Review

George Anderson*, Cathy Vaillancourt, Michael Maes and Russel J. Reiter

Breastfeeding and the gut-brain axis: is there a role for melatonin?

DOI 10.1515/bmc-2017-0009
Received March 2, 2017; accepted June 5, 2017

Abstract: The benefits of breastfeeding over formula feed are widely appreciated. However, for many mothers breastfeeding is not possible, highlighting the need for a significant improvement in the contents of formula feed. In this article, the overlooked role of melatonin and the melatonergic pathways in breast milk and in the regulation of wider breast milk components are reviewed. There is a growing appreciation that the benefits of breastfeeding are mediated by its effects in the infant gut, with consequences for the development of the gut-brain axis and the immune system. The melatonergic pathways are intimately associated with highly researched processes in the gut, gut microbiome and gut-brain axis. As the melatonergic pathways are dependent on the levels of serotonin availability as a necessary precursor, decreased melatonin is linked to depression and depression-associated disorders. The association of breastfeeding and the gut-brain axis with a host of medical conditions may be mediated by their regulation of processes that modulate depression susceptibility. The biological underpinnings of depression include increased levels of pro-inflammatory cytokines, oxidative stress, kynurenine pathway activity and dysregulation of the hypothalamic-pituitary adrenal axis, all of which can decrease melatonergic pathway activity. The inclusion of the melatonergic pathways in the biological interactions of breast milk and gut development has significant theoretical and treatment implications, as well as being important to the prevention of a host of infant-, child- and adult-onset medical conditions.

***Corresponding author: George Anderson,** CRC Scotland & London, Eccleston Square, London SWIV 1PG, UK,
e-mail: anderson.george@rocketmail.com
Cathy Vaillancourt: INRS-Armand-Frappier Institute and Center for Interdisciplinary Research on Well-Being, Health, Society and Environment (CINBIOSE), Laval, QC, Canada
Michael Maes: Deakin University, Department of Psychiatry, Geelong, Australia
Russel J. Reiter: UT Health Science Centre, San Antonio, TX, USA

Keywords: breastfeeding; breast milk components; gut-brain axis; gut microbiota; gut permeability; infancy; melatonin; sudden infant death syndrome.

Introduction

Breastfeeding is highly recommended, with benefits for both infant and mother. However, breastfeeding rates are variable across countries as well as across different ethnic groups within a country (1). In the USA, 30% of mothers exclusively breastfeed, with another 30% partially breastfeeding (2). Most mothers in the USA, and most Western countries, predominantly use formula feed. This has a number of medical consequences for the susceptibility of the infant to an array of medical conditions and, consequently, significant economic implications (3).

Breastfeeding affords protection against a wide variety of medical conditions that may emerge at different time-points over the lifespan, including hospital admissions for respiratory infections and neonatal fever (4, 5), offspring childhood obesity and cancer (6), sudden infant death syndrome (SIDS) (7), as well as an array of other medical conditions, such as cardiovascular disease, obesity, hyperlipidemia, hypertension and types 1 and 2 diabetes (8). Such an array of benefits seem partly mediated by the impacts of breastfeeding on processes regulating metabolism and thereby on the risk of offspring metabolic dysregulation and obesity (9). Consequently, given that metabolic dysregulation increases the risk of a host of adult-onset medical conditions, breastfeeding would be expected to decrease the risk of Alzheimer's disease and other neurodegenerative disorders (10). Metabolic dysregulation is also strongly associated with an increased risk of depression (10), with breastfeeding decreasing the risk of adolescent depression and wider psychopathology (11). It is also of note that the pathophysiological changes associated with depression overlap with, and may act to prime, the pathophysiological processes evident in Alzheimer's disease and other medical conditions (12). As such, the benefits of breastfeeding may be mediating alterations in the offspring's metabolism

that contributes to depression, which, in turn, may interact with susceptibility genes and other epigenetic developmental processes to determine the risk of a host of medical conditions over the lifespan. However, it should be noted that these are indirect links, although based on current evidence, have still to be investigated.

In this article, the benefits of breastfeeding are reviewed, particularly in the context of the impact of breast milk in the infant gut, and thereby on the development of the gut-brain axis and the immune system. The role of the melatonergic pathways in these processes are highlighted. Firstly, the gut-brain axis and the melatonergic pathways are overviewed.

The gut-brain axis

Enhanced levels of gut permeability and associated alterations in gut microbiota are linked to the etiology and/or course of an array of medical conditions, including multiple sclerosis (13), Parkinson's disease (12), dementia (14), schizophrenia (15), bipolar disorder (16), the autistic spectrum (17) and depression (18). As noted above, the high rates of comorbid depression, often prior to symptom exacerbation, in these conditions suggests that gut-brain axis alterations may mediate some of their associations with such an array of medical presentations via raised levels of depression.

The general model proposed to drive these wider impacts of altered gut microbiota and increased gut permeability emphasizes the importance of immune-inflammatory processes. Many of the effects of immune-inflammatory processes are driven by increased levels of pro-inflammatory cytokines. Such cytokines induce indoleamine 2,3-dioxygenase (IDO), which takes tryptophan away from the serotonin and melatonin pathways by driving it down to the kynurenine pathway, including to the synthesis of tryptophan catabolites (TRYCATs) (19). An array of different TRYCATs can be produced, including immune and neuroregulatory TRYCATs, such as the excitotoxic quinolinic acid and the more protective kynurenic acid. Peripheral increases in such TRYCATs lead to increased levels of somatization (20) as well as increasing the availability for kynurenine and kynurenic acid to be taken up over the blood-brain barrier, in turn altering neuroregulation centrally (21). Such increases in IDO, as well as the stress hormone cortisol-induced tryptophan 2,3-dioxygenase (TDO), not only increase peripheral and central TRYCATs, but, by decreasing serotonin availability, also decrease the activity of the melatonergic pathway, which requires serotonin as a precursor (22). Alterations in the melatonergic pathways will be covered in more detail below. Suffice to note that gut permeability changes may not only regulate immune-inflammatory responses, but also have central effects via neuroregulatory TRYCATs and the inhibition of the serotonergic and melatonergic pathways.

Increased levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS) are intimately associated with enhanced levels of immune-inflammatory activity, with ROS and RNS contributing to driving the necessary plasticity changes in response to inflammation. However, prolonged ROS and RNS, in the absence of adequate or depleted endogenous antioxidants, lead to an increase in oxidative and nitrosative stress (O&NS), including lipid peroxidation-mediated damage to membranes and oxidative damage of DNA. DNA damage induces the DNA repair system, including poly(ADP-ribose) polymerase-1, which by depleting nicotinamide will decrease sirtuin levels, with consequent impacts on mitochondrial functioning (23). Recent work proposes that mitochondria may be a significant hub for interactions among TRYCATs, melatonergic pathways, alpha 7 nicotinic receptors (a7nAChR) and the dioxin receptor, the aryl hydrocarbon receptor (24). As such, these are key effector processes that may mediate the association of alterations in gut microbiota and gut permeability with a wide array of pathophysiological processes that occur across a host of medical conditions. Ultimately, it would seem that breastfeeding, at least in part via the gut, will modulate such processes.

