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Non-Reproductive Long-Term Health Complications of Gonad Removal in Dogs as Well as Possible Causal Relationships with Post-Gonadectomy Elevated Luteinizing Hormone (LH) Concentrations

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Abstract:

Throughout most of the developed world, surgical sterilization via gonadectomy has become a common tool for combating the overpopulation of unwanted dogs as well as to eliminate the risk of reproductive diseases in pet dogs. However, if a surgical sterilization method is chosen that enables a dog to keep its gonads intact while still preventing reproduction, thismay avoid the problems discussed in this article. In the dog as in other normal adult mammals, the hypothalamus secretes gonadotropin-releasing hormone (GnRH), which stimulates the anterior pituitary gland to release of luteinizing hormone. Luteinizing hormone (LH) stimulates the secretion of gonadal steroid hormones (testosterone in males and estrogen/progesterone in females). These gonadal steroid hormones then negatively feedback to the hypothalamus and anterior pituitary to decrease the secretion of GnRH and LH, respectively. However, in the gonadectomized mammal, there is no negative feedback, which results in supraphysiologic circulating concentrations of LH. In gonadectomized dogs, LH concentrations are more than thirty times the concentrations found in normal adult dogs. Although the main role of LH is for reproductive functions (e.g. ovulation, corpus luteum formation), there are LH receptors present throughout the body, not just limited to the reproductive tract. The purpose of LH receptors in non-reproductive tissues is not known but may induce cell division and stimulate nitric oxide release. With constant activation following gonadectomy, these receptors are up regulated, further magnifying the effects of the extremely high LH concentrations in non-reproductive tissues. Canine gonadectomy increases the risk of several non-reproductive long-term disorders caused by extremely high LH including obesity, urinary incontinence, urinary calculi, diabetes mellitus, hypothyroidism, hip dysplasia, cranial cruciate ligament rupture, aggressive and fearful behavior, cognitive dysfunction syndrome, prostate adenocarcinoma, transitional cell adenocarcinoma,

osteosarcoma, hemangiosarcoma, lymphosarcoma, and mastocytoma. In this review, the relationship between LH receptor activation in these non-reproductive target tissues will be discussed.

Keywords: Behavior; Cranial Cruciate Ligament Rupture; Diabetes Mellitus; Hip Dysplasia; Hypothyroidism; Longevity; Neoplasia; Obesity; Urinary Incontinence.

Introduction

Throughout most of the developed world, surgical sterilization has become a common tool for combatting the overpopulation of unwanted dogs [1-6]as well as toeliminatethe risk of reproductive diseases in pet dogs (e.g. mammary gland cancer and prostate hyperplasia /infection)[7].In the United States, 64% of dogs have been surgically-sterilized [8**].** For the purposes of this review, ovariectomy and ovariohysterectomy (spay) or castration (neuter) will be collectively referred to as gonadectomy, since each of these methods for surgical sterilization include gonad removal (ovaries or testes).

In the normal adult mammal, thehypothalamus secretes gonadotropin-releasing hormone (GnRH), which stimulates the anterior pituitary gland to release of luteinizing hormone [9]. Luteinizing hormone (LH) stimulates the secretion of gonadal steroid hormones (testosterone in males and estrogen/progesterone in females). These gonadal steroid hormones then negatively feedback to the hypothalamus and anterior pituitary to decrease the secretion of GnRH and LH, respectively (Figure 1A). However, in the gonadectomized mammal, there is no negative feedback, which results in supraphysiologic circulating concentrations of LH (Figure 1B).In gonadectomized dogs, LH concentrations are more than thirty times the concentrations found in normal adult dogs [10].

Although the main role of LH is for reproductive functions (e.g. ovulation, corpus luteum formation), there are LH receptors present throughout the body, not just limited to the reproductive tract (Table 1). The purpose of LH receptors in non-reproductive tissues is not known but may induce cell division and stimulate nitric oxide release [11]. With constant activation following gonadectomy, these receptors are up regulated, further magnifying the effects of the supraphysiologic LH concentrations in non-reproductive tissues. In this review, we have summarized several non-reproductive long-term health complications resulting from canine gonadectomy as well as discussed the possibility of how these effects are mediated by LH receptor activation in these non-reproductive target tissues.

