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Breast pumping and lactational state exert differential effects on ethanol pharmacokinetics

Julie A. Mennella, PhD¹ and M. Yanina Pepino, PhD^{1,2}

¹Monell Chemical Senses Center, Philadelphia, PA

²Washington University, School of Medicine, St. Louis, MO

Abstract

Prior research revealed that breast stimulation altered the way the lactating body handles alcohol. Its effects depended upon when it occurred relative to drinking. The goal of the present study was to determine whether breast pumping works independently of the physiological and metabolic changes that accompany lactation. To this end, we tested 12 women when they were exclusively breastfeeding 3- to 5-month-old infants and then again months after lactation had ceased. Subjects were randomly assigned to one of two groups which differed in the timing of breast pumping relative to drinking a 0.4g/kg dose of alcohol: one group breast pumped 0.6 hr after drinking (Pumped After (PA) Group) and the other pumped 1 hour before drinking (Pumped Before (PB) Group). For each reproductive stage, subjects were tested on 2 separate days, consuming a standardized meal one hour before drinking during one test day and remaining fasted during the other. Breath alcohol levels (BrAC) and temperature readings were obtained before and at fixed intervals after drinking. Pumping before drinking significantly decreased BrAC during both reproductive stages whereas pumping after drinking resulted in different BrAC time curves during lactation when compared to after lactation. That is, levels were significantly lower during the descending phase of the time curve during than after lactation. The interactions between pumping and reproductive stage were most apparent during fed condition. Further, women were more sensitive to hypothermic effects of both fasting and drinking alcohol during lactation. These findings add to the growing literature that lactating women metabolize alcohol differently, in part, due to the frequent breast stimulation during breastfeeding and the pronounced physiological changes that accompany one of the most energetically costly mammalian activities.

Key Word List

Lactation; Pharmacokinetics; Temperature; women's health; breastfeeding; alcohol

Introduction

Lactation is the consequence of complex and highly synchronized endocrine and neuroendocrine processes which begin during late pregnancy to prepare both the body and brain for motherhood (Russell et al., 2001). Mammary gland development (i.e., lactogenesis)

Corresponding author and author to whom requests for reprints should be sent: Julie A. Mennella Ph.D., 3500 Market Street, Philadelphia, PA 19104-3308, phone: 267-519-4880, fax: 215-898-2084, mennella@monell.org.

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begins in late pregnancy in response to the complex milieu of reproductive hormones (e.g., estrogen, progesterone, prolactin, oxytocin) that act directly on the mammary gland, and metabolic hormones (e.g., glucocorticoids, insulin, growth hormone, and thyroid hormone) which act indirectly by altering nutrient flux to the mammary gland. Following parturition, endocrine events that sustain lactation are triggered by suckling. Breast stimulation (by an infant or a breast pump) causes transient release of the hormones necessary to produce and eject milk (Mennella et al., 2005; Lucas et al., 1980; Noel et al., 1974; Pang and Hartmann, 2007).

Perhaps less well known than its effect on milk production are the effects on the brain-gut axis. Associated with lactogenesis is an increase in the size and complexity of the digestive tract (Hammond, 1997), and altered nutrient metabolism in adipose tissues, skeletal muscles and liver (Bell, 1995; Tigas et al., 2002). Similar to the effects of sham feeding (Holst et al., 1986; Uvnas-Moberg et al., 1987; Eriksson et al., 1987), suckling causes a vagal release of hormones (e.g., increase in insulin, gastrin, CCK, decrease in somatostatin) which regulate digestive processes such as gastric emptying rates (Holst et al., 1986; Franceschini et al., 1990; Winberg, 2005; Widstrom et al., 1984; Linden et al., 1987; Fleming et al., 1997). The evolution of common neural and endocrine regulation of lactation and energy balance (Wade and Schneider, 1992; Illingworth et al., 1986) ensures a sufficiently large flux of nutrients is mobilized to mammary tissues to support milk synthesis (Dewey, 1997; Prentice and Prentice, 1988; Illingworth et al., 1986). These common regulatory mechanisms suggest that suckling may exert similar effects on ethanol pharmacokinetics (and perhaps other drugs) as does food consumption, a hypothesis that we recently tested in a series of studies (Pepino and Mennella, 2008; Pepino et al., 2007).

