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ORIGINAL ARTICLE

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Distribution of cytokeratin filaments and vimentin in developing human taste buds

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Abstract Taste buds in humans originate from approximately the 8th postovulatory week under the influence of ingrowing nerve fibers. Since they develop from local epithelium, it is of interest whether or not prospective taste cells maintain or develop characteristics of epithelial cells that are different from those of the adjacent epithelium during differentiation. The aim of this study was to monitor changes of the distribution of the cytokeratin filaments (CKs) 8, 18, 19 and 20 ("gastrointestinal" type), CK 7 ("ductal" type), and CK 13 (maturation "mucosa type"), as well as vimentin in developing human taste buds and adjacent squamous epithelium. With the exception of CK13, which remains negative in taste bud anlagen and adult taste buds, all cytokeratins tested were present in taste cells. With the progress of development, the distribution of CKs becomes more and more restricted to taste cells and salivatory ducts as well as Ebner gland cells. Only CK20 is exclusively specific to taste bud anlagen and sometimes to individual bipolar cells occurring in early stages (week 8–9). Vimentin was located mainly in mesodermal derivatives but also in perigemmal epithelial cells during all stages of development. The occurrence of vimentin in "borderline" epithelia that interface with underlying connective tissue, i.e., in a region of discontinuity, may be associated with particular events in development, cell migration or even dedifferentiation.

Key words Gustatory papillae · Embryonic development · Fetal development · Immunohistochemistry · Innervation

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Introduction

Taste buds are clusters of specialized epithelial cells that occur predominantly in three distinct locations within the lingual epithelium, namely in fungiform, foliate and circumvallate papillae. During development, unspecialized lingual epithelial cells begin to polarize (7th to 8th postovulatory week) and adopt a bipolar shape (Witt and Reutter 1996). Simultaneously, some of the taste bud primordial cells connect synaptically with ascending nerve fibers, which indicates forthcoming sensory properties of the cells. By week 14, most taste bud primordia possess taste pores that enable them to communicate directly with the environment of the oral cavity. Although questioned in recent reports concerned with amphibians (Barlow et al. 1996), it seems that mammalian taste organs are induced and maintained by nerve fibers (Vintschgau and Hönigschmied 1877; Hosley et al. 1987; Nosrat et al. 1997; Oakley et al. 1998). Recent work on the expression of specific molecules with developing or regenerating taste buds might give hints regarding the origin and dynamics of development (e.g., cell adhesion molecules and neurotrophic factors: Nolte and Martini (1992); Smith et al. (1993, 1994); Nosrat and Olson (1995). Since taste buds develop from local epithelium, it is of interest if prospective taste bud cells maintain phenotypic characteristics of epithelial cells or develop ones that are different from those of the adjacent epithelium in which they are integrated during differentiation. Among the cytoskeleton filaments, the most important differentiation markers in various tissues are intermediate filaments, especially the family of cytokeratin (CK) filaments, from which 20 types have been isolated and characterized so far (Moll 1993). The distribution pattern of CKs 7, 8, 18, 19 and 20 in taste bud cells is different from that in adjacent non-taste epithelia (Oakley et al. 1994). One of the most unique general "marker" proteins for mammalian taste buds is CK 20 (Zhang and Oakley 1996) the occurrence of which has been observed almost exclusively in endodermally derived tissues, except for Merkel cells and urothelial cells

(Moll 1993). If CK 20 is a very early protein in differentiating taste bud primordial cells, we might find a direct relation between nerve supply and CK 20 expression. If CK 20 were to be found earlier than nerve fibers in association with taste buds, we might assume a non-neuronally induced development of taste organs. To obtain sufficient information on the distribution of CK filaments in the course of early development, we applied a battery of monoclonal antibodies directed against CKs 7, 8, 13, 18, 19, and 20. Nerve fibers were detected with antibodies against protein gene product 9.5 (PGP 9.5) (Witt and Reutter 1997) and CD57 (Leu-7), an oligosaccharide antigen first identified on a subset of normal lymphocytes (Abo and Balch 1981) that also recognizes the myelin-associated glycoprotein of central and peripheral glia cells (McGarry et al. 1983).

In order to study the possible interaction between derivatives of endoderm and mesoderm in terms of taste bud development, we investigated the distribution of another intermediate filament, vimentin, that occurs mainly in fibroblasts, endothelial cells and other derivatives of mesoderm (Franke et al. 1978).

Materials and methods

Thirty human fetal tongues were obtained from legal and spontaneous abortions from the 6th until the 20th week of gestation (Table 1), performed in the Department of Gynecology and Obstetrics of the Medical Academy of Dniepropetrovsk (Ukraine). Specimens of late gestation and adult tongues were obtained from the Department of Pathology, Technical University of Dresden. The specimens were collected according to the regulations published in the "Declaration of Helsinki" (1995).

