Smell and taste in the preterm infant

Frank H. Bloomfield[a,b,*], Tanith Alexander[a,c], Mariana Muelbert[a], Friederike Beker[d,e]

[a] Liggins Institute, University of Auckland, Auckland, New Zealand
[b] Newborn Services, National Women's Health, Auckland City Hospital, Auckland, New Zealand
[c] Neonatal Unit, Middlemore Hospital, Counties Manukau Health, Auckland, New Zealand
[d] Department of Newborn Services, Mater Mothers' Hospital, Brisbane, QLD, Australia
[e] Mater Research Institute, The University of Queensland, Brisbane, QLD, Australia

ARTICLE INFO

ABSTRACT

Olfaction and gustation are critical for the enjoyment of food but also have important metabolic roles, initiating the cephalic phase response that sets in train secretion of hormones important for metabolism and digestion before any food is actually ingested. Smell and taste receptors are functional in the fetus and there is evidence for antenatal learning of odours. Despite enteral nutrition and metabolism being major issues in the care of very preterm infants, often little consideration is given to the potential role of smell and taste in supporting these processes, or in the role they may have in encoding hypothalamic circuitry in a way that promotes healthy metabolism in the post-neonatal period. This review will discuss the evidence for the role of smell and taste in the newborn infant.

1. Introduction

The importance of the olfactory and gustatory senses for the enjoyment and metabolism of food has been recognised for well over 120 years. Henry Fincks wrote *"To which of our senses are we most indebted for the pleasures of the table? To name the sense of taste in answer to this question would be quite as incorrect as to assert we go to the opera to please our eyes. More incorrect, in fact, because many do attend the opera chiefly on account of the spectacle; whereas, in regard to gastronomic delights it is safe to say that at least two-thirds of our enjoyment is due to the sense of smell."* [1]. Pavlov's experiments in dogs with exteriorised oesophagi demonstrated that the presence of food in the mouth, without it ever reaching the stomach, stimulated copious gastric secretions; in contrast, if bread was inserted into the stomach via tube without the dog being aware, gastric secretions were substantially less and the bread remained in the stomach undigested for over an hour [2]. The activation of the pathways involved in digestion in anticipation of food is now known as the cephalic phase response. The cephalic phase response increases gut motility and the secretion of enzymes and hormones such as ghrelin, insulin, leptin, glucagon-like peptide-1, cholecystokinin, pancreatic polypeptide and gastrin that result in tighter regulation of blood glucose concentrations and enhanced digestion [3]. Gastro-intestinal motility, digestion and metabolic control are major issues in nutrition of the preterm infant [4], yet the standard mode of

enteral feeding before sucking feeds are established is to provide milk via a gastric tube, at intervals and volumes decided by the clinician, usually without any accompanying smell or taste. A recent survey of Australian and New Zealand neonatal units found that, even in moderate-late preterm babies, only approximately 30% of units routinely provided smell or taste before feeds (Alexander and Bloomfield, unpublished data). This brief review will discuss the potential role of smell and taste in the nutritional care of the preterm infant.

2. Ontogeny of olfaction and gustation

The olfactory system is complex and, in most mammals, consists of the main or primary olfactory system, located in the upper part of the nasal cavity, and the vomeronasal organ, located in the nasal septum and of uncertain significance in humans. The primary olfactory receptors are present by the eighth week of gestation and have a mature appearance by the end of the second trimester [5,6]. Olfactory marker protein, considered to correlate with neuroreceptor functionality and connectivity with the main olfactory bulb, is expressed in the olfactory mucosa by 28 weeks' gestation and in the main olfactory bulb by 32–35 weeks' gestation [7]. Taste receptors detect the five tastes and flavours (bitter, sweet, sour, salty and umami) and begin to develop at 7–8 weeks' gestation, maturing by the middle of the second trimester [8,9]. Fetal swallowing of small amounts of amniotic fluid begins at the

