REVIEW

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Massage stimulation's effect on melatonin levels in preterm infants via vagal activity

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ABSTRACT

Massage stimulation has been suggested to be used to promote the growth and development of preterm and low birth weight (LBW) infants. Some experts believe that infant massage can help develop the central nervous system, which increases vagal activity, improves hormone secretion, triggers the release of melatonin, and increases its production. Rhythmic endogenous melatonin secretion appears in term infants around 2-3 months of age, whereas preterm infants have delayed melatonin secretion, which persists after correction for 8 to 9 months of gestation. Massage stimulation increases vagal activity, which causes an increase in melatonin. Vagal activity then modulates pineal and extrapineal activity, resulting in melatonin production. Based on scientific evidence, current reviews suggest that massage stimulation can provide health benefits to newborns, particularly preterm infants. This article aims to review that massage stimulation can increase melatonin levels by activating vagal mechanisms.

Keywords: Massage stimulation, melatonin, preterm, vagal activity.
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INTRODUCTION

Low birth weight (LBW) and preterm infant growth and development both improved from massage stimulation as an intervention.[1] According to some studies, baby massage can aid in the maturation of the central nervous system by restoring normal function, increasing the secretion of neuroendocrine substances required for growth, and increasing vagal activity, which helps with the secretion of digestive hormones and can cause the release of melatonin and increase its production.[2–5] Results were noticeably better in the massaged group in a study investigating the impact of massage therapy on the rhythm of melatonin 6-sulphatoxyymelatonin secretion at night. The previous study stated that 14 days of massage resulted in regular sleep, including nocturnal sleep consolidation and reduced REM (rapid eye movement) sleep which was associated with increased melatonin levels.[6,7]

Both rats and infants have been used to demonstrate melatonin's antioxidant, anti-inflammatory, and anti-excitotoxic properties. Experimental evidence demonstrates that melatonin protects against prenatal brain injury in animal models.[8–10] The development of neurological and developmental impairments in preterm newborns is thought to be correlated with long-term endogenous melatonin deficit. For the first 8 to 16 weeks after birth, term infants cannot synthesize melatonin; this period is known as transient melatonin deficit. Babies born preterm do not show the same development pattern as infants at term; 12 weeks after birth, preterm infants do not have a rhythm of melatonin production even after the appropriate gestational age correction, and preterm infants have a slow development of melatonin rhythm.[11–13]

Further research showed that abnormal development in the brain, lung and respiratory systems was most common in preterm infants. Data from earlier studies indicate that this might be connected to a persistent low level of melatonin in the pineal, which can be corrected by melatonin supplementation.[10,14,15] Numerous researchers are examining the positive benefits of melatonin on infant free radical disease, including hypoxia, respiratory distress syndrome, surgical procedures, and sepsis, during the perinatal period, when it is utilized in the treatment of many diseases.[16] Current research focuses on melatonin supplementation in premature infants, but few studies have investigated the increase in endogenous melatonin through massage stimulation. It is known that massage stimulation can increase melatonin through increased vagal activity after massage.

Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) is the most diverse natural biological signal and was described as the first biological signal to appear in the most primitive organisms.[14] The main physiological function of melatonin is related to hormonal properties, though it can also exhibit autocrine or paracrine properties, such as in the retina or gastrointestinal tract.[17] Scientists have reclassified melatonin from being exclusively a hormone to a multi-tasking molecule due to the presence of the essential enzyme melatonin synthesis in many tissues, the presence of melatonin receptors in different tissues, and the discovery of the antioxidant and anti-inflammatory properties of melatonin.[18,19]

Pineal Melatonin is synthesized via polysynaptic innervation pathways, and the stimuli produced are transmitted to the suprachiasmatic nucleus via the retinohypothalamic tract (SCN). The SCN transmits messages to the paraventricular

nucleus (PVN), whose fibers connect with the intermediolateral column of the thoracic spinal cord (IML). IML projects to the superior cervical ganglia (SCG), and postganglionic SCG sympathetic fibers innervate the pinealocytes, releasing norepinephrine specifically during the night's dark phase, triggering the enzymatic conversion of tryptophan to melatonin.[20]

