PHYSIOLOGY

Is Lactic Acid a Primary Chemosignal Molecule for Pair Bonding in Humans?

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ABSTRACT

Objective: **We propose a hypothesis that lactic acid may be a primary chemosignal molecule for pair bonding (both, mother-baby and romantic pair) in humans.**

Method: **Published studies in humans which provided quantitation of lactic acid (or lactate) in seven body fluids, reviews on lactic acid metabolism and relevant publications which promoted the concept of putative pheromones were analyzed.**

Results: **A total of 22 studies in humans which had quantitated lactic acid (or lactate) values in seven body fluids (breast milk, lacrimal tear, saliva, semen, sweat, urine and vaginal fluid) were analyzed. The determination method had varied among these 22 studies. Colorimetry, enzymatic, oxidation and titration, capillary electrophoresis with amperometric detection, gas chromatography and HPLC were the mainly used methods for lactic acid determination. A definite pattern of the presence of lactic acid in all the body fluids receives recognition. Six reasons for why lactic acid is a primary chemosignal for humans in mother-baby bonding and romantic pair bonding are suggested.**

Conclusions: **Our hypothesis invite further attention on the functional versatility of lactic acid in all the body fluids of humans, and its contribution to the emotional states of excitement during pair bonding.**

KEY WORDS

lactic acid bacteria, metabolism, mother-baby, odor, pheromone

INTRODUCTION

Lactic acid is a vital endogenous compound, engaged in intermediary metabolism of cells. Table 1 provides a select list of 13 reviews on lactic acid and its currently recognized physiological roles[1-13]. In 2004, Gladden[3] had inferred: 'From 1930s to early 1970s, lactic acid was considered as a dead end waste product of glycolysis due to hypoxia, and a major cause of muscle fatigue. Since 1970s, the lactate paradigm shifted and lactate came to be considered as an important intermediate in wound repair and regeneration process.' In addition, the role of lactic acid (lactate) as a signaling molecule has gained prominence lately[10,12,13].

The definition of pair bonding, meant in this study, is 'Development of a strong and long-lasting closeness and emotional attachment or bonding between two lovers or between parent and child' as presented by Francoeur[14]. As such, we include both, mother-baby bonding and romantic pair bonding under the large frame 'pair bonding'. Similar nurturing behaviors such as gazing, holding, hugging, feeding and kissing represent both types of bonding. In presenting a new pair bonding paradigm in the 20th century, Pinsof[15] included 7 set of factors involving ability to

(1) attach to another human being
(2) love another person
(3) select an appropriate partner
(4) commit to an intimate relationship
(5) maintain a certain level of personal integrity, morality and responsibility
(6) get along with another person over an extended period of time
(7) regulate emotion (particularly anger) and impulses (particularly sexuality)

We have arranged these 7 ability factors, in an ascending order of progress in pair bonding. While discussing the biology underlying pair bond formation, Walum and Young[16] had proposed that pair bonding is the evolutionary antecedent of romantic love and that pair bond is an essential element of romantic love.

The influence of 7 body fluids in mother-baby bonding and romantic pair bonding is presented in Table 2. Based on the assembled quantitative and experimental evidence on the ubiquitous distribution of lactic acid in all the body fluids, we propose a hypothesis that lactic acid may be a primary chemosignal molecule for pair bonding in humans.

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Table 1: Select list of reviews on Lactic acid and its related physiological roles

Year	Topic	Reference
1932	Lactic acid in the living organism	Himwich[1]
1981	Vaginal odors and secretions	Huggins & Preti[2]
2004	Lactate metabolism ─ a new paradigm	Gladden[3]
2012	Lactate in human sweat	Derbyshire *et al*.[4]
2012	Brain lactate metabolism	Dienel *et al*.[5]
2015	Lactate as a signaling molecule in the brain	Mosienko *et al*.[6]
2017	Vaginal microbiota and host defence	Smith & Ravel[7]
2017	Lactic acid, *Lactobacillus* and vaginal health	Tachedjian *et al*.[8]
2017	Lactobacilli in human vaginal microbiota	Witkin & Linhares[9]
2017	Lactic acid and glycolysis	Sun *et al*.[10]
2018	Science and translation of Lactate shuttle theory	Brooks[11]
2020	lactate signaling in malignancy	Baltazar *et al*.[12]
2020	lactate signaling	Certo *et al*.[13]