* Corresponding author at: Liggins Institute, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand.
E-mail addresses: f.bloomfield@auckland.ac.nz (F.H. Bloomfield), t.alexander@auckland.ac.nz (T. Alexander), m.muelbert@auckland.ac.nz (M. Muelbert), Friederike.Beker@mater.org.au (F. Beker).

end of the first trimester and reaches up to 750 mL/day by 34 weeks' gestation, when the gastrointestinal tract is beginning to develop mature migrating motor complexes that will result in directional cranial-caudal peristalsis [10]. Thus, fetal smell and taste receptors are exposed to the components of amniotic fluid for many weeks before birth and at comparable gestations to preterm infants.

Odour of amniotic fluid is known to be important for recognition of kin in a variety of animals; for example, newborn lambs and rat pups are preferentially attracted to areas impregnated with their own amniotic fluid rather than to areas impregnated with amniotic fluid from an unrelated female [11]. Healthy, 3-day old term newborns preferentially turn their heads towards a pad impregnated with their own amniotic fluid rather than towards a pad impregnated with unfamiliar amniotic fluid [6]. Interestingly, this occurs similarly in both breast-fed babies (who may be re-exposed to similar volatiles through mothers' milk) and bottle-fed infants [6]. In two-day old term newborns, the duration of head orientation to pads impregnated with amniotic fluid or colostrum is similar and significantly greater than orientation towards a control stimulus of water. However, by four days after birth, babies exhibit a clear preference for mothers' milk over amniotic fluid, although a preference for amniotic fluid over water remains [11]. That these preferences are related to prenatal, rather than postnatal, olfactory learning is demonstrated by a study performed in healthy term babies immediately after birth before the routine use of skin-to-skin at birth [12]. Babies were washed in water containing 0.05% potassium permanganate and placed in a cot until the placenta was delivered. One of mother's nipples/areolae was randomly assigned to be treated with amniotic fluid and the baby placed prone in the midline on the mother's chest. Twenty-three out of thirty babies chose the breast treated with amniotic fluid, 21 of whom were observed to examine both sides of the mother's chest before making a choice. Twenty-two of the thirty babies successfully grasped a nipple and began to suck without help; 17 of these chose the nipple treated with amniotic fluid. These data suggest that the odour of amniotic fluid is a stronger attractant for a newborn baby than simply the mother's odour. Memory of prenatal olfactory learning appears to persist for some time after birth. Babies separated from their mothers immediately after birth and fed formula via bottle for 10–14 days without contact with their mothers, generated greater expression pressure, suck frequency and suck efficiency during a bottle feed at 10–14 days when exposed to filter paper impregnated with expressed mothers' milk rather than with formula or water [13]. Similarly, babies of mothers who drank carrot juice in the last trimester but not during lactation demonstrated fewer negative facial expressions in response to weaning cereals prepared with carrot juice, again presumably indicating memory of flavour of amniotic fluid [14]. Perinatally-acquired odours also generate long-term memory, as babies exposed to a camomile balm used prophylactically to prevent sore nipples exhibited preference for camomile odour over violet odour at both 7 and 21 months of age [15].

Thus, babies born at term demonstrate prenatal functioning of olfactory receptors that retain memory of amniotic fluid volatile constituents into the post-natal period and beyond. Although some of the volatile fingerprints have been identified in breast-milk [16], further research is needed to understand which components generate the greatest response from babies.

3. Olfaction in preterm newborns

More recent evidence indicates that olfaction is also important in preterm newborns. Some innovative approaches have been taken to investigate the effect of stimulation with odour on preterm infants' non-nutritive sucking behaviour. Bingham has developed an 'olfactometer' which can be controlled remotely to deliver test or control odours through a programmed schedule (non-contingent) or contingent upon infant sucking [17]. In 7 moderately preterm newborns (33–34 weeks' gestation), stimulation with breast-milk odour during a tube feed