The retina, gastrointestinal tract, skin, platelets, bone marrow, and other organs serve as the pineal gland's secondary sources of the hormone melatonin, which is also released by the pineal gland.[21] The pineal gland is the primary source of melatonin under physiological circumstances. Both noradrenergic and parasympathetic cholinergic fibers innervate the pineal gland.[22] While exposure to light stimulates the sympathetic nervous system and decreases pineal melatonin production, other environmental factors (such as stress or insulin-induced hypoglycemia) that alter the autonomic nervous system or trigger the release of epinephrine from the adrenal medulla may override the inhibitory effects of light and increase melatonin synthesis. In animal models of seizures, there is concrete evidence that acupuncture raises melatonin levels in the pineal gland and subsequently in the blood.[23]

With the discovery of hydroxy indole-O-methyltransferase (HIOMT), now known as N-acetyl serotonin-O-methyltransferase (ASMT), in these tissues, early research suggested the existence of a non-pineal source of retinal-associated melatonin. Vlahakes and Wurtman later showed the presence of ASMT in the mouse Harderian glands in 1972. In addition, melatonin was discovered in the retina, harderian gland, and cerebellum of mice with a pinealectomy. These findings, along with the identification of alkylamine-N-acetyltransferase (AANAT) and ASMT, suggest this network's potential for melatonin synthesis independent of the pineal.[18]

Melatonin is secreted in the gastrointestinal tract by enterochromaffin cells, which contain melatonin precursors (5-oxytryptophane, tryptamine, serotonin, and mexamine).[24] Melatonin was found in enterochromaffin cells of the intestinal mucosa in 1976 by Raikhlin et al., using immunocytochemical analysis. They estimate that there is 400 times more melatonin in the gastrointestinal tract than in the pineal gland and 10–100 times more in plasma. It was first discovered that cycles in food intake, rather than photoperiod, regulated melatonin levels in the gastrointestinal tract. Melatonin was discovered in pinealectomy mice's plasma and urine around the same time.[19] However, fasting caused the melatonin levels in the blood of pinealectomized rats to decline during the day, suggesting that blood melatonin may come from dietary sources. Most melatonin is found in foods, and when consumed, this indoleamine is absorbed by the intestines and reaches the bloodstream. At the same time, melatonin was found in pinealectomy mice's plasma and urine. A putative dietary source of blood melatonin is supported by the fact that daytime melatonin levels in the blood of pinealectomized rats decreased after fasting.[18]

