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Breast Feeding and Melatonin: Implications for Improving Perinatal Health

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Abstract

The biological underpinnings that drive the plethora of breastfeeding benefits over formula-feeding is an area of intense research, given the cognitive and emotional benefits as well as the offsetting of many childhood- and adult-onset medical conditions that breast-feeding provides. In this article, we review the research on the role of melatonin in driving some of these breastfeeding benefits. Melatonin is a powerful antioxidant, anti-inflammatory and antinociceptive as well as optimizing mitochondrial function. Melatonin is produced by the placenta and, upon parturition, maternal melatonin is passed to the infant upon breastfeeding with higher levels in night-time breast milk. As such, some of the benefits of breastfeeding may be mediated by the higher levels of maternal circulating night-time melatonin, allowing for circadian and antioxidant effects, as well as promoting the immune and mitochondrial regulatory aspects of melatonin; these actions may positively modulate infant development. Herein, it is proposed that some of the benefits of breastfeeding may be mediated by melatonin's regulation of the infant's gut microbiota and immune responses. As such, melatonin is likely to contribute to the early developmental processes that affect the susceptibility to a range of adult onset conditions. Early research on animal models has shown promising results for the regulatory role of melatonin.

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Introduction

Although highly recommended, breastfeeding rates vary across countries, with 30% of USA mothers exclusively breastfeeding, and a further 30% partially breastfeeding [1]. Consequently, the majority of women in the USA and most western countries predominantly use formula-feeding, with a number of negative impacts, as compared to breastfeeding, for the developing infant.

Breastfeeding has many benefits, including: lower rates of hospital admissions for respiratory infections [2]; lower hospital admissions for neonatal fever [3]; decreased levels of childhood obesity at age 2 years [4]; decreased levels of offspring cancer [5], as well as a range of other medical conditions, including type 1 and 2 diabetes, obesity, hypertension, cardiovascular disease and hyperlipidemia [6]. Such benefits to infant outcome result in substantial financial benefits to countries, at least in part mediated by the improvements in health, cognition and IQ that breastfeeding confers [7,8].

Such benefits are likely to impact on the susceptibility to a number of other adult onset conditions, including Alzheimer's disease and depression [9,10], suggesting that breastfeeding may decrease the susceptibility to Alzheimer's disease in the offspring, as well as in the mother [11]. Such offspring benefits are likely to be partly mediated via the positive impacts of breastfeeding on offspring obesity and metabolic dysregulation [12]. Breastfeeding may also confer some psychoneuroimmunological benefits to mothers ([13].

Biological Benefits of Breastfeeding

The biological components and processes that drive the benefits of breastfeeding are the subject of intense investigation. Some of these benefits are thought to be mediated by the effects of immune-associated factors in the maternal milk, which may be modulated by levels of maternal stress [14]. These immune-linked factors include cytokines, chemokines, whole cells, immunoglobulins, various growth factors, lysozyme, lactoferrin, oligosaccharides and microbiota [15,16]. Such breast milk derived growth factors, cytokines and chemokines, are proposed to have important roles in the infant's gastrointestinal and immune development [17,18], with these factors contributing to the immune influence on the maturation and integrity of the gastrointestinal tract, including in part, via the regulation of the infant's inflammatory responses [19]. Classical T helper 1 (Th1) cytokines are pro-inflammatory and include interleukin (IL)-1β, IL-18 and gamma-interferon (IFNγ), whilst classical Th2 cytokines, such as IL-10, are generally anti-inflammatory. The levels and balance of such cytokines in breast milk will modulate many aspects of infant development [19]. Chemokines are also important players in the regulation of immune responses, primarily via their capacity to chemo attract an array of different immune cells, including neutrophils, monocytes, and lymphocytes. An array of chemokines are found in breast milk [20].

Cytokines, chemokines, and growth factors, such as brain-derived neurotrophic factor (BDNF), are thought to prime intestinal immune cells, contribute to angiogenesis, help develop the intestinal epithelial barrier function, and generally suppress inflammation [21]. Human milk has significant levels of secreted immunoglobulin A (IgA), which plays an important role in the gut's mucosal immune defence, with infant gut microbiota eventually inducing secreted (s)IgA as the infant's immune system develops [22]. This may be of some importance as sIgA may have a significant role in the selection of 'good' and 'bad' gut microbiota [23]. As such, breastfeeding, via a variety of factors, impacts on the development of the infant's immune system, including in the regulation of the gut and gut microbiota. This is likely to be of crucial relevance to infant brain development, given the growing body of data showing the importance of the gut-brain axis to an array of psychiatric and neurodegenerative conditions [24-26]. The impacts of breastfeeding on such processes may be even more important in premature infants, where only limited in utero development of such physiological processes occurs [22].