Non-Reproductive Tissues	Species	Reference
Adrenal cortex	Dog, human, rat, rhesus macaque	128-130
Blood vessels (endothelial cells, vascular smooth muscle cells)	Human	121; 120; 131
Brain (hippocampus, hypothalamus, cerebellum, brain stem, cortex)	Guinea pig, rat	89; 132
Fibroblasts	Human	131
Gastrointestinal tract (enteric neurons, smooth muscle)	Human, rat	133-135
Lower urinary tract (bladder and urethra)	Dog, human	39,Ponglowhapan, Church, Khalid, 2008; 114
Lymphoid tissues (thymus and lymphocytes)	Hamsters, human	136
Skin (epidermis, hair follicle, sebaceous glands, sweat glands)	Dog, human	36; 125
Striated muscle cells	Human	131
Thyroid gland	Human	62

Table 1: Luteinizing hormone receptors are found in several tissues outside of the reproductive tract. In the dog, activation of these receptors may be responsible for the long-term health complications following gonad removal.

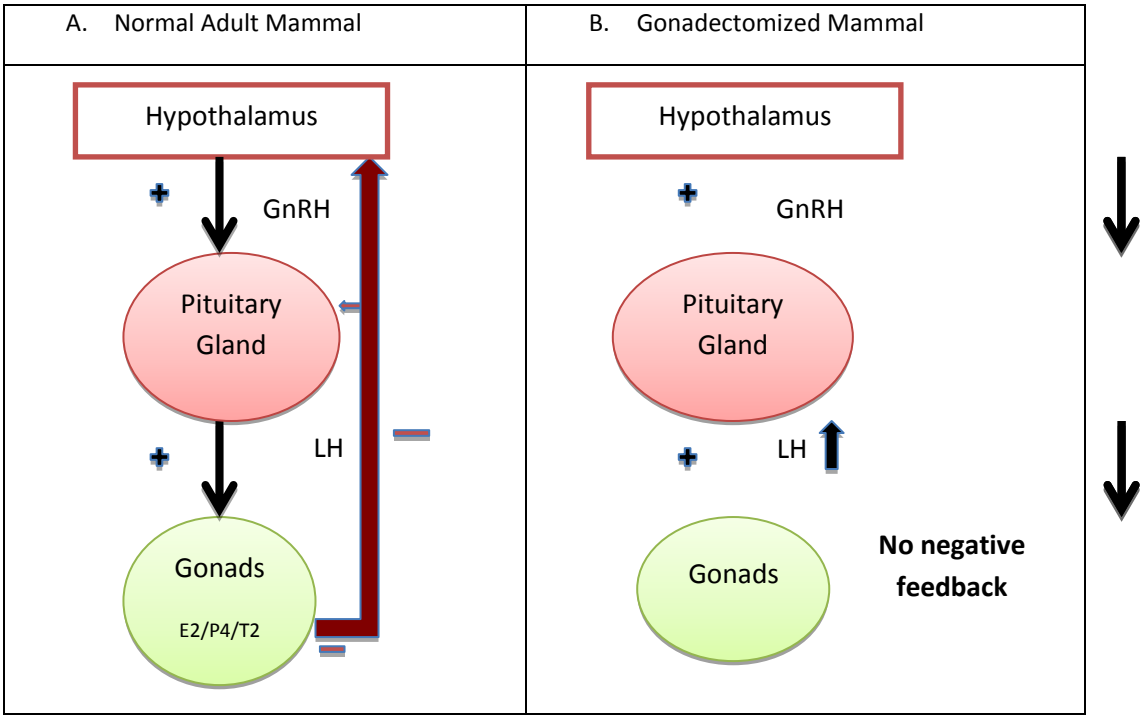

Figure 1: A: In the normal adult mammal, the hypothalamus secretes gonadotropin-releasing hormone (GnRH), which stimulates the anterior pituitary gland to release of luteinizing hormone. Luteinizing hormone (LH) stimulates the secretion of gonadal steroid hormones (testosterone (T2) in males and estrogen (E2)/progesterone (P4) in females). These gonadal steroid hormones then negatively feedback to the hypothalamus and anterior pituitary to decrease the secretion of GnRH and LH, respectively. B: In the gonadectomized mammal, there is no negative feedback, which results in supraphysiologic circulating concentrations of LH.