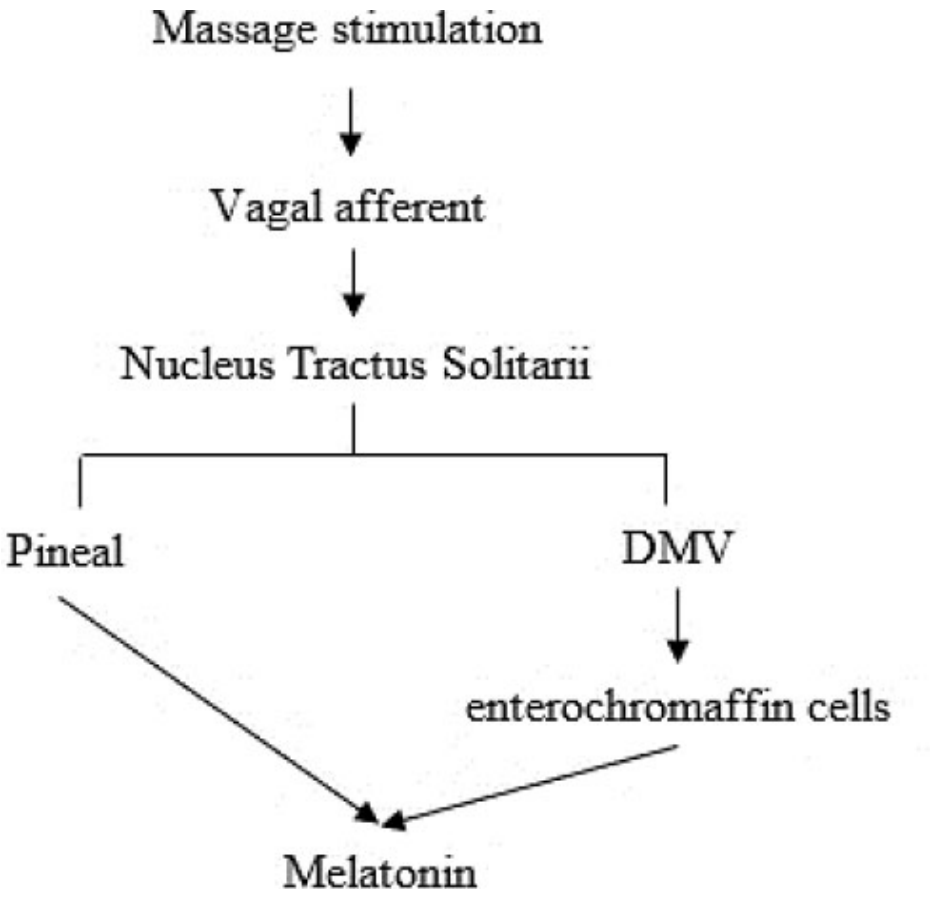

Figure 1. a schematic overview of melatonin modulation by vagus sensory stimulation via massage stimulation.

Melatonin in Newborn

There have been several studies on melatonin secretion in children, but few on melatonin synthesis in term and preterm infants. Melatonin levels in the urine of preterm infants were found to be lower three months after birth.[8,25] Endogenous melatonin begins to secrete rhythmically in term infants between 2-3 months of age, and nightly melatonin levels may revert to normal within 48 hours of delivery. Melatonin secretion is delayed in preterm newborns and continues even after adjustment for 8 to 9 months of gestation.[8] Preterm newborns do not begin to synthesize melatonin until at least 52 weeks following conception, according to some research. Melatonin is delivered to the fetus from the mother via the placenta during its development. The existence of circadian rhythms in the absence of maternal melatonin depends mostly on brain development and relatively little on the environment. Therefore, term infants only exhibit transient melatonin insufficiency, whereas

preterm infants may develop melatonin deficiency. The neurological pathways of the melatonin-secreting brain circuit are not fully developed until after birth, despite the fact that prenatal structures like the suprachiasmatic nucleus and pineal gland perform well.[15,26]

In the first several weeks of life, plasma melatonin levels in term infants are low and exhibit little diurnal change. While the adult circadian pattern of melatonin production is only seen at 2-3 months of life, which is further delayed in preterm infants, there is very little excretion of the metabolite 6-sulfatoxymelatonin during the first six weeks in neonates. The delay in melatonin secretion was two to three times greater and even longer in newborns who were sick at delivery (with a history of fetal distress and pre-eclampsia).[27,28] After hypoxic-ischemic illnesses, both adults and critically ill children produce more endogenous melatonin.[29] Endogenous melatonin levels increased 6 to 15 times in perinatal piglets, a model for asphyxia, during periods of hypoxia-ischemia and reperfusion, indicating that melatonin may protect the fetus and newborn from neurodegenerative diseases even before pineal melatonin synthesis begins.[30]

