SPLASH!® milk science update
February 2016 Issue

INTERNATIONAL MILK GENOMICS CONSORTIUM

This month's issue features milk as a sleep aid for the elderly, breast milk's effect on infant's circadian rhythms, fermentation of proteins in kefir, and how a lactation hormone also affects the intestines.

Medicating the Elderly with Night Milk

- **Insomnia is common among the elderly, and is often due to lower production of the hormone melatonin in old age.**
- **Dietary melatonin supplements are known to aid sleep in old age.**
- **Milk from cows milked at night, which contains much more melatonin than day milk, improves sleep, too—at least in animal studies.**
- **Combining night-milk consumption with physical activity in old age should help sleep substantially.**

Elderly people often have trouble sleeping. For those afflicted, it's more than mere annoyance: insomnia in old age is associated with a range of health difficulties. What's worse, many medications that are commonly prescribed to elderly people only add to the problem—including beta blockers, which treat hypertension. This is because they lower the levels of a hormone called melatonin. Yet, melatonin levels can be increased by consuming foodstuffs that contain the hormone. One key source is milk collected from cows in the middle of the night.

The idea that the gradual ebbing of melatonin production in later years is frequently responsible for many elderly people's insomnia has been around for some time. More than twenty years ago, a highly cited study [1] with just a dozen participants found that elderly people with sleep problems are far more likely to sleep well—that is, to sleep without waking up repeatedly—when they receive a melatonin supplement as opposed to a placebo.

The amount of melatonin in those supplements was quite a bit above what is available naturally in milk. But that doesn't necessarily mean that natural milk levels are too low to have an effect. One problem is that milk containing relatively high levels of melatonin—and of melatonin's precursor, the amino acid tryptophan—isn't easy for suburban consumers to come by. Cow's milk that sits on a supermarket shelf typically comes from a cow that was milked during the day.

The difference between milk collected during the night and typical supermarket milk is so stark, it's as different as night and day. In 2014, a study of Holstein cows at the Federal University of Viçosa, in the Brazilian state of Minas Gerais, put the melatonin levels of day milk at about a 10th of those in night milk [2]. Animals milked at 2 a.m. in the study produced, on average, 39.43 picograms (pg) of melatonin per liter of milk. In comparison, milk from the same animals collected during the day (at 3 p.m.) contained only 4.03 pg per liter. In other words, switch the milking schedule, and you shift the components of milk. (Indeed, melatonin concentrations as high as 56.4 pg per liter have been recorded in cow's milk, by altering the photoperiod to which the cows were exposed.)

Using this knowledge to benefit humans doesn't require experiments in rodents for the usual reason in medical research—that of getting an idea whether a treatment is likely to work before a full side-effect profile has been established. Since humans have consumed milk for millennia, its safety is assured. Instead, studies in mice and rats offer a means to isolate the physiological effects of melatonin-rich milk from the possibly muddling influence of psychology. Unlike humans, rodents haven't grown up with the understanding that drinking a glass of warm milk before bed will aid sleep.

The same group at the Federal University of Viçosa followed up their analysis of the melatonin concentration of day and night milk with a study to check that the differences were reflected in blood. They report that Wistar rats that drank cow's milk collected at 2 a.m. had elevated melatonin levels in their blood plasma—a big jump up, compared to when they drank day milk [2].

In a more detailed study in 2015, the behavior of mice in response to different concentrations of night milk (and thus, melatonin) was closely monitored [3]. The mice that drank the most melatonin were those that reduced their activity and fell asleep quickest, and most easily lost their footing in a laboratory balance test. The effect was so large it was comparable to that of diazepam, the sedative.

And yet, while the rodent studies serve a purpose, it is in humans that most researchers in the field are ultimately hoping

to see an effect. Very few trials of night milk have been attempted in humans.

One noteworthy study for elderly readers comes from Japan [4]. There, researchers have studied the effect of elderly people's daily levels of physical activity on their sleep, in combination with their consumption of different dairy products. Both physical activity and consuming melatonin-containing milk are thought to aid sleep, so what about both together?

The results were much as imagined. Day milk—even with its quite low level of melatonin—improved the quality of participants' sleep on its own. Adding exercise into the mix aided this effect [4]. These results would most likely have been more impressive, however, if night milk were specifically used.

