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Chapter VII

The Pineal Gland, Melatonin and Scoliosis*

Gregory Day*† *and Bruce McPhee
University of Queensland, Brisbane, Australia

Abstract

Over the past 25 years, chicken studies implicated experimental pinealectomy as acause of scoliosis. The nature of the scoliosis was demonstrated to be similar to that of human idiopathic scoliosis. Subsequent research involved a primate (Rhesus monkey) experimental pinealectomy model. Scoliosis was not induced by pinealectomy. In a recent Australian study, no causal link was established between pineal lesions and the development of idiopathic scoliosis. Melatonin is the only known hormone secreted by the pineal gland in humans. Previous research concluded that melatonin secretion was similar in those with idiopathic scoliosis and aged-matched controls. A recent Korean study concluded that permanent melatonin deficiency was not a causative factor in the aetiology of (AIS) adolescent idiopathic scoliosis. Over a period of

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† Correspondence: Gregory Day, MD, Professor, Level 5, St Andrew's Place, 33 North Street, Spring Hill, Queensland, Australia 4000. E-mail: *ggandlda@bigpond.net.au*.

25 years, research involving the production of scoliosis following pinealectomy in small animal models has not been reproducible in the human model. The search for a scientifically sound human model to investigate the etiology of idiopathic scoliosis continues.

Introduction

The existence of the pineal gland was postulated nearly two millennia ago. It was not until 1958 that discovery of the active pineal hormone, melatonin, opened the way into researching the functions of the pineal gland [1,2]. Subsequently, Axelrod was able to elucidate the biochemical cascade for the synthesis of melatonin in the pinealocytes [3]. The pineal gland's anatomical location and function are now established. It is known to exert a physiological effect through a variety of actions such as an endocrine gland, a transducer, and a regulator of hormones and as a damped circadian oscillator. Melatonin is thought or known to mediate all of these functions. Animal research has demonstrated a relationship between the production of melatonin and the modulation of circadian rhythm and sleep regulation. In addition, melatonin is suspected of influencing reproductive physiology, cardiovascular function, immunological regulation, and psychiatric disorders. It is not clear to what extent the results from animal studies can be extrapolated to humans. Perhaps one of the most unusual and unexpected findings is the relationship between the pineal gland, melatonin and scoliosis in experimental animals.

Experimental Scoliosis – Pinealectomy and Melatonin

Research involving the production of experimental scoliosis in chickens and rodents commenced following a serendipitous experiment in France 40 years ago [4].

Experimental pinealectomy in three-day-old white leghorn chickens of both genders led to the development of thoracic scoliosis, [5] whereas a sham procedure did not [6]. Between 50 and 100% of pinealectomized chickens developed scoliosis [4,6]. The prevalence of scoliosis in chickens pinealectomized between 2 and 18 days after hatching was not significantly different [7]. However, scoliosis was only occasionally observed after older chickens underwent experimental pinealectomy [8]. The critical step involved

removing the entire pineal gland and/or stalk [9,10]. The induced scoliosis appeared to be similar to human idiopathic scoliosis [11,12]. However, angular thoracic scoliosis was also observed in some pinealectomized chickens as well as controls [11,13,14]. Intra-muscular auto-transplantation of the pineal gland into pinealectomized chickens prevented the scoliosis developing in 90%, [12] but the results of this research were subsequently repudiated [15,16].