Antibodies

The antibodies used are listed in Table 2.

Tissue preparation

Small tongues (<8th postovulatory week) were left in the mandible; others were removed and fixed in buffered formalin for 2–4 h. The samples were dehydrated in a series of graded ethanols, cleared in xylene and embedded in Paraplast.

Immunohistochemistry

Serial sections (5–7 μm) were mounted on siliconized glass slides and pre-treated with microwaves (800 Watt) or pronase (1:20, Table 2). Antibodies were diluted 1:20 to 1:200 in phosphate buffered saline (PBS, pH 7.2) containing 0.7% bovine serum albumin (BSA) for 1 h at room temperature. After washing in PBS, the sections were exposed to appropriate biotinylated antisera (Vector, Burlingame, Calif., USA) for 1 h at room temperature. The reaction product was visualized by an avidin-biotin-peroxidase-complex (ABC, Vercastain-Elite, Vector) followed by incubation with DAB/H_2O_2. The sections were counterstained with hematoxylin.

For indirect immunofluorescence, tongues (week 6–week 18) were fixed in freshly prepared 4% paraformaldehyde in phosphate buffer for 2–4 h, then washed in phosphate buffer and cryoprotected in a mixture of 15% sucrose and TRIS-buffered saline (TBS). Frozen sections of 20 μm were prepared, air-dried, and incubated with TBS containing 1% BSA, 10% normal serum, and 0.5% Triton X-100 for 1 h at room temperature. After a rinse with TBS, the sections were treated with antibodies (Table 2) overnight at 4° C. Then the sections were incubated with FITS- and CY3-conjugated secondary antibodies for 1 h at room temperature, rinsed in buffer, and mounted with TBS-glycerine. Laserscan images were examined and analyzed with a Leica TCS NT microscope.

Controls

The following controls were performed: (1) omission of the first antibody in order to rule out non-specific binding of the secondary

Table 1 The number of tongues examined in immunohistochemical studies on the development of papillae and taste buds

Postovulatory week	6–7	8–10	11–13	14–19	20–31	Perinatal	Adult
Tongues (*n*)	7	7	5	2	4	1	4

Table 2 Monoclonal antibodies used for the detection of intermediate filaments and nerve fibers in developing human taste buds (*CK* cytokeratin, *IF* immunofluorescence)

Antibody	Source	Dilution	Pretreatment	Section material
MNF 116 (CKs 5,6, 8, 19)	Dako	1:100	Pronase	Paraffin, ABC
CK 7	Progen	1:25	Pronase	Paraffin, ABC
CK 8	Dako	1:50	Microwave	Paraffin, ABC
CAM 5.2	Becton Dickinson	1:20	Microwave	Paraffin, ABC
CK 13	Progen	1:100	Pronase	Paraffin, ABC
CK 18 (KS18.04)	Progen	1:20	Pronase	Paraffin, ABC
CK 19	Dako	1:100	Pronase	Paraffin, ABC
CK 20	Progen	1:200	Microwave	Paraffin, ABC
Vimentin (V3B4)	Progen	1:200	Microwave	Paraffin, ABC
Vimentin (V9)	Boehringer	1:100	Pronase	Paraffin, ABC
PGP 9.5 (polyclonal)	Anawa	1:1000	Microwave	Paraffin, ABC;
		1:500	–	Frozen; IF
Leu-7	Becton Dickinson	1:100	–	Paraffin, ABC

Table 3 Subjectively estimated binding intensities of antibodies to intermediate filaments in the developing human gustatory epithelium (– no reaction, +++ maximal reaction, *TB* taste buds, *Epith.* epithelium, *Ebner* Ebner glands, *MC* marginal cells, *bas* basal cell layer, *sup* superficial cell layer, *n.d.* not determined)

Age (weeks)	6–7			8–10			11–13			14–19			20–30			31–birth			Age		
Cytokeratin	TB	Epith.	Ebner	TB	Epith.	Ebner	TB	Epith.	Ebner	TB	Epith.	Ebner	TB	Epith.	Ebner	TB	Epith.	Ebner	TB	Epith.	Ebner
CK7		+		+	+			+		+	+bas	+++	+++	(+)	+++	n.d.	–	++	–	–	–
CK8		+		+	+																
CAM 5.2		sup+[a]		++	++		+	+	+	+	–	(+)	++	(+)	+	n.d.	–	+		+++	+++
MNF 116		+[a]		++	++		++	++	++	+	++bas	++	n.d.	n.d.	n.d.	n.d.	–	++			
CK13		++		–	++		–	++	–	–	+++	–	+	+	+	n.d.	++	+	–	++	++
CK18		+		++	+		+	++	++	+	(+)	++	++	+++	++	++	–	++		+++	–
CK19		+		++	++		+	+++	+++	+	+	+	–	–	++	++	(+)	++		+	
CK20		–		+	–		+	–	–	++	–	–	++	–	(+)+	+	–	–	+	–	++
															–				++		
Vimentin	++			++	–		++						+++			+			–	(+)	–
	MC						MC														

[a] 6th week: negative

antibody; (2) incubation of known immunoreactive structures, usually epidermis, to check the activity of the primary antibody.