More research into how elderly people respond to night milk would be welcome. One study more than a decade old looked at how demented patients sleep in response to drinking night milk [5], with mixed results. It had nothing to say about non-demented elderly people.

Somewhere out there, an entrepreneur with a dairy herd could fill in a potentially gaping market niche: delivering night milk to elderly people, served up as a soporific tonic. This is expectation from the animal data—and indeed from the Japanese study since it found that milk consumption improved sleep on its own. The title of the Brazilian milk melatonin-production paper implies the possibility: 'Night milking adds value to cow's milk'. That may be true in more than an economic sense, but first more data is needed.

1. Garfinkel, D. et al. (1995) Improvement of sleep quality in elderly people by controlled-release melatonin. The Lancet 346, 541-544.
2. Milagres, M. P. et al. (2014) Night milking adds value to cow's milk. J Sci Food Agric 94, 1688–1692.
3. dela Peña, I. J. I. et al. (2015) Milk collected at night induces sedative and anxiolytic-like effects and augments pentobarbital-induced sleeping behavior in mice. J Med Food 18 (11), 1255–1261.
4. Kitano, N. et al. (2014) Association between difficulty initiating sleep in older adults and the combination of leisure-time physical activity and consumption of milk and milk products: a cross-sectional study. BMC Geriatrics, 14:118
5. Valtonen, M. et al. (2005) Effect of melatonin-rich night-time milk on sleep and activity in elderly institutionalized subjects. Nordic Journal of Psychiatry 59 (3), 217-221.

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Milk, the Synchronizer

- **Breast milk contains various components that oscillate in their levels over the course of the day.**
- **One of the most important circadian changes in breast milk appears to be in the levels of the amino acid tryptophan, which peaks at about 3 a.m.**
- **These subtle changes in the composition of breast milk help infants to train their own circadian rhythms, with potential consequences for their brain development.**
- **Infant formulas that imitate the circadian shifts in breast milk have been shown to improve bottle-fed infants' sleep.**

Consuming a glass of warm milk before bed is supposed to make you sleep well. This old wives' tale is repeated on websites that offer health and nutritional advice, often backed up by the detail that milk contains tryptophan, the amino acid that is the reason eating turkey purportedly makes you sleepy. But the reality is much more complex. In fact, several compounds in milk appear to have a soporific effect. And perhaps the most intriguing thing about them is that their levels alter with the time of day that the milk is produced.

The list of milk components thought to promote sleep includes melatonin, vitamin B12, nucleosides (as well as their phosphorylated cousins, nucleotides such as 5′-adenosine monophosphate and 5′-guanosine monophosphate)—and tryptophan. For most of these, there is good data suggesting that their concentration in milk fluctuates with a circadian rhythm [1, 2].

Take, for example, the hormone melatonin, which is manufactured from tryptophan in a gland about the size of a pea that is located deep in the brain. In 2005, a team of Spanish researchers at the University of Extremadura, in Badajoz, measured the amount of 6-sulfatoxymelatonin (a metabolite of melatonin that is excreted in urine) in one group of exclusively breastfed infants and in another group of bottle-fed infants. All participants were twelve weeks-old [3]. The researchers also monitored the levels of tryptophan in the milk that each breastfed infant was consuming, and put wrist monitors on all of the infants to record various sleep parameters.

The results underscored that breastfed infants sleep better than those given formula: in this study [3], they slept for nighttime stretches almost an hour and a half longer than formula-fed infants. The key difference between the two groups was that the levels of 6-sulfatoxymelatonin in the urine of the breastfed infants appeared to oscillate in a way that implied it was being entrained by the circadian rhythm of tryptophan in breast milk. The breast-milk tryptophan content peaked at

around 3 a.m., leading its consumers' 6-sulfatoxymelatonin levels to hit a maximum just before 6 a.m.—in other words, enough time for their tiny bodies to absorb the tryptophan, make melatonin from it, and have their kidneys filter out the waste products of that process. The formula-fed infants didn't exhibit nearly as clear a circadian pattern in their 6-sulfatoxymelatonin excretion.