Melatonergic pathways

Methoxyindole N-acetyl-5-methoxytryptamine (melatonin) is present in most plants and animals. Melatonin has been most widely investigated following its night-time release by the mammalian pineal gland, a process that intimately involves melatonin in circadian rhythm regulation (25). However, melatonin is produced by an array of cell types, including astrocytes, placental trophoblasts, immune cells and enterochromaffin gut cells (26–29). Following a meal, gut melatonin synthesis can be 400-fold that of the pineal gland night-time peak release (30). Melatonin has been proposed to be produced in all mitochondria-containing cells (31), with recent work suggesting that melatonin may be produced within mitochondria (32). Melatonin synthesis is, therefore, widespread.

Melatonin has a number of significant effects, being an antioxidant, anti-inflammatory, antinociceptive and immune regulator, as well as optimizing mitochondrial functioning and inducing endogenous antioxidants (33). Such effects allow melatonin to have clinical efficacy across a wide diversity of medical conditions, including neurodegenerative and psychiatric disorders (34) as well as in the management of cancers (35).

The synthesis of melatonin requires tryptophan to be converted to serotonin by tryptophan hydroxylase, with serotonin then converted by arylalkylamine N-acetyltransferase to N-acetylserotonin (NAS), which is enzymatically converted to melatonin by hydroxyindole O-methyltransferase. NAS and the metabolites of melatonin are also powerful antioxidants, with NAS also a brain-derived neurotrophic factor (BDNF) mimic via its activation of the BDNF receptor tyrosine kinase receptor-B (36). Both melatonin and NAS are amphiphilic, being able to diffuse across the extracellular space and over cell membranes, allowing them to have receptor-independent effects. Given that melatonergic pathway activation is highly dependent on serotonin availability, factors that drive tryptophan to TRYCATs production, such as stress and immune-activated TDO and IDO, will decrease melatonergic pathway activity. Likewise, factors that enhance serotonin breakdown by monoamine oxidase, such as chronic stress, will also decrease serotonin availability. As such, factors that act to mediate changes in the gut-brain axis by increasing TRYCATs, by virtue of taking tryptophan away from serotonin synthesis, will also concurrently lower melatonergic pathway activation.

As well as being highly produced in the gut, melatonin acts to maintain gut-barrier integrity, including when this is challenged by stress and dietary factors (37). One species of intestinal bacteria, *Enterobacter aerogenes*, significantly increases its swarming behavior to melatonin (38), indicating that the high levels of melatonin release in the gut following a meal are intimately linked to the interactions of the microbiome with the host. It requires investigation as to whether gut bacteria synthesize melatonin, including as to the role of host dietary factors in this. Some of the protection afforded by melatonin in gut-barrier maintenance is mediated by the a7nAChR (39), the level and activity of which can be upregulated by melatonin (40). Consequently, TRYCATs pathway activation that increases the a7nAChR antagonist, kynurenic acid, may also act to negate the gut-barrier effects of melatonin.

Overall, the melatonergic pathway may be intimately associated with gut regulation as well as the processes driving the immune-inflammatory interactions of the gut-brain axis. Such interactions of TRYCATs with the melatonergic pathways and immune-inflammatory processes form the backdrop of the gut-brain axis upon which the constituents of breast milk will act.

Breastfeeding: physiological processes

The impact of breastfeeding on the physiological processes that underpin its many benefits are the subject of intense investigation. A host of immune-associated factors in maternal milk have been proposed to drive these breastfeeding benefits, including in preclinical investigations. Murine data indicates that maternal immune cells may act to compensate for the infant's inadequate adaptive immune system (41). Cabinian and colleagues showed that breast milk leukocyte survival in the suckling infant can occur, with most breast milk lymphocytes, predominantly T lymphocytes and cytotoxic T cells, establishing themselves in specific intestinal areas, called Peyer's patches. These authors suggest that maternal cytotoxic T cells in breast milk are directed to the Peyer's patches where they compensate for the infant's immature adaptive immune system, especially against constant oral infectious risks that are evident postnatally (41). Such work has provided impetus to the search for breastfeeding-driven alterations in the developing immune system in mediating human breastfeeding benefits.

A multitude of immune-associated factors can be present, and transferred, in human breast milk, including whole cells, cytokines, chemokines, immunoglobulins (Igs), lysozymes, lactoferrin, human milk oligosaccharides and microbiota, as well as prebiotic glycans and various growth factors (42, 43). These breast milk-derived factors are important, due, in part, to their role in the infant's gastrointestinal and immune system development (44). As such, alterations in the infant gut seems to be an important mediator of breastfeeding benefits.

Breastfeeding: modulation of the gut and gut-brain axis

Recent work by Sordillo and colleagues in human infants revealed four underlying bacterial co-abundance groups: the first predominantly composed of Firmicutes (Lachnospiraceae/Clostridiales), the second predominantly composed of Proteobacteria (Klebsiella/Enterobacter), the third predominantly composed of Bacteriodetes and the

fourth predominantly composed of Veillonella (45). Using these co-abundance groups, these authors measured outcomes in regression models, with prenatal/birth and demographic characteristics as independent predictors, finding that race, mode of delivery, breastfeeding and cord blood vitamin D levels are significantly associated with the composition of the infant gut microbiome (45). Although such a single study does considerably simplify the associations of prenatal factors and breastfeeding with the infant's gut microbiome, it is important to note that variations in vitamin D may also modulate levels of serotonin availability for the melatonergic pathways, with vitamin D increasing levels of tryptophan hydroxylase and, therefore, serotonin synthesis (46). Other work supports a role for breastfeeding in the regulation of the gut microbiome, including in interaction with other factors, such as tobacco use and exposure to pets in pregnancy (47). Such data indicates the relevance of early developmental processes, including breastfeeding, to the development of the gut, with consequences for the modulation of the gut-brain axis and developing immune system.

The World Allergy Association recently recommend the use of prebiotics in high-risk pregnancies, including when breastfeeding, highlighting the growing appreciation of the role of the gut in infancy to alterations in the immune response that contribute to later allergy susceptibility (48). Such a perspective would also indicate that increasing gut melatonin, to increase gut bacteria swarming (38), may also have utility in the early modulation of allergy risk. Generally, breastfeeding is associated with a significant decrease in an array of allergies (49). However, the composition of human breast milk is a modulatory factor, with infants receiving human milk with low lacto-N-fucopentaose-III concentrations (<60 μM) being more likely to become affected with cow's milk allergy when compared to high lacto-N-fucopentaose-III-containing milk (50). Allergies are one means by which alterations in gut microbiota may modulate the gut-brain axis, with relevance to an array of adult-onset disorders, including dementia, schizophrenia and bipolar disorder (51, 52). Chen and colleagues showed that a predisposition toward allergies increased the risk of hypertension, dyslipidemia and diabetes mellitus among patients with schizophrenia or bipolar disorder (51). Alterations in gut microbiota are strongly associated with the emergence of such metabolic syndrome-associated factors (53), with the adjunctive use of melatonin in the treatment of psychosis decreasing the emergence of such metabolic factors (54). As to whether these benefits of melatonin are mediated via the gut and the gut microbiome requires investigation in this patient group. It is also of note that variations in melatonin levels in breast milk are also likely to be relevant, which is discussed in more detail below. Overall, the specific composition of breast milk is of importance to later alterations in the gut-brain axis and immune system responses.

Other aspects of breastfeeding may also be relevant; for example, some mothers with inactive secretor genes have altered human milk oligosaccharide composition and quantities in their breast milk. A recent study by Smith-Brown and colleagues highlighted the relevance of secretor status interactions with breastfeeding on microbiota composition at 2–3 years of age (55). Breastfeeding also modulates the infant's response to routine Rotarix childhood immunization at 8 and 15 weeks of age (56). These authors showed that breastfeeding reduced both stool vaccine shedding and the IgA seroresponse, with reduced rotavirus gut replication and shedding after the first vaccine dose suggested to lower serum IgA response. As such, breastfeeding is intimately associated with alterations in immune responses.

