ORIGINAL ARTICLE

The role of melatonin in the pathogenesis of adolescent idiopathic scoliosis (AIS)

M. Girardo · N. Bettini · E. Dema · S. Cervellati

Abstract The cause of adolescent idiopathic scoliosis (AIS) in humans remains obscure and probably multifactorial. At present, there is no proven method or test available to identify children or adolescent at risk of developing AIS or identify which of the affected individuals are at risk of progression. Reported associations are linked in pathogenesis rather than etiologic factors. Melatonin may play a role in the pathogenesis of scoliosis (neuroendocrine hypothesis), but at present, the data available cannot clearly show the role of melatonin in producing scoliosis in humans. The data regarding human melatonin levels are mixed at best, and the melatonin deficiency as a causative factor in the etiology of scoliosis cannot be supported. It will be an important issue of future research to investigate the role of melatonin in human biology, the clinical efficacy, and safety of melatonin under different pathological situations. Research is needed to better define the role of all factors in AIS development.

Keywords Scoliosis · Melatonin · Chicken · Melatonin receptor · Pineal gland

Introduction

The cause of adolescent idiopathic scoliosis (AIS) in humans remains obscure and probably multifactorial. A number of suggestions concerning the etiology of AIS have been proposed including neuromuscular, genetic, mechanical, growth-related, and developmental, but no single factor has been identified so far.

Research into the etiology of idiopathic scoliosis has focused on multiple areas and has demonstrated the complex pathophysiology of this disorder: connective tissue abnormality, abnormal biomechanical forces, neurophysiologic predisposition, genetic, and increase of calmodulin or decrease of melatonin during the puberty.

The role of melatonin in human biology concerns circadian rhythm, sleep disturbances, affective disorders, sexual maturation, aging and age-related diseases, tumors growth (malignancy), cardiovascular system, bone structure, interaction with calmodulin, AIS.

Synthesis and receptors of melatonin

The melatonin is produced mainly in the pineal gland and a small portion in the retina. The synthesis and release of melatonin are stimulated by darkness, melatonin is the "chemical expression of darkness" and inhibited by light [56]. Photic information from the retina is transmitted to the pineal gland through the suprachiasmatic nucleus of the hypothalamus (SCN) and the sympathetic nervous system [10, 24]. The activity of arylalkylamine N-acetyltransferase (AANAT), the enzyme that regulates the rate of melatonin synthesis, is increased, initiating the synthesis and release of melatonin.

The synthesis of melatonin from serotonin is catalyzed by two enzymes [arylalkylamine N-acetyltransferase (AANAT) and hydroxyindole-O-methyltransferase (HIOMT)] that are largely confined to the pineal gland. Melatonin is rapidly metabolized, chiefly in the liver, by hydroxylation to

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6-hydroxymelatonin. The urinary excretion of 6-sulfat-oxymelatonin (the chief metabolite of melatonin) closely parallels serum melatonin concentrations [24].

Serum melatonin concentrations vary considerably according to age: infants younger than 3 months of age secrete very little; 1–3 years: peak nocturnal 325 pg/ml; after decline gradually: 10–15% per decade; young adult: peak nocturnal 10–60 pg/ml [30].

In humans, melatonin has diurnal variations. The hormone secretion increases soon after the onset of darkness, peaks in the middle of the night, between 2 and 4 a.m., and gradually falls during the second half of the night [33].

Melatonin receptors have been located in the suprachiasmatic nucleus, the pars tuberalis, and in the cerebellum [17, 58]. Two membrane-bound melatonin-binding sites belonging to distinct groups have been identified: ML1 (high-affinity) and ML2 (low-affinity) receptors [17, 45]. There are two subtypes of a high-affinity melatonin receptor (ML1) cloned from several mammals including humans: the Mel1a and Mel1b receptors, which are now referred to as the MT1 and MT2 receptors, respectively [2, 57]. Several major actions of melatonin are mediated by the membrane receptors MT1 and MT2. They belong to the superfamily of G-protein coupled receptors containing the typical seven transmembrane domains. MT1 receptors activate protein kinase C-b, whereas MT2 receptors inhibit the soluble guanylate cyclase pathway while stimulating protein kinase C [24, 29, 57]. The ML2 receptors are coupled to the stimulation of phosphoinositide hydrolysis, are a distinct molecular species, but their distribution has not been determined. The ML2 (also named MT3) receptor was poorly characterized and enigmatic until a recent study identified it as a form of quinone reductase [24, 62].

Melatonin may play a role in the pathogenesis of AIS?