In the decade since that study was published, researchers have been exploring its corollaries. One logical consequence of breastfed infants sleeping for longer than formula-fed infants is that their parents do, too. This bears out in the data. In a study by Therese Doan and her colleagues at the University of California's School of Nursing in San Francisco, parents of infants who were breastfed in the evening or at night gained an average of 40–45 minutes of sleep over parents who gave their offspring formula at the same time [4]. The quality of parental sleep was also higher—it was interrupted less.

A second logical consequence of breastfed infants sleeping more is that they may be at an advantage when it comes to brain development. This research on development is much more recent, and the conclusions, therefore, are more tentative, but the argument makes intuitive sense.

In the womb, a fetus is exposed to the day-night rhythms of its mother's body, principally via the melatonin and cortisol (a metabolic hormone) circulating in placental blood. As such, it's possible to record diurnal rhythms in a fetus's heart rate, respiratory rate, and sleep activity from 22 weeks' gestation onward.

After birth, however, this influence is lost, and infants born at term typically sleep for about 16 hours per day. Unlike adults, their sleep states cannot be categorized into rapid eye movement (REM) and S-wave (non-REM) types, instead newborns are understood to have "active sleep" (which later develops into REM), quiet sleep (which develops into non-REM), and what is obscurely called "indeterminate sleep." The relative amount of time spent in each of these sleep states shifts substantially in young bodies: a term newborn spends half of its sleeping time in "active sleep" (preemies as much as 80–90%), but by the time a child is ready for preschool, active sleep's equivalent, REM, makes up just 20% of sleep.

The establishment of the proper patterns of sleep is thought to be important for healthy brain development. Active sleep is known to encourage the formation of synaptic connections that compose the brain's basic circuitry. Meanwhile, quiet sleep consolidates information gleaned about the world during waking hours. This explains why a stable balance of the two sleep states, with clear and rhythmic shifts between them, is understood to be a sign of a maturing central nervous system.

As described in a paper [2] by researchers at the University of Turin, Italy, this understanding raises a number of points, given earlier work by the University of Extremadura group [3]. Most straightforwardly, women who pump and store their milk might benefit their infant's brain development if they label their bottles "night milk" and "day milk," being careful to give their infants milk that was pumped at night during the night—and milk that was pumped during the day, during the day. Breast milk banks might want to do the same.

Infant formula manufacturers are already taking note of this field of research, some adding tryptophan to create a product for use at night [5]. This development is largely attributable to work by the University of Extremadura team, who followed their 2005 study with a double-blind prospective trial, testing whether formula with extra ingredients that were intended to imitate daytime and nighttime breast milk could help bottle-fed infants sleep better [6].

In the study, daytime formula was used during the hours of 6 a.m. to 6 p.m. It contained low levels of tryptophan, but high levels of proteins and some of the nucleotides that are present at high levels in breast milk during the day. Nighttime formula was used from 6 p.m. to 6 a.m. It had high levels of tryptophan and of a different set of nucleotides that are present in breast milk during the night. As per the 2005 study, the infants taking part all wore wrist monitors to capture their sleep patterns. The same group of infants was followed for a week while they consumed unmodified formula, for a week while they consumed unmodified formula during the day and "night formula" at night, and for a week while they consumed day and night formulas at the appropriate times.

The diurnal recipes were a great success. The day and night formula routine was associated with a full hour of extra nighttime sleep for the infants compared with normal formula, which acted as an experimental control. Feeding with night formula during the night and unmodified formula during the day also led to improvements in sleep.

So, for parents who care about their sleep, paying attention to the daily changes in breast milk—or looking out for specially designed night milk formulas—should make life easier, as well as benefit their infant's development. And as for their own "warm glass of milk before bed," drinking milk that was pumped from a cow at night—which is also when cow-milk tryptophan content peaks—may have greater soporific benefits than basic, supermarket milk. A helpful tip for parents with their own cow to milk.