Obesity:

Obesity is serious medical problem defined as an excessive accumulation of fat beyond the physical and skeletal limits [12]. Gonadectomy is the single largest risk factor for the development of obesity in dogs [7, 13]. Up to 68% of gonadectomized dogs are obese [14 – 19]. Gonadectomy induces obesity through two main mechanisms: increased appetite and decreased metabolic rate. Gonadectomy stimulates food intake [20] and increases indiscriminate appetite [21]. In unaltered dogs, food intake suppresses the secretion of gastrointestinal hormones (cholecystokinin and glucagon) resulting in satiety (alleviation of hunger)[22]. However, within 1 week following gonadectomy, food intake increases by 20% and then persists [23, 24]. It is possible that stimulation of LH receptors present in the gastrointestinal tract following gonadectomy suppresses cholecystokinin and/orglucagon release. It is also possible that LH receptors in the hypothalamus are involved in the increase in [25]as lesions within the ventromedial hypothalamus result in hyperphagia [26].

Gonadectomy also results in a 30% decrease in daily energy requirements [24]. The underlying mechanism for decreased energy requirements is not known but is likely due to decreased physical activity [27-30]. Within the first 90 days after gonadectomy, dogs will gain a significant amount of weight [23]. Weight gain results from a decrease in activity without a corresponding decrease in food intake [23]. Of course, with an increased appetite from gonadectomy, decreasing food intake leaves the dog in an unpleasant and perpetual state of hunger.

Urinary System:

Urinary incontinence: Urinary incontinence is an involuntary leakage of urine resulting from either a weakened or complete loss of urinary sphincter control. The association between urinary incontinence and gonadectomy in female dogs was first described by Jo [31]. Urinary incontinence is a common long-term health complication of gonadectomy in female dogs with a reported incidence ranging from 5-30% [32-35].Early age gonadectomy (under 5 months of age) may further increase the risk of occurrence of urinary incontinence [35-37]. LH receptors are expressed in all regions the canine lower urinary tract, from the body and neck of the bladder to the proximal and distal urethra [38, 39]. Gonadectomized female dogs with urinary incontinence have a significantly higher number of LH receptors in the lower urinary tract compared to unaltered females[40]. Urinary continence can be restored in gonadectomized females by reducing circulating LH concentrations using estrogens [34, 41-44], GnRH agonists [45, 46] or GnRHimmunization [47,48].

Urinary calculi: Urinary calculi are solid particles (concretions) in the urinary system, usually composed of mineral salts that can form in any part of the urinary tract [49]. Urinary calculi may be large enough to obstruct the flow of urine or small enough to be passed with the urine. After evaluating records from more than two million dogs, Banfield Pet Hospital found that all urinary calculi (urine crystals,kidney stones, and bladder stones), occurred at a rate three times higher in gonadectomized dogs compared to unaltered dogs [50].Under normal circumstances, there is a balance of urinary calculi promoters and inhibitors. However, this balance appears to be disrupted under the influence of an abundant LH environment.

Endocrine System:

Diabetes Mellitus: Diabetes mellitus results from the impaired secretion of insulin with variable degrees of peripheral insulin resistance leading to hyperglycemia. In dogs, the incidence of diabetes mellitus is 0.4-1.2% [51] and has been increasing over the past 30 years [52,53].Gonadectomy doubles the risk for developing diabetes mellitus in dogs [53]. Although gonadectomy increases the risk for obesity, the increased prevalence for diabetes mellitus in gonadectomized dogs is unrelated to obesity [54, 55] and may be a direct effect of LH on the pancreas.

Hypothyroidism: Hypothyroidism is a common endocrine disorder in which the thyroid gland does not produce sufficient quantities of thyroid hormone (thyroxin, T4) [56, 57]. Gonadectomy has a profound effect on thyroid function [58] and is the most significant cause for the development of hypothyroidism in dogs [59].Thirty percent more gonadectomized dogs develop hypothyroidism compared to unaltered dogs [60]. Women who have undergone gonadectomy are also at an increased risk for developing hypothyroidism [61]. LH receptors are expressed in normal and adenomatous human thyroid glands [62] and presumably also present in the canine thyroid gland. Because thyroid stimulating hormone concentrations remain similar for both gonadectomized and unaltered dogs [63], research is needed to determine the effects of LH receptor activation in unaltered and gonadectomized dogs.

