

Melatonin Therapy for Canine Alopecia

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Melatonin is a hormone synthesized in the pineal gland, mainly at night, and is a product of the multistep conversion of L-tryptophan to serotonin and subsequently melatonin. It has been implicated in the regulation of a wide range of physiological and behavioral processes in a wide array of vertebrate species. These processes include modulation of reproduction, especially in species that are seasonally reproductive; photoreception; thermoregulation; skin and pelage coloration; and fur growth cycles. In humans, clinical and basic research on the effects of melatonin involves antiaging, antioxidant (its free radical scavenger properties appear more powerful than those of vitamin E), anesthetic properties, sleeping disorders, jet lag syndrome, depression, and contraception.

Most knowledge regarding melatonin has been attained in the last two decades. Because of the wide array of its potential effects, a vast literature has developed on the topic; a Medline search on the keyword "melatonin" yielded more than 3,000 references for articles published from the late 1980s to the late 1990s. However, melatonin is barely mentioned in human dermatology literature. This is interesting considering that the hormone was first isolated from bovine pineal glands in 1958 by Dr. Aaron Lerner, a dermatologist studying its effect on skin pigmentation. Although melatonin causes lightening of the skin of amphibian frogs (because of rapid melanosomal aggregation around the nucleus of the dermal melanocytes), and is responsible for growth of white winter pelage in weasels and Siberian hamsters (probably because of its antimelanocyte-stimulating hormone effect), it does not seem to play a major role in human skin pigmentation. Concurrently, the anesthetic properties of melatonin are being actively evaluated in human patients with cancer, especially melanoma. Longer survival time has been reported in patients with melanomas treated with interleukin-2 (IL-2) and melatonin compared with patients treated with IL-2 alone. In addition, advanced solid neoplasms resistant to IL-2 may become responsive to IL-2 therapy by a concomitant administration of melatonin, which could act by enhancing IL-2 antitumor immune effect or by increasing the susceptibility of cancer cells to the cytotoxicity mediated by IL-2-induced cytotoxic lymphocytes, or both.

It has even been postulated that increased daily retinal exposure to artificial light in the 20th century, in contrast with earlier times, has resulted in decreased melatonin secretion, which, in turn, has contributed to an increased incidence of melanomas and other cancers.

In veterinary dermatology, little attention has been paid to melatonin. This substance is involved in the neuroendocrine control of photoperiod-dependent molting or pelage color in many mammals. However, the mechanism by which melatonin induces molting and fur growth is not entirely understood. The hormone may act directly on hair follicles, or within the central nervous system to alter

secretion of melanocyte-stimulating hormone or prolactin secretion, or both.

Effects of melatonin on fur growth have been studied in mink and foxes. There are indications of a synergistic effect of prolactin and melatonin, two photoperiod-dependent hormones, at the level of the hair follicle. The melatonin secretion pattern is an inverse function of day length, and circulating melatonin levels correlate inversely with prolactin levels. Melatonin secretion occurs during the hours of darkness, so the amount of melatonin biosynthesis is directly related to the length of the daily dark period. The quantity continues to increase in autumn until winter solstice.

Mink exhibit a seasonal fur growth cycle regulated by photoperiod. As the length of the photoperiod decreases, an increase in melatonin concentration (and a decrease in prolactin) results, initiating growth of the winter pelage, which begins in September in northern latitudes. In spring, the opposite occurs: the length of the photoperiod increases, resulting in an increase in prolactin concentration (and a decrease in melatonin), initiating the spring molt. Mink treated with implants of melatonin in June, when natural melatonin production is low, or exposed to an artificial 6L: 18D photoperiod, or treated with bromocriptine, a dopamine antagonist, have suppressed prolactin production and exhibit an early onset of autumn molt and produce prime winter pelage by mid-October, 6 to 8 weeks earlier than normal. For this reason, melatonin implants have been commercially available for several years to the fur industry for use in mink and foxes. This is to the best of this author's knowledge, the only commercial application of melatonin in veterinary dermatology. However, melatonin was implicated in the 1960s in the treatment of canine acanthosis nigricans. Recently, it has been used experimentally in dogs with recurrent flank alopecia, pattern baldness, and alopecia-X of Nordic breeds.