1. Sánchez, C. L. et al. (2009) The possible role of human milk nucleotides as sleep inducers. Nutr. Neurosci. 12(1), 2-8.
2. Arslanoglu, S. et al. (2012) Potential chronobiotic role of human milk in sleep regulation. J. Perinat. Med. 40, 1–8.
3. Cubero, J. et al. (2005) The circadian rhythm of tryptophan in breast milk affects the rhythms of 6-sulfatoxymelatonin and sleep in newborn. Neuroendocrinol. Lett. 26(6), 657–661.
4. Doan, T. et al. (2007) Breast-feeding increases sleep duration of new parents. J. Perinat. Neonat. Nurs. 21(3), 200–206.
5. Bravo, R. et al. (2013) Chapter 28: Components in formula milks that improve sleep. in the handbook of nutrition, diet and sleep. Editors: Preedy, V. R. et al. Springer, London.
6. Cubero, J. et al. (2007) Chrononutrition applied to formula milks to consolidate infants' sleep/wake cycle. Neuroendocrinol. Lett. 28(4), 360-366.

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Kefir Microorganisms Break Down Milk Proteins

- **Kefir is a fermented dairy beverage produced when milk is incubated with "kefir grains"—a mix of sugar, proteins, lactic acid bacteria, and yeast.**
- **The kefir microorganisms ferment milk lactose, but it is unclear how they affect milk proteins.**
- **A new study finds that milk proteins are extensively broken down during kefir fermentation, producing 609 peptides unique to kefir and changing the abundance of more than 1,500 peptides.**
- **Twenty-five of the kefir peptides were previously identified to have a variety of biological activities, including antimicrobial, antihypertensive, and immunomodulatory functions.**
- **The fact that kefir fermentation breaks down proteins could make kefir a helpful food option for people who have trouble digesting proteins.**

Kefir is a fermented dairy drink that is becoming increasingly popular in the United States, and has been shown to have beneficial health effects [1]. The drink is made by incubating heat-treated milk with "kefir grains," which contain sugars, proteins, lactic acid bacteria, and yeast [2-4]. The kefir microorganisms are known to ferment milk lactose, but it is still unclear how they affect milk proteins and whether they break these proteins down into peptides.

"It's sort of this black box," says David Dallas at Oregon State University. In a new study, Dallas and his team conducted the most exhaustive analysis to date of the milk peptides released during kefir fermentation [5]. "We wanted to find out what's going on during the kefir fermentation, and what kind of functional peptides are produced," he says.

The researchers found that the kefir microorganisms extensively digested milk proteins during kefir fermentation, resulting in the release of a large number of peptides. "It was surprising to find that there were thousands of peptides there, and all sorts of protein changes that are not visible to the eye but visible with a mass spectrometer," Dallas says. "I think that's pretty cool," he says.

Dallas's group identified 1,591 peptides released during kefir fermentation, out of which 609 were unique to kefir, and they also saw changes in the abundance of more than 1,500 peptides. "I think it's just really interesting to see that these kefir microorganisms are basically chopping up so much of these proteins with these external proteases that they produce, and using those for their growth," says Dallas. "It's not just this lactose fermentation picture that we had been looking at for such a long time," he says.

The researchers then checked whether any of the identified peptides were known to have biological activity. "We basically took all of the peptide sequences that we found and then we compared them to a list that we put together from the literature," says Dallas.

The group identified 25 peptides with a variety of biological functions, including antimicrobial, antihypertensive, immunomodulatory, and anti-oxidative peptides [6]. "People have a lot of different health beliefs about kefir, and it's possible that some of those are coming from the peptides as opposed to other components," says Dallas.

The fact that milk proteins are broken down during kefir fermentation may have implications for digestive health. "The other potential implication is that because you have at least some degree of digestion happening here, that kefir, or other things like it, these could be ideal foods for people who have trouble digesting proteins," says Dallas [7-10].

Undigested proteins can survive all the way into the colon, where they can serve as a food source for bacteria that produce inflammatory or toxic metabolites. "Clearly that's something that you want to avoid," says Dallas. "So if you have problems digesting—people who have different problems like ulcerative colitis or inflammatory bowel disease, people with antacid medication, or the elderly—this might be a good food for them," he says.

Dallas plans to look in more detail at how protein digestion affects the health, immunity, and microbial profile of the gut.

Researchers could compare the effects of kefir to those of other foods with more intact proteins, he says.