Consistent with this hypothesis, the systemic availability of alcohol was diminished during lactation (Pepino et al., 2007; da-Silva et al., 1993). After drinking a moderate dose of alcohol, the resultant breath alcohol concentrations (BrAC) were significantly lower in lactating women than women who were formula-feeding similarly aged infants as well as nulliparous women (Pepino et al., 2007). By experimentally manipulating the timing of breast pumping relative to drinking, we found that pumping an hour before drinking significantly decreased blood alcohol concentration and alcohol bioavailability, whereas pumping after drinking appeared to speed up elimination and attenuate alcohol-induced hypothermia (Pepino and Mennella, 2008). The effects were more pronounced when alcohol was ingested following a meal than on an empty stomach.

The present study builds upon these findings to determine whether breast pumping works synergistically with the physiological and metabolic changes that accompany lactation in the metabolism of alcohol. To this end, we assessed alcohol pharmacokinetics and alcohol-induced temperature changes in the same women while they were lactating and then again after lactation had ceased.

Methods

Subjects

Lactating women (N=12) who were exclusively breastfeeding 3- to 5-month-old infants were recruited. Exclusion criteria included smoking, pregnancy, lifetime alcohol abstinence, alcohol dependence, diabetes and obesity. Pregnancy tests were administered to confirm non-pregnancy, and breath carbon monoxide levels were measured to verify non-smoking status. All procedures were approved by and in accordance with the ethical standards of the Office of Regulatory Affairs at the University of Pennsylvania and with the Helsinki Declaration of 1975, as revised in 1983 and each subject gave informed written consent prior to testing.

The women (6 Caucasian, 4 African American, and 2 Other/Mixed Ethnic Group) were 33.0 ± 1.2 years of age with a mean body mass index (BMI) of $23.1 \pm 0.9 \text{ kg/m}^2$ at the start of testing (during lactation) and $23.6 \pm 1.0 \text{ kg/m}^2$ at the after-lactation testing visit. The groups were matched for age (PB vs PA: 34.0 ± 1.6 vs 31.4 ± 1.9 years; $F(1,10)=1.15$; $p=0.31$), time since parturition (PB vs PA: 4.0 ± 0.3 vs 4.1 ± 0.3 months; $F(1,10)=0.14$; $p=0.71$) and drinking habits (PB vs PA: 7.8 ± 3.3 vs 5.2 ± 3.9 drinks per month during lactation; $F(1,10)=0.26$; $p=0.62$). They breastfed their infants for, on average, 10.5 ± 1.1 months, and reported that alcohol intake was negligible during pregnancy but increased during lactation to 6.7 ± 2.5 standard drinks per month.

Procedures

Each woman was tested during two reproductive stages: while exclusively breastfeeding a 3- to 5-month-old infant (hereafter referred to as “during lactation”) and then several months (16.8 ± 3.6) after lactation had ceased (hereafter referred to as “after lactation”). When tested during lactation, each woman was exclusively breastfeeding and consequently had not yet resumed menstruation. Although research revealed that no significant effects of menstrual cycle phase on alcohol pharmacokinetics (Corrêa et al., 2004; Haddad et al., 1998; Mumenthaler et al., 1999), cycle phase was nevertheless controlled for after lactation such that women were tested during the follicular phase of the menstrual cycle.

On the first testing day, subjects were randomly assigned to one of two groups which differed in the timing of breast pumping relative to drinking alcohol (Pumped Before; PB (N=5), Pumped After; PA (N=7); see below). The data obtained from the during lactation period for some subjects have been reported elsewhere (Pepino and Mennella, 2008). Each woman was tested at each reproductive stage (i.e., during or after lactation) on two days separated by one week. For the during lactation period, women arrived having last nursed or breast pumped 2.7 ± 0.8 hours prior to the start of the study. For all testing days, women arrived at the Center at 0800 hours having been instructed to abstain from alcohol for 36 hours and food for 12 hours. At approximately 0830 hours, capillary blood glucose was measured to ensure subjects had fasted, as indicated by blood glucose levels less than 99 mg/dl. As shown in Figure 1, although both groups used an electric breast pump (Medela, Crystal Lake, IL) for 16 minutes, the timing differed between the groups (Pepino and Mennella, 2008). Group “Pumped Before” (Group PB) breast pumped an hour before drinking whereas Group “Pumped After” (Group PA) did not begin pumping until 0.6 hrs after alcohol consumption. Although women reported that pumping after lactation felt awkward because no milk was produced, they felt no pain or discomfort.