Melatonin (N-acetyl-5-methoxytryptamine) is the only known hormone secreted by the poultry pineal gland [17]. Pinealectomy on three-day-old chickens resulted in reduced melatonin levels and elimination of the melatonin circadian rhythm [18]. Although a low serum melatonin level was reported to be associated with scoliosis in pinealectomized chickens, [18] other researchers were unable to validate the association [7,19]. Induced melatonin suppression by constant light resulted in the development of scoliosis in 15% of white Leghorn chickens, [20] but it had no effect on Nihon chickens [21]. Intra-peritoneal injections of melatonin (2.5 mg/100 mg body weight) into pinealectomized white Leghorn chickens for a period of three weeks prevented scoliosis in 80% [18], but injections of melatonin (2.5 mg/1 kg body weight) had no effect on pinealectomized Mountain Hubbard chickens [22]. The latter dose was believed to restore melatonin levels to a more physiological range. Daily intra-peritoneal injections of 5-hydroxy-l-tryptophan (a precursor of both serotonin and melatonin) into white Leghorn pinealectomized chickens retarded scoliosis development in 30% [23]. Pinealectomy in young chickens resulted in a loss of diurnal variation in serum melatonin levels and a reduction in melatonin receptor affinity whether or not scoliosis developed. Low melatonin levels and reduced spinal cord melatonin binding were believed to be not the sole factors in the etiology of scoliosis in pinealectomized chickens [24].

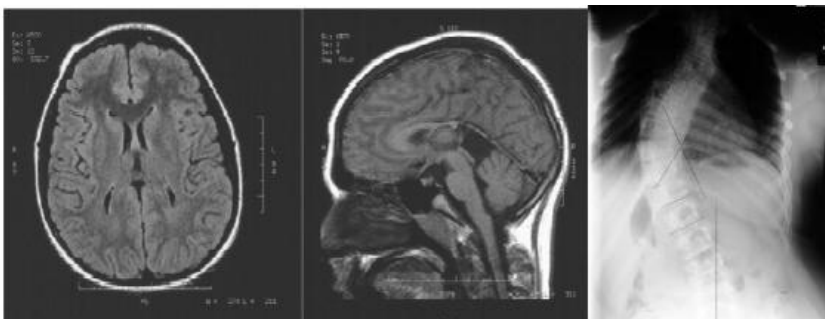

Figure 1. (a) Magnetic resonance images of the brain of a 12-year-old male with a pineal cyst. (b) Plain AP radiograph demonstrating his right thoracic scoliosis.

Other experimental animal pinealectomy models (e.g., hamsters) also produced scoliosis [25]. Scoliosis did not develop in pinealectomized quadrupedal rats but developed in all pinealectomized bipedal male Sprague-Dawley rats, implying a postural mechanism [26]. Scoliosis was observed in 64% of a bipedal model of a strain of mouse that exhibited depressed melatonin levels in plasma and the pineal gland, including some with double curves, after 40 weeks [27]. Bipedal ambulation in a standard mouse was associated with scoliosis in only 25%, all with single curves. When combined with pinealectomy, the incidence of scoliosis in the bipedal standard mouse increased to 70%, some with double curves, comparable with bipedal melatonin-deficient mice. Daily intraperitoneal injections of melatonin prevented the development of scoliosis in the bipedal model of the melatonin-deficient mouse and pinealectomized standard mouse [28]. Hence, melatonin deficiency in bipedal mice appeared to play significant role in the development of scoliosis. Scoliosis did not develop in young pinealectomized Rhesus monkeys with a mean follow-up of 28 (range 10 to 41) months [29]. Because none of the monkeys developed scoliosis, it was postulated that the aetiological factors leading to scoliosis in lower animals may differ from idiopathic scoliosis in primates.

Pineal tumours and related conditions in humans are rare [30-33], including the case of a girl with a hypothalamic hamartoma and precocious puberty having melatonin levels low for her chronological age but appropriate for her pubertal status [34]. Scoliosis following pineal ablation in children has been reported in only one patient (Figure 1) [35-38].

Anatomic Similarities and Differences between Animal Models and Idiopathic Scoliosis

The scoliosis resulting from experimental pinealectomy in chickens and various bipedal animal models is believed to be similar to human idiopathic scoliosis. Chicken scoliosis is three-dimensional, involving rotation of the thoracic spine, producing a rib hump [39]. Single and double curves occur in both chicken and human scoliosis. The vertebral bodies in chicken and human idiopathic thoracic scoliosis are laterally wedged at the apex of the curve [13,40,41]. The vertebral wedging may result from anatomic changes in the

vertebral growth plates [42]. Differential pressures on the quadrants of the vertebral growth plates can lead to the anatomic changes [42,43].