It should be noted that there is a rapid alteration in the infant fecal microbiome following the transition from breastfeeding to other nutrition, including cow's milk. In circumstances when *Clostridium difficile*, the most common known cause of antibiotic-associated diarrhea, is present, this bacterium can disappear over early development, in the absence of any symptoms (57). This is unusual, as at later developmental time-points antibiotic-induced increases in *C. difficile* lead to the release of toxins A and B, which cause significant tissue damage in the host, with symptoms that range from mild diarrhea to pseudomembranous colitis and toxic megacolon. As somewhere between 10% and 50% of infants are asymptomatic carriers of *C. difficile*, this suggests that the infant gut is a distinct environment. The role of intrapartum antibiotics, which occurs in about 50% of pregnancies, in the regulation of the offspring's gut is the subject of current investigation (58).

As well as the gut microbiome influencing the host immune system by increasing gut permeability, it is important to note that gut microbiota are a metabolically active biomass that can weigh 2 kg in adult humans, with microbiota-derived molecules significantly influencing the metabolism of the host (59). The host takes up and utilizes an array of bacterial metabolites, including a major energy source in the form of short chain fatty acids, as well as folic acid and vitamins (60). LeBlanc and colleagues also propose that such bacterial metabolites interact with the mammalian epigenetic machinery, including histone modifications and DNA methylation, thereby influencing the host's chromatin state and active gene expression (60). As such, the effects of breastfeeding and the variations in

its constituents modulate a complex array of physiological processes and systems.

A plethora of other physiologically relevant factors may also be variably present in breast milk, including T helper 1 (Th1) cytokines, which are generally pro-inflammatory, and the more anti-inflammatory Th2 cytokines. The levels and ratio of these cytokines in breast milk may modulate many aspects of infant development, including from their modulation of the infant's gut (61), with maternal intake of probiotics significantly regulating breast milk levels of cytokines and secretory IgA (62). Maternal gut microbiota, by influencing the constituents of breast milk, will therefore modulate the development of the infant gut, including infantile colic and regurgitation (62), suggesting an across-generational gut bacteria communication. Chemokines, by virtue of chemo-attracting an array of various immune cells, are also important modulators of immune responses. A number of different chemokines are evident in breast milk (63).

A multitude of growth factors are also evident in breast milk, including BDNF, glial cell line-derived neurotrophic factor (GDNF) and nerve growth factor (NGF) (64), which, along with the omega-3 polyunsaturated fatty acid, docosahexaenoic acid (DHA), show alterations in the breast milk of women with preeclampsia (65). Preeclampsia is a risk factor for a wide array of offspring medical conditions, including schizophrenia (66). Levels of circulating serum BDNF in the infant positively correlate with neurodevelopmental outcomes, being proposed to contribute to the association of breastfeeding with offspring cognition (67). DHA levels also positively correlate with many markers of immune function in infants, including when DHA has been added to formula feed (68). Both DHA (69) and GDNF (70) contribute to the maintenance of the gut barrier. However, stress-mediated increases in gut permeability in rodents are driven by increased NGF release from neighboring mast cells (71), suggesting that trophic factors may also contribute to the plasticity processes associated with increased gut permeability.

Breast milk-derived trophic factors, as with cytokines and chemokines, have been proposed to mediate their effects by priming intestinal immune cells and helping to develop intestinal epithelial barrier function, as well as contributing to angiogenesis and generally suppressing immune-inflammation (42). Human milk also contains high levels of other immune factors, including IgA (72). IgA has an important function in the gut, especially in regard to mucosal immune defence. Over the course of development of the infant's immune system, gut microbiota eventually induce secreted IgA (sIgA) (73), which, given the importance of sIgA in the selection of beneficial and less beneficial microbiota, is likely to be of some significance in the development of the gut and gut-brain axis (74). As to how these immune-regulatory factors in breast milk interact with the development of the infant's sIgA response and wider mucosal immunity is the subject of current investigation (75). The effects of such factors in breast milk may be even more important in premature infants (7).

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 (76), including in premature infants (77). As the adaptive immune system develops, gamma-delta T cells continue to be significant modulators of gut responses, including the activity levels of Th1 and Th17 cells, with gamma-delta T cells being subject to negative feedback effects by regulatory T cells (78). Consequently, as well as breastfeeding modulating infant gamma-delta T cells responses, breastfeeding may also epigenetically regulate the nature of gamma-delta T cell interactions with the adaptive immune system over the lifespan (79). It requires investigation as to whether this is mediated by alterations in the levels and/or regulation of the TNF-like cytokine TL1A, which is highly expressed in the gut (80), where it acts to regulate mucosal Th1, Th2, Th17 and regulatory T cells (81, 82) as well as gamma-delta T cells and the microbiome (80). The induction of TL1A is via the activation of the transcription factor, nuclear factor-kappa B (NF-kB) (83), suggesting that the numerous factors that act to regulate NF-kB in breast milk, including melatonin (84), DHA (85) and NGF (86), may directly, or via the growth of an optimized microbiome, act to regulate TL1A. Probiotics also act to inhibit the levels of NF-kB activation (87), suggesting impacts on TL1A regulation.

The evolution of human breastfeeding has resulted in a circadian modulation of the contents of breast milk, including in the levels of breast milk melatonin (88). It is of note that many of the factors in breast milk can act to regulate melatonin, suggesting that the varying breast milk constituents may differentially modulate levels of gut melatonin, with relevance to bacterial swarming (38) as well as melatonin's maintenance of the gut barrier (39). For example, breast milk constituents, including tryptophan and omega-3 polyunsaturated fatty acids, inhibit monoamine oxidase, and thereby increase serotonin availability as a precursor for the melatonergic pathways (89, 90). It is also notable that breastfeeding acts to attenuate the infant's hypothalamic-pituitary adrenal (HPA) axis response (91), which is likely to inhibit the chronic effects of cortisol that can increase monoamine

oxidase, which melatonin prevents (92). This requires investigation in early development, as the infant's HPA axis can be unpredictably active (93), allowing stress to have early impacts in the gut and gut-brain axis. It is also of note that maternal stress and anxieties prenatally also act to modulate the infant's HPA axis response (94). As to how prenatal stressors interact with maternal postnatal stress in the modulation of the infant microbiome and the composition of breast milk require further investigation, including as to the relevance of alterations in the melatonergic pathways to this. The role of the melatonergic pathways in the perinatal period and infancy are looked at next, including as to the relevance of melatonin in breast milk.