Numerous clinical research has suggested that melatonin may effectively act as a neuroprotective agent. Infants receiving melatonin for hypoxia as well as those with respiratory distress syndrome and bronchopulmonary dysplasia had lower serum concentrations of oxidative stress markers.[31,32] Melatonin may also have an effect on neocortical functional synaptic plasticity. Melatonin has been shown in adult animals to be neuroprotective in focal cerebral ischemia, and in neonatal mice to reduce white matter cyst development following acute excitotoxic brain injury. Melatonin, an antioxidant with anti-inflammatory and anti-apoptotic properties, can protect the human fetus from free radical brain damage that occurs during times of elevated oxidative stress during pregnancy (such as pregnancies complicated by pre-eclampsia, intrauterine growth restriction, infection, and preterm birth).[33]

Melatonin's antioxidant properties protect the brain from oxidative stress-induced damage. Melatonin administration was associated with significant reductions in microglial and astrocytic activation in a growth retardation model of intrauterine induced by unilateral uterine artery ligation and in a cerebral hypoxia-ischemia model.[34] In response to acute Utero asphyxia, post-asphyxia melatonin therapy reduces apoptotic cell death while attenuating inflammatory markers such as increased production of activated microglia and 8-isoprostane.[35]

Melatonin administration to the mother has been shown to be beneficial for the offspring, in addition to direct administration to the fetus and neonate, which has been associated with neuroprotective effects. Melatonin was shown to reduce ischemia-reperfusion-induced oxidative damage in the brain of preterm fetal rats when given to pregnant rats immediately before an acute ischemic episode and on a regular basis throughout pregnancy.[14] Melatonin was given to ewes as a preventative measure, and both the increase in primary and secondary hydroxyl radicals disappeared. Melatonin administration also prevented increased lipid peroxidation products and brain injury.[36] Melatonin administration to pregnant rats increased superoxide dismutase and glutathione peroxidase activity in the brains of preterm infants and term fetuses. Melatonin's modulatory and neuroprotective action is due to more than just the binding of hydroxyl radicals and the increased activity of intracerebral antioxidant enzymes.[37]

Massage Stimulation

Massage has been used as a recovery therapy since Hippocrates' time. Infant massage has been practiced in China since the twentieth century. Massage stimulation in newborns has been widely used in various populations of premature infants and infants with special needs since its introduction in America in the early 1970s. According to previous study, massage stimulation in infants is a process that uses touch and motion stimuli with various variations of massage movements. Parents or trained medical personnel can perform this baby massage stimulation.[4]

Recent research has shown that the amount of massage given to infants has a significant effect, so a distinction is being made between massage with moderate pressure movements and massage with light pressure movements. Light movement techniques are synonymous with gentle stimulation (gentle human touch). Gentle stimulation has a comfortable effect that can be felt immediately, according to research conducted in 1990.[38,39] There are two major theories about infant massage that have been investigated. The first theory is a protocol developed by Tiffany Field in Miami, which includes a 3–5 minute phase. The first and third parts are touch stimuli with moderate massage movements, while the second part is motion stimulation with upper and lower limb flexion and extension movements. The second theory involves multisensory intervention, which includes hearing, touch, vision, and balance (auditory, tactile, visual, and vestibular).[38,40]

Mothers are taught to massage their infants. Massage by mothers improved their infants' circadian sleep rhythms.[6] Another study asked mothers to massage their newborns for 10 minutes before bedtime every day for a month. The infants' sleep became more organized, as evidenced by longer sleep periods, fewer night waking, and more hours of sleep. This causes mothers to sleep more organized because their infants are sleeping rather than waking them, and it may also be due to the benefits of stimulating pressure on their hands following a massage.[41] In a quasi-experimental study of 45 premature infants admitted to the neonatal intensive care unit (NICU) in Iran, subjects received 15 minutes of field massage per day for 5 days. Sleep status scores improved after receiving a massage. Additionally, after receiving a massage, the scores on wakefulness, restlessness, and motor activity decreased.[42]