However, anatomic differences between normal human and chicken spines might overshadow the comparison of the scoliosis [6,39]. Most lumbar and thoracic vertebrae in chickens spontaneously fuse with spinal growth [39], whilst human vertebrae do not fuse. In chickens, the thoracic spine is naturally lordotic, whilst in humans, it is kyphotic. Moreover, the presence of thoracic hypokyphosis or lordosis is believed to be significant in the pathogenesis of the deformity of idiopathic thoracic scoliosis [44]. Plain imaging and magnetic resonance imaging studies of idiopathic scoliosis support a theory that relative overgrowth of the anterior elements of the human spine result in thoracic hypokyphosis or lordosis [45,46]. Chicken scoliosis may have no predilection for gender or side, whilst human idiopathic scoliosis commonly occurs predominantly on the right side of female thoracic spines. Scoliosis in pinealectomized chickens is seen only in the thoracic or thoraco-lumbar spines [11,47]. Human idiopathic scoliosis can also be present in the lumbar spine.

Unilateral visual impairment did not have a significant effect on the incidence and magnitude of scoliosis of pinealectomized chickens but affected the laterality of the curves. Visually impaired chickens had a significantly higher likelihood of left thoracic curves, tending to be as frequent as the right thoracic curves, regardless of the side of blindness. By comparison, right thoracic scoliosis predominated in visually unimpaired chickens [48].

Genetic Considerations in Animal Models and Idiopathic Scoliosis

A 55 to 90% prevalence of scoliosis was observed in highly inbred white leghorn chickens [49-51]. A study of inherited scoliosis in chickens implicated three major autosomal, recessive genes with variable expression due to incomplete penetrance, the additional effect of minor modifying genes and the environment [52]. A higher incidence of severe scoliosis in the rooster was attributed to sex-influence rather than sex-linkage inheritance [53]. Scoliosis was experimentally enhanced in genetically engineered chickens by dietary means, including feeding aminonitriles or by deprivation of trace elements such as copper, vitamin B-6, or manganese [54,55]. Interestingly, serum zinc levels significantly declined eight weeks following pinealectomy in three day-old Hydro Broiler chickens [56].

Genetic studies of adolescent idiopathic scoliosis indicated that about 11% of first-degree relatives were affected, 2.4% in second-degree relatives, and 1.4% in third-degree relatives [57-59]. Monozygous twins had a high concordance rate of idiopathic scoliosis (about 73%) compared to dizygous twins [60-62]. Genetic linkages to chromosomes 6p, 10q, 18q [63], 19p13 [64], 17p11 [65], and X [66] have been reported in adolescent idiopathic scoliosis.

Melatonin and Adolescent Idiopathic Scoliosis

Adolescents [67-69] with progressive idiopathic scoliosis were observed to have reduced night-time serum levels of melatonin, although these findings have not been supported [70-73]. In some studies, methods for identifying melatonin secretion varied and included night-time and day-time serum levels as well as 24-hour urinary excretion measurements. Because the ages of scoliotic subjects varied between reports, it was postulated that melatonin levels could influence pre-menarchal scoliotic development rather than in adolescence [74]. It was recently reported that pineal gland metabolism was similar in idiopathic scoliosis patients and controls [75].

An abnormality of melatonin receptors was implicated in a study of Hereditary Lordoscoliotic Rabbits [76]. Polymorphism of melatonin 1A receptor on chromosome 4q was not linked to human idiopathic scoliosis [77,78], but polymorphism of melatonin 1B receptor was [79]. Impaired melatonin signalling was observed in human idiopathic scoliosis but melatonin receptors were reported as being normal [80]. ASMT (Acetyl-serotonin methyl-transferase) is responsible for the final phase of synthesis of melatonin [81]. The gene is located on the pseudo-autosomal region of the short arms of the X and Y chromosomes. An unpublished study demonstrated low expression of ASMT in the vertebral growth plates in congenital and idiopathic scoliosis [82]. Tryptophan hydroxylase 1 is also a critical enzyme in melatonin synthesis. Polymorphism of this gene was observed to be associated with an incidence of idiopathic scoliosis [83].