Table 2: Influence of Body Fluids in Mother-Baby Bonding and Pair Bonding

Body Fluid	Mother-Baby Bonding[1]	Romantic Pair Bonding[2]
Breast milk (♀ only)	positive	negative
Lacrimal tears	positive	positive
Saliva	negative	positive
Semen (♂ only)	negative	positive
Sweat	negative	positive
Urine	positive	'marginal'
Vaginal fluid (♀ only)	negative	positive

[1]Signals are provided by the mother to baby via breast milk; signals provided by the baby to mother via lachrimal tears and urine. Tough a mother kisses her baby, in all probabilities, saliva is not exchanged during kissing, as opposed to romantic pair-bonding relationship.

[2]Signals are provided by courting couple via body fluids equally such as saliva, sweat, semen(♂)and vaginal fluid(♀). During foreplay, saliva is exchanged between pairs during kissing. Semen and vaginal fluid are exchanged during oral sex. Sweat is generated during coitus act. Anecdotal evidence for women shedding tears during climax of coitus act prevails. 'Marginal' indicates marginally positive, in paraphilia cases of urolagnia or undinism.

METHOD

Published studies in humans which provided quantitation of lactic acid (or lactate) in seven body fluids, reviews on lactic acid metabolism and relevant publications which promoted the concept of putative pheromones were analyzed. We have excluded studies which reported merely the presence of lactic acid (or lactate) in body fluids, without quantification.

RESULTS

A total of 22 studies in humans which had quantitated lactic acid (or lactate) values in seven body fluids, between 1927 and 2011, are summarized in Table 3. These include, breast milk (5 studies)[17-21], lacrimal tear (1 study)[22], saliva (2 studies)[23,24], semen (4 studies)[25-28], sweat (4 studies)[29-32], urine (2 studies)[21,33] and vaginal fluid (4 studies)[34-37]. All seven body fluids are either released or excreted. As one would expect, the determination methods had varied among these 22 studies. Colorimetry, enzymatic, oxidation and titration, capillary electrophoresis with amperometric detection, gas chromatography and HPLC were the mainly used methods. As such, reported lactic acid (lactate) values in all the body fluids cannot be calibrated with precision. Nevertheless, a definite pattern of the presence of lactic acid in all the body fluids receives recognition.

DISCUSSION

First, we comment on the available quantitative data on the lactic acid content of human body fluids. Table 3 shows that among the 7 body fluids studied, compared to other body fluids, reported data on lacrimal tears are inadequate. Even the only available study by van Haeringen and Glasius[22] is five decades old. This is partly reflected by the difficulty in collecting lacrimal tears from human subjects. While inferring that the lactate levels of 1-5 mmol/L in tears are higher than the normal blood levels (0.5-0.8 mmol/L), Van Haeringen and Glasius[22] had failed to indicate the age range and sex of their 10 subjects from whom samples were collected.

Though four androstene steroids (androstenone, androstanol, androstadienone and estratetraenol) have been promoted as human pheromones for pair bonding during the past two decades, Wyatt had criticized strongly such overenthusiastic promotions for false positive data, lack of methodological rigor and statistical doubts[38,39]. For mother-baby bonding, Vaglio *et al*.[40] had identified 5 putative pheromone chemicals (Table 4): 1-dodecanol (lauryl alcohol), 1-1 oxybis octane, isocurcumenol, a-hexyl cinnamic aldehyde and isopropyl myristate. But, quantitative data on these putative pheromone chemicals is missing. The molecular weights of these 5 chemicals range between 186 and 270, and their boiling points range between 167℃ to 350℃. Compared to these five chemicals, lactic acid has a lower molecular weight of 90 and lower boiling point of 122℃.

As for the origin of human pheromones, Alex Comfort postulated 50 years ago, 'Many mammalian pheromones seem to be urinary, though specialized secretions are also common. Contact with urine plays little part in human relations, though it may be emphasized in paraphilias. More likely vehicles in man are the skin, including axillary and pubic apocrine glands and hair tufts, which resemble the deer's tarsal organ and the smegma"[41]. As indicated in Table 2, Comfort had partially erred in not identifying the role played by baby's urine in mother-baby bonding. Even though blood (as a body fluid) is not released, except under traumatic situations of injury, one study reports a significant increase in plasma lactic acid in healthy boys (1-3 years old) who had cried and resisted induction of anesthesia prior to undergoing circumcision[42].