CANINE RECURRENT FLANK ALOPECIA

Clinical Features

Canine recurrent flank alopecia (CRFA) is a recently recognized skin disorder of unknown cause that is characterized by episodes of truncal hair loss that often occurs on a recurrent basis. It has previously been described under several synonyms: *seasonal flank alopecia*, *seasonal growth hormone deficiency*, *canine idiopathic cyclic flank alopecia*, *cyclic follicular dysplasia*, and *follicular dysplasia*. CRFA is most commonly seen in Boxers, bulldogs, and Airedale terriers but also occurs in several other breeds. Dogs of either sex and any reproductive status can be affected. CRFA is characterized by a nonscarring alopecia that is most often confined to the thoracolumbar region. Lesions are usually bilaterally symmetrical, but in acca-

sional dogs (or episodes), only one side of the body is affected, or one side is more affected than the other. The alopecic lesions are amular, or "geographic" in shape with well-demarcated borders. The alopecic skin is often markedly hyperpigmented. Mean age at the onset of the first episode is 3.8 years, but can be variable (range: 8 months to 11 years). The onset of alopecia is not confined to the fall and winter months in males or to the spring months in females as was first reported. Instead, when all cases are combined, the majority of dogs have an onset of alopecia between November and March in the Northern hemisphere. The month of onset does not seem to be affected by breed, age, sex, or sexual status.

Spontaneous regrowth of hair occurs in 3 to 8 months in most cases and usually consists of normal pelage density, even though some dogs may grow darker hair in the previously affected areas (particularly boxers) or may grow a golden color (aurotrichia) as seen in some miniature Schnauzers. However, after several consecutive episodes of alopecia, some of the affected dogs will not experience complete hair regrowth before the onset of the next episode. Approximately 20% of these dogs will only have one isolated episode of flank alopecia in their life span in the experience of this author. However, the majority will develop recurrent alopecic episodes for years. Other dogs have an occasional year when the alopecia does not recur. The degree of alopecia is variable, with some dogs having a virtually identical hair loss (size and duration) year after year, and other dogs developing larger areas or longer episodes of hair loss, or both, as years go by.

Cause and Pathogenesis

The cause of CRFA remains obscure. To date, underlying causes, such as endocrinopathies, have not been identified. The seasonal nature and recurrence of CRFA suggests that photoperiod may be involved in the process. It is the author's belief that there is a higher incidence of CRFA at higher latitude (i.e., north of the 45th parallel), suggesting that CRFA might indeed be caused by a genetically influenced melatonin deficiency that is responsible directly or indirectly (by its effect on prolactin, androgen, estrogen, or growth hormone, or a combination) for the recurrent alopecia.

Treatment

Although several therapeutic agents have erroneously been proclaimed effective in treating CRFA, no treatment has yet been confirmed effective. Nevertheless, melatonin holds promise in the treatment of CRFA because initial therapeutic trials have produced encouraging results. However, the unpredictable course of CRFA and the spontaneous regrowth of hair render the evaluation of any therapeutic agent, used either to prevent or shorten an episode of alopecia, in CRFA extremely difficult. The only subjective reference we have used is the knowledge that a dog who has suffered at least three consecutive episodes of CRFA has a high likelihood (>80%) of having the alopecia recur the following year.

In the initial trial conducted to evaluate the efficacy of

melatonin treatment in preventing CRFA, nine dogs who had previously suffered three or more consecutive episodes of CRFA were used (Paradis, 1995). Around the autumnal equinox (approximately 2 months before the next "expected" episode of CRFA) each received melatonin: three dogs received two SC injections of 12.5 mg of melatonin in soybean oil (2.5 mg/ml; this formulation is not available commercially) at 2-week intervals, and six dogs received three constant-release implants impregnated with 12 mg of melatonin (36 mg total, based on the 12 mg/fox dose) SC. None of the nine dogs treated with melatonin in the fall experienced large areas of alopecia in the winter after the melatonin treatment as they had done the previous years. Instead, two (two large male Airedale terriers) had a very discrete, unilateral, 1.5- to 2-cm-diameter area of hypotrichosis of less than a month's duration, which was different from their previous much larger areas of alopecia that usually lasted several months. One older female boxer who had had six consecutive episodes, with incomplete regrowth after the most recent, had no hair regrowth of that relatively small area of alopecia that had remained after melatonin administration, but did not develop new area of alopecia. Also of interest, several owners reported an overall noticeably denser hair coat than usual following melatonin administration.