At approximately 0900 hours (shortly after Group PB breast pumped), subjects, in randomized order, consumed a standard meal during one session (Fed Condition) and remain fasted during the other (Fasted Condition) (Ramchandani et al., 2001). The meal which contained 530 calories was consumed within a 20-minute period (Ramchandani et al., 2001; Pepino et al., 2007). One hour later (hereafter referred to as time 0), subjects drank a 0.4 g/kg dose of alcohol. The beverage, a 15% v/v solution of 100% alcohol mixed with a non-caloric Strawberry-Kiwi flavored drink (Crystal Lite, Kraft Food Inc., Northfield, IL), was aliquoted into two equal volumes, and each aliquot was consumed within consecutive 5-minute periods.

BrAC were determined by breathing into a fuel-cell sensor analyzer (Alco-Sensor IV, St. Louis, MO) at fixed intervals before (-90, 0) and after (25, 35, 45, 55, 65, 75, 85, 95, 105, 115, 125, 135, 145, 175, 205 min) alcohol consumption (Mumenthaler et al., 2000; Ramchandani et al., 2001). From the raw BrAC data, we determined time-to-peak, peak values, area under the blood alcohol time curve concentration (AUC; g-hr/L) and elimination rate (R) for each subject and condition. AUCs were estimated by using a software program (OriginLab® Corporation, Northampton, MA) based on the trapezoidal rule. The alcohol elimination rate (R), expressed

as the amount of alcohol eliminated per kg of the body per hour was calculated as $R=\beta_{60}/\text{body weight}$.

Because lactation may modify postprandial thermogenesis (Illingworth et al., 1986; Motil et al., 1990) and because alcohol consumption can affect body temperature (Danel et al., 2001 but see Desruelle et al., 1996; Martin and Cooper, 1978), we measured ear temperatures (Thermoscan pro-LT, Braun; Thermoscan, Inc., San Diego, CA) at fixed intervals (-90, 0, 25, 35, 45, 55, 65, 75, 85, 115, 145, 175, 205 min) throughout the study in all but one subject. Delta temperature scores from baseline were also calculated.

Data Analyses

For each measure, separate mixed ANOVAs with group (PA, PB) as the between-subjects factor and food condition (fed, fasted), reproductive stage (during lactation, after lactation) and time since alcohol consumption (when applicable) as the within-subject factors were conducted. When the ANOVAs revealed significant effects or interactions, post-hoc Fisher Least Significant Difference analyses were conducted. The critical value for significance was $P<0.05$.

Results

BrAC Time Curve

BrAC levels was significantly affected by the following factors: group ($F(1,10)=4.99$; $p=0.05$), condition ($F(1,10)=339.59$; $p<0.0001$) and time ($F(14, 140)=193.37$; $p<0.0001$). As shown in Figure 2 and Table 1, BrAC levels were significantly lower and the systemic availability of alcohol, as determined by AUC, was smaller when alcohol was consumed after a meal than when it was consumed on an empty stomach for both groups and during both reproductive stages. Further, regardless of group or reproductive stage, elimination rates were faster during fed (0.12 ± 0.01) than fasted (0.09 ± 0.01 ; $F(1,7)=100.8$; $p<0.0001$) condition.

Also observed were the following significant two-way interactions: reproductive stage by time ($F(14,140)=3.67$; $p<0.0001$) and condition by time ($F(14,140)=21.95$; $p<0.0001$) and three-way interactions: food condition by group and time ($F(14, 140)=2.10$; $p=0.015$) and reproductive stage by group and time ($F(14,140)=7.67$; $p<0.0001$) for the BrAC time curve. To better understand these significant effects, in particular the two- and three-way interactions, we executed sequential ANOVAs for each condition. Therefore, each three-way ANOVA included reproductive stage, group and time.