According to research on premature baby massage, massage can be used as an additional therapy for premature babies who are being treated in the NICU.[43] Some of the advantages of baby massage include reduced stress, increased weight, stimulation of motor development and brain development, improved sleep patterns, increased immune system, babies returning home from the hospital faster, and babies feeling more comfortable with

touch and closeness to the mother.[38,44,45]

Massage therapy reduced the average gastric residual volume, frequency of vomiting, abdominal circumference, and average gastric residual number in preterm infants in a meta-analysis of 528 reviewed articles investigating the effect of massage on feeding intolerance in preterm infants.[46] A total of 644 infants participated in the meta-analysis of 13 studies on daily weight gain. The study's findings revealed that massaged infants gained slightly more weight.[47] In the meta-analysis research conducted by Wang et al., 2013, 611 articles were taken and 17 studies were eligible. Massage stimulation increased daily weight gain by 5.32 g while decreasing the length of stay by 4.41 days.[48]

Massage stimulation also influences neurodevelopment. In a quasi-experimental study, 66 infants were recruited from two university hospitals with tertiary-level NICUs; 32 infants were massaged by their mothers, and the neuro-developmental outcome (Bayley score) was assessed at 12 months of corrected age. It was discovered in this study that babies who were massaged had higher cognitive scores after 12 months of correction.[48] In a meta-analysis study, three studies used the Bayley infant's mental and motor development scale, two studies used the Test for Infant Motor Performance (TIMP) scale, and one study used psychomotor development to assess infant development. The results of three studies using the Bayley scale with 261 participants revealed that massaged infants' mental development improved by 7.89 points but not their motor development.[47]

Massage Stimulation Physiology

Touch is one of the key elements of engagement between a baby and a caregiver. A haptic perception process allows infants to sense information by moving their hands, fingers, and mouths (based on touch sensation). Unlike other sensory systems, the haptic system can investigate the surroundings. Lifting, holding, squeezing, poking, or playing with one's fingers are all examples of active exploration known as touch, which involves the skin and kinesthetic sensors (movements of muscles and joints).[49]

In their most basic forms, warmth, touch, and light pressure induce relaxation and well-being. This can happen in noninteractive situations like eating and being warm and in interactive situations like closeness, breastfeeding, or sexual interactions. Thick myelinated fibers of the Ab type are involved, as well as a subpopulation of slowly conducting C-fibers. Furthermore, some cutaneous afferents from the ventral side override the spinal cord to reach the NTS's vagal sensory area via the nodose ganglion. In situations of close individual physical contact, this latter type of sensory fiber should be particularly necessary for inducing well-being and relaxation.[40]

When the ventral physical contact between the mother and the newborn is induced, both simple hormonal neurogenic reflexes and more complicated central processes participate in mediating and expressing relaxation and well-being. The activation of cutaneous vagal afferents, which project to the nucleus tractus solitarius, in addition to the typical sensory fibers that mediate the feelings of touch, warmth, and light pressure. At the NTS level, sensory input causes a physiologically calming effect by decreasing sympathetic neuron activity and raising parasympathetic tone. This causes a decrease in blood pressure, an improvement in peripheral circulation, and the activation of the gastrointestinal tract's endocrine system.[40,50]

The second stage involves activating the noradrenaline (NA) route that is directed from the NTS to the hypothalamus. Decreased plasma cortisol levels show that the hypothalamic-pituitary-adrenal (HPA) axis is suppressed as a result. It is interesting to note that preterm infants who had skin-to-skin contact also displayed reduced levels of gastrointestinal hormones regulated by the vagal nerve in addition to a decrease in the hormone cortisol. This demonstrates that central physical contact affects the vagal nerve's activity.[40]