The neonate is highly dependent on the innate immune system in the first 6 months, prior to the full maturation of the adaptive immune system, which is also compensated for by increased activity of gamma-delta T cells [27,28]. As such, neonates and early infancy is associated with a distinct pattern of immune responses, including in the regulation of the intestine. Consequently, a fuller protection requires human milk. Complex carbohydrates and glycans are rich in human milk and, being prebiotics, increase the gut colonization by probiotic bacteria. Glycans are therefore part of an array of milk component factors that drive the nature of the infants immune response, particularly via effects in the gut [21]. Early developmental influences on gut microbiota are being increasingly recognized as important for the susceptibility to adult onset disorders, at least in part by subtle changes in the nature of the

immune response that influence the development of an array of different tissues and organs, at least in part driven by increased gut permeability and the leakage of gut microbiota and/or tiny fragments of partially digested food, which lead to low level systemic inflammation [29]. Some of the benefits of breastfeeding may be mediated by elevated infant night-time melatonin [30].

Melatonergic Pathways

Melatonin (N-acetyl-5-methoxytryptamine) is a methoxyindole that is present in most plants and animals, with recent work suggesting that it may be expressed in all mitochondria-containing cells [31,32]. In mammals, melatonin has been primarily studied in the context of its night-time release by the pineal gland, which gives it a powerful role in driving circadian rhythms [33]. However, as reflected by its possible expression in all mitochondria-containing cells, melatonin has been shown to be released by a growing number of cells, including placental trophoblasts, astrocytes, immune cells and enterochromaffin gut cells [34,35]. In fact, melatonin production by the gut can be up to 400-fold greater than the amount produced by the pineal gland [36]. As well as a role in circadian regulation, melatonin is also a powerful antioxidant, anti-inflammatory and antinociceptive, contributing to its crucial role as an immune regulator and optimizer of mitochondrial functioning [37]. As such, melatonin is a key regulator of immune defenses and cellular energy processes [38,39], which requires investigation as to the relevance of melatonin's impact on breastmilk constituents. Melatonin also induces endogenous antioxidant enzymes [40], with these increases being mediated via melatonins induction of the transcription factor NF-E2-related factor 2 (Nrf2) [32,41]. Many melatonin effects seem to be via its regulation of homeostatic processes, contributing to its clinical utility across a wide range of medical conditions.

N-acetylserotonin (NAS) is the precursor of melatonin and is also a powerful antioxidant, immune regulator and modulator of mitochondria functioning [42]. NAS is also a BDNF mimic, via its activation of the BDNF receptor, tyrosine kinase receptor-B (TrKB) [43]. The synthesis of NAS and melatonin are highly dependent on serotonin availability, given that serotonin is the immediate precursor of NAS. Serotonin is converted to NAS by the enzyme, arylalkylamine N-acetyltransferase (AANAT), with hydroxyindole O-methyltransferase (HIOMT), (also referred to as acetylserotonin methyltransferase), converting NAS to melatonin [44]. The melatonergic pathways are therefore highly dependent on tryptophan availability for serotonin synthesis, with lower levels of serotonin, as in depressive episodes or in the course of immune activation, restricting NAS and melatonin synthesis. Both melatonin and NAS are amphiphilic, readily diffusing through the extracellular space and across cell membranes and organelles. Consequently, neither is entirely dependent on plasma membrane receptors for their cellular effects [45].

Many of the melatonin metabolites also have anti-inflammatory and antioxidative, as well as immune system modulatory effects, as previously summarized [41]. As a consequence, melatonergic pathway activation produces an array of antioxidants, including Nrf2-induced endogenous antioxidant enzymes, with implications for a host of medical conditions [46], as well as in pregnancy and infancy [47].

With the early developmental period being increasingly recognized as an important factor in the etiology of a host of medical conditions, it is of note that single nucleotide polymorphisms (SNP) in melatonin receptors (MT1r and MT2r) as well as the melatonergic pathway enzymes increase the susceptibility to a wide array of medical conditions, including depression [48], cancer [49,50], multiple sclerosis [51,52] and bipolar disorder [53]. The role of early developmental melatonin in the modulation of the epigenetic processes that contribute to the risk of such medical conditions is an area of intense investigation, including as to the role of gut microbiota, gut dysbiosis, gut permeability and bacterial translocation in this early developmental etiology [29].