The techniques used in the study could also have implications for kefir manufacturing. “You could use peptidomics as a way to monitor the kefir that you’re producing to see how much variation there is from batch to batch,” says Dallas. “Perhaps you could ferment longer to produce more peptides, or select which bacteria you want to use for your fermentation to produce peptides,” he says.

“I think that there could be lot of interesting research in that area, to make specialized kefir,” says Dallas. “I think there’s a lot of ideas that could be followed up on,” he says.

1. Sando L. (2015). Kefir Consumption—a Growing Culture. SPLASH! milk science update: September 2015. (http://milkgenomics.org/article/kefir-consumption-a-growing-culture/)
2. Angulo, L., Lopez, E., & Lema, C. (1993). Microflora present in kefir grains of the Galician region (North-West of Spain). Journal of Dairy Research, 60(2), 263–267.
3. Leite, A. M., Miguel, M. A., Peixoto, R. S., Rosado, A. S., Silva, J. T., Paschoalin, V. M., & De Oliveira Leite, A. (2013). Microbiological, technological and therapeutic properties of kefir: A natural probiotic beverage. Brazilian Journal of Microbiology Braz. J. Microbiol., 44(2), 341-349.
4. Wang, S.-Y., Chen, K.-N., Lo, Y.-M., Chiang, M.-L., Chen, H.-C., Liu, J.-R., & Chen, M.-J. (2012). Investigation of microorganisms involved in biosynthesis of the kefir grain. Food Microbiology, 32(2), 274–285.
5. Dallas, D. C., Citerne, F., Tian, T., Silva, V.L., Kalanetra, K.M., Frese, S.A., Robinson, R.C., Mills, D.A., & Barile, D. (2016) Peptidomic analysis reveals proteolytic activity of kefir microorganisms on bovine milk proteins. Food Chemistry, 197(Pt A), 273-84
6. Clare, D. A., & Swaisgood, H. E. (2000). Bioactive milk peptides: a prospectus. Journal of Dairy Science, 83(6), 1187–1195.
7. Vass, A., Szakaly, S., & Schmidt, P. (1983). Experimental study of the nutritional biological characters of fermented milks. Acta Medica Hungarica, 41(2–3), 157–161.
8. Puri, P., Mahapatra, S., Bijlani, R., Prasad, H., & Nath, I. (1994). Feed efficiency and splenic lymphocyte proliferation response in yogurt-and milk-fed mice. International Journal of Food Sciences and Nutrition, 45(4), 231–235.
9. Breslaw, E. S., & Kleyn, D. H. (1973). In vitro digestibility of protein in yogurt at various stages of processing. Journal of Food Science, 38(6), 1016–1021.
10. Lee, H., Friend, B. A., & Shahani, K. M. (1988). Factors affecting the protein quality of yogurt and acidophilus milk. Journal of Dairy Science, 71(12), 3203–3213.

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Prolactin Targets Intestines Too

- **Prolactin is a hormone that PROmotes LACTation.**
- **During puberty and pregnancy, prolactin promotes mammary development.**
- **After the birth of offspring, prolactin promotes milk production.**
- **New research demonstrates that prolactin acts in the intestines as well as in the mammary gland.**
- **In lactating rats, prolactin enhances calcium absorption in the intestines by increasing the surface area of the mucosal lining and upregulating the expression of genes responsible for transporting calcium from intestines to the bloodstream.**

Prolactin (PRL) is a hormone that, as its name clearly indicates, PROmotes LACTation. Although it is best known for initiating milk production in the mammary glands, prolactin actually targets numerous other tissues throughout the body during lactation. One important target is the gut, where prolactin is believed to influence calcium absorption. A new study confirms this hypothesis, demonstrating that prolactin increases the ability of the intestines to absorb calcium and transfer it to the bloodstream [1]. These important findings show that although PRL may have the important job of telling the mammary glands to make milk, it also plays a critical role in making sure that milk has all of the necessary ingredients.

Prolactin and the mammary gland

The hormone PRL is found in both male and female vertebrates and has over 300 known physiological functions [2]. It was named in the early 1930s after researchers demonstrated that a protein secreted from the pituitary gland could induce milk secretion in rabbits that had never been pregnant [3]. Since that time, animal models have been critical in determining the scope of PRL’s action on mammary tissue.