resulted in a greater median number of sucks compared with control. In 29 preterm babies with a mean gestational age of 30 weeks, tested at a mean corrected gestational age of 33 weeks, exposure to milk odour via a specially adapted and instrumented pacifier resulted in increased measures of suck pressure and burst activity in those receiving breast milk odour compared with formula odour [18]. Similarly, in a very small non-blinded study, exposure of preterm infants to breast-milk odour once a day for five days, commencing the day before first attempting breast-feeding at 35 weeks' post-conceptional age resulted in longer sucking bouts, increased numbers of long sucking bouts and increased milk intake (assessed by weighing immediately before and after feeds) [19]. Exposed babies also were discharged home significantly earlier. Interpretation of these studies is complicated by the very small number of participants.

Two randomised controlled trials and one observational cohort study have assessed the impact of early colostrum administration in preterm babies on clinical and feeding outcomes [20–22]. These have reported that administration of small amounts of oral colostrum to extremely preterm or extremely low birthweight (ELBW) infants commencing within the first three days after birth is safe. A cohort study reported increased rates of receiving breastmilk as the majority of enteral feeds six weeks later [22] and a randomised trial of sixteen ELBW babies reported a significantly shorter time to full enteral feeds of 150 mL·kg^{-1}·day^{-1} (14 vs 24 days) [21]. The intervention in this study was 0.2 mL oral colostrum every 2 h for 48 consecutive hours, beginning 48 h after birth. The magnitude of the effect seems extremely large for such a brief intervention and it is not clear that the blinding method described (syringes covered with tape) would have been effective. A larger randomised, placebo-controlled trial of 48 babies born before 28 weeks' gestation who received 0.2 mL oropharyngeal colostrum or water every 3 h for 72 h from 48 to 96 h after birth did not find any difference in time to full enteral feeds or to hospital discharge [20]. However, there was a statistically significant reduction in clinical (but not proven) sepsis (12/24 vs 22/24), although rates in the placebo group were extremely high. Nevertheless, significantly greater urinary levels of secretory immunoglobulin A, and lower levels of salivary transforming growth factor β and interleukin 8, at one and two weeks suggest that there may be an underlying mechanism that would support such an effect that is worthy of further study. A large RCT ($n = 622$) designed to address the question of whether oropharyngeal mother's milk in extremely low birthweight babies will reduce the incidence of sepsis and necrotising enterocolitis is underway [23].

Longer exposure of tube-fed preterm babies to smell or to smell and taste may shorten time to full enteral feeds, although further research is needed. A trial of 51 infants < 29 weeks' gestation randomised babies to smell and taste of milk before each feed or no olfactory/gustatory exposure to milk until 32 weeks' gestation [24]. Babies in the intervention group tended to reach full enteral feeds earlier (median 13.5 vs 15.5 days). Similarly, a trial of 80 preterm babies between 28 and 34 weeks' gestation reported that administration of breast milk odour during tube feeds three times a day until oral feeds were attained led to full oral feeding 3 days earlier and a four day reduction in hospital stay [25]. Neither of these trials was blinded.

4. Smell, taste and the potential impact on metabolism

In addition to the potential for improving tolerance of enteral feeds through stimulation of the digestive tract, olfaction also may impact upon the central appetite-regulatory pathways. Information on odour is passed from the olfactory bulbs to the primary olfactory cortex via the lateral olfactory tract. Functional MRI studies in adults demonstrate activation of the lateral and anterior orbito-frontal gyri [26]. From there, information passes to the orbito-frontal cortex, where conscious perception of smell occurs, and also to the hypothalamus via the amygdala of the limbic system. Near-infrared spectroscopy (NIRS) studies in term and preterm neonates have demonstrated changes in