Many biological factors, including those in breast milk such as tryptophan and omega-3 polyunsaturated fatty acids, act to regulate serotonin and therefore melatonin availability, including via the regulation of monoamine oxidase (MAO), which degrades monoamines such as serotonin [54,55]. Chronic stress-induced hypothalamus-pituitary-adrenal (HPA) axis activation, leading to cortisol production, can also increase MAO, as well as increasing tryptophan 2,3-dioxygenase (TDO), which drives tryptophan to tryptophan catabolite (TRYCAT) synthesis and away from serotonin and melatonin synthesis [29]. As breastfeeding can limit infant HPA axis cortisol responses [56], this is another means by which breastfeeding is likely to optimize the infant's serotonin and melatonin availability.

Overall, melatonin has many effects, including being: an optimizer of mitochondria functioning; a powerful antioxidant and inducer of endogenous antioxidants; an anti-inflammatory; a regulator of immune and glial cell reactivity; as well as being a circadian rhythm regulator [33,36,37,40,41]. The melatonergic pathway is present in many cell types and tissues/organs, especially in the gut [36]. All of these factors are crucial over the course of infancy, suggesting that variations in the presence of melatonin in breast and formula feeding is likely of some importance.

Melatonin: Perinatal and Infancy

Melatonin is highly produced, in a non-circadian fashion, by the placenta, leading to the maintenance of high melatonin levels in the pregnant mother and foetus [57,58]. Upon birth, such continuous melatonin provision ceases, for both the mother and the newborn. However, a growing body of data has highlighted the utility of melatonin during the first year of life.

Melatonin increases survival in struggling premature infants, with melatonin being shown to have adjunctive efficacy in the management of neonatal sepsis [59,60]. Melatonin also has utility in the management of perinatal asphyxia [61], with melatonin decreasing levels of subsequent seizures and white matter damage, as well as preventing the expression of indicants of developmental delay at 6 month follow up [62]. Increased levels of melatonin are evident in labor-associated birth (versus caesarean section), which is suggested to decrease the oxidant challenge in the neonate [63]. As such, the increasing placental melatonin production over the course of pregnancy and its efficacy in a number of critical neonatal conditions suggests that melatonin is likely to have utility and a high safety profile in the perinatal period [59]. Further investigation of this area is, however, urgently warranted.

Melatonin and Breastfeeding

Given the night-time rise in pineal melatonin synthesis levels, there is an increase in circulating melatonin levels in the mother. Consequently, breastfeeding during the night results in the transfer of melatonin, NAS and melatonin metabolites to the suckling infant [30]. As such, night-time breastfeeding results in differences in the contents of the mother' milk, with a small sample study showing increased night-time melatonin in the milk of preterm mothers, which correlated with the circulating levels of the antioxidant enzyme, glutathione peroxidase [64]. It is not unlikely that such melatonin-containing night-time breast milk will have an impact on the entrainment of the infant's circadian rhythms, as well as providing powerful antioxidant, anti-inflammatory and immune regulatory effects. It is also likely that melatonin will impact on the maturation of gut microbiota and gut permeability, thereby suggesting possible impacts on how such gut microbiota influence infant development [65], including via modulation of the circadian rhythm and the patterning of circadian genes expressed. Circadian genes are important regulators of immune system responses [66].

In the central nervous system (CNS), NAS, melatonin and its antioxidant metabolites may all increase levels of neurogenesis, as shown in a wide range of preclinical studies [67]. As such, it requires investigation as to whether the positive effects of breastfeeding on cognition and IQ [68] are mediated, at least in part, via the melatonin contained in the night-time feed. Melatonin may also have impacts on many other aspects of development [69], including via its regulation of circadian genes [70].

To ensure maximal levels of melatonin in breast milk at night, the mother should sleep in a dark room and, likewise, breast feed under very subdued lighting [71]. Avoiding blue wavelengths of light, which are present in polychromatic light sources, is of special importance since these light wavelengths are maximally inhibitory to pineal melatonin synthesis [71].