Why lactic acid seems an optimal compound for a role as primary chemosignal in the bonding process of humans? We suggest following reasons.

(1) It's ubiquity in all body fluids makes it an optimal choice to satisfy the parsimony principle favored in evolution. Simply put, frugality in the use of body's resources[43,44]. This is best illustrated in vaginal niche, where lactic acid serves multiple functions, including microbicidal activity[2,36,45] and anti-inflammatory effect on cervico-vaginal epithelia to mitigate HIV transmission in vivo[45]. Such multi-functional deeds have yet to be proved empirically for other touted 'putative pheromone' molecules.

(2) It complies with the definition of a pheromone signal, in eliciting a specific reaction such as a stereotyped behavior in the recipient[38]. For instance, in mother-baby bonding, lactic acid in the breast milk elicits baby's nose and mouth towards the breast. Lactic acid in the lacrimal tears of a baby elicits immediate comforting reaction from the mother.

(3) It is released from the human body regions identified by Comfort[41], namely skin, axillary and pubic apocrine glands, penis and vagina. Among all other mammals, women are unique in having lactic acid at high levels in vagina during their reproductive years, relative to pre-puberty and post-menopausal phases[47].

(4) Low molecular weight (90.1) and relatively low boiling point (122℃) makes lactic acid air dispersal within short intimate distance easier.

(5) In dissolved state, lactic acid has a mild odor of soured milk or yogurt[2].

(6) As a chemosignal, 2.2 fold increase in the concentration of lactic acid in vaginal fluid has been demonstrated during sexual stimulation[2].

Table 3: Quantitation of Lactic Acid in Human Body Fluids involved in Bonding

Subject No	Age(yr)	Lactic Acid	Reference
breast milk			
62♀	21-45	30 - 173 µg/ml (mean 96 µg/ml)	Ohta[17]
26♀	30.5 ± 4.4	60 µg/ml (baseline)	Wallace *et al*.[18]
		256 µg/ml (10 min post-exercise)	
		267 µg/ml (30 min post-exercise)	
9♀	34.4 ± 5.1	0.1 mM	Carey *et al*.[19]
24♀	25 - 45	8.1 µg/ml (pre-maximal exercise)	Wright *et al*.[20]
		18.9 µg/ml (post-maximal exercise)	
3♀	27 - 33	4.8 - 16.5 µg/ml	Zhang *et al*.[21]
		28.9 - 92.5 µg/ml (10 min post-exercise)	
		6.4 - 35.8 µg/ml (30 min post-exercise)	
		4.5 - 17.0 µg/ml (60 min post-exercise)	
lacrimal tear			
10	n.m	1 - 5 mmol/L (as lactate)	van Haeringen & Glasius[22]
saliva			
9	22.2	0.2 - 1.7 mM (as lactate)	Segura *et al*.[23]
18♂	17.3	0.48 ± 0.08 mM/L (before training)	Volodchenko *et al*.[24]
		1.95 ± 0.14 mM/L (after 2h training)	
Semen			
50♂	n.m.	0.95 - 1.37 mg/ml	McCarthy *et al*.[25]
n.m.	n.m.	0.9 - 1.0 mg/ml	Goldblatt[26]
9♂	n.m.	1.46 mg/ml	Ackerman & Roussel[27]
5♂		11.48 ± 1.7 mg/ml (low fertility)	Lay *et al*.[28]
8♂		19.13 ± 1.1 mg/ml (medium fertility)	
11♂		16.11 ± 0.8 mg/ml (high fertility)	
sweat			
3♂	28-39	0.34 - 0.97 mg/ml	Mosher[29]
8?	30-60	2.85 ± 0.2 mg/ml	Thurmon & Ottenstein[30]
4♂	19-33	3.36 ± 0.0 mg/ml	
3	n.m	2.13 ± 0.2 mg/ml (dry heat)	Lyburn[31]
30	n.m.	0.87 ± 0.0 mg/ml (wet heat)	
1♀	22	8.28 mg/ml	Sugase & Tsuda[32]
7♂	21-24	8.73 - 24.39 mg/ml	
urine			
3♀	27-33	19.4 - 31.4 µg/ml	Zhang *et al*.[21]
61	0-134 day	6.4 mmol/mol creatinine	Haschke-Becher *et al*.[33]
45	30 d - 2.5 y	39.9 mmol/mol creatinine	
	2.5 - 4	10.1 mmol/mol creatinine	
59	2.5 - 4	5.5 mmol/mol creatinine	
vaginal fluid*			
5♀	n.m	0.658 mg/g secretion (unstimulated)	Preti *et al*.[34]
		1.482 mg/g secretion (self stimulation to orgasm)	
59♀	18-30	9.5 ± 11.9 mg/24 hr (OC non users)	Bauman *et al*[35]
82♀	18-30	15.4 ± 10.0 mg/24 hr (OC users)	
48♀	18-45	111 ± 22 mM	O'Hanlon *et al*.[36]
77♀	31	0.11 mmol/l (healthy control)	Beghini *et al*.[37]
43♀	29	0.02 mmol/l (bacterial vaginosis patients)	
52♀	28	0.13 mmol/l (vulvovaginal candidiasis patients)	
21♀	32	0.31 mmol/l (cytolytic vaginosis patients)	

