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## Smell and taste in the preterm infant

Frank H. Bloomfield<sup>a,b,\*</sup>, Tanith Alexander<sup>a,c</sup>, Mariana Muelbert<sup>a</sup>, Friederike Beker<sup>d,e</sup><sup>a</sup> Liggins Institute, University of Auckland, Auckland, New Zealand<sup>b</sup> Newborn Services, National Women's Health, Auckland City Hospital, Auckland, New Zealand<sup>c</sup> Neonatal Unit, Middlemore Hospital, Counties Manukau Health, Auckland, New Zealand<sup>d</sup> Department of Newborn Services, Mater Mothers' Hospital, Brisbane, QLD, Australia<sup>e</sup> Mater Research Institute, The University of Queensland, Brisbane, QLD, Australia

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## 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](mailto:f.bloomfield@auckland.ac.nz) (F.H. Bloomfield), [t.alexander@auckland.ac.nz](mailto:t.alexander@auckland.ac.nz) (T. Alexander), [m.muelbert@auckland.ac.nz](mailto:m.muelbert@auckland.ac.nz) (M. Muelbert), [Friederike.Beker@mater.org.au](mailto:Friederike.Beker@mater.org.au) (F. Beker).<http://dx.doi.org/10.1016/j.earlhumdev.2017.09.012>

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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-conceptual 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<sup>-1</sup>·day<sup>-1</sup> (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  $\beta$  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

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