Breastfeeding and melatonin

Over the course of pregnancy, the placenta produces increasing levels of melatonin, in a non-circadian fashion (27). The melatonergic pathways are, therefore, activated throughout pregnancy, with beneficial effects in both the mother and the fetus as well as the placenta (95). At parturition, such continuous placental melatonin provision ceases for the mother and the newborn baby. An aspect of the transition from fetus to newborn is the loss of continuous protection afforded by placental melatonin. This is not insignificant, as melatonin has many early postnatal benefits, including increasing survival in cases of perinatal asphyxia and neonatal sepsis (96, 97). A broad array of data shows melatonin to have beneficial effects for the mother and the infant, including in decreasing the susceptibility to preeclampsia in the mother, and the consequences of this for both mother and infant (7, 96, 97). Being a natural substance, it is important to note that no significant side-effects have been noted. To some degree, the loss of placental melatonin is compensated in the neonate by its presence in breast milk, as well as the constituents for melatonin's endogenous synthesis by the infant. It should be noted that infants do not show a circadian production of melatonin until they are 3–5 months old, which is about the time corresponding to the cessation of breastfeeding for many women, perhaps indicative of an adaptive response in infants that are no longer receiving melatonin from breast milk, or even an indicant that infants may not require melatonin until this age. However, in many non-Western cultures, breastfeeding is maintained until the infant is aged 1 year and above, indicating that the demands on women in Western culture are likely to underpin their earlier cessation of breastfeeding, rather than being an evolutionary derived process (1, 8).

The night-time rise in pineal melatonin increases circulating maternal melatonin levels, which are transferred in the breast milk to the sucking infant, along with NAS and various melatonin metabolites (88). Consequently, night-time breast milk has higher levels of melatonergic pathway products that may, among other effects, act to entrain the infant's developing circadian rhythms. Night-time breast milk is therefore likely to have higher antioxidant, anti-inflammatory and immune regulatory effects (98), including as arising from the impact of breast milk melatonin in the infant's developing microbiome and gut permeability, with consequences for immune system development, which is significantly regulated by circadian factors (99). Given the importance of the gut microbiome to an array of childhood and adult-onset disorders (100), including metabolic dysregulation (101), night-time breast milk melatonin is likely to be of some importance to the etiology of a wide array of medical conditions, including SIDS (7).

Many of the breast milk components that have been modeled as underpinning breastfeeding's biological benefits are regulated by melatonin (102) and NAS (103), suggesting that maternal circadian melatonergic pathway activity will modulate the benefits of wider breast milk components. Regulators of breast milk components also show circadian variation, including microRNAs (104), which can regulate the transcription of many genes. Some of melatonin's effects are modulated by miR-16 (105), which is expressed in a circadian rhythm in breast milk (104), indicating interactions of melatonin, circadian rhythm and mRNAs in determining the constituents and effects of breast milk. As maternal stress modulates many breast milk components (106), as well as gut permeability, melatonin will be important to the inhibition of these stress effects, both in the mother and infant. Overall, alterations in the regulation of the melatonergic pathway will have significant impacts on the constituents of breast milk, and therefore in the regulation of the infant gut and immune system.

Melatonin addition to formula feed

The role of melatonin in night-time breast milk, and its influence on the other components of breast milk, urgently requires further investigation, including as to the role of the melatonergic pathways in the regulation of the infant gut, and therefore on the developing gut-brain axis and

immune system. Recently, we proposed that melatonin should be added to a night-time specific formula feed, in order to bring formula feed closer to the benefits of breast milk (7). The absence of melatonin in formula feeds is a major deviation from the evolutionary forces that underpin the presence of melatonin in night-time breast milk. Some of the effects of breast milk melatonin in the infant gut are likely to be direct, both in regard to the swarming of different gut bacteria (38) and in the maintenance of the gut barrier. As indicated above, indirect effects will arise from the effects of melatonin on the levels of other beneficial breast milk components. Variation in the levels of maternal melatonin synthesis is also likely to be important to the general levels of wider breast milk circadian, antioxidant and immune-associated beneficial factors, as limited data would suggest (98). Although, highly likely to prove beneficial, the addition of melatonin to breast milk would have to be investigated cautiously, as it would be likely to modulate wider aspects of normal infant development.

The addition of melatonin to formula feed may be most beneficial in premature infants, paralleling the common addition of proteins, fats and carbohydrates to breast milk for babies born preterm (107). The period to full term that is lost in premature infants would have been a period of high, continuous exposure to placental melatonin, perhaps indicating that all pretermer feeds should contain melatonin. It is not uncommon for premature infants to suffer from necrotizing enterocolitis, which is still a devastating intestinal disease in preterm neonates and involves disruption of the development of gut microbiota, usually as a consequence of organ immaturity, antibiotic use and the hospital microbial environment (108). Given the array of benefits of melatonin and other melatonergic pathway products, it is highly likely that melatonin will prove beneficial in the management of necrotizing enterocolitis in premature infants, as has been proposed (109), following its efficacy for this condition in preclinical models (110).

As some of the benefits of melatonin may be mediated via its induction of the a7nAChR (39), it requires investigation as to whether the adjunctive use of choline, an a7nAChR agonist, would prove useful. A number of studies have indicated the utility of adding choline to infant feed (111). The addition of choline, as well as melatonin, to infant feeding requires investigation, especially as to whether there are any synergistic effects, including in the gut and in the regulation of the gut-brain axis, as preclinical data would suggest (39).

It will also be important to determine as to how variations in melatonin, including its addition to formula feed, interact with the master infant colonizer, bifidobacteria, and human milk oligosaccharides from breast milk, the importance of which has been recently highlighted (112). Evidence indicates a role for bifidobacteria, when used as a prebiotic in the management of irritable bowel syndrome, in the modulation of melatonin (113), suggesting interactions of bifidobacteria with melatonin.

Future directions

A number of future directions are indicated by the integration of the melatonergic pathways with the biological underpinnings of the gut and gut-brain axis, including the role of melatonin in breastfeeding's modulation of the early developmental formation of the gut-brain axis. Future directions include investigations as to whether:

- gut microbiota produce melatonin and as to whether variations in melatonin synthesis are evident across specific microbiota species.
- night-time breast milk feeding modulates the development of the infant gut, gut-brain axis and immune system.
- variations in maternal melatonin production and content in breast milk modulate the infant gut and the susceptibility to an array of childhood and adult medical conditions, as well as childhood and adult cognitive ability.
- the addition of melatonin would bring formula feed closer to the benefits of breast milk.
- premature infants would further benefit from the addition of melatonin to all feeds.
- the addition of choline and melatonin to formula feed would have additive or synergistic benefits, especially in premature infants.
- the addition of melatonin to formula feed might lower SIDS risk.
- melatonin in breast milk modulates not only the immune response but also the effector pathways involving alterations in the levels of specific TRYCATs.
- the association of breast milk is mediated, in part, via the effects of melatonin and choline on depression susceptibility, with the biological underpinnings of depression increasing the risk of a host of other medical conditions.
- and how breast milk melatonin variations interact with the role of prenatal sleep disturbance, linked to maternal stress, depression and anxiety in the prenatal period as well as postpartum depression, require investigation.

Conclusions

The integration of the melatonergic pathways into the biological underpinnings of the interaction of breastfeeding with the development of the gut, gut-brain axis and immune system may be important, both theoretically and clinically. As indicated by the collated data above, it is not unlikely that the melatonergic pathways will prove to be an important regulator of the early developmental etiology of a host of medical conditions. This suggests that targeting the melatonergic pathway in breastfeeding and the gut will be valuable in the prevention of a host of infant-, childhood- and adult-onset medical conditions.

Conflict of interest statement: The authors declare that no conflict of interests concerning this article exists.