Results

The results of this investigation are summarized in Table 3.

CK 7

CK 7 is detected by week 6 in the superficial epithelial cell layer (not shown) and early taste bud primordia from week 8 on (Figs. 1a, c, e, 2b).

CK 8, 18

In early gestation, CK 18-like immunoreactivity (IR) is confined to cells of the apical layer of the epithelium, and to a subset of the taste bud primordial cells (Fig. 1b). CK 8 is also expressed by cells of the basal cell layer. Later, from approximately week 12 until adulthood, CK 8 and 18 are restricted to taste bud primordial cells and Ebner glands (Figs. 1d, f, 2a, c). In the newborn (Figs. 3a, 4a) and senile (not shown) gustatory papilla, only taste bud cells and Ebner's glands are immunoreactive. Adjacent epithelial cells lack CK 18.

MNF 116 (CKs 5, 6, 8, 19)

MNF 116 labels superficial and basal epithelium from week 7 onwards (Fig. 3b). MNF reactivity is present in all epithelial structures including taste bud cells, excretory ducts of Ebner gland cells and non-gustatory epithelial cells during all developmental periods investigated.

CK 19

At 8–9 weeks of gestation, CK 19-like IR is found in cells of both superficial and basal epithelial cells of the lingual surface and in cells of the taste bud primordia (Fig. 3c). In advanced stages (week 13), all cell layers are CK 19-positive (Fig. 3d), including excretory duct cells and a subpopulation of Ebner gland cells. Later (week 18 until birth), CK 19 remains expressed by taste bud cells, ductal cells of Ebner glands and the epithelium opposite to circumvallate papillae, but barely in the papillae themselves (Figs. 3e, 4b). In the adult tongue, CK 19 is restricted to taste buds and Ebner glands (not shown).

CK 20

CK 20 IR occurs exclusively in taste bud anlagen of the posterior and the anterior lingual epithelia (Fig. 3f). In