Melatonin also regulates many of the milk-associated factors thought to drive the biological benefits of breastfeeding [72,73], and is likely to attenuate the effects of maternal stress on such milk-derived factors [74]. Maternal melatonin also has a role in the regulation of the maternal production of such proposed beneficial factors [73], indicating that it may also regulate the levels of the infant's endogenous synthesis of these factors. As to whether the circadian regulation of such milk-derived beneficial factors is driven by melatonin in the night-time breast milk requires investigation.

Overall, the role of melatonin in the night-time breastfeed has been significantly under-investigated.

Given the lack of melatonin in formula feeds, it could be argued that this is a significant deviation from the evolutionary driven forces that led to the night-time feed containing melatonin. It also requires investigation as to whether variations in maternal melatonin modulate the circadian, antioxidant and immune-associated beneficial factors in the night-time breast feed over the course of normal development.

Consideration should be given to the possibility of supplementing infant formula for use at night-time feeding with melatonin. Thus, there could be both daytime and night-time formulas, differing in their melatonin levels. Indeed, one author (RJR) of the current report was asked about this possibility by a major producer of infant formula.

The utility of melatonin in early infancy, however, may be especially relevant in premature infants. It is common to add protein, fat and carbohydrate fortifiers to breastmilk for premature infants [75]. Given that melatonin is highly produced by the placenta [35], it is highly likely that premature infants may gain from the addition of melatonin to all feeds, and not solely to night-time feeds. There is a growing utilization of banked human donor milk for premature babies, which is usually pasteurized by the Holder method [72]. As to whether such milk should be fortified with melatonin, as mentioned above, either as a whole or in a sub-sample solely for night-time feeding has still to be investigated. It should also be noted that very low birthweight infants often have little access to breastfeeding [76] and may also benefit from the addition of melatonin to human donor milk or formula feed, as would be the case in situations where the mother is unable to breast feed.

Preclinical studies indicate that providing the dam with melatonin in pregnancy prevents offspring postnatal corticosteroid-induced hypertension [77]. This suggests that the addition of melatonin to human donor milk for premature infants may have utility in decreasing the effects of corticosteroids given to women at increased risk of a preterm birth, including the reduced levels of cognition and increased risk of hypertension that are linked to corticosteroid-associated preterm births [78]. Placental melatonin is decreased in preeclampsia, which is significantly associated with intrauterine growth restriction and preterm birth [35]. This may be of particular relevance in women with preexisting diabetes and nephropathy or microalbuminuria, where complications such as severe preeclampsia and preterm delivery are still common [79]. An SNP in the melatonin receptor, MT2, is a genetic susceptibility factor for gestational diabetes [80], with preclinical studies showing that melatonin decreases the increased risk of neural tube defects in gestational diabetes [81]. However, it should be noted that it still requires thorough investigation as to the utility and safety of exogenous melatonin during human pregnancy, although there is increasing evidence that melatonin may be beneficial for ensuring successful pregnancy [82]. However, it should be noted that an array of medical conditions with a suspected early developmental etiology, such as hypertension and obesity, were evident prior to the development of formula feed in the nineteenth century, indicating that such disorders are multifactorial and not simply due to decreased melatonin provision in early infancy.

Future Directions

General practitioners (GPs) need to improve their knowledge regarding breastfeeding, as their support of breastfeeding significantly increases its rates [83]. Perinatologists, neonatologists and pediatricians, as well as GPs also need to improve their knowledge regarding the effects of melatonin, given that little is known other than in regard to its utility in management of 'jet lag'. In this context, it also of note that the benefits of breastfeeding extend to the mother, with psychoneuroimmunological benefits [13], including alterations in pro-inflammatory cytokines and altered stress hormone responses, which are thought to contribute to a decreased risk of Alzheimer's disease [11].

There a number of gaps in the available data on the utility of melatonin in humans, including its use during the perinatal period and infancy. However, an extensive preclinical and limited human literature indicate that there are many potential benefits of perinatal and postnatal melatonin that are likely to be relevant not only to the optimization of infant development, but also for the susceptibility to adult onset disorders [77,78]. As such, many of the benefits of breastfeeding would seem to be mimicked by the effects of melatonin. Much of the data on melatonin has been derived from preclinical studies and is in need of careful investigation in human studies.

Breastfeeding is consistently associated with increased levels of cognition and IQ in the offspring [68]

and it requires investigation as to whether such positive cognitive benefits are mediated, perhaps in part, by the melatonin contained in the night-time feed or its effects on the content of breast milk or indeed from their interaction.