List of abbreviations

a7nAChR	α7 nicotinic receptors
BDNF	brain-derived neurotrophic factor
DHA	docosahexaenoic acid
GDNF	glial cell line-derived neurotrophic factor
HPA	hypothalamic-pituitary adrenal
IDO	indoleamine 2,3-dioxygenase
Ig	immunoglobulin
NAS	N-acetylserotonin
NF-κB	nuclear factor-κB
NGF	nerve growth factor
O&NS	oxidative and nitrosative stress
RNS	reactive nitrogen species
ROS	reactive oxygen species
SIDS	sudden infant death syndrome
TDO	tryptophan 2,3-dioxygenase
Th	T helper
TRYCATs	tryptophan catabolites

References

1. Hendrick CE, Potter JE. Nativity, country of education, and Mexican-origin women's breastfeeding behaviors in the first 10 months postpartum. Birth 2017; 44: 68–77.
2. Smith LA, Geller NL, Kellams AL, Colson ER, Rybin DV, Heeren T, Corwin MJ. Infant sleep location and breastfeeding practices in the United States, 2011–2014. Acad Pediatr 2016; 16: 540–9.
3. Walters D, Horton S, Siregar AY, Pitriyan P, Hajeebhoy N, Mathisen R, Phan LT, Rudert C. The cost of not breastfeeding in Southeast Asia. Health Policy Plan 2016; 31: 1107–16.
4. Dagvadorj A, Ota E, Shahrook S, Baljinnyam Olkhanud P, Takehara K, Hikita N, Bavuusuren B, Mori R, Nakayama T. Hospitalization risk factors for children's lower respiratory tract infection: a population-based, cross-sectional study in Mongolia. Sci Rep 2016; 6: 24615.
5. Netzer-Tomkins H, Rubin L, Ephros M. Breastfeeding is associated with decreased hospitalization for neonatal fever. Breastfeed Med 2016; 11: 218–21.
6. Zalewski BM, Patro B, Veldhorst M, Kouwenhoven S, Crespo Escobar P, Calvo Lerma J, Koletzko B, van Goudoever JB, Szajewska H. Nutrition of infants and young children (one to three years) and its effect on later health: a systematic review of current recommendations (EarlyNutrition project). Crit Rev Food Sci Nutr 2017; 57: 489–500.
7. Anderson G, Vaillancourt C, Maes M, Reiter RR. Breastfeeding and melatonin: implications for improving perinatal health. J Breastfeeding Biol 2016; 1: 8–20.
8. Binns C, Lee M, Low WY. The long-term public health benefits of breastfeeding. Asia Pac J Public Health 2016; 28: 7–14.
9. Moser VA, Pike CJ. Obesity and sex interact in the regulation of Alzheimer's disease. Neurosci Biobehav Rev 2016; 67: 102–18.
10. Slyepchenko A, Maes M, Machado-Veira R, Anderson G, Solmi M, Sanz Y, Berk M, Köhler CA, Carvalho AF. Intestinal dysbiosis, gut hyperpermeability and bacterial translocation: missing links between depression, obesity and type 2 diabetes? Curr Pharm Des 2016; 22: 6087–106.
11. Hayatbakhsh MR, O'Callaghan MJ, Bor W, Williams GM, Najman JM. Association of breastfeeding and adolescents' psychopathology: a large prospective study. Breastfeed Med 2012; 7: 480–6.
12. Anderson G, Seo M, Berk M, Carvalho AF, Maes M. Gut permeability and microbiota in parkinson's disease: role of depression, tryptophan catabolites, oxidative and nitrosative stress and melatoninergic pathways. Curr Pharm Des 2016; 22: 6142–51.
13. Rodriguez M, Wootla B, Anderson G. Multiple sclerosis, gut microbiota and permeability: role of tryptophan catabolites, depression and the driving down of local melatonin. Curr Pharm Des 2016; 22: 6134–41.
14. Bekkering P, Jafri I, van Overveld FJ, Rijkers GT. The intricate association between gut microbiota and development of type 1, type 2 and type 3 diabetes. Expert Rev Clin Immunol 2013; 9: 1031–41.
15. Severance EG, Yolken RH, Eaton WW. Autoimmune diseases, gastrointestinal disorders and the microbiome in schizophrenia: more than a gut feeling. Schizophr Res 2016; 176: 23–35.
16. Hamdani N, Boukouaci W, Hallouche MR, Charron D, Krishnamoorthy R, Leboyer M, Tamouza R. Resolution of a manic episode treated with activated charcoal: evidence for a brain-gut axis in bipolar disorder. Aust N Z J Psychiatry 2015; 49: 1221–3.
17. Iovene MR, Bombace F, Maresca R, Sapone A, Iardino P, Picardi A, Marotta R, Schiraldi C, Siniscalco D, Serra N, de Magistris L, Bravaccio C. Intestinal dysbiosis and yeast isolation in stool of subjects with autism spectrum disorders. Mycopathologia 2017; 182: 349–63.
18. Jiang H, Ling Z, Zhang Y, Mao H, Ma Z, Yin Y, Wang W, Tang W, Tan Z, Shi J, Li L, Ruan B. Altered fecal microbiota composition in patients with major depressive disorder. Brain Behav Immun 2015; 48: 186–94.
19. Morris G, Carvalho AF, Anderson G, Galecki P, Maes M. The many neuroprogressive actions of tryptophan catabolites (TRYCATs) that may be associated with the pathophysiology of neuroimmune disorders. Curr Pharm Des 2016; 22: 963–77.
20. Anderson G, Maes M, Berk M. Inflammation-related disorders in the tryptophan catabolite pathway in depression and somatization. Adv Protein Chem Struct Biol 2012; 88: 27–48.