Musculoskeletal System

Hip Dysplasia: Canine hip dysplasia is associated with the abnormal joint structure and laxity of the muscles, connective tissue, and ligaments that would normally support the hip[25, 64, 65]. As hip joint laxity increases, the articular surfaces between the pelvic tubar coxae and head of the femur lose contact with each other, resulting in subluxation. Over time, subluxation results in a significant change in the size and shape of both articular surfaces and varying severity of osteoarthritis. It is important to note that most dogs with hip dysplasiaare born with normal hips but then develop hip dysplasia secondary to intrinsic and/or extrinsic factors. The incidence of hip dysplasia can be as high as 40-83% in giant and large breed dogs [64-68]. Independent of the occurrence of obesity, gonadectomy significantly increases the incidence of canine hip dysplasia [68]. Compared to unaltered dogs, gonadectomy increases the by 1.5 [64] to 2 times [69] the occurrence in unaltered dogs. The mechanism for the increased incidence is not known but possibly results from an increase in LH receptor expression and/or activation in the structural support tissues within the hip joint.

Cranial Cruciate Ligament Rupture

The cranial cruciate ligament serves to prevent cranial displacement of the tibia relative to the femur, to limit internal rotation of the tibia relative to the femur, and to prevent stifle hyperextension [70, 71]. Cranial cruciate ligament rupture is another musculoskeletal disorder that initially involves the degeneration of the cranial cruciate ligament, which leads to a partial rupture and then progresses to a complete rupture following an unspectacular traumatic event [72, 73]. Similar to hip dysplasia, most dogs with cranial cruciate ligament ruptures are born with normal stifle joints but then develop the tendency for cranial cruciate ligament rupture secondary to intrinsic and/or extrinsic factors.Gonadectomy significantly increases the prevalence of cranial cruciate ligament rupture [74], doubling the occurrence reported for unaltered dogs [75]. With an incidence as high as 5.1% and 7.7% in males and females, respectively [69].Prepubertalgonadectomy delaystibial growth plate closure [76], which extends the length of tibia and the steepness of the tibial plateau [77,78]. Increased steepness of the tibial plateau can increase the cranial tibial thrust, which is a risk for cranial cruciate ligament rupture [79, 80]. Despite the skeletal deformations that occur with pre-pubertal gonadectomy, even dogs post-pubertallygonadectomized have an increased risk for cranial cruciate ligament rupture [69]. There is some evidence that hormones (estrogen and relaxin) may play a role in altering cranial cruciate ligament laxity and may be modifiable risk factors in humans [81, 82]. The role for LH and its receptor in the etiopathogenesis of canine cruciate ligament rupture should not be overlooked.

Behavior and Cognition

The role of gonadectomy on behavior is complex and evidence for benefits as well as detriments following gonadectomy has been reported. Reproductive-related behaviors (such as urine marking in house, mounting, and roaming) are all reduced or eliminated following gonadectomy [83, 84, 30].However, fear and aggression tend to be exacerbated [85].

Fear of storms, fear of gunfire, fear of noises, fear biting, timidity, separation anxiety, and submissive urination all increase significantly following gonadectomy. Gonadectomized females are also more reactive to the presence of unfamiliar humans and dogs [86]. Although some dogs may become less aggressive following gonadectomy [84], dominance aggression [87]and owner-directed aggression [21, 88] occur with a significantly higher frequency in gonadectomized dogs compared to unaltered dogs. The hippocampus and hypothalamus both play important roles in controlling behaviors, especially those pertaining to fear and aggression. Luteinizing hormone receptors are abundant in hippocampus and hypothalamus [89-91]. In addition, administration of supraphysiologic concentrations of LH to gonadectomized animals can induce aggression and other behavioral changes [92-94].

Cognitive dysfunction syndrome is a neurodegenerative disorder of senior dogs, which is characterized by both cognitive changes and neurophysiological pathologies [95, 96]. Memory impairment, poor problem solving skills, social disconnect, confusion, and day-night reversal may occur as the condition progresses. Gonadectomy significantly increases the development and progression of cognitive dysfunction syndrome in dogs. Increases in luteinizing hormone are associated with declines in cognitive performance [97]. In addition, elevated LH concentrations increase beta amyloid plaque formation and are implicated in the development of Alzheimer's syndrome in humans [98, 99]. Male sex hormones and systemic inflammation in Beta amyloid plaques are also involved in the pathogenesis of cognitive dysfunction syndrome in dogs [100, 51]. Therefore, it is possible that LH and its receptor are important in the development of cognitive dysfunction syndrome in gonadectomized dogs.