Since the initial study, several veterinary dermatologists have used melatonin in CRFA either to prevent recurrence or to shorten the duration of an alopecic episode. Apparent success was obtained in several cases with melatonin administered either orally (tablets or capsules) or subcutaneously (aqueous injections or implants). To document the real benefit of melatonin therapy in this disorder, one should selectively treat dogs before or shortly after the onset of alopecia (although the use of melatonin as a preventive treatment is limited, considering that the chance of recurrence is 60 to 70% in any given year). A placebocontrolled, double-blinded study using oral melatonin is warranted, since this seems to be the treatment of choice for most owners and veterinarians.

CANINE PATTERN BALDNESS

Clinical Features

Canine pattern baldness (CPB) is a relatively common but poorly defined disorder. Three different syndromes have been recognized in dogs. The most common syndrome typically consists of an acquired alopecia developing at the postauricular regions; along the ventral neck, thorax, and abdomen; and on the caudomedial thighs. It is seen primarily in dachshunds but is also recognized in several short-coated breeds: Chihuahuas, miniature pinschers, whippets, greyhounds, Boston terriers, boxers, and so on. The hair loss usually starts around 6 months of age and gradually progresses over the following year but remains restricted to the described areas.

Treatment

Because CPB is a purely aesthetic problem, not much energy has been spent in finding a possible treatment for it. To date, no effective treatment has been reported aside

from the possible beneficial effect of melatonin. Indeed, in this author's study evaluating the efficacy of melatonin in CRFA, two boxers with concurrent CPB experienced impressive hair growth in those areas in which the hair coat was previously sparse to absent (more specifically the chest and ventral neck). Based on these unexpected findings, a pilot study was conducted to evaluate the efficacy of melatonin in the treatment of canine CPB (Paradis, 1996). Eleven purebred dogs affected with CPB as described were treated either with one to three constant-release implants impregnated with 12 mg of melatonin (7 dogs) SC, or with one capsule containing 5 mg of melatonin in a lactose base given PO, every 24 hours for 30 days (4 dogs). All 11 dogs experienced hair growth (varying from mild to significant) in affected areas that was noticed as early as 1.5 months after the initiation of the treatment. Maximal growth was achieved 3 to 4 months later. Most owners were pleased with the results, and several reported an overall denser and more attractive hair coat. Results were less impressive in the two dachshunds and the two miniature pinschers of the trial, and for all dogs hair growth on the sternum was negligible, perhaps because of premature wearing or irreversible follicular atrophy.

Since the initial study, other CPB cases have been treated with melatonin by several veterinary dermatologists. Good results have been observed in several dogs (but not all), including Dachshunds and Boston terriers.

ALOPECIA-X OF THE NORDIC BREEDS

This is the name several veterinary dermatologists are now using to refer to the following diseases: pseudo-Cushing, adult-onset growth hormone deficiency, hyposomatotropism of the adult dog, growth hormone-responsive alopecia, castration-responsive dermatosis, gonadal sex hormone dermatoses, sex-hormone alopecia, sex hormone/ growth hormone dermatosis, biopsy-responsive alopecia, adrenal sex hormone imbalance, congenital adrenal hyperplasia-like syndrome, Lysodren-responsive dermatosis, follicular dysplasia of Nordic breeds, Siberian husky follicular dysplasia, follicular growth dysfunction of the plush-coated breeds, and others.

A number of patients with "that disease" have been treated with melatonin by several veterinary dermatologists with apparent success in more than 50% of the cases. Criteria have not yet been established regarding the responsiveness for any given breed, sex, age, and so on.