For both fed and fasted conditions, reproductive stage significantly interacted with group and time (Fed condition: $F(14,140)=2.86$; $p<0.001$; Fasted condition: $F(14,140)=5.93$; $p<0.0001$). Figure 2A illustrates the interaction between reproductive stage, pumping group and time when women were tested under fed conditions. As shown in Figure 2A, BrAC time curve of PB group were lower than PA Group at time 0-55 min when women were tested during lactation and at time 45-105 min when women were tested after lactation. Although no differences were observed between during and after lactation states for group PB, we did find that group PA women had higher BrAC levels at time 25-35 min and lower BrAC levels at time 65, 85 and 105 min during lactation than after lactation (Figure 2A).

Figure 2B illustrates the interaction between reproductive stage, pumping group and time when women were tested under fasted conditions. Differences in BrAC between PA and PB groups were only different at one time point. In PA group, BrAC were lower at 45 min during lactation and higher at 25 min after lactation when compared to the PB group. Similarly to the results observed during the fed condition, effects of reproductive stage were more apparent in the PA than in the PB group.

Temperature

There were significant interaction effects between reproductive stage, condition and time on ear temperatures ($F(12,108)=1.84$; $p=0.05$). As shown in Figure 3A and Table 1, women had significantly lower temperatures and were more sensitive to hypothermic effects of both fasting and drinking alcohol while they were lactating than after lactation ($p's<0.0001$). Figure 3B further highlights the differences between lactating and postlactating women's temperature response to fasting and alcohol, as depicted by delta temperature changes relative to respective baseline values. Peak and nadir temperatures were lower during lactation than after lactation (peak: $p=0.0004$; nadir: $p=0.0003$) and during fasted when compared to fed conditions (peak: $p=0.0001$; nadir: $p=0.008$; see Table 1). There was also a main effect of group such that PA group had overall higher ear temperatures than PB group ($p=0.0001$).

Conclusions

The present study revealed that the effects of breast pumping on ethanol pharmacokinetics were independent of lactation when women pumped before drinking and worked synergistically with lactation when women pumped after drinking. Consistent with previous findings (Pepino and Mennella, 2008), the effects of pumping were more pronounced when alcohol was consumed with a meal thus suggesting that food and breast stimulation have additive effects on ethanol metabolism and further highlighting the role that suckling stimulation has on the brain-gut axis. It is well known that food increases the metabolism of ethanol during its first passage through the gut and liver before reaching the systemic circulation (i.e., first pass metabolism). It does so directly, by speeding up ethanol elimination through enhanced blood flow to the liver and/or activity of ethanol-metabolizing enzymes, or indirectly by delaying gastric emptying which decreases the rate of intestinal absorption (Levitt, 2002; Gentry, 2000; Hahn et al., 1994). We speculate here on the mechanisms underlying the effects of suckling stimulation.

The effects of pumping on ethanol metabolism were both time- and reproductive stage-dependent. For women who breast pumped before drinking (PB Group), there was a tendency for the systemic availability of alcohol to be reduced relative to those who pumped after drinking (PA Group) both during lactation and after lactation. The mechanism by which pumping exerted these effects may be due to the changes in the hormonal milieu of the women as well as the physiological adaptations of lactation. Pumping shortly before drinking has short-acting effects on ethanol pharmacokinetics during both reproductive stages, perhaps as a result of the neural and hormonal responses triggered by breast stimulation (via pumping). Within a half hour (Widstrom et al., 1988) after suckling stimulation begins, there is vagal release of hormones (e.g., increase in insulin, gastrin, cholecystokinin; decrease in somatostatin) which regulate digestive processes such as gastric emptying rates (Holst et al., 1986; Franceschini et al., 1990; Winberg, 2005; Widstrom et al., 1984; Linden et al., 1987; Fleming et al., 1997).