Neoplasia

Prostate Adenocarcinoma

Unlike the condition in men, the aggressive nature of the canine prostate adenocarcinoma and the lack of a screening test make the identification of dogs with early-stage prostate cancer extremely problematic [101]. In dogs, gonadectomy is the largest risk factor for the development of prostate adenocarcinoma[102, 103]. Luteinizing hormone receptors are abundant in the prostate gland and increase in expression following gonadectomy [104, 105]. Prostate carcinomas in dogs are associated with a high rate of metastasis at presentation and too poor of a prognosis to recommend aggressive local therapies [101]. Prostatectomy is associated with significant postoperative morbidity, in particular urinary incontinence, without significantly extending survival times [106,107].

Transitional Cell Carcinoma

Transitional cell carcinomas can arise from the bladder or urethra, including the prostatic urethra [108-112]. Even with surgical removal, radiation treatment and chemotherapy, the prognosis for dogs with transitional cell carcinomas is poor with only 16% of treated dogs surviving for over one year [113]. Gonadectomized dogs have a significantly higher risk of developing a transitional cell carcinoma compared with unaltered dogs [113]. Luteinizing hormone receptors are widely distributed throughout the bladder and urethra[39, 105,114] and increase in expression following gonadectomy [115].

Osteosarcoma

Osteosarcoma is a highly metastatic cancer of bone tissue. Despite many advances over the past 20 years, survival times for dogs diagnosed with osteosarcoma have not changed, with the principal cause of mortality being the development of pulmonary metastases [116]. Osteosarcoma occurs with significantly higher frequency in gonadectomized dogs [117]. The incidence of osteosarcoma in gonadectomized dogs is 1.3-2.0 times higher than in unaltered dogs [118]. It is not known if LH receptors exist in the bone or if LH could be using an indirect mechanism to mediate the increased incidence of osteosarcoma.

Hemangiosarcoma

Hemangiosarcoma is a rapidly growing, highly invasive cancer arising from the lining of blood vessels and occurring almost exclusively in dogs. Primary tumors can arise in any vascular tissue but the spleen and heart are the most common locations for hemangiosarcoma to develop. Even with surgical removal, the mean life expectancy *is* 86 days (range, 10–202 days) without adjunctive chemotherapy and 189 days (range, 118–241 days) with adjuvant chemotherapy [119]. Many studies have confirmed the presence of LH receptors in vascular endothelial and smooth muscle cells [120, 121]. Gonadectomized female dogs have two times the risk for developing splenic hemangiosarcoma and five times the risk for developing cardiac hemangiosarcoma compared to unaltered females [122, 85]. Research is needed to determine if canine hemangiosarcomas possess LH receptors and if adjunctive therapy targeting these receptors would extend life expectancy.

Lymphosarcoma

Lymphosarcoma is a cancer of lymphocytes and/or lymphoid tissues. Lymphosarcoma is the most common cancer diagnosed in dogs accounting for up to 24% of all canine cancers. LH receptors are present in lymphocytes and lymphoid tissue (medulla of thymus) [123]. Gonadectomy increases the incidence of lymposarcoma [85]. Gonadectomized males are three times more likely to develop lymphosarcoma than unaltered males and about 1 in 10 neutered males will develop lymphosarcoma [69].

Mastocytoma

Mastocytomais the most common skin tumor in dogs [124]. Luteinizing hormone receptors are abundant in the skin [38, 125]. Several studies have documented an increased risk for developing mastocytoma following gonadectomy in dogs [69, 126,85].

Conclusion

Unrelated to any particular disease or major cause of death, years of gonad exposure prolong longevity [127]. Based upon the review of the literature, it becomes clear that canine gonads are not merely reproductive organs but critical to endocrine, musculoskeletal, behavior, and anti-neoplastic health. Among the non-reproductive functions of gonads, suppression of LH secretion and resulting LH receptor over expression appear necessary in maintaining homeostasis. Therefore, a surgical sterilization method that enables the dog to keep gonads intact while still preventing reproduction is likely to prolong its health.

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