SOURCE OF MELATONIN

Melatonin is easily synthesized and is therefore a relatively cheap hormone that can be administered orally (tablets or capsules) or systemically using aqueous SC injections or constant-release SC implants. Interestingly, melatonin is also present naturally in some plants. However, to absorb 3 mg of melatonin, one would have to eat 120 bananas or 30 large bowls of rice!

Melatonin tablets are sold over the counter in health stores and drugstores in the United States and several other countries, where it is considered a dietary supplement rather than a drug (so it is not regulated as such). It is

found as 2- or 3-mg tablets under several brand names. However, only licensed products have guaranteed purity. Although less practical, capsules can be made from melatonin crystalline powder purchased at Sigma Chemical Company (P.O. Box 14508, St. Louis MO, USA, 63178-9916; approximately 40 US dollars per gram). The major concern with oral administration of melatonin is its short half-life and dose-dependent bioavailability. In a study, its apparent half-life in dogs was 18.6 minutes following administration of 3 mg/kg IV. An injectable aqueous melatonin (made from melatonin crystalline powder dissolved in ethanol and mixed with water and DMSO) has been available for several years, through Rickards Research Foundation (18001 Euclid Avenue, Cleveland, OH 44112) and has been used in the past for the treatment of acanthosis nigricans (Scott et al, 1995). This could be a valuable option, although no pharmacokinetic data are available. Constant-release implants impregnated with 2.5 mg and 12 mg of melatonin have been approved in several countries for use in mink and foxes, respectively, and are commercially available from Wildlife Pharmaceuticals (Fort Collins, Colorado 80524-2778). Unfortunately, some dogs who received the subcutaneous implants experienced sterile abscesses or granulomas at the site of implantation. This seems particular to dogs; in the fur industry, more than 10 million minks and foxes have received subcutaneous melatonin implants with no reports of adverse local reactions.

CLINICAL USE OF MELATONIN

The use of melatonin in dogs must be considered experimental at this time. There is no information on possible harmful long-term side effects in dogs or any other species. When human volunteers were fed 6 g (6,000 mg) of melatonin every night for 30 days, stomach discomfort and some residual sleepiness were the only reported side effects. Since melatonin has been shown to regulate light-mediated reproductive events in mammals, it is best to avoid its use in breeding dogs. However, since CRFA, CPB, and alopecia-X of Nordic breeds are most likely genetically programmed, it is better to avoid proliferating dogs affected with those conditions. For melatonin to be a valuable therapeutic option in some types of canine alopecia, its long-term effects will have to be evaluated. Myriad questions remain, such as: What is the optimal dose and route of administration, length of treatment, and the best time of year (or time of day for oral administration) for treatment to be initiated? It is not known whether its efficacy depends on a sustained high level or only a peak of melatonin produced in the initial stage, nor do we know the minimal number of days that the presence of melatonin is required to initiate the growth of hair. Finally, it is also not known if the animal will become insensitive or refractory to the formerly inductive melatonin signal after an extended period of exposure to high melatonin concentrations.

Studies are needed to corroborate the results of these preliminary trials investigating the effectiveness of melatonin therapy for various types of canine alopecias. Meanwhile, if one wishes to try melatonin in dogs with alopecia, this author's recommendations for the time being are as follows: use 12-mg implants SC at the rate of one to four

per dog. This is purely empirical and is based on the 12 mg/fox dose, which successfully produces precocious winter fur growth in that species. It has the advantage of being sustained-release, and it is possible that this may be important for therapeutic efficacy. Melatonin is released over a few months in foxes, so it may be administered once (CRFA) or twice (CPA?) a year, depending on the disease being treated. If implants are not an option, one can use oral melatonin, given daily for 4 to 6 weeks at as high a dose and frequency that one dares (e.g., 3 to 6 mg every 8 to 12 hours). It may later be revealed that this treatment regimen is excessive in dosage and duration. However, these current recommendations are based on the short half-life of orally administered melatonin in dogs, and on the knowledge that in mink, activation of hair follicles by melatonin occurs during a 4- to 6-week period. This photoperiodic signal does not seem necessary for later pelage growth and maturation. Melatonin appears to be safe, but owners should be made aware of the experimental nature of the treatment and sign a release form accordingly.

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