Melatonin and Calmodulin

Calmodulin is a critical mediator of cellular calcium function and a regulator of many enzymes. Melatonin binds to calmodulin with high affinity

and is believed to be a calmodulin antagonist [84]. Administration of calmodulin antagonists (tamoxifen, trifluoperozine) reduced the incidence and magnitude of scoliosis in experimental pinealectomy chicken and bipedal mouse models [85,86].

Elevated platelet calmodulin levels were observed in children with progressive scoliosis [87,88]. However, genetic expression of calmodulin was significantly lower in the vertebral articular processes and the convex-side paraspinal muscles in idiopathic scoliosis patients compared to congenital scoliosis and controls [89,90]. Platelet disorders may reflect a basic cellular pathology and a secondary change attributable to the spinal curvature or the cause of the deformity. Platelets from adolescents with minimal curve scoliosis showed significantly more deviations from normal than healthy control subjects. The most frequent of these platelet anomalies did not predict curve progression at two- to 3.5-year follow-up [91]. A number of structural and functional anomalies were observed in platelets of patients with adolescent idiopathic scoliosis [92]. Subsequently, no significant differences in platelet parameters were observed between adolescent idiopathic scoliosis patients and a control group [93]. Current controversy focuses on the lack of control data and the large variability of baseline platelet morphological and biological anomalies and platelet calmodulin levels in patients with idiopathic scoliosis [94].

Melatonin, Growth and Maturation

Animal studies have shown that melatonin has a regulatory role in reproduction by down-regulating the gonadotrophin-releasing hormone gene [95-97]. Consequently, levels of melatonin and the gonadotrophins are inversely related. The demonstration of sex hormone receptors in the pineal gland and melatonin receptors in the reproductive organs is evidence of a complex relationship between melatonin, the hypothalamus, the pituitary, the pineal and the gonads during pubertal growth [98,99].

Gonadotrophin-releasing hormone (GRH) is secreted in a pulsatile manner by neurons in the hypothalamus. Activation of GRH receptors in the pituitary gland controls the release of luteinizing hormone and follicle-stimulating hormone and thus gonad activity. Melatonin has an inhibitory effect on the hypothalamic-pituitary-gonad axis by down-regulating gonodatrophin-releasing hormone gene expression [97,100]. Serum melatonin levels are high during childhood but subsequently decline below a threshold value, signalling

the hypothalamus to secrete gonodatrophin-releasing hormone, triggering the onset of puberty [101]. The action of melatonin on the gonads is an indirect effect as pubertal growth and maturation occurs through the action of the sex hormones on other receptors. The inhibitory effect on growth hormone signalling is an effective means of preventing precocious puberty.

Experimentally, it has been demonstrated that melatonin may act directly on the pituitary Gland, inducing growth hormone (GH) and prolactin (PRL) release [17,102,103]. On the other hand, melatonin has been shown to act indirectly on suprachiasmatic nucleus neurons through its receptor inducing the expression of Growth Hormone-Releasing Peptide and related peptides, thus stimulating GH and PRL release from the pituitary [104]. This difference may be species specific.

High levels of melatonin have been found in women with amenorrhoea and in delayed onset of puberty, while low levels have been reported in precocious puberty [105,106]. However, the incidence of scoliosis in precocious puberty appears to be no different from the general population. Human models of endocrine-related disturbances of growth and maturation with a significantly high incidence of scoliosis are limited. There are some notable clinical syndromes with growth disturbance and precocious or delayed puberty, which may provide some insight into the hypothalamic-pituitary-gonad axis.