For the PA Group, pumping resulted in different BrAC time curves during the two reproductive stages. That is, levels were significantly lower during the descending phase of the time curve, peak BrAC occurred earlier and the systemic availability was smaller during than after lactation, thus suggesting that the neural/hormonal consequences of breast stimulation interact with some of the physiological (e.g. gastrointestinal) and metabolic adaptations which accompany lactation during the time when BrAC levels are peaking or descending, which, in turn, affects ethanol elimination.

We acknowledge that the present study has several limitations. Ideally, additional control groups (e.g., parous women who are formula feeding similarly aged infants, women tested in both pumping conditions and during both reproductive stages) are needed to separate the effect of recent parturition on ethanol metabolism. Moreover, because ethanol was orally

administered in the present study, we could not differentiate the effects of reproductive stage and breast stimulation on ethanol absorption separately from their effects on elimination. Therefore, future research, employing ethanol clamp (Ramchandani et al., 2006) or paracetamol (Willems et al., 2001) techniques, is needed to investigate the mechanisms by which lactational state and breast stimulation affect how the drug is absorbed separately from how it is eliminated. And finally, we acknowledge that there are better and more sensitive methods to measure the effects of alcohol ingestion on thermoregulatory responses, an area of research which has yielded variable findings in humans (Desruelle et al., 1996; Martin and Cooper, 1978).

Despite the latter limitation, we found that, regardless of when pumping occurred, women had significantly lower temperatures and were more sensitive to hypothermic effects of both fasting and drinking alcohol while they were lactating than when after lactation. Such findings may have been the result of the pronounced physiological and thermoregulatory changes that accompany one of the most energetically costly mammalian activities (Prentice and Prentice, 1988). That is, to meet the high energetic demands of lactation, mammalian females adopt a diverse range of behavioral, anatomical, and physiological strategies, many of which are initiated during late pregnancy, to meet the demands of the growing fetus, and then augmented by the endocrine changes that initiate and sustain lactation (Prentice and Prentice, 1988; Dufour and Sauther, 2002). Paralleling the proliferation of the mammary glands, are increases in the size and complexity of the digestive tract (Hammond, 1997) and altered nutrient metabolism in adipose tissues, liver and skeletal muscles (Bell, 1995). Depending on the environmental circumstances, such anatomical changes can be associated with increased body fat utilization and reliance on energy-sparing adaptations. Although there are considerable variations between and within populations, energy can be spared by reducing physical activity or increasing metabolic efficiency or both (Dufour and Sauther, 2002; Prentice and Prentice, 1988).

These findings add to the growing literature that lactating women metabolize alcohol differently due, in part, to the frequent breast stimulation during breastfeeding and the pronounced physiological changes that accompany one of the most energetically costly mammalian activities. In the past, many health professionals have interpreted the reduced systemic availability of ethanol in lactating women (Pepino et al., 2007) as an indication that lactation protects the mother and infant from ethanol exposure. Such clinical interpretations, along with the epidemiological findings that women have a greater vulnerability to alcohol than men (Baraona et al., 2001; Mann et al., 2005; Brienza and Stein, 2002), make knowledge of ethanol pharmacokinetics during lactation particularly important. Providing insights from evidence-based research will continue to aid in the development of scientifically-sound guidelines for ethanol consumption by nursing women as well as to shed light on how breast pumping or breast feeding affects the availability and elimination of ethanol, and perhaps other drugs, during lactation, an area that has received little scientific attention despite the increasing numbers of lactating women who need to take medications (Wisner et al, 2002; Stowe, 2007).

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Time of Day	8:30	8:46	9:00	9:30	10:00	10:10	10:25	10:35-10:53	10:53-12:25	12:55	13:25
Time Relative to Drinking Beverage (min)	-90	-76	-60	-30	0	10	25	35-52	53-145	175	205
Events	Glucose test Pregnancy test	Breast pump for 16 min (For Group Pumped Before)	Breakfast (Fed Condition) or No Breakfast (Fasted Condition)		Start drinking	End drinking		Breast Pump for 16 min (For Group Pumped After)			
BrAC	x			x (-1 min)			x	x x	xxxxxxxxxxxx	x	x
Ear Temperature	x			x			x	x x	xxxxxxx		

Figure 1.