Numerous hormones influence lactation during development and lactation. In order to understand the specific role of PRL, researchers have developed a very neat biological trick. Rather than trying to figure out what PRL does, they look at what happens (or does not happen, as the case may be) when PRL is not present. This is accomplished by inactivating or “knocking out” the genes responsible for PRL communication with the mammary gland [4]. During puberty and pregnancy, mice without PRL targets on mammary tissue do not develop alveoli, the structures in the mammary glands that contain milk-secreting cells [4]. If PRL expression is inhibited at delivery, the alveoli are structurally normal but do not secrete milk [4]. Thus, PRL directs both the development and function of milk-secreting structures within the mammary gland.

Trust your gut

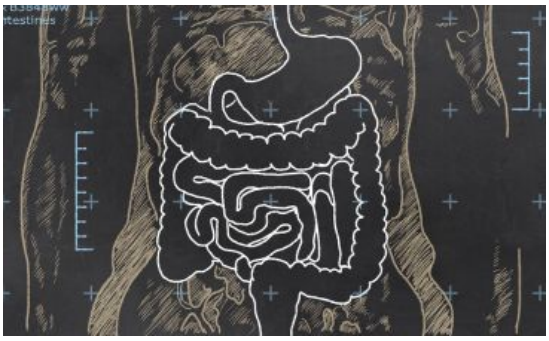
Whereas the pituitary pumps out PRL to initiate and maintain lactation, the mammary glands are not the only organs responding to the hormone's signal. Protein receptors specific to PRL are found on cells throughout the body, including reproductive organs (e.g., ovaries) as well as many organs—like the intestines—that are usually not considered critical for lactation. But as it turns out, without PRL acting on the intestines, milk may lack some key ingredients.

PRL has long been known to be active in the intestines during lactation [1,3,5]. Indeed, there is a suspected connection between the gut and the mammary gland, often referred to as the entero-mammary pathway. For example, immunoglobulins (or antibodies) produced in the guts of non-lactating females or males simply stay in the gut to fight off pathogens. But in lactating females, these immunoglobulins have a special homing mechanism to the mammary gland, a process controlled in large part by the actions of PRL [6,7]. As a result, milk immunoglobulins represent the mother's pathogen experience, providing protection to the offspring against the very pathogens they are most likely to encounter.

Immunity is not the only connection between the gut and the mammary glands modulated by PRL. During pregnancy and lactation, intestinal absorption of calcium increases to supply this essential mineral to the fetal and infant skeleton. PRL has always been implicated in this process, but its specific actions on the intestines were not clear [1,5,8].

Higher peaks and deeper valleys

A major clue about what PRL may do in the intestines came from the observation that PRL communicates directly with cells that line the inside, or mucosal surface, of both the small and large intestines [1]. Although we might picture food moving through the intestines like water through pipes, a more apt analogy might be a roller coaster. The mucosal surface of the intestines is a series of peaks (called villi) and valleys (called crypts), and it is along this surface that nutrients (including proteins, fats, carbohydrates, vitamins and minerals) are absorbed into the intestines for eventual transfer into the bloodstream. This roller coaster-like structure is a rather ingenious way of getting more surface area for nutrient absorption; the higher the peaks and the deeper the valleys, the more cells for food to contact for absorption.



In a newly published study, Wongdee et al. [1] tested the hypothesis that PRL enhances calcium absorption by increasing the height of the peaks and the depths of the valleys. To do so, they compared the intestinal landscapes of nulliparous (= never been pregnant) rats, lactating rats, and lactating rats treated one week prior to the analysis with bromocriptine, a drug that inhibits the production of prolactin by the pituitary. This last experimental group was critical—just like the knockout mice, this group would be able to highlight the specific actions of PRL. Lactating rats had higher villi and deeper crypts in their intestinal mucosa, resulting in a greater surface area, compared with those of the nulliparous rats [1]. The similarities in mucosal measurements between nulliparous and bromocriptine-treated rats confirmed their hypothesis that these changes in the mucosal surface were PRL dependent [1].