Prader-Willi syndrome is a genetic hypothalamic-hypophyseal disorder in which growth hormone secretion us usually decreased. Puberty is usually delayed. Up to 80% of Prader-Willi subjects develop scoliosis. Whether there is a corresponding over-secretion of melatonin causing suppression of growth hormone secretion is unknown. The prevalence and magnitude of the scoliosis is not influenced by growth hormone treatment [107]. Likewise, the frequency and severity of the scoliosis in Turner's syndrome (short-statured children), which has 28% prevalence of scoliosis, is not affected by growth hormone therapy [108,109]. Growth hormone does not appear to be a promoter or agent of modification of scoliosis. Recent research suggests that polymorphism at the promoter region of calmodulin-1 gene and the homozygous genotype of growth hormone receptor gene may be associated with high susceptibility to AIS [110]. Scoliosis, sleep disorders and precocious puberty are commonly observed in female patients with Rett syndrome. Three quarters of Rett syndrome patients develop scoliosis by the age of 13 years [111-113]. Studies of children with Rett syndrome showed that the peak secretion of melatonin was normal, but the peak value was at a lower limit for normal children [114,115]. Although scoliosis in Rett syndrome has long been considered

neurogenic in type [116], the findings may indicate an underlying melatonin deficiency associated with a high incidence of scoliosis in a genetic condition that affects females.

McCune-Albright syndrome and Jaffe-Lichtenstein syndrome are genetic conditions associated with precocious puberty and endocrine changes, with a high frequency of scoliosis. In a study of patients with polyostotic fibrous dysplasia, the estimated prevalence of scoliosis was 40 to 52% [117]. Half the patients had precocious puberty with no relationship to the presence of scoliosis. The scoliosis was possibly related to the presence of spinal lesions and pelvic obliquity, and biochemically to phosphaturia and hyperparathyroidism, rather than a specific endocrine disorder. Although a neuroendocrine-related association with scoliosis was not evident in this study, a possible melatonin deficiency has been postulated as a potential association in fibrous dysplasia-like disorders by virtue of the failure of melatonin to bind to its RZR/ROR receptors, resulting in changes in the levels of activity of nuclear cAMP that lead to alteration of expression of bone sialoprotein [118].

Scoliosis and precocious or late puberty are common in Neurofibromatosis Type 1. The prevalence of scoliosis is 10 to 20%, with the majority evident before the age of seven years [119,120]. Precocious puberty is usually associated with an optic pathway glioma (OPG). Of the 5% to 25% of NF1 patients who have an OPG [121], up to 39% have precocious puberty [122]. Biochemical analysis of hormones secreted by the pituitary have demonstrated numerous hormonal irregularities [122-125]. Although there has been no research into the possible association of these hormone irregularities and melatonin, is has been postulated that melatonin deficiency, increased serotonin level with disturbed melatonin-serotonin interactions and calmodulin antagonism could be responsible for progression of spinal deformities in neurofibromatosis 1 [126,127].

Lesions of the hypothalamus are frequently associated with precocious puberty, including gliomas, hamartomas, and arachnoid cysts [128,129]. A number of hormonal abnormalities arising from the hypothalamic-pituitary axis have been reported. The studies have concentrated on the pituitary hormones with a systemic effect rather than what effect the tumor may have on melatonin secretion and whether altered melatonin secretion might be related to any systemic hormonal change. Hamartomas may induce precocious puberty either by having gonadotrophin-releasing hormone (GRH) activity or interfere with the antagonists of the normal hypothalamic GRH pulse generator. Melatonin has this potential as a GRH antagonist. Low levels of

melatonin have been reported in a case of hypothalamic hamartoma with precocious puberty [34].

The is currently no evidence that genes regulating the synthesis of growth hormone or the gonadotrophins predispose to or modify the development of adolescent idiopathic scoliosis. Although melatonin appears to have an inhibitory role on the gonadotrophin-releasing hormone generator in the hypothalamus, its role as a primary factor or a secondary effect in precocious or delayed puberty and associated scoliosis is unproven. Hormone regulation in growth and maturation and its effect of the development of scoliosis is clearly complex. Future studies of hormonal changes in precocious puberty should include analysis of melatonin levels.