There are a number of theories on the etiology and pathogenesis of idiopathic scoliosis. These include genetic, skeletal, myogenic, metabolic and chemical factors, and abnormalities of the central nervous system [25, 68]. Experiments on various animal models have suggested possible anatomical or functional influences for each of these elements in the etiology of idiopathic scoliosis [1, 7, 51, 52].

Machida and Dubousset have found that pinealectomy in chickens, shortly after hatching, consistently produces scoliosis which has similar anatomical features to those of human idiopathic scoliosis [15, 35]. The intramuscular implantation of the pineal body into pinealectomised chickens prevented the development of this experimentally induced scoliosis. The intramuscular implantation of the pineal body into pinealectomised chickens prevented the development of this experimentally induced scoliosis [36].

Their previous studies strongly support the hypothesis that a defect of the neurohormonal system of the pineal body plays a major role in the development of such scoliosis.

In another report, the authors studied the possible role of melatonin deficiency in experimentally induced scoliosis in 90 chickens underwent pinealectomy on the third day after hatching: 30 were treated with serotonin, 30 with melatonin, and 30 received no therapy; the findings suggest that melatonin deficiency contributes to the etiology of this experimental scoliosis, probably by interfering with the normally symmetrical growth of the proprioceptive system involving the paraspinal muscles and the spine [34].

In another study, they found significantly decreased levels of melatonin (actual serum levels with multiple regular overnight samples) in five adolescents with progressive curves, while those with stable curves were similar to controls [37].

Hilibrand, to determine whether melatonin production is decreased in AIS, compared melatonin production in female patients with and without AIS; previous authors have produced experimental scoliosis in chickens after pinealectomy, preventable by administration of melatonin. He suggested that a defect in melatonin synthesis might be involved in the pathogenesis of human idiopathic scoliosis, and using morning and evening urine samples assayed for melatonin tried to confirm differences between adolescent females with idiopathic scoliosis and controls. Although melatonin deficiency may cause scoliosis in the chicken, and contrary to his hypothesis this study suggests that it is not a mechanism in the pathogenesis of AIS in humans [26].

Later Bagnall also measured melatonin levels in adolescents with idiopathic scoliosis, to compare serum melatonin levels in patients with AIS and matched control subjects during the day and in the middle of the night. He was unable to show statistically significant differences in melatonin levels with 2 a.m. and 2 p.m. serum samples; no significant differences were found in serum melatonin levels between experimental and control groups either during the day, when melatonin levels were low, or during the night, when melatonin levels were high. He suggested that melatonin's activity may be through the intermediation of growth hormone [4, 24].

Fagan measured the 24-h urinary melatonin production in patients with AIS, to address the controversy over the role of melatonin deficiency in AIS by measuring total melatonin production over a 24-h period. No significant difference in diurnal, nocturnal, or total urine was found between adolescent patients with idiopathic scoliosis and controls of similar age and gender [16].

Brodner examined the circadian pattern of secretion of melatonin and the urinary excretion of 6-hydroxy-melatonin-sulfate (6-OH-MLTs) in patients with AIS and in age- and gender-matched healthy control subjects; 6-OH-MLTs

is the principal metabolite of melatonin. He studied nine adolescent patients who had been admitted to our department for the surgical correction of scoliosis; there were no statistically significant differences in the secretion of serum melatonin or the excretion of urinary 6-OH-MLTs between the patients and the control group [8].

The hypothesis of melatonin deficiency as a causative factor in the etiology of AIS cannot be supported by the data.

Experimental animal model of scoliosis

Surgical removal of the pineal gland or cutting of the pineal stalk in young chickens produced scoliosis that closely resembled that of AIS in human beings [20]. In 2003, Turgut et al. [63] reviewed the incidence of scoliosis development and found it to vary between 50 and 60% by most researchers, and between 80 and 100% by Machida and Colliard and Rivard. Our recent studies also revealed an incidence of 54% [11, 13]. Because pinealectomy reduces melatonin secretion, low circulating melatonin level has been implicated as a possible cause for scoliosis [31, 40].

In another experiment with rats, two questions were addressed: Does pinealectomy have the same effect in mammals as shown in the chicken? Is the bipedal condition important for the development of the scoliosis? [38]. He studied whether pinealectomy has the same effect in mammals as shown in the chicken and to determine whether the bipedal condition is important for development of scoliosis. The study provides an additional dimension for experimentally induced scoliosis by showing that melatonin deficiency secondary to pinealectomy alone does not produce scoliosis if the quadrupedal condition is maintained. The bipedal condition, such as that in the chicken or human, plays an important role in the development of scoliosis [38].