Schedule of Events. Two groups of women were tested on two days separated by one week at two time periods: during and after lactation. Conditions were the same during both time periods. At time 0, women drank a 0.4 g/kg body weight dose of alcohol following a 12-hour overnight fast during one test session (Fasted Condition) or 1 hr after the consumption of a standard breakfast during the other (Fed Condition). Group PB breast pumped for 16 minutes one hour before circles) whereas Group PA breast pumped for 16 minutes beginning 35 min (0.6 hours) after (triangles) drinking alcohol. The symbol × denotes timing and number of breath alcohol concentrations (BrAC) and ear temperature measurements.

A. Fed Condition

A. Fasted Condition

Figure 2.

BrAC curves over time in two groups of women tested during (open symbols) and after lactation (solid symbols). Group PB breast pumped one hour before (N=5; circles) whereas Group PA breast pumped beginning 0.6 hours after (N=7; triangles) drinking a 0.4g dose of ethanol per kg of body weight. Panel A depict values obtained during Fed Condition and Panel B depict values obtained after an overnight Fasted Condition. Timing of breast pumping is indicated by hatched box and meal ingestion (for Fed Condition) by arrow. For both food conditions, reproductive stage significantly interacted with group and time (Fed condition: $F(14,140) = 2.86$; $p < 0.001$; Fasted condition: $F(14,140) = 5.93$; $p < 0.0001$). See text for further analyses.

Figure 3A.

Figure 3B

Figure 3.

Temperature Response to Fasting and an Alcohol Challenge.

Panel A. Ear temperature (°C) before and after women (Groups PA and PB combined) drank a 0.4g/kg dose of alcohol (at time 0) during fed (solid) and fasted (open) conditions.

Temperature readings taken during lactation are depicted as squares and those taken after lactation are depicted as triangles. There were a significant interaction between reproductive stage (during lactation, after lactation, condition (fed, fasted) and time since alcohol consumption ($F(12,108)=1.84$; $p=0.05$). See text for further analyses.

Panel B. Delta temperature scores relative to respective baseline values during fed (solid) and fasted (open) conditions and during lactation. Delta temperatures from lactating women are depicted as squares and those of women post lactation are depicted as triangles.

Table 1

Effects of Timing of Breast Pumping Stimulation Relative to Alcohol Consumption (Pumping Group), Condition (Fed, Fasted) and Reproductive State (During Lactation, After Lactation) on Alcohol Pharmacokinetics and Ear Temperatures.

Condition	Fed				Fasted				Statistical Effects	
	PB		PA		PB		PA		Interaction	Main
Reproductive State:	During Lactation	After Lactation	During Lactation	After Lactation	During Lactation	After Lactation	During Lactation	After Lactation		
Outcomes:										
<i>Pharmacokinetics</i> *										
AUC (g·hr/L)	0.64±0.06	0.59±0.06	0.82±0.07	0.84±0.07	1.25±0.08	1.27±0.05	1.39±0.10	1.37±0.06		Group: p=0.07; Condition: p<0.0001
Time-to-peak BAC (hr)	0.97±0.12	1.01±0.13	0.82±0.14	0.92±0.15	0.58±0.07	0.44±0.05	0.62±0.08	0.68±0.06		Condition: p=0.004
<i>Temperature</i> **										
Peak Temperature (C°)	36.0±0.1	36.4±0.1	36.2±0.1	37.1±0.1	35.4±0.1	36.3±0.1	36.0±0.1	36.7±0.2	State × Condition: p=0.03; State × Condition × Group: p=0.004	Group: p=0.0002; State: p=0.004 Condition: p=0.0001
Nadir Temperature (C°)	34.9±0.1	35.6±0.2	35.6±0.1	36.3±0.2	34.4±0.1	35.5±0.2	35.3±0.1	36.1±0.2		Group: p=0.005; State: p=0.0003 Condition: p=0.008

* Plus-minus values represent Means ±SEM of 7 women in Group PB and 5 women in Group PB

** Plus-minus values represent Means ±SEM of 6 women in Group PB and 5 women in Group PB.