Melatonin, Osteoblasts and Osteoporosis

Melatonin may have a direct effect on osteoblasts and osteoclasts in experimental animals [130,131]. Melatonin has been shown to stimulate the differentiation of both human and animal osteoblasts in cell culture in a dose-dependent manner with a demonstrable increase in procollagen production [132,133]. Its effect on bone homeostasis is due in part to promotion of bone synthesis and in part to down regulation of (receptor activator of nuclear factor KB) RANK-mediated osteoclastic bone resorption [134]. Both melatonin and estrogen retard bone resorption following ovariectomy in experimental animals [135]. The effect of estrogen was augmented by the addition of melatonin in preventing bone resorption [130]. Significanty lower bone mineral densities and lower numbers of osteocytes have been reported in the vertebrae of pinealectomized chickens, almost all of which developed scoliosis, compared with a control group of pineal-intact chickens [136]. The number of osteoblasts was similar in both groups. Experimentally, an association between the pineal deficiency, melatonin deficiency, reduced osteoblast differentiation, reduced bone density and scoliosis has been demonstrated.

Low Bone Mineral Density is a generalized phenomenon in adolescent idiopathic scoliosis [137-140]. The prevalence of adolescent idiopathic scoliosis with osteoporosis is approximately 20 to 38% [141]. Follow-up studies indicated that osteopenia in patients with adolescent idiopathic scoliosis persists [139,142]. No correlation was noted between the severity of the deformity and the bone density [143]. Melatonin and estrogens play a role in the normal vertebral remodelling during the pubertal growth period.

Osteoblast differentiation is probably mediated by melatonin activation of MT2 melatonin receptors. Melatonin is known to inhibit the accumulation of induced cAMP in normal cells due to the coupling of melatonin receptors to an inhibitory protein [144,145]. Normal osteoblasts in cell culture show a dose-dependent decrease in cAMP cell levels with increasing concentrations of melatonin. The response of osteoblasts from idiopathic scoliosis is different, the effect ranging from an increased production of cAMP to a low-grade proportional reduction in cAMP [80]. Because accumulation of high levels of cAMP suppresses osteoblastic function, these findings suggest that melatonin signaling is impaired in osteoblasts isolated from idiopathic scoliosis patients. Such a defect may result in deregulation of osteoblast differentation and reduced bone density. Whether the resultant osteoporosis is a primary cause of the scoliosis or a secondary effect has not been determined.

Idiopathic Scoliosis and Brain Dysfunction/Lesions

MRIs of the brain and spinal cord can help in the investigation of abnormalities of proprioception, postural equilibrium control, oculo-vestibular function, and vibratory sensation for the purpose of clinical neuromotor assessment of children with idiopathic scoliosis [146-150]. Younger children with progressive idiopathic scoliotic curves with and without neuromotor signs are more likely to have brain stem abnormalities such as Arnold-Chiari type-1 malformation, syringomyelia, or cerebellar tonsillar ectopia [151-156]. However, lesions involving the suprasellar region and pineal gland in juveniles and adolescents have not been implicated in the etiology of idiopathic scoliosis [157].

Conclusion

Although the pineal gland, and in particular melatonin, have been observed to play a major role in the development of scoliosis in experimental animal models, melatonin has no clear role in the etiology of idiopathic scoliosis in humans. The etiology of idiopathic scoliosis remains obscure but is clearly more complex than animal models. Its causal factors and progression are likely to be multifactorial, possibly including genetically predisposed

growth receptors susceptible to plasma levels of and/or a balance between the various hormones, involved in pubertal growth, including melatonin. Alteration in melatonin levels due to hypothalamic or pineal pathologies or possible genetic syndromes do not appear to increase the incidence of idiopathic scoliosis. In humans, the role of melatonin and the pineal gland may be permissive, rather than an apparently more direct influence, observed in the animal model. Even then, scoliosis only develops in the majority of experimental animals suggesting that other factors, including genetic susceptibility, may also influence the development of their spine/spinal deformities.

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