21. Speciale C, Hares K, Schwarcz R, Brookes N. High-affinity uptake of L-kynurenine by a Na^+-independent transporter of neutral amino acids in astrocytes. J Neurosci 1989; 9: 2066–72.
22. Maes M, Anderson G. Overlapping the tryptophan catabolite (TRYCAT) and melatoninergic pathways in Alzheimer's disease. Curr Pharm Des 2016; 22: 1074–85.
23. Bai P, Cantó C, Oudart H, Brunyánszki A, Cen Y, Thomas C, Yamamoto H, Huber A, Kiss B, Houtkooper RH, Schoonjans K, Schreiber V, Sauve AA, Menissier-de Murcia J, Auwerx J. PARP-1 inhibition increases mitochondrial metabolism through SIRT1 activation. Cell Metab 2011; 13: 461–8.
24. Anderson G. Linking the biological underpinnings of depression: role of mitochondria interactions with melatonin, inflammation, sirtuins, tryptophan catabolites, dna repair and oxidative and nitrosative stress, with consequences for classification and cognition. Prog NeuroPsyol Pharmacol Bio Psychiatry 2017; pii: S0278–5846: 30383–9.
25. Erren TC, Reiter RJ. Melatonin: a universal time messenger. Neuro Endocrinol Lett 2015; 36: 187–92.
26. Liu YJ, Zhuang J, Zhu HY, Shen YX, Tan ZL, Zhou JN. Cultured rat cortical astrocytes synthesize melatonin: absence of a diurnal rhythm. J Pineal Res 2007; 43: 232–8.
27. Lanoix D, Beghdadi H, Lafond J, Vaillancourt C. Human placental trophoblasts synthesize melatonin and express its receptors. J Pineal Res 2008; 45: 50–60.
28. Muxel SM, Pires-Lapa MA, Monteiro AW, Cecon E, Tamura EK, Floeter-Winter LM, Markus RP. NF-κB drives the synthesis of melatonin in RAW 264.7 macrophages by inducing the transcription of the arylalkylamine-nacetyltransferase (AA-NAT) gene. PLoS One 2012; 7: e52010.
29. Raikhlin NT, Kvetnoy IM, Tolkachev VN. Melatonin may be synthesised in enterochromaffin cells. Nature 1975; 255: 344–5.
30. Huether G. The contribution of extrapineal sites of melatonin synthesis to circulating melatonin levels in higher vertebrates. Experientia 1993; 49: 665–70.
31. Tan DX, Manchester LC, Liu X, Rosales-Corral SA, Acuna-Castroviejo D, Reiter RJ. Mitochondria and chloroplasts as the original sites of melatonin synthesis: a hypothesis related to melatonin's primary function and evolution in eukaryotes. J Pineal Res 2013; 54: 127–38.
32. He C, Wang J, Zhang Z, Yang M, Li Y, Tian X, Ma T, Tao J, Zhu K, Song Y, Ji P, Liu G. Mitochondria synthesize melatonin to ameliorate its function and improve mice oocyte's quality under in vitro conditions. Int J Mol Sci 2016; 17. pii: E939.
33. Reiter RJ, Tan DX, Galano A. Melatonin: exceeding expectations. Physiology (Bethesda) 2014; 29: 325–33.
34. Anderson G, Rodriguez M. Multiple sclerosis: the role of melatonin and N-acetylserotonin. Mult Scler Relat Disord 2015; 4: 112–23.
35. Reiter RJ, Tan DX, Fuentes-Broto L. Melatonin: a multitasking molecule. Prog Brain Res 2010; 181: 127–51.
36. Jang SW, Liu X, Pradoldej S, Tosini G, Chang Q, Iuvone PM, Ye K. N-acetylserotonin activates TrkB receptor in a circadian rhythm. Proc Natl Acad Sci USA 2010; 107: 3876–81.
37. Anderson G, Maes M. The gut-brain axis: the role of melatonin in linking psychiatric, inflammatory and neurodegenerative conditions. Adv Integr Med 2015; 2: 31–7.
38. Paulose JK, Cassone VM. The melatonin-sensitive circadian clock of the enteric bacterium Enterobacter aerogenes. Gut Microbes 2016: 1–4.
39. Sommansson A, Nylander O, Sjöblom M. Melatonin decreases duodenal epithelial paracellular permeability via a nicotinic receptor-dependent pathway in rats in vivo. J Pineal Res 2013; 54: 282–91.
40. Markus RP, Silva CL, Franco DG, Barbosa EM Jr, Ferreira ZS. Is modulation of nicotinic acetylcholine receptors by melatonin relevant for therapy with cholinergic drugs? Pharmacol Ther 2010; 126: 251–62.
41. Cabinian A, Sinsimer D, Tang M, Zumba O, Mehta H, Toma A, Sant'Angelo D, Laouar Y, Laouar A. Transfer of maternal immune cells by breastfeeding: maternal cytotoxic T lymphocytes present in breast milk localize in the Peyer's patches of the nursed infant. PLoS One 2016; 11: e0156762.
42. Newburg DS, Walker WA. Protection of the neonate by the innate immune system of developing gut and of human milk. Pediatr Res 2007; 61: 2–8.
43. Munblit D, Treneva M, Peroni DG, Colicino S, Chow L, Dissanayeke S, Abrol P, Sheth S, Pampura A, Boner AL, Geddes DT, Boyle RJ, Warner JO. Colostrum and mature human milk of women from London, Moscow, and Verona: determinants of immune composition. Nutrients 2016; 8. pii: E695.
44. Groer MW, Gregory KE, Louis-Jacques A, Thibeau S, Walker WA. The very low birth weight infant microbiome and childhood health. Birth Defects Res C Embryo Today 2015; 105: 252–64.
45. Sordillo JE, Zhou Y, McGeachie MJ, Ziniti J, Lange N, Laranjo N, Savage JR, Carey V, O'Connor G, Sandel M, Strunk R, Bacharier L, Zeiger R, Weiss ST, Weinstock G, Gold DR, Litonjua AA. Factors influencing the infant gut microbiome at age 3–6 months: findings from the ethnically diverse vitamin D antenatal asthma reduction trial (VDAART). J Allergy Clin Immunol 2017; 139: 482–91.
46. Kaneko I, Sabir MS, Dussik CM, Whitfield GK, Karrys A, Hsieh JC, Haussler MR, Meyer MB, Pike JW, Jurutka PW. 1,25-Dihydroxyvitamin D regulates expression of the tryptophan hydroxylase 2 and leptin genes: implication for behavioral influences of vitamin D. FASEB J 2015; 29: 4023–35.
47. Levin AM, Sitarik AR, Havstad SL, Fujimura KE, Wegienka G, Cassidy-Bushrow AE, Kim H, Zoratti EM, Lukacs NW, Boushey HA, Ownby DR, Lynch SV, Johnson CC. Joint effects of pregnancy, sociocultural, and environmental factors on early life gut microbiome structure and diversity. Sci Rep 2016; 6: 31775.
48. Forsberg A, West CE, Prescott SL, Jenmalm MC. Pre- and probiotics for allergy prevention: time to revisit recommendations? Clin Exp Allergy 2016; 46: 1506–21.
49. Huang C, Liu W, Cai J, Weschler LB, Wang X, Hu Y, Zou Z, Shen L, Sundell J. Breastfeeding and timing of first dietary introduction in relation to childhood asthma, allergies, and airway diseases: a cross-sectional study. J Asthma 2017; 54: 488–97.
50. Seppo AE, Autran CA, Bode L, Järvinen KM. Human milk oligosaccharides and development of cow's milk allergy in infants. J Allergy Clin Immunol 2017; 139: 708–11.e5.
51. Chen MH, Li CT, Lin WC, Wei HT, Chang WH, Chen TJ, Pan TL, Su TP, Bai YM. A predisposition for allergies predicts subsequent hypertension, dyslipidemia, and diabetes mellitus among patients with schizophrenia or bipolar disorder: a nationwide longitudinal study. Schizophr Res 2014; 159: 171–5.
52. Daulatzai MA. Non-celiac gluten sensitivity triggers gut dysbiosis, neuroinflammation, gut-brain axis dysfunction, and vulnerability for dementia. CNS Neurol Disord Drug Targets 2015; 14: 110–31.