Similarly, it requires investigation as to the relevance of melatonin in breast milk for the many other adult onset conditions that are positively regulated by breastfeeding, including: decreased hospital admissions for respiratory infections [2] and neonatal fever [3]; lower levels of childhood obesity [4]; and lower rates of offspring cancer [5]; as well as a range of other medical conditions, including type 1 and 2 diabetes, obesity, hypertension, cardiovascular disease and hyperlipidemia [6]. Melatonin is known to positively modulate all of these medical conditions [70], suggesting possible beneficial effects prenatally and in infancy.

Many of the benefits of melatonin may ultimately be mediated by its positive effects on mitochondrial functioning [84,85], in turn optimizing cellular functioning, including that of immune cells [86,87]. Many of the benefits of melatonin are mediated via its induction of the alpha-7 acetylcholine receptor (a7nAChR), which has cognitive enhancing effects [88], as well as being a significant immune [89] and mitochondrial [90] regulator. It is unknown as to whether any benefits of breastfeeding are mediated via the increased levels and activation of the a7nAChR. This is in need of investigation, especially given the role of the a7nAChR in the regulation of gut permeability [91].

It should also be noted that the constituents of breast milk are highly variable between individuals, with postnatal age and gestational length (preterm versus term) being important predictors of breast milk content [92]. It will be important to investigate how variable this is across day- versus night-time breast milk constituents, and as to whether variations in maternal and/or non-circadian melatonin contribute to such individual variance.

Given that the night-time breast feed is likely to have its content determined by circadian factors and that melatonin is significant circadian regulator, there is a need to study the influence of the administration of melatonin to the mother, on the content and benefits of breast milk. Cesarean section and other pro-inflammatory events in the mother are likely to drastically decrease the levels of maternal pineal gland melatonin production [93]. Should melatonin benefits in breast milk and/or its influence on the contents of breast milk be prevented by such maternal pro-inflammatory processes, primarily driven by increased levels of pro-inflammatory cytokines, it is likely that the use of melatonin by the mother at night or its addition to breast milk or formula feed would compensate its transient cessation. However, it should be emphasized that supplementation with melatonin should not occur until the content of breastmilk has been thoroughly examined to identify the amount of melatonin that is being transferred during feeding, and the subsequent melatonin serum levels of infants. A safe level of any melatonin supplement for an infant has also yet to be determined.

SIDS

Sudden infant death syndrome (SIDS) is most common between the ages of 1-6 months, the period of time when infant levels of circulating melatonin are often still to develop a circadian rhythm [94,95]. A recent review and meta-analysis found breastfeeding to decrease the risk of SIDS [96,97]. The biological underpinnings of such protection afforded by breastfeeding are still to be determined. A Canadian study indicates that up to 41.4% of gastrointestinal infections, 26.1% of hospitalizations from lower respiratory tract infections and 24.6% of SIDS cases could be prevented in native Canadian infants if they received any breastfeeding [98]. Given the beneficial effects of melatonin against oxidative stress [99], mitochondrial functioning [32], infections [100], gut microbiota/permeability [29] and diaphragm muscle fatigue [101], which are all suspected to contribute to SIDS pathophysiology [102-106], it requires investigation as to whether the efficacy of breastfeeding is mediated, to some degree, by melatonin. If so, this could suggest that the addition of melatonin to the night-time formula feed would lower SIDS cases, as may its administration to the mother following cesarean section. The decreased levels of melatonin (and its precursor serotonin) in SIDS [107] is partly mediated by microglia activation [108] and is prevented by melatonin [109], suggesting that melatonin may well lower the incidence of SIDS and strengthens the case for melatonin inclusion in night-time formula feeds as well as its optimization in breast milk. The role of melatonin in SIDS, including as to whether melatonin would have any efficacy in preventing SIDS cases, is in urgent need of investigation.

Conclusions

The biological underpinnings of the many benefits of breastfeeding over formula feeding is an important and active area of research. The research reviewed above suggests that variations in melatonin may well be an important aspect of the many breastfeeding benefits. As indicated, there are a number of easily achievable investigations that would clarify the role of melatonin in breast milk, including in the regulation of gut microbiota and in the early developmental processes that bias the susceptibility to a range of adult onset conditions. Given that the four major pathophysiological processes associated with SIDS are inhibited by melatonin, it will be important to determine as to whether melatonin in breast milk, or its addition to a night-time formula feed, decreases the incidence of SIDS.

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