From a previous series of experimental studies, we have proposed that a deficiency of melatonin may contribute to the etiology of experimental scoliosis in chickens [36] and rats [38, 40] and the bipedal condition may also be an important factor for its development. O'Kelly et al. [48] tried to produce scoliosis following pinealectomy in quadrupedal models (rats and hamsters), but significant spinal curvature was not observed. In 2003, Machida et al. investigated the pathological mechanism of idiopathic scoliosis in experimentally induced scoliosis in rats. A total of 30 rats were divided into three groups: 10 bipedal rats with a sham operation, which served as the control; 10 quadrupedal rats with pinealectomy; and 10 bipedal rats with pinealectomy. Scoliosis developed only in pinealectomized bipedal rats and not in pinealectomized quadrupedal rats. These deformities of lordoscoliosis in pinealectomized bipedal rats were similar to human idiopathic scoliosis. Lordosis or lordotic tendency was sufficient to cause the spine to rotate to the side. The disturbance of equilibrium and other postural mechanisms secondary to a deficiency of melatonin after pinealectomy may promote development of lordoscoliosis with vertebral rotation especially in the bipedal posture [39].

Later Oyama et al. investigated whether bipedal ambulation in C57BL/6J mice has the same effects on spinal deformity as those seen in pinealectomized bipedal rats. The results confirm the observations in rats, and also support our hypothesis that melatonin as well as the bipedal ambulation appear to play a critical pathogenic role in scoliosis in experimental mammals [49].

There are physiologic reasons why the chicken model cannot be simply extrapolated to the human situation [24]. The distribution of melatonin receptors in the chicken is widespread: in the brainstem and in the dorsal gray matter of the signal cord, particularly in the lumbar region. Receptors have even been demonstrated in the chicken ovary and testicle. In humans, there is no extrapineal source of melatonin production. Its actions appear to differ between humans, other mammals, and other vertebrates [4, 8].

Cheung in a new study tried to reproduce these findings in a bipedal nonhuman primate (monkeys) model with surgical pinealectomy and showing a decrease in the melatonin level. None of the 18 pinealectomised monkeys developed scoliosis in a mean follow up period of 28 months. This study proved that the possible etiologic factors producing idiopathic scoliosis in lower animals are different from primates and that findings in lower animals cannot necessarily be extrapolated to human beings [12].

But, in 2009, Gorman and Breden stated that than bipedalism per se, expression of idiopathic-type scoliosis is dependent on normal spinal loading applied along the cranio-caudal axis that interacts with an unknown factor causing the primary curve. In this regard, a comparative biological approach using a simplified teleost model will promote discovery of basic processes integral to idiopathic-type scoliosis in teleosts and humans, and highlight human-specific aspects of the deformity.

Experimental studies

The data regarding human melatonin levels are mixed at best and the melatonin deficiency as a causative factor in the etiology of scoliosis cannot be supported. The biological relevance of melatonin in AIS is controversial. These considerations led to look instead at the melatonin signal transduction pathway because a defect of melatonin signaling activity could generate effects similar to a melatonin deficiency. Moreau et al. studied if there are a dysfunction

of the melatonin-signaling pathway in tissues targeted by this hormone is involved in AIS. For the study, cells isolated from patients with AIS and patients suffering from other type of spinal deformity were compared owing to the property of melatonin to inhibit the accumulation of cAMP-induced by forskolin in normal cells due to the coupling of melatonin receptors to inhibitory guanine nucleotide-binding (Gi) proteins [6, 9, 28, 44, 50, 60, 64]. Experimental data showed a melatonin signaling dysfunction in osteoblasts isolated from 100% of the patients with AIS tested; and among possible causes, abnormalities in Gi proteins (serine residues phosphorylation) function could be involved in AIS pathogenesis [44].

Further investigation led us to conclude such a signaling defect was not caused by a deregulation or mutations of MT1 and MT2 melatonin receptor subtypes as also demonstrated by the works of Morcuende et al. [43] and other reports on the natural and engineered mutations of MT1 or MT2 receptor subtypes [21, 43]. Azeddine et al. focused our attention on the next possible target: G inhibitory proteins (Gi) coupled to both melatonin receptors. The study reconciled the role of melatonin in AIS by demonstrating a melatonin signaling dysfunction occurring in osteoblasts derived from AIS patients, which contrasted with similar cells isolated from healthy subjects. The difference is caused in AIS cells by increased phosphorylation of serine residues affecting the activity of G inhibitory proteins normally associated with melatonin cell surface receptors. These interactions include those between Protein Kinase C delta (PKC D) and MT2 melatonin receptors or PKC D and the receptor for activated Protein C Kinase 1 [3].

Two types of mammalian melatonin receptors have been cloned and characterized, melatonin receptor 1A (MTNR1A) and melatonin receptor 1B (MTNR1B), respectively [65].