n.m = not mentioned; OC = oral contraceptives;

*Beghini *et al*.'s study provided assayed median values of L-isomer and D-isomer of lactic acid for healthy controls and women suffering from three clinical conditions. What is shown in the table are the values for L-isomer.

Table 4: Signal Molecules from mother to baby during bonding in Humans

Signal molecule[a]	Formula	Mol. Wt.	boiling point (°C)
1) 1-dodecanol (lauryl alcohol)	$C_{12}H_{26}O$	186.34	259
2) 1-1'oxybis octane	$C_{16}H_{34}O$	242.44	286.5
3) Isocurcumenol	$C_{15}H_{22}O_2$	234.33	350
4) α-hexyl cinnamic aldehyde	$C_{15}H_{20}O$	216.3	174
5) Isopropyl myristate	$C_{17}H_{34}O_2$	270.45	167
Lactic Acid[b]	$C_3H_6O_3$	90.1	122

[a]Signal molecules (putative pheromones) 1-5, identified by Vaglio *et al.*[40] from sweat-patch picked at para-axillary and nipple-areola regions of 20 women (aged 30-40 years, mean age 36.8 years) during pregnancy and childbirth. But, concentration of these 5 chemicals in the nipple-areola regions were not quantitated; only mean proportional rates (in percent) were presented.

[b]Based on the molecular weight, boiling point and odor profile, we propose that lactic acid can also be a primary signal molecule in nipple-areola region. For concentration range of lactic acid in breast milk (μg/ml), see Table 3.

Two prevailing limitations for this study needs mention. First, is the lack of a single publication in which the lactic acid content of all body fluids have been assayed, using the same quantitation method. Secondly, our hypothesis can neither be enhanced nor discredited due to an irritating tendency of psychologists using attention grabbing terms like 'pheromones' or 'chemical signals' in body odor studies[48-50)], without specifically identifying what these chemicals are. It could be that psychologists who flagrantly promote such usage either do not have expertise to identify such molecules in their labs or patience to chemically check such molecules via available service vendors, prior to publication. We suggest that such vanities need to be restrained to the minimum.

CONCLUSION

It is appropriate to state three sentences on what Wyatt had observed in 2015, related to 'best candidate human pheromone': 'Historically, human pheromone research has focused on sex pheromones, but given our other highly developed senses in adulthood, sex may not be the right place to look first. Instead, suckling is one behavior in mammals where smell is known to be ubiquitously important. The secretion produced by lactating human mothers from areola (Montgomery's) skin glands around their nipple may contain a good candidate human pheromone'[38)]. Similar thought was repeated by Wyatt two years later[51)]. We question the need to look for two different signal chemicals in the breast of women and reproductive organs of men and women. Lactic acid perfectly fits the bill as a 'two-in-one' signal chemical for mother-baby bonding and romantic pair bonding. A connecting link between mother-baby bonding and romantic pair bonding is the role played by woman's breast. As such, the chemosignal role played by lactic acid present in breast milk and vaginal fluid deserve attention. Previously, Newton and Newton[52)] had inferred that the physiologic responses in lactation and coitus are closely related, including occurrence of (1) uterine contractions, (2) nipple erection, and (3) milk ejection.

In conclusion, our hypothesis invite further attention on the functional versatility of lactic acid in all the body fluids (lacrimal tears, saliva, sweat, breast milk, semen and vaginal fluid) of humans, and its contribution to the emotional states of excitement during pair bonding.

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