Massage stimulation increases vagal activity

Physical contact between mother and baby will induce hormonal neurogenic reflexes and central mechanisms that play a role in mediating and expressing the baby's sense of comfort and relaxation. Warmth and gentle pressure on the skin also activate vagal afferents, which are then sent to the NTS along with sensory fibers that mediate the touch experience. By boosting parasympathetic tone and decreasing sympathetic nerve activity, sensory stimulation causes a physiologically calming effect in NTS, which lowers blood pressure. The stimulation of baroreceptors and mechanoreceptors, which activates afferent and efferent vagal pathways and activates the parasympathetic nervous systems of the cardiovascular and gastrointestinal systems, is thought to be the potential mechanism in preterm infants that causes a significant increase in body weight in response to tactile-kinesthetic stimulation.[40]

Studies demonstrating that combined tactile/kinesthetic stimulation causes an increase in cardiac vagal activity, which is connected to an increase in stomach motility and can raise preterm birth weight, support this process. Weight growth in preterm infants is mediated through additional pathways by tactile and kinesthetic stimuli.[4] Animal studies show that pressure receptor stimulation activates the vagus, which releases food absorption hormones and ornithine decarboxylase. The randomized research assessed potential underlying mechanisms by measuring gastric motility and sympathetic and parasympathetic nervous system activity in response to massage therapy. Premature neonates who received massage therapy had increased body weight, vagal tone, and gastric motility during and immediately after treatment.[50] These results are in line with research demonstrating that tactile stimulation can increase vagal activity in adults and research showing that preterm infants who receive both tactile and kinesthetic stimulation show higher vagal activity.[4,22]

Baroreceptors and mechanoreceptors in the skin are stimulated by tactile stimulation, which stimulates vagal efferent fibers that innervate the digestive system. Vagal afferent fibers, the primary input source for vagal efferent neurons, innervate baroreceptors and cutaneous mechanoreceptors. These vagal efferent functions mostly as parasympathetic control of the central neuronal system,

including the gastrointestinal system.[4] Vagal activity and newborn development have been linked in numerous studies. Age was positively linked with vagal baseline activity in preterm and term infants, paralleling the typical maturation of the autonomic nervous system. Similarly, infant vagal activity has been linked to the autonomic nervous system's maturity and integrity. Compared to term infants, preterm infants have lower levels of early vagal activity, and infants with lower levels of early vagal activity are more likely to have suboptimal neurodevelopmental outcomes.[50]

A group in Korea measured responses to stimulation, including basic vagal activity, heart rate, and oxygen saturation in the infant massage stimulation study (tactile and kinesthetic stimulation). Preterm infants were randomly assigned to either a massage group or a standard care control group for ten days. In the experimental group, vagal activity was significantly greater after the massage than before, whereas no changes occurred in the control group. The treatment group also spent significantly more time awake and active. Thus, basic vagal activity is associated with increased attention and more structured behavior.[50,51]

Massage stimulation increases melatonin

In a study conducted by Ferber et al, 2002, regarding massage in 21 infants, there was an increase in melatonin in infants who were massaged once a day for 30 minutes for 10 days. The underlying mechanism is thought to be that increased vagal activity after massage causes an increase in melatonin. Massage stimulation in preterm infants helps neurological maturation by the presence of vagal activity which then modulates the parasympathetic nervous system including the pineal and extrapineal glands to synthesize melatonin.[6,52]

The pineal gland is the primary source of melatonin under physiologic conditions. Noradrenergic parasympathetic and cholinergic parasympathetic fibers innervate the pineal gland. Melatonin synthesis occurs via electrical signals that the SCN sends to the pineal gland in the complex autonomic nervous circuit. The activation of melatonin production via b1-adrenergic receptors, results in the release of norepinephrine from post-ganglionic sympathetic nerve terminals to pinealocytes.[53] Environmental factors can alter the autonomic nervous system or induce the adrenal medulla to secrete epinephrine, which overrides light's inhibitory action and accelerates melatonin synthesis. Stimulation of the afferent branch of the vagal nerve is then transmitted to the nucleus solitarius. The limbic and autonomic nervous systems, as well as the pineal gland, are then engaged by neurons in the solitary nucleus via mono- or multisynaptic connections.[52]