53. Marotz CA, Zarrinpar A. Treating obesity and metabolic syndrome with fecal microbiota transplantation. Yale J Biol Med 2016; 89: 383–8.
54. Anderson G, Maes M. Melatonin: an overlooked factor in schizophrenia and in the inhibition of anti-psychotic side effects. Metab Brain Dis 2012; 27: 113–9.
55. Smith-Brown P, Morrison M, Krause L, Davies PS. Mothers secretor status affects development of childrens microbiota composition and function: a pilot study. PLoS One 2016; 11: e0161211.
56. Bautista-Marquez A, Velasquez DE, Esparza-Aguilar M, Luna-Cruz M, Ruiz-Moran T, Sugata K, Jiang B, Parashar U, Patel M, Richardson V. Breastfeeding linked to the reduction of both rotavirus shedding and IgA levels after Rotarix® immunization in Mexican infants. Vaccine 2016; 34: 5284–9.
57. Davis MY, Zhang H, Brannan LE, Carman RJ, Boone JH. Rapid change of fecal microbiome and disappearance of *Clostridium difficile* in a colonized infant after transition from breast milk to cow milk. Microbiome 2016; 4: 53.
58. Simioni J, Hutton EK, Gunn E, Holloway AC, Stearns JC, McDonald H, Mousseau A, Schertzer JD, Ratcliffe EM, Thabane L, Surette MG, Morrison KM. A comparison of intestinal microbiota in a population of low-risk infants exposed and not exposed to intrapartum antibiotics: the baby & microbiota of the intestine cohort study protocol. BMC Pediatr 2016; 16: 183.
59. Mischke M, Plösch T. The gut microbiota and their metabolites: potential implications for the host epigenome. Adv Exp Med Biol 2016; 902: 33–44.
60. LeBlanc JG, Milani C, de Giori GS, Sesma F, van Sinderen D, Ventura M. Bacteria as vitamin suppliers to their host: a gut microbiota perspective. Curr Opin Biotechnol 2013; 24: 160–8.
61. Garofalo R. Cytokines in human milk. J Pediatr 2010; 156 (Suppl. 2): S36–40.
62. Baldassarre ME, Di Mauro A, Mastromarino P, Fanelli M, Martinelli D, Urbano F, Capobianco D, Laforgia N. Administration of a multi-strain probiotic product to women in the perinatal period differentially affects the breast milk cytokine profile and may have beneficial effects on neonatal gastrointestinal functional symptoms. A Randomized Clinical Trial. Nutrients 2016; 8. pii: E677.
63. Bosire R, Guthrie BL, Lohman-Payne B, Mabuka J, Majiwa M, Wariua G, Mbori-Ngacha D, Richardson B, John-Stewart G, Farquhar C. Longitudinal comparison of chemokines in breastmilk early postpartum among HIV-1-infected and uninfected Kenyan women. Breastfeed Med 2007; 2: 129–38.
64. Li R, Xia W, Zhang Z, Wu K. S100B protein, brain-derived neurotrophic factor, and glial cell line-derived neurotrophic factor in human milk. PLoS One 2011; 6: e21663.
65. Dangat K, Kilari A, Mehendale S, Lalwani S, Joshi S. Higher levels of brain derived neurotrophic factor but similar nerve growth factor in human milk in women with preeclampsia. Int J Dev Neurosci 2013; 31: 209–13.
66. Byrne M, Agerbo E, Bennedsen B, Eaton WW, Mortensen PB. Obstetric conditions and risk of first admission with schizophrenia: a Danish national register based study. Schizophr Res 2007; 97: 51–9.
67. Nassar MF, Younis NT, El-Arab SE, Fawzi FA. Neuro-developmental outcome and brain-derived neurotrophic factor level in relation to feeding practice in early infancy. Matern Child Nutr 2011; 7: 188–97.
68. Richard C, Lewis ED, Field CJ. Evidence for the essentiality of arachidonic and docosahexaenoic acid in the postnatal maternal and infant diet for the development of the infant's immune system early in life. Appl Physiol Nutr Metab 2016; 41: 461–75.
69. Willemsen LE, Koetsier MA, Balvers M, Beermann C, Stahl B, van Tol EA. Polyunsaturated fatty acids support epithelial barrier integrity and reduce IL-4 mediated permeability in vitro. Eur J Nutr 2008; 47: 183–91.
70. Meir M, Flemming S, Burkard N, Bergauer L, Metzger M, Germer CT, Schlegel N. Glial cell line-derived neurotrophic factor promotes barrier maturation and wound healing in intestinal epithelial cells *in vitro*. Am J Physiol Gastrointest Liver Physiol 2015; 309: G613–24.
71. Barreau F, Cartier C, Leveque M, Ferrier L, Moriez R, Laroute V, Rosztoczy A, Fioramonti J, Bueno L. Pathways involved in gut mucosal barrier dysfunction induced in adult rats by maternal deprivation: corticotrophin-releasing factor and nerve growth factor interplay. J Physiol 2007; 580(Pt 1): 347–56.
72. Weaver LT, Arthur HM, Bunn JE, Thomas JE. Human milk IgA concentrations during the first year of lactation. Arch Dis Child 1998; 78: 235–9.
73. Bridgman SL, Konya T, Azad MB, Sears MR, Becker AB, Turvey SE, Mandhane PJ, Subbarao P; CHILD Study Investigators., Scott JA, Field CJ, Kozyrskyj AL. Infant gut immunity: a preliminary study of IgA associations with breastfeeding. J Dev Orig Health Dis 2016; 7: 68–72.
74. McLoughlin K, Schluter J, Rakoff-Nahoum S, Smith AL, Foster KR. Host selection of microbiota via differential adhesion. Cell Host Microbe 2016; 19: 550–9.
75. Planer JD, Peng Y, Kau AL, Blanton LV, Ndao IM, Tarr PI, Warner BB, Gordon JI. Development of the gut microbiota and mucosal IgA responses in twins and gnotobiotic mice. Nature 2016; 534: 263–6.
76. Gibbons DL, Haque SF, Silberzahn T, Hamilton K, Langford C, Ellis P, Carr R, Hayday AC. Neonates harbour highly active gammadelta T cells with selective impairments in preterm infants. Eur J Immunol 2009; 39: 1794–806.
77. Weitkamp JH, Rosen MJ, Zhao Z, Koyama T, Geem D, Denning TL, Rock MT, Moore DJ, Halpern MD, Matta P, Denning PW. Small intestinal intraepithelial TCR$\gamma\delta+$ T lymphocytes are present in the premature intestine but selectively reduced in surgical necrotizing enterocolitis. PLoS One 2014; 9: e99042.
78. Yurchenko E, Levings MK, Piccirillo CA. $CD4^+$ $Foxp3^+$ regulatory T cells suppress $\gamma\delta$ T-cell effector functions in a model of T-cell-induced mucosal inflammation. Eur J Immunol 2011; 41: 3455–66.
79. Schmolka N, Wencker M, Hayday AC, Silva-Santos B. Epigenetic and transcriptional regulation of $\gamma\delta$ T cell differentiation: programming cells for responses in time and space. Semin Immunol 2015; 27: 19–25.
80. Tougaard P, Skov S, Pedersen AE, Krych L, Nielsen DS, Bahl MI, Christensen EG, Licht TR, Poulsen SS, Metzdorff SB, Hansen AK, Hansen CH. TL1A regulates TCR$\gamma\delta^+$ intraepithelial lymphocytes and gut microbial composition. Eur J Immunol 2015; 45: 865–75.
81. Jia LG, Bamias G, Arseneau KO, Burkly LC, Wang EC, Gruszka D, Pizarro TT, Cominelli F. A novel role for TL1A/DR3 in protection against intestinal injury and infection. J Immunol 2016; 197: 377–86.
82. Thomas LS, Targan SR, Tsuda M, Yu QT, Salumbides BC, Haritunians T, Mengesha E, McGovern DP, Michelsen KS. The TNF family member TL1A induces IL-22 secretion in committed human Th 17 cells via IL-9 induction. J Leukoc Biol 2017; 101: 727–37.