cerebral oxygenation in the pre-frontal area in response to odour stimulation [27–29]. This is assumed to reflect changes in blood flow and, therefore, neuronal activity. Term infants demonstrate greater changes in cerebral oxygenation in response to maternal breast milk odour than to formula odour [29] and decreased oxygenation, thought to reflect deactivation, has been demonstrated in preterm infants in response to unpleasant odours associated with neonatal intensive care such as detergent and disinfectant [27]. In newborn rabbit pups, the maternal mammary pheromone upregulates expression of the Fos protein, a regulator of cell proliferation and differentiation, to a greater extent than a control odour in the posterior piriform cortex and the lateral hypothalamus [30]. The posterior piriform cortex is an associative cortex, thought to play a role in encoding responses to odour through learning and anticipation [31]. The lateral hypothalamus is a key area for feeding behaviour, with output neurons to a variety of brain areas including the arcuate nucleus, part of the hypothalamic appetite-regulatory centre [32]. Hypothalamic circuitry largely develops antenatally in humans and primates, with neurogenesis occurring in the first trimester and circuit formation beginning in the late second trimester and extending throughout the third trimester [33,34]. Development of the hypothalamic appetite-regulatory pathways has been demonstrated to be affected by nutritional signals during fetal life, even from very early pregnancy. For example, maternal periconceptional undernutrition in sheep leads to epigenetically-regulated changes in glucocorticoid receptor and pro-opiomelanocortin expression in the ventral hypothalamus, which includes the arcuate nucleus, in the late gestation fetus that persist through to adult life [35,36]. In rats, maternal undernutrition leads to postnatal hyperphagia and increased fasting leptin and insulin concentrations [37]. The postnatal phenotype could be reversed by neonatal leptin administration during the first two weeks after birth [38]. In rats, the hypothalamic circuit development that occurs in utero in humans occurs in the early postnatal period [39], indicating that leptin and insulin may be important hormones in encoding hypothalamic appetite-regulatory and metabolic pathways. Increased levels of insulin during this critical period of hypothalamic differentiation have been associated with altered development of cholecystokinin, galanin and neuropeptide Y (NPY) neurons [40,41], all of which are involved in appetite regulation. The immature regulation of insulin transport across the blood brain barrier during the neonatal period in rats provides a mechanism by which the developing hypothalamus can be exposed to elevated levels of insulin.

It therefore is reasonable to postulate that ordinary fluctuations of metabolic hormones, such as insulin and leptin, in the neonatal period might be important in determining healthy encoding of the hypothalamic pathways. This might particularly be the case in preterm infants who are ex utero at a time when critical development of circuitry is occurring. The cephalic phase response mentioned above is active in the newborn and is important for initiating secretion of these hormones. In addition to systemic secretion, these hormones also are present in saliva, secretion of which, of course, is stimulated by smell and taste [42]. Indeed, salivary concentrations of NPY2 receptor, involved in hunger signalling, have been reported to have a 95% positive predictive power for feeding immaturity (defined as inability to sustain full oral feeds), although the negative predictive power was weak [43]. A randomised controlled trial (sample size 180 extremely preterm infants) to determine whether pulsed orocutaneous intervention simultaneous with feeding will accelerate time to full oral feeds (ClinicalTrials.gov NCT02696343) is underway [44]. A randomised factorial experiment (sample size 530 moderate-late preterm infants) is investigating whether the simpler approach of providing smell and taste before all tube feeds will have a similar effect, as well as mitigating the increased fat mass seen by term-corrected age in preterm infants [45,46] (Australia and New Zealand Clinical Trials Registry ACTRN12616001199404).

5. Conclusion

Smell and taste are powerful sensory inputs that develop during fetal life and are important in the transition to postnatal feeding. In addition to the importance of smell in recognition of the mother, smell and taste initiate metabolic pathways that promote digestion and metabolic control. Feed intolerance in the newborn period is a major problem in the extremely low preterm baby and even moderate-late preterm birth carries increased risk of impaired metabolic health in later life [47,48]. Further research should investigate whether exposing tube-fed preterm infants to smell and taste of mother's milk may improve these outcomes for future extremely preterm babies.

Conflict of interest statement

F H Bloomfield is the Principal Investigator of the randomised factorial trial referred to in the penultimate paragraph (ACTRN12616001199404) which is funded by the Health Research Council of New Zealand. He holds numerous other research grants.