Xu Sheng Qiu et al. analyzed, with a genetic study, whether melatonin receptor 1B (MTNR1B) gene polymorphisms are associated with the predisposition and/or disease severity of AIS. The study was carried out in 2-stage case–control analysis: initial screening (472 cases and 304 controls) and separate replication test (342 cases and 347 controls) to confirm results in the screening. The conclusion was that the polymorphisms of the promoter of MTNR1B gene were associated with AIS, but not with the curve severity in AIS patients. This suggested that MTNR1B was an AIS predisposition gene [54].

Same authors in another study tried to determine whether the MTNR1A gene promoter polymorphism is associated with the predisposition and/or disease severity of AIS. A total of 226 AIS girls and 277 normal controls were recruited. The MTNR1A gene was not associated with occurrence or curve severity of AIS and not be involved in the etiopathogenesis [53].

Melatonin exerts its biologic effects primarily through specific, high affinity membrane-band receptors. The diversity of melatonin's response within the body may be attributed to the fact that its receptors are expressed in a wide variety of tissues [67]. Despite many studies on the role of paravertebral muscle in the pathogenesis of scoliosis [18, 19, 23, 41, 42], there is no research on the expression of melatonin receptors in the paravertebral muscles of patients with AIS. Theoretically, asymmetry of expression of melatonin receptors in bilateral paravertebral muscles could influence the balance of growth and development of paravertebral muscle and lead to scoliosis [55]. Melatonin receptor mRNA expression in bilateral paravertebral muscles in AIS, congenital scoliosis, and control were studied. The MT2 mRNA expression on the concave side of paravertebral muscle was higher than that on the convex side both in AIS. The ratio of MT2 mRNA expression on the concave side compared with the convex side in cases with Cobb angle >50° and cases with Cobb angle <50° showed no significant difference. The melatonin receptor expression in bilateral paravertebral muscles in AIS is asymmetric, which may be a secondary change [55].

Several lines of evidence show that melatonin deficiency is closely associated with AIS, although there are still doubts and debates. Some polymorphisms in Tryptophan-Hydroxylase 1 (TPH1) and AANAT, the genes of two critical enzymes involved in melatonin biosynthesis, may contribute to variability of melatonin production in pineal glands.

Other investigators could not find the deficiency of melatonin in AIS patients and viewed that the physiologic melatonin had no effect in preventing scoliosis [5, 16]. Therefore, Wang et al. investigated the relationship between melatonin deficiency and the development of AIS with genetic analysis, and they made a genetic association study of Tryptophan Hydroxylase 1 gene (TPH1) and AANAT gene with AIS. They found that Tryptophan Hydroxylase 1 gene (TPH1) polymorphisms were associated with the occurrence of AIS and is an AIS predisposition gene; AANAT gene polymorphisms were not associated with the occurrence of AIS [66].

Clinical experience

The relationship between pinealectomy, melatonin levels, and development of scoliosis is controversial, and the results from animal studies are contradictory. Melatonin deficiency after a pinealectomy has been investigated in animals; however, in humans, this status can be assessed solely by investigating patients with a tumor originating in the pineal gland. Pineal tumors and related conditions in humans are rare [24, 47, 59, 61]. A retrospective study of scoliosis in children with a variety of pineal lesions may be the closest human model to compare with experimental pinealectomy in animals.

Murata et al. [46] analyzed secretion of melatonin and pituitary hormones in 14 patients with germinoma originating in the pineal or the hypothalamic-neurohypophyseal region. Germinoma cells originating from the pineal gland impair the production of melatonin by pineocytes and consequently induce a permanent melatonin deficiency in those patients, but these patients don't developed idiopathic scoliosis [24].

In another study, the pineal pathology was varied from cysts and epidermoid to teratoma, germinoma, pineocytoma, and glioblastoma. Treatment ranged from biopsy/extirpation to radiotherapy. 38 boys and 10 girls with pineal lesions were identified. Pineal ablation is not related to the development of idiopathic scoliosis in humans [14].

Conclusion

Melatonin is not a simple hormone. It has many complex functions, which are only recently being defined. Model cannot be simply extrapolated to humans. No permanent deficiency of secretion of melatonin occurs in patients with AIS.

The etiology of AIS continues to elude investigators, although research has provided much useful information, which has been presented in this review.

The consensus is that the etiology is multifactorial. With time, continued research will lead to the identification of the various factors involved in the causation of this disorder, which affects so many children and adolescents. Early identification will lead to earlier treatment and perhaps eventually to eradication of the disease itself [32].

Conflict of interest None.

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