Research on the effects of acupuncture on melatonin has shown that acupuncture can stimulate the vagal nerve which then causes an increase in melatonin in adult patients with anxiety disorders.[23] The study induces seizures in rats by injecting benzylpenicillin into the hippocampus, followed by electroacupuncture. After ten biweekly acupuncture sessions, acupuncture increased nighttime levels of the urinary melatonin metabolite 6-sulfatoxymelatonin (a6MTs). Furthermore, After a 5-week intervention of two acupuncture procedures per week, nocturnal levels for the same urinary metabolite were observed to be higher.[22]

In addition to pineal modulation, vagal nerve stimulation can also increase melatonin by modulating extrapineal melatonin secretion. Melatonin is secreted from several different places in addition to the pineal gland, including the retina, gastrointestinal system, bone marrow, skin, kidneys, ovaries, testes, and circulating leukocytes. These extrapineal sources of melatonin not only contain a significant amount of the hormone overall, but some of them also contain melatonin in high concentrations, such as those found in the gastrointestinal tract and bone marrow. Both sources have melatonin concentrations that are 2 to 3 times higher than the blood's melatonin level and more than 400 times higher than the pineal glands. The release of melatonin from this extrapineal source is not regulated by the photoperiod since it is innervated by the vegetative nervous system.[53-54]

Patients with neurological disorders characterized by tetraplegia or lesions of the cervical spinal cord or superior cervical ganglion and sympathetic nerves, as well as patients undergoing sympathectomy surgery or receiving beta-blocker treatment, exhibit very low levels of melatonin production. Extrapineal melatonin synthesis occurs via the same metabolic pathway as described in the pineal gland, but it is not regulated by photoperiod in some tissues, such as the retina, where there is generally no day and night variation.[14,55]

The effect of vagal stimulation on the gastrointestinal tract is to increase the endocrine system of enterochromaffin. Vagal efferent stimulation of enterochromaffin results in the release of serotonin and melatonin. The response of the proximal duodenal enterochromaffin cells to nerve stimulation is to release melatonin, which binds to the MT2 receptor. The gastrointestinal mucosa's enterochromaffin cells can release melatonin either directly into blood vessels or diffusely to reach the outer layers of smooth muscle.[56] Melatonin is produced in the lower gastrointestinal system and is what causes the rise in blood melatonin after eating, according to pig research.[18,57]

Non-invasive stimulation approaches have been investigated in addition to studies that directly stimulate structures in the pineal sympathetic innervation pathway. The researchers looked at how unilateral transcutaneous vagus auricular nerve stimulation affected pineal melatonin levels in Zucker lean and obese diabetic Zucker rats (ZDO).[23] Notably, the researchers investigated the impact of trans auricular vagus nerve stimulation (taVNS) on pinealectomised ZDO rats and discovered acute rises in plasma melatonin levels comparable to intact ZDO rats. A year later, using bilateral taVNS, similar results were obtained. Because melatonin levels remained elevated even after the pineal gland was removed, this suggests that vagus nerve stimulation stimulates melatonin secretion from extrapineal sites rather than the gland itself (Figure 1). This could be due to the 20% of the circulating melatonin being produced extrapineally.[58]

CONCLUSION

Increased vagal activity during massage stimulation can increase melatonin levels. Baroreceptors and mechanoreceptors in

the skin can be stimulated by massage to affect the vagal efferent fibers that innervate the digestive and pineal systems. Skin baroreceptors and mechanoreceptors are innervated by vagal afferent fibers, which are the primary afferent input to neurons that give rise to vagal efferent fibers that provide the majority of the parasympathetic control of the pineal and gastrointestinal systems. Thus, increased vagal activity may underlie the effect of massage therapy on increasing melatonin levels. Therefore, massage stimulation is recommended for all growing preterm.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTION

All author had contributed for manuscript writing and agreed for the final version of the manuscript for publication.

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