An increased surface area impacts the absorption of all nutrients, not only calcium. So why the emphasis on calcium absorption? Wongdee et al.'s [1] experimental model also found that, in addition to inducing morphological changes in the intestine, PRL increased the expression of genes involved in transporting calcium across cells and into the bloodstream. A higher rate of gene expression equates to more protein production. In this instance, the proteins are responsible for moving calcium across the cells of the intestines and into the bloodstream, where they can be transferred to the mammary glands. Many hands make quick work; so having more proteins means an increased rate of cellular transfer.

Perhaps the most interesting finding by Wongdee et al. [2], however, has to do with another hormone, called FGF-23. This hormone actually has the opposite effect of PRL by preventing the intestines from absorbing too much calcium. With so much emphasis on effects that result in getting as much calcium as possible from the intestines, it may seem surprising that the investigators found that the intestines of lactating rats had increased expression of FGF-23. That's right, in addition to stimulating calcium absorption, PRL promotes expression of a hormone that inhibits calcium absorption. Wongdee et al. [2] proposed that the purpose of FGF-23 expression is to keep serum calcium from reaching dangerous levels [2]. While too little calcium may spell problems for infant skeletal development, too much calcium can cause issues for the mother.

From mice to men

Taken together, the findings of Wongdee et al. [2] highlight that PRL does much more than simply influence calcium absorption during lactation. PRL actually regulates the process. But their findings were in rodents—is it possible to take these findings and assume they apply to PRL in women? The big assumption here is that evolution has conserved the

function of PRL across distantly related mammals. This assumption is certainly confirmed when considering the role of PRL on mammary development and milk production [3]. In fact, PRL plays a role in production of crop milk in pigeons and doves, suggesting a very old evolutionary role in “milk” production [8].

Although it is not possible to replicate Wongdee et al.’s [2] study in human subjects, confirming their findings in other animal models—particularly one that is more similar in reproductive physiology to that of humans—would support a shared action of PRL across mammals. Might pigs hold the answer? Next month’s SPLASH! will look at a study on genetic expression of PRL targets throughout the body in a pig model and will point to many shared functions between pigs and humans (and even ties to rodents)! Stayed tuned.

1. Wongdee K, Teerapornpuntakit J, Sripong C, Longkunan A, Chankamngoen W, Keadsai C, Kraidith K, Krishnamra N, Charoenphandhu N. 2016. Intestinal mucosal changes and upregulated calcium transporter and FGF-23 expression during lactation: contribution of lactogenic hormone prolactin. Archives of Biochemistry and Biophysics 590: 109-117.
2. Schenninck A, Trott JF, Manjarin R, Lemay DG, Freking BA, Hovey RC. 2015. Comparative genomics reveals tissue-specific regulation of prolactin receptor gene expression. Journal of Molecular Endocrinology 54: 1–15.
3. Akers RM. 2002. Lactation and the Mammary Gland. Ames: Iowa State Press.
4. Briskin C, Kaur S, Chavarria TE, Binart N, Sutherland RL, Weinberg RA, Kelly PA, Ormandy CJ. 1999. Prolactin controls mammary gland development via direct and indirect mechanisms. Developmental Biology 210: 96-106.
5. Teerapornpuntakit J, Wongdee K, Thongbunchoo J, Krishnamra N, Charoenphandhu N. 2012. Proliferation and mRNA expression of absorptive villous cell markers and mineral transporters in prolactin-exposed IEC-6 intestinal crypt cells. Cell Biochemistry and Function 30: 320-327.
6. Boumahrou N, Chevaleyre C, Berri M, Martin P, Bellier S, Salmon H. 2012. An increase in milk IgA correlates with both pIgR expression and IgA plasma cell accumulation in the lactating mammary glad of PRM/Alf mice. Journal of Reproductive Immunology 96: 25-33.
7. Brandtzaeg P. 2002. Current understanding of gastrointestinal immunoregulation and its relation to food allergy. Annals of the New York Academy of Science 964: 13-45.
8. Wongdee K, Charoenphandu N. 2013. Regulation of epithelial calcium transport by prolactin: from fish to mammals. General and Comparative Endocrinology 181: 235-240.

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Funding provided by California Dairy Research Foundation and the International Milk Genomics Consortium