F H Bloomfield is the Abbot Nutrition Lecturer at the 2017 Perinatal Research Society (USA). The lecture is on a topic largely unrelated to this manuscript (the role of nutrition on development of the pancreas).

References

[1] H.T. Fincks, The gastronomic value of odours, Contemp. Theatr. Rev. 50 (Nov 1886) (1886) 680–695.
[2] I. Pavlov, Ivan Pavlov - Nobel Lecture: Physiology of Digestion, Nobel Media AG, 2014.
[3] M.L. Power, J. Schulkin, Anticipatory physiological regulation in feeding biology: cephalic phase responses, Appetite 50 (2–3) (2008) 194–206.
[4] J.E. Harding, B.E. Cormack, T. Alexander, J.M. Alsweiler, F.H. Bloomfield, Advances in nutrition of the newborn infant, Lancet 389 (10079) (2017) 1660–1668.
[5] S.V. Lipchock, D.R. Reed, J.A. Mennella, The gustatory and olfactory systems during infancy: implications for development of feeding behaviors in the high-risk neonate, Clin. Perinatol. 38 (4) (2011) 627–641.
[6] B. Schaal, L. Marlier, R. Soussignan, Olfactory function in the human fetus: evidence from selective neonatal responsiveness to the odor of amniotic fluid, Behav. Neurosci. 112 (6) (1998) 1438–1449.
[7] M.I. Chuah, D.R. Zheng, Olfactory marker protein is present in olfactory receptor cells of human fetuses, Neuroscience 23 (1) (1987) 363–370.
[8] R.M. Bradley, I.B. Stern, The development of the human taste bud during the foetal period, J. Anat. 101 (Pt 4) (1967) 743–752.
[9] M. Witt, K. Reutter, Scanning electron microscopical studies of developing gustatory papillae in humans, Chem. Senses 22 (6) (1997) 601–612.
[10] F.H. Bloomfield, J.E. Harding, Fetal nutrition, in: W.W. Hay, Jr.P.J. Thureen (Eds.), Neonatal Nutrition and Metabolism, Cambridge University Press, Cambridge, 2006, pp. 1–22.
[11] L. Marlier, B. Schaal, R. Soussignan, Neonatal responsiveness to the odor of amniotic and lacteal fluids: a test of perinatal chemosensory continuity, Child Dev. 69 (3) (1998) 611–623.
[12] H. Varendi, R.H. Porter, J. Winberg, Attractiveness of amniotic fluid odor: evidence of prenatal olfactory learning? Acta Paediatr. 85 (10) (1996) 1223–1227.
[13] K. Mizuno, A. Ueda, Antenatal olfactory learning influences infant feeding, Early Hum. Dev. 76 (2) (2004) 83–90.
[14] J.A. Mennella, C.P. Jagnow, G.K. Beauchamp, Prenatal and postnatal flavor learning by human infants, Pediatrics 107 (6) (2001) E88.
[15] M. Delaunay-El Allam, R. Soussignan, B. Patris, L. Marlier, B. Schaal, Long-lasting memory for an odor acquired at the mother's breast, Dev. Sci. 13 (6) (2010) 849–863.
[16] Z. Jiang, Y. Liu, Y. Zhu, J. Yang, L. Sun, X. Chai, Y. Wang, Characteristic chromatographic fingerprint study of short-chain fatty acids in human milk, infant formula, pure milk and fermented milk by gas chromatography-mass spectrometry, Int. J. Food Sci. Nutr. 67 (6) (2016) 632–640.
[17] P.M. Bingham, D. Churchill, T. Ashikaga, Breast milk odor via olfactometer for tube-fed, premature infants, Behav. Res. Methods 39 (3) (2007) 630–634.
[18] P.M. Bingham, S. Abassi, E. Sivieri, A pilot study of milk odor effect on nonnutritive sucking by premature newborns, Arch. Pediatr. Adolesc. Med. 157 (1) (2003) 72–75.
[19] C. Raimbault, E. Saliba, R.H. Porter, The effect of the odour of mother's milk on breastfeeding behaviour of premature neonates, Acta Paediatr. 96 (3) (2007) 368–371.
[20] J. Lee, H.S. Kim, Y.H. Jung, K.Y. Choi, S.H. Shin, E.K. Kim, J.H. Choi, Oropharyngeal colostrum administration in extremely premature infants: an RCT, Pediatrics 135 (2) (2015) e357–66.
[21] N.A. Rodriguez, M.W. Groer, J.M. Zeller, J.L. Engstrom, L. Fogg, H. Du, M. Caplan, A randomized controlled trial of the oropharyngeal administration of mother's