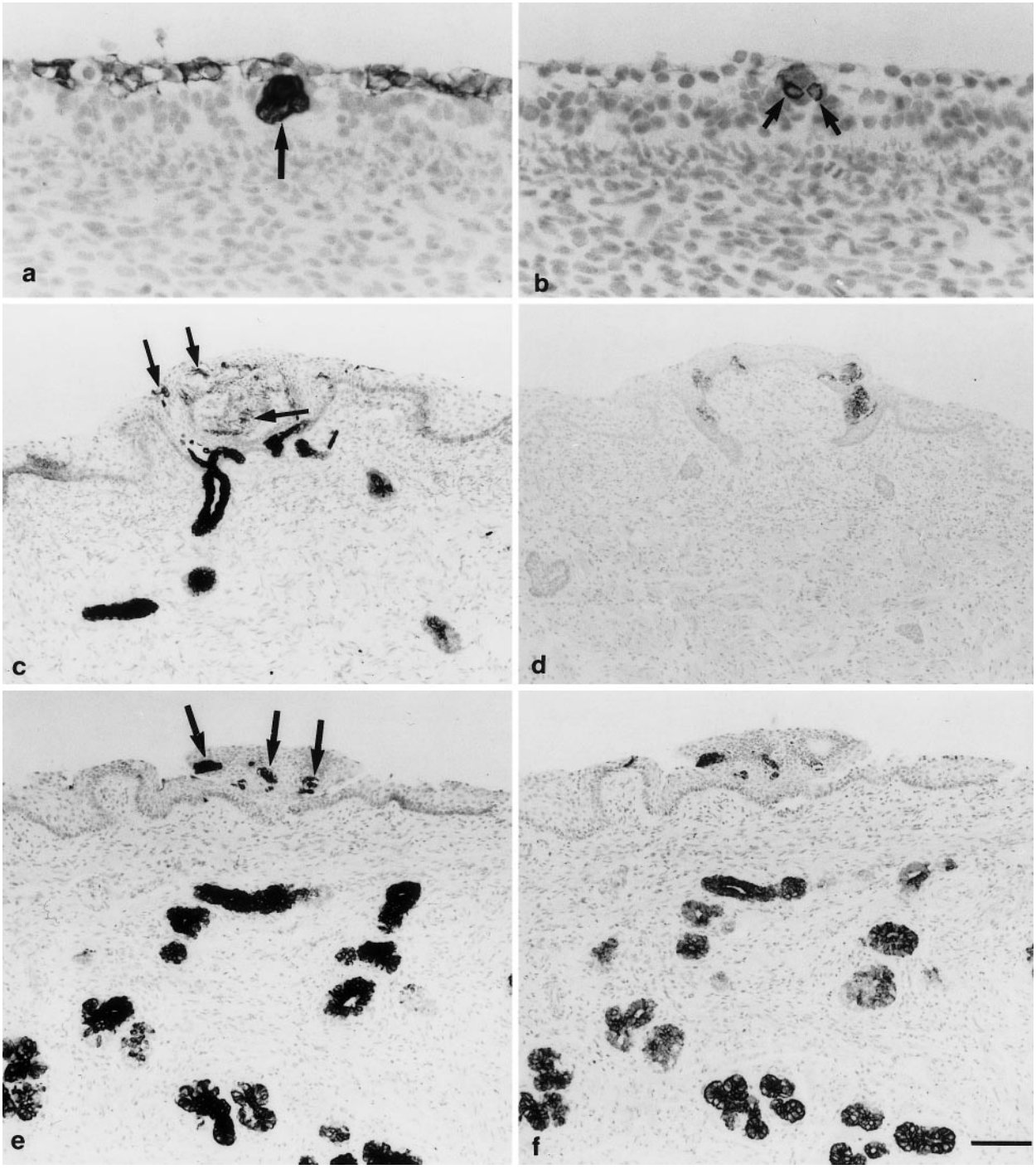


Fig. 1a–f Immunohistochemical detection of cytokeratin filaments (CK) 7, 8, 18 in human embryonic and fetal taste bud primordia. Counterstained with hematoxylin. *Bar* **a, b** 20 μm, **c–f** 80 μm. **a, b** Anterior part of the tongue, postovulatory week 8. CK7 is located in clustered taste bud cells (*arrow*). The superficial cell layer of the lingual epithelium is also labeled (**a**). In the adjacent section to **a**, CK18 is present in only two cells of this early corpuscle (*arrows*, **b**). **c, d** Circumvallate papilla, week 18. CK7 occurs predominantly in excretory ducts of Ebner glands (**c**). Also cells of taste buds are detectable (*arrows*). CK8 occurs only in taste bud cells (**d**, adjacent section). The epithelium is negative, and Ebner glands barely react. **e, f** Circumvallate papilla, week 21. CK7 is detected in Ebner glands and taste bud primordial cells (**e**, *arrows*). The immunoreactivity of CK18 in the adjacent section (**f**) is somewhat less pronounced. The circumvallate papilla of **e, f** is depicted at higher magnification in Fig. 2b, c