83. Endo K, Kinouchi Y, Kakuta Y, Ueki N, Takahashi S, Shimosegawa T. Involvement of NF-κB pathway in TL1A gene expression induced by lipopolysaccharide. Cytokine 2010; 49: 215–20.
84. Shao G, Tian Y, Wang H, Liu F, Xie G. Protective effects of melatonin on lipopolysaccharide-induced mastitis in mice. Int Immunopharmacol 2015; 29: 263–8.
85. Zhao J, Shi P, Sun Y, Sun J, Dong JN, Wang HG, Zuo LG, Gong JF, Li Y, Gu LL, Li N, Li JS, Zhu WM. DHA protects against experimental colitis in IL-10-deficient mice associated with the modulation of intestinal epithelial barrier function. Br J Nutr 2015; 114: 181–8.
86. Prencipe G, Minnone G, Strippoli R, De Pasquale L, Petrini S, Caiello I, Manni L, De Benedetti F, Bracci-Laudiero L. Nerve growth factor downregulates inflammatory response in human monocytes through TrkA. J Immunol 2014; 192: 3345–54.
87. Dai C, Zheng CQ, Meng FJ, Zhou Z, Sang LX, Jiang M. VSL#3 probiotics exerts the anti-inflammatory activity via PI3k/Akt and NF-κB pathway in rat model of DSS-induced colitis. Mol Cell Biochem 2013; 374: 1–11.
88. Illnerová H, Buresová M, Presl J. Melatonin rhythm in human milk. J Clin Endocrinol Metab 1993; 77: 838–41.
89. Chen HF, Su HM. Fish oil supplementation of maternal rats on an n-3 fatty acid-deficient diet prevents depletion of maternal brain regional docosahexaenoic acid levels and has a postpartum anxiolytic effect. J Nutr Biochem 2012; 23: 299–305.
90. Anderson G, Maes M. Pharmaceutical and nutrition benefits in Alzheimer's disease via convergence on the Melatoninergic Pathways. In: Atta-Ur-Rahmanr, editor. Frontiers in clinical drug research-Alzheimer disorder, Chapter 3, Vol. 78. Bentham Press e-books 2015: 50–127.
91. Beijers R, Riksen-Walraven JM, de Weerth C. Cortisol regulation in 12-month-old human infants: associations with the infants' early history of breastfeeding and co-sleeping. Stress 2013; 16: 267–77.
92. Stefanovic B, Spasojevic N, Jovanovic P, Jasnic N, Djordjevic J, Dronjak S. Melatonin mediated antidepressant-like effect in the hippocampus of chronic stress-induced depression rats: regulating vesicular monoamine transporter 2 and monoamine oxidase A levels. Eur Neuropsychopharmacol 2016; 26: 1629–37.
93. Jansen J, Beijers R, Riksen-Walraven M, de Weerth C. Cortisol reactivity in young infants. Psychoneuroendocrinology 2010; 35: 329–38.
94. Tollenaar MS, Beijers R, Jansen J, Riksen-Walraven JM, de Weerth C. Maternal prenatal stress and cortisol reactivity to stressors in human infants. Stress 2011; 14: 53–65.
95. Soliman A, Lacasse AA, Lanoix D, Sagrillo-Fagundes L, Boulard V, Vaillancourt C. Placental melatonin system is present throughout pregnancy and regulates villous trophoblast differentiation. J Pineal Res 2015; 59: 38–46.
96. Gitto E, Karbownik M, Reiter RJ, Tan DX, Cuzzocrea S, Chiurazzi P, Cordaro S, Corona G, Trimarchi G, Barberi I. Effects of melatonin treatment in septic newborns. Pediatr Res 2001; 50: 756–60.
97. Aly H, Elmahdy H, El-Dib M, Rowisha M, Awny M, El-Gohary T, Elbatch M, Hamisa M, El-Mashad AR. Melatonin use for neuroprotection in perinatal asphyxia: a randomized controlled pilot study. J Perinatol 2015; 35: 186–91.
98. Katzer D, Pauli L, Mueller A, Reutter H, Reinsberg J, Fimmers R, Bartmann P, Bagci S. Melatonin concentrations and antioxidative capacity of human breast milk according to gestational age and the time of day. J Hum Lact 2016; 32: NP105–10.
99. Dumbell R, Matveeva O, Oster H. Circadian clocks, stress, and immunity. Front Endocrinol (Lausanne) 2016; 7: 37.
100. Matamoros S, Gras-Leguen C, Le Vacon F, Potel G, de La Cochetiere MF. Development of intestinal microbiota in infants and its impact on health. Trends Microbiol 2013; 21: 167–73.
101. Wang M, Monaco MH, Donovan SM. Impact of early gut microbiota on immune and metabolic development and function. Semin Fetal Neonatal Med 2016; 21: 380–7.
102. Rahman SA, Castanon-Cervantes O, Scheer FA, Shea SA, Czeisler CA, Davidson AJ, Lockley SW. Endogenous circadian regulation of pro-inflammatory cytokines and chemokines in the presence of bacterial lipopolysaccharide in humans. Brain Behav Immun 2015; 47: 4–13.
103. Iuvone PM, Boatright JH, Tosini G, Ye K. N-acetylserotonin: circadian activation of the BDNF receptor and neuroprotection in the retina and brain. Adv Exp Med Biol 2014; 801: 765–71.
104. Floris I, Billard H, Boquien CY, Joram-Gauvard E, Simon L, Legrand A, Boscher C, Rozé JC, Bolaños-Jiménez F, Kaeffer B. miRNA analysis by quantitative PCR in preterm human breast milk reveals daily fluctuations of hsa-miR-16-5p. PLoS One 2015; 10: e0140488.
105. Li C, Chen S, Li H, Chen L, Zhao Y, Jiang Y, Liu Z, Liu Y, Gao S, Wang F, Yu J, Wang H, Rao J, Zhou X. microRNA-16 modulates melatonin-induced cell growth in the mouse-derived spermatogonia cell line GC-1 spg cells by targeting Ccnd1. Biol Reprod 2016; 95: 57.
106. Thibeau S, D'Apolito K, Minnick AF, Dietrich MS, Kane B, Cooley S, Groer M. Relationships of maternal stress with milk immune components in African American mothers of healthy term infants. Breastfeed Med 2016; 11: 6–14.
107. Rochow N, Fusch G, Choi A, Chessell L, Elliott L, McDonald K, Kuiper E, Purcha M, Turner S, Chan E, Xia MY, Fusch C. Target fortification of breast milk with fat, protein, and carbohydrates for preterm infants. J Pediatr 2013; 163: 1001–7.
108. Cassir N, Simeoni U, La Scola B. Gut microbiota and the pathogenesis of necrotizing enterocolitis in preterm neonates. Future Microbiol 2016; 11: 273–92.
109. Marseglia L, D'Angelo G, Manti S, Aversa S, Reiter RJ, Antonuccio P, Centorrino A, Romeo C, Impellizzeri P, Gitto E. Oxidative stress-mediated damage in newborns with necrotizing enterocolitis: a possible role of melatonin. Am J Perinatol 2015; 32: 905–9.
110. Guven A, Uysal B, Gundogdu G, Oztas E, Ozturk H, Korkmaz A. Melatonin ameliorates necrotizing enterocolitis in a neonatal rat model. J Pediatr Surg 2011; 46: 2101–7.
111. Maas C, Franz AR, Shunova A, Mathes M, Bleeker C, Poets CF, Schleicher E, Bernhard W. Choline and polyunsaturated fatty acids in preterm infants' maternal milk. Eur J Nutr 2017; 56: 1733–42.
112. Katayama T. Host-derived glycans serve as selected nutrients for the gut microbe: human milk oligosaccharides and bifidobacteria. Biosci Biotechnol Biochem 2016; 80: 621–32.
113. Wong RK, Yang C, Song GH, Wong J, Ho KY. Melatonin regulation as a possible mechanism for probiotic (VSL#3) in irritable bowel syndrome: a randomized double-blinded placebo study. Dig Dis Sci 2015; 60: 186–94.