colostrum to extremely low birth weight infants in the first days of life, Neonatal Intensive Care 24 (4) (2011) 31–35.

[22] R. Snyder, A. Herdt, N. Mejias-Cepeda, J. Ladino, K. Crowley, P. Levy, Early provision of oropharyngeal colostrum leads to sustained breast milk feedings in preterm infants, Pediatr. Neonatol. (2017).

[23] N.A. Rodriguez, M. Vento, E.C. Claud, C.E. Wang, M.S. Caplan, Oropharyngeal administration of mother's colostrum, health outcomes of premature infants: study protocol for a randomized controlled trial, Trials 16 (2015) 453.

[24] F. Beker, G. Opie, E. Noble, Y. Jiang, F.H. Bloomfield, Smell and taste to improve nutrition in very preterm infants: a randomized controlled pilot trial, Neonatology 111 (2017) 260–266.

[25] A. Yildiz, D. Arikan, S. Gozum, A. Tastekin, I. Budancamanak, The effect of the odor of breast milk on the time needed for transition from gavage to total oral feeding in preterm infants, J. Nurs. Scholarsh. 43 (3) (2011) 265–273.

[26] L.M. Levy, R.I. Henkin, A. Hutter, C.S. Lin, D. Martins, D. Schellinger, Functional MRI of human olfaction, J. Comput. Assist. Tomogr. 21 (6) (1997) 849–856.

[27] M. Bartocci, J. Winberg, G. Papendieck, T. Mustica, G. Serra, H. Lagercrantz, Cerebral hemodynamic response to unpleasant odors in the preterm newborn measured by near-infrared spectroscopy, Pediatr. Res. 50 (3) (2001) 324–330.

[28] M. Bartocci, J. Winberg, C. Ruggiero, L.L. Bergqvist, G. Serra, H. Lagercrantz, Activation of olfactory cortex in newborn infants after odor stimulation: a functional near-infrared spectroscopy study, Pediatr. Res. 48 (1) (2000) 18–23.

[29] S. Aoyama, T. Toshima, Y. Saito, N. Konishi, K. Motoshige, N. Ishikawa, K. Nakamura, M. Kobayashi, Maternal breast milk odour induces frontal lobe activation in neonates: a NIRS study, Early Hum. Dev. 86 (9) (2010) 541–545.

[30] N.Y. Schneider, C. Piccin, F. Datiche, G. Coureaud, Spontaneous brain processing of the mammary pheromone in rabbit neonates prior to milk intake, Behav. Brain Res. 313 (2016) 191–200.

[31] M. Kadohisa, D.A. Wilson, Separate encoding of identity and similarity of complex familiar odors in piriform cortex, Proc. Natl. Acad. Sci. U. S. A. 103 (41) (2006) 15206–15211.

[32] G.D. Stuber, R.A. Wise, Lateral hypothalamic circuits for feeding and reward, Nat. Neurosci. 19 (2) (2016) 198–205.

[33] B.E. Grayson, S.E. Allen, S.K. Billes, S.M. Williams, M.S. Smith, K.L. Grove, Prenatal development of hypothalamic neuropeptide systems in the nonhuman primate, Neuroscience 143 (4) (2006) 975–986.