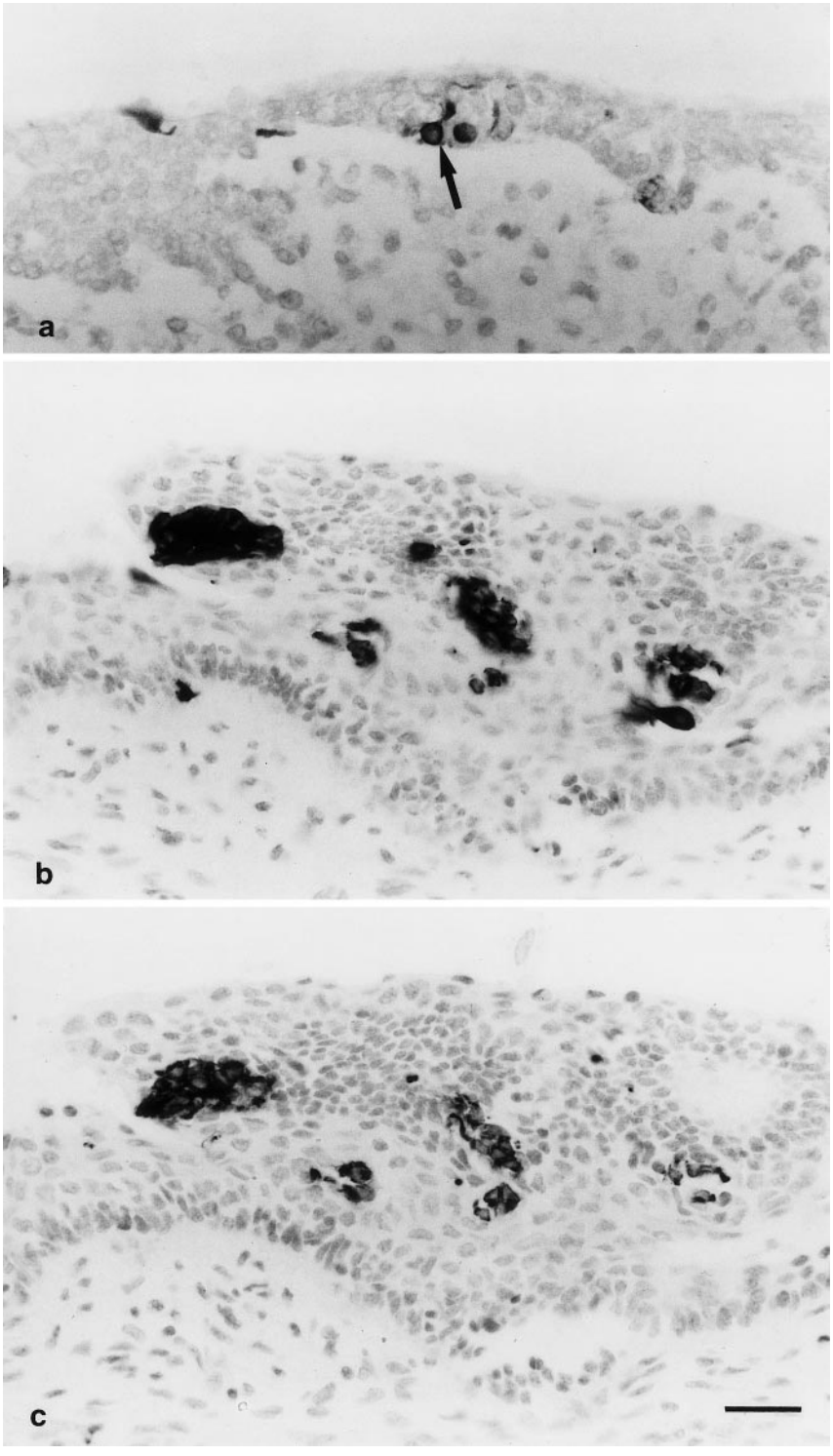
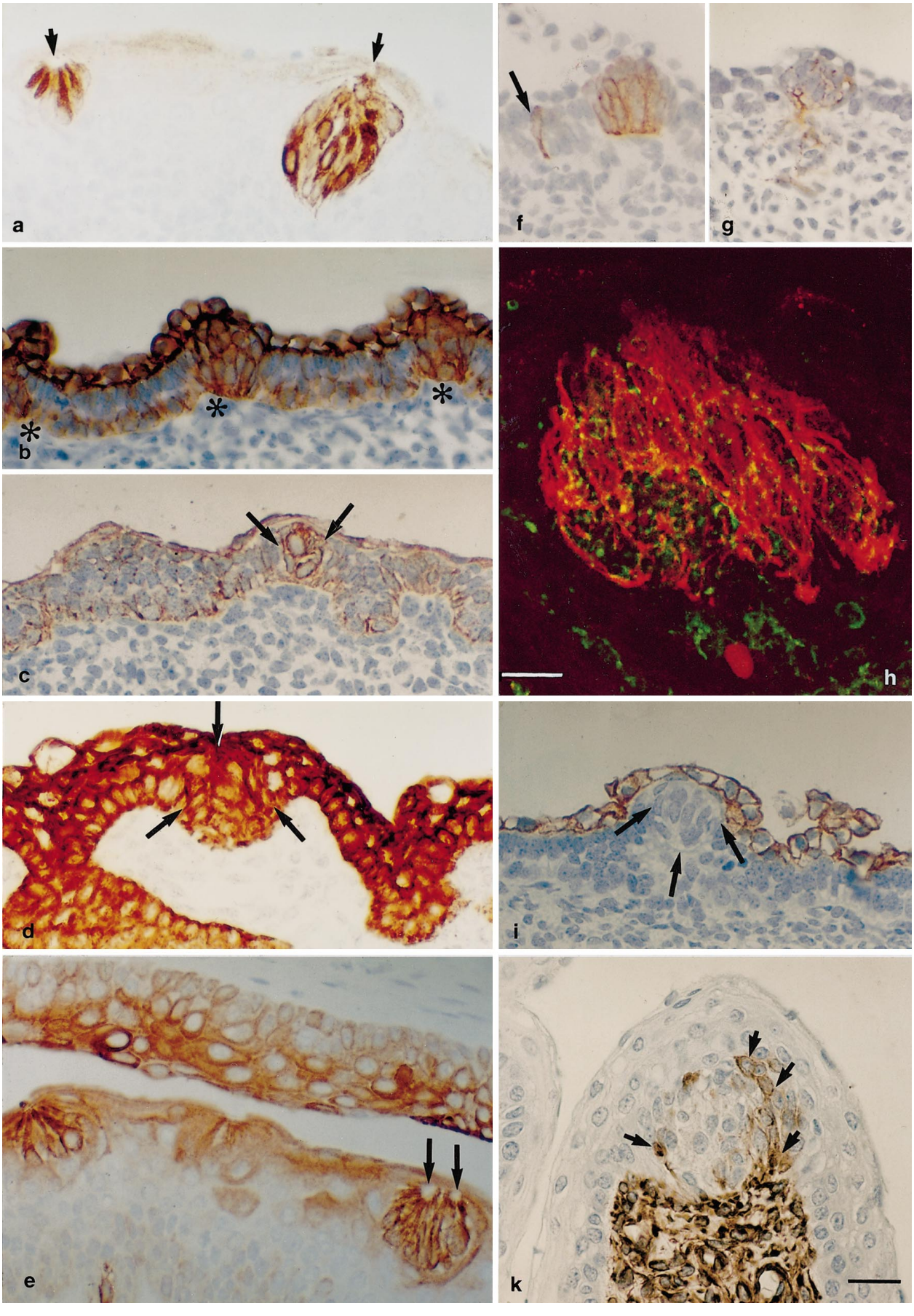


Fig. 2 **a** Circumvallate papilla, week 13. CK 18 is located in two cells of an early taste bud anlage. One of them is already bipolar shaped (*arrow*). **b, c** Circumvallate papilla, week 21. The same specimens as shown in Fig. 1e, f at higher magnification. CK7 (**b**) seems not to be present in more bud primordial cells than CK 18. (**c**). Counterstained with hematoxylin. *Bar* 20 μm

early stages (week 8–9), the taste bud primordia are located in part within pre-formed papilla, and in part in non-elevated epithelial formations. However, some elongated epithelial cells outside taste bud primordia are observed in early developmental stages (Fig. 3f). Also in later stages CK 20 remains restricted to taste bud cells (Fig. 3h).

CK 13

From early stages on (week 8–9) CK 13 is detected in the superficial cell layer of epithelium, but not in taste bud primordial cells (Fig. 3i). In specimens of adult tongues, the occurrence of CK 13 is restricted to the stratum germinativum, but not to the basal cell layer and not to epidermal sections near a taste bud (not shown).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Vimentin

Vimentin occurs in interstitial mesenchymal cells, endothelial cells and is most densely distributed in mesenchymal structures of dermal papillae just underneath the epithelium. In early developmental stages it can be found in epithelial cells immediately adjacent to taste bud primordia (marginal cells) and also within taste bud primordia. Between 13 and 20 weeks vimentin is usually located in marginal cells rather than in taste bud cells proper (Fig. 3k).

Nerve fibers

Nerve fibers, detected with antibodies against protein gene product 9.5 (PGP 9.5) and CD57 (Leu-7), are present in the lingual mesenchyme by week 6, but do not enter the epithelium before week 8. Nerve fibers in early taste bud primordia were seen to penetrate the basal lamina preferentially in regions where dermal indentations (early papillae) are preformed (Fig. 3g). Later, a dense nerve fiber plexus in the dermal papilla develops whose fibers intensely intermingle with intragemmal cells (Fig. 3h). Intragemmal cells are not reactive to any neuronal marker.

Fig. 3 Immunohistochemistry for cytokeratins (**a–i**) and vimentin (**k**) in developing human taste buds. Counterstained with hematoxilin. *Bar* **a–g, i, k** 20 µm, **h** 10 µm. **a** Circumvallate papilla, newborn. CK18 is present in all sectioned taste bud cells, however, at different reaction intensities. Slender cells converge into the taste pit (*arrows*). Adjacent section to that depicted in **e**. **b** Anterior part of the tongue, week 8. MNF 116 (pankeratin antibody) labels the still unpolarized, bi-layered taste bud primordial cells and the basal and superficial cell layer (out of 3 cell layers) of the epithelium. The dermal indentations demarcate the locations where later gustatory papillae arise (*asterisks*). **c** Same specimen as shown in **b**. CK19 has the same distribution pattern as revealed by pankeratin antibody MNF 116 (**b**). A taste bud anlage is indicated by *arrows*. **d** Fungiform papilla, week 13. CK19 is uniformly distributed in all epithelial cells, including a taste bud anlage (*arrows*). **e** Circumvallate papilla, newborn (same specimen as shown in **a**). CK19 is present in two taste buds. The deviding right taste bud displays two taste pits (*arrows*). Cells of the opposite epithelium of the circumvallate trench are also labeled (cf Fig. 4). **f** Anterior part of the tongue, week 8, CK20. Same specimen as **b** and **c**. CK20 is present in a subset of taste bud primordial cells (right cluster). One individual bipolar cell reaches from the basal lamina up to the thin superficial layer of the epithelium (*arrow*). **g** Anterior part of the tongue, week 8, Leu-7. Same specimen as **b, c, f.** The antibody labels an ascending nerve fiber bundle, the finest ramifications of which enter a taste bud primordium. **h** Laserscan projection of a fungiform papilla, week 18, immunoreactive for CK20 and protein gene product 9.5 (PGP 9.5). The cells of the taste bud anlage are positive for CK20 (*red* fluorescence); nerve fibers (*green* fluorescence) are located between the intragemmal cells. **i** Anterior part of the tongue, week 8, CK13, same specimen as **b, c, f.** Only the superficial epithelial cells are marked. The taste bud anlage (outlined by *arrows*) lacks CK13. **k** Fungiform papilla, week 20, vimentin. The mesenchyme is strongly labeled, but most of the epithelium of the papilla remains free of immunoreactivity. Only epithelial cells situated at the interface between mesenchyme/taste bud anlage and adjacent epithelium/taste bud anlage expresses vimentin (*arrows*)

In summary, the CKs studied appear selectively in slender taste bud primordial cells, but not before nerve fibers invade the prospective gustatory epithelium. Those CK subtypes which also mark adjacent epithelial regions during early gestation (<12th week) become more and more restricted to taste cells (or subpopulations) and Ebner glands in the course of time.

Two exceptions from this rule are evident: (1) CK20 is exclusively specific to taste bud primordia and adult taste buds; (2) taste buds usually lack CK13, with a short positive interval around the 13th week of gestation. In older stages, the squamous epithelium is strongly CK 13-positive, with the exception of all gustatory papillae that contain a taste bud.

Vimentin appears at about the same time as CKs, but remains restricted to marginal cells of the taste bud primordium, especially in later periods of gestation.

Discussion

Developmental alterations in taste organs are complex events that are not restricted to the gestational periods. In order to document the wide range of various events and a possible temporal correlation with the development of nerve fibers we studied the distribution of various intermediate filaments, which were described as markers for different classes of epithelia or mesenchymal cells and stages of differentiation (Moll 1993).

Intermediate filaments comprise a large multigene family that can be subdivided into several classes. The epithelium-specific "cytokeratin catalogue" contains a set of 20 polypeptides that are each encoded by a single gene (Moll et al. 1982). CKs are of vital necessity, because they serve a stabilizing, mechanical role for the cell. Experimental defects revealed by experimental knockouts for several CKs cannot be compensatory by other intermediate filaments (Galou et al. 1997). Many CKs are expressed by specific epithelial cell classes, including their malignant tumours, and have gained diagnostic value (Moll 1993). According to their origin and most common distribution, CKs have been classified into several groups: (1) epithelia of the gastrointestinal system are characterized by CKs 8, 18, 19, and 20; (2) CK 7 occurs prevalently in ductal cells of the large intestinal glands; (3) CK 13 is known as a "mucosa-specific" maturation CK (Moll et al. 1982; Moll 1993).

Cytokeratins in oral epithelia and taste buds

Antibodies against several CKs have already been used as markers for taste cells and associated epithelia in adult rodents (Takeda et al. 1988; Wong et al. 1994; Zeng et al. 1995; Zhang et al. 1995) and human tongues (Zhang and Oakley 1996). For example, CK 18 has been shown to occur in older subpopulations of taste cells in rats (Zhang et al. 1995). In non-gustatory oral epithelia, CK 8, 18, and 19 occur in basal cells (Moll 1993), but our own observa-

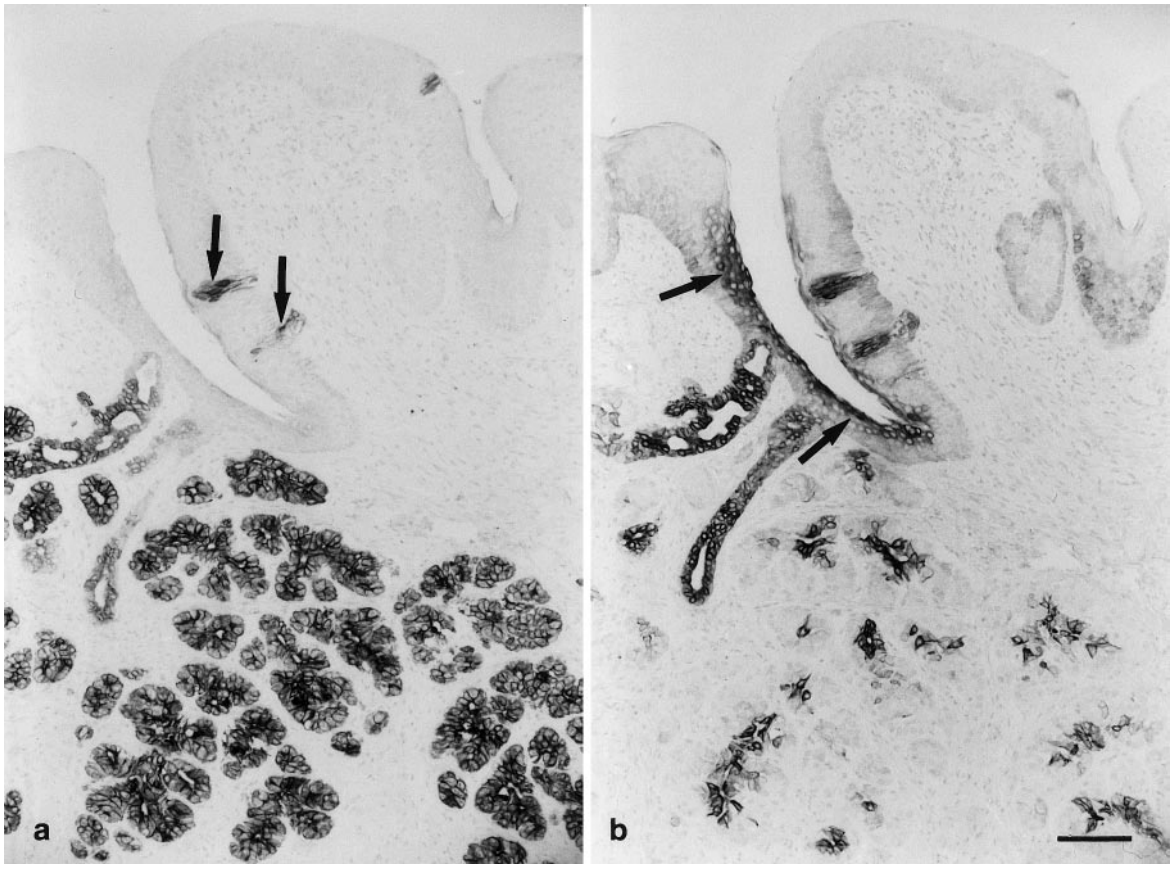

Fig. 4 Circumvallate papilla, newborn. Comparison between the distribution of CK18 (**a**) and CK19 (**b**). CK18 is present in taste buds (*arrows*), in acinar cells of Ebner glands and, to a lesser degree, in excretory duct cells. In contrast, CK19 occurs mainly in cells of the excretory duct system that also includes the outer wall of the circumvallate trench (*arrows*). In both cases, the nongustatory epithelium is largely unreactive for both antibodies at this stage. Compare with Fig. 3a, e. *Bar* 80 μm

tions showed a staining of the superficial cell layer rather than the basal one. Furthermore, the occurrence of CKs in adjacent, non-gustatory epithelium tends to decrease in the course of development, which is in agreement with earlier studies of CK distribution patterns during development (Pelissier et al. 1992). In contrast, the occurrence of CKs in taste cells remains constant during different developmental stages. This indicates the strong spatio-functional interrelationship of small sensory organs with a relatively large adjacent epithelial region.

CK20 provides the most restrictive expression of all cytokeratins in the upper gastrointestinal tract (Moll 1993; Zhang and Oakley 1996). CK20 occurs only in endodermal derivatives except Merkel cells and urothelial umbrella cells (Moll 1993). However, in accord with results of Zhang et al. (1995) we observed CK20-positive taste bud cells also in fungiform papillae, which are part of the ectodermally derived anterior tongue. Zhang et al. (1995) discuss a migratory potential of putative taste precursor cells. Interestingly, indvidual slender epithelial cells outside of, but in immediate spatial vicinity to, preformed taste bud primordia are also CK20-positive. They resemble solitary chemosensory cells observed in fish (Whitear 1992) or in mouse palate epithelium. This remarkable distribution of CK20-positive cells supports our earlier observation (Witt and Reutter 1997) that taste bud primordia in humans are not necessarily associated with gustatory papillae as seems to be the case in rodents (Farbman and Mbiene 1991).

These and previous studies show that nerves apparently do not invade the gustatory epithelium *after* taste bud-selective determinants known so far have been detected – e.g., CK20, CD44 in marginal cells (Witt and Kasper 1998) – thus putting non-neuronal inductive factors considered so far in question. However, the rarely occurring "solitary" CK20-positive cells might point to a non-neuronal dependency of taste bud development, provided CK20 is exclusively associated with gustatory cells in the tongue as observed by Zhang and Oakley (1996) and in this study.

Vimentin distribution in taste bud anlagen

Vimentin is normally expressed by mesodermal derivatives (e.g., endothelial cells, muscle cells, fibroblasts; Franke et al. 1978). It also occurs in "borderline" epithelia that interact with underlying connective tissue. One of the factors leading to vimentin expression in epithelial cells is the discontinuity or disturbance of the epithelium, e.g., in cell culture (Franke et al. 1982) or during development and cell migration (Ramaekers et al. 1983).

For a detailed discussion on vimentin co-expression in epithelial cells see Kasper (1992). Although there is a low predictability for cell-typing based on vimentin expression alone, we speculate that the close connection of taste bud cells to marginal extragemmal cells might reflect a common role of these cells with regard to cell lineage. Cranial structures develop from unique combinations of embryonic tissues, