of 6 to 18 months, from not having impairments in any behavioral category to having impairments in 1 category or to having impairments in ≥ 2 categories and that progressed from having impairments in 1 behavioral category to having impairments in ≥ 2 categories. *See* Figure 1 for key.

The difference between sexually intact male dogs and neutered dogs was not attributable to a major difference in age of the dogs at the time of the first interview, as 14 of the 29 (49%) sexually intact male dogs, 25 of the 47 (53%) castrated male dogs, and 37 of the 63 (59%) spayed female dogs were 11 to 12 years old at the time of the first interview. The difference was also not a reflection of major differences in follow-up time. Mean follow-up times for spayed female, castrated male, and sexually intact male dogs with impairments in 1 behavioral category at the time of the first and second interviews were 13.1 months (SD, 5.3 months; n = 9), 17.0 months (SD, 2.1 months; 4), and 17.0 months (SD, 2.8 months; 6), respectively. Mean follow-up times for spayed female and castrated male dogs that progressed from impairments in 1 behavioral category at the time of the first interview to impairments in ≥ 2 categories were 16.3 months (SD, 5.2 months; n = 9) and 15.9 months (SD, 0.8 months; 4), respectively.

Percentages of dogs with visual and hearing impairments, arthritis, or dental problems did not differ between sexually intact male dogs and neutered dogs. Of the 6 sexually intact male dogs with impairments in 1 behavioral category at the first and second interviews, 4 (67%) had arthritis, 1 (17%) had dental disease, 5 (83%) had visual impairments, and 5 (83%) had hearing impairments. Of the 13 neutered dogs with impairments in 1 behavioral category at the first and second interviews, 6 (46%) had arthritis, 1 (8%) had dental disease, 10 (77%) had visual impairments, and 12 (92%) had hearing impairments. Of the 13 neutered dogs that progressed from impairments in 1 behavioral category at the time of the first interview to impairments in ≥ 2 categories at the time of the second interview, 5 (38%) had arthritis, 6 (46%) had dental disease, 11 (85%) had visual impairments, and all 13 (100%) had hearing impairments. Although these problems were not necessarily verified by examination by a veterinarian, results suggest that differences between sexually intact male and neutered dogs were likely attributable to differences in cognitive function and not a reflection of the owners' perceptions of their dogs' overall health.

Discussion

Results of previous studies[1,8] of behavioral changes in aging dogs performed at the same institution as the present study indicated that abnormalities in 4 behavioral categories (disorientation in the home and yard, disturbances in social interactions, impairment of house training, and disruption of the sleep-wake cycle) can be evaluated by use of a structured telephone interview format. These behavioral signs presumably reflect disruptions of cognitive function, have a gradual onset, and progress over time. All 4 of these behavioral categories involve learning or memory in one way or another, and signs associated with these categories comprise most of the behavioral signs improved by use of selegiline in aging dogs.[7]

In the present study, the percentage of sexually intact male dogs with impairments in house training at the time of the second interview (ie, when dogs were 13 to 15 years old) was significantly less than the percentage of neutered dogs. No other differences between groups were detected at the first or second interview; however, the low percentages of dogs with impairments in any particular category may have precluded detection of differences.

When results for the first and second interviews were compared, there were no significant differences among groups in regard to percentages of dogs that progressed from not having any impairments to having impairments in 1 category or to having impairments in ≥ 2 categories. However, percentage of dogs that progressed from being mildly impaired (ie, impairments in 1 behavioral category) at the time of the first interview to being severely impaired (ie, impairments in ≥ 2 categories) at the time of the second interview was significantly higher for neutered than sexually intact male dogs. Thirteen of the 27 (48%) neutered dogs progressed from being mildly impaired to being severely impaired, whereas none of the 6 sexually intact male dogs did.

There were not any differences among groups in regard to prevalence of owner-reported visual or hearing impairment, arthritis, or dental problems suggesting that owners of sexually intact male dogs did not perceive their dogs as being in better overall health. Also, there were no differences among groups in regard to age or follow-up time that could explain the difference between sexually intact male and neutered dogs. Thus, the difference in percentage of dogs that progressed from mild to severe impairment was likely a reflection of hormone-related differences in cognitive function, suggesting that the presence of circulating testosterone in the sexually intact male dogs may have slowed the progression of cognitive impairment in dogs that already had signs of mild impairment. This finding is in line with current research on the neuroprotective roles of testosterone and estrogen at the cellular level and the role of estrogen in preventing Alzheimer's disease in human females. One would predict that estrogens would have a similar protective role in sexually intact female dogs; unfortunately, too few sexually intact female dogs were available for inclusion in the present study to test this hypothesis.

Clearly, more work is needed to confirm and extend these findings. While the veterinary community is waiting for additional research on this subject to be performed, the implications of these findings on the practice of early spaying and neutering of dogs that are kept into their senior years as family companions should be considered. First, it should be pointed out that only a small percentage of dogs progress to the level of severe cognitive impairment. Thus, the risk associated with loss of the protective effects of gonadal hormones may be a small price to pay for the advantages of gonadectomy (eg, prevention of ovarian, uterine, and testicular cancer). For some dog owners, however, the increased likelihood of progression to severe cognitive impairment may be more of a concern, particularly given the higher prevalence of impairments in house training among neutered dogs, compared with sexually intact male dogs. It may also be a concern in working dogs for which a high level of cognitive function is required, such as those used for police work, to provide assistance to the disabled, and for scent detection.

Results of the present study may also stimulate a search for alternative means of fertility control that leave gonadal hormone production intact. Tubal (oviduct) ligation could be used in females and vasectomy could be used in males, but both of these procedures have drawbacks, in that female dogs that undergo tubal ligation will still cycle into estrus and will not be protected from uterine disease or mammary cancer, and male dogs that undergo vasectomy would not receive the advantages of decreased likelihood of problem aggression, urine marking, and sexual behavior associated with castration.[52] Alternatively, the benefits of hormonal replacement therapy in senior gonadectomized male and female dogs should be determined, or the benefits of prophylactic treatment with appropriate drugs to reduce the likelihood of cognitive impairment should be investigated.

[a]Anipryl, Pfizer Animal Health, Exton, Pa.

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