[34] Y. Koutcherov, J.K. Mai, K.W. Ashwell, G. Paxinos, Organization of human hypothalamus in fetal development, J. Comp. Neurol. 446 (4) (2002) 301–324.

[35] A. Stevens, G. Begum, A. Cook, K. Connor, C. Rumball, M. Oliver, J. Challis, F. Bloomfield, A. White, Epigenetic changes in the hypothalamic proopiomelanocortin and glucocorticoid receptor genes in the ovine fetus after periconceptional undernutrition, Endocrinology 151 (8) (2010) 3652–3664.

[36] G. Begum, A. Davies, A. Stevens, M. Oliver, A. Jaquiery, J. Challis, J. Harding, F. Bloomfield, A. White, Maternal undernutrition programs tissue-specific epigenetic changes in the glucocorticoid receptor in adult offspring, Endocrinology 154 (12) (2013) 4560–4569.

[37] M.H. Vickers, B.H. Breier, W.S. Cutfield, P.L. Hofman, P.D. Gluckman, Fetal origins of hyperphagia, obesity and hypertension and its postnatal amplification by hypercaloric nutrition, Am. J. Phys. 279 (2000) E83–E87.

[38] M.H. Vickers, P.D. Gluckman, A.H. Coveny, P.L. Hofman, W.S. Cutfield, A. Gertler, B.H. Breier, M. Harris, Neonatal leptin treatment reverses developmental programming, Endocrinology 146 (10) (2005) 4211–4216.

[39] S.G. Bouret, Nutritional programming of hypothalamic development: critical periods and windows of opportunity, Int. J. Obes. Suppl. 2 (Suppl. 2) (2012) S19–24.

[40] A. Plagemann, T. Harder, A. Rake, K. Melchior, W. Rohde, G. Dorner, Increased number of galanin-neurons in the paraventricular hypothalamic nucleus of neonatally overfed weanling rats, Brain Res. 818 (1) (1999) 160–163.

[41] A. Plagemann, A. Rake, T. Harder, K. Melchior, W. Rohde, G. Dorner, Reduction of cholecystokinin-8S-neurons in the paraventricular hypothalamic nucleus of neonatally overfed weanling rats, Neurosci. Lett. 258 (1) (1998) 13–16.

[42] S. Zolotukhin, Metabolic hormones in saliva: origins and functions, Oral Dis. 19 (3) (2013) 219–229.

[43] J.L. Maron, K.L. Johnson, J.A. Dietz, M.L. Chen, D.W. Bianchi, Neuropeptide Y2 receptor (NPY2R) expression in saliva predicts feeding immaturity in the premature neonate, PLoS One 7 (5) (2012) e37870.

[44] S.M. Barlow, J.L. Maron, G. Alterovitz, D. Song, B.J. Wilson, P. Jegatheesan, B. Govindaswami, J. Lee, A.O. Rosner, Somatosensory modulation of salivary gene expression and oral feeding in preterm infants: randomized controlled trial, JMIR Res. Protoc. 6 (6) (2017) e113.

[45] M.L. Gianni, P. Roggero, N. Liotto, O. Amato, P. Piemontese, D. Morniroli, B. Bracco, F. Mosca, Postnatal catch-up fat after late preterm birth, Pediatr. Res. 72 (6) (2012) 637–640.

[46] M.L. Gianni, P. Roggero, F. Taroni, N. Liotto, P. Piemontese, F. Mosca, Adiposity in small for gestational age preterm infants assessed at term equivalent age, Arch. Dis. Child. Fetal Neonatal Ed. 94 (5) (2009) F368–72.

[47] C. Crump, M.A. Winkleby, K. Sundquist, J. Sundquist, Risk of hypertension among young adults who were born preterm: a Swedish national study of 636,000 births, Am. J. Epidemiol. 173 (7) (2011) 797–803.

[48] C. Crump, M.A. Winkleby, K. Sundquist, J. Sundquist, Risk of diabetes among young adults born preterm in Sweden, Diabetes Care 34 (5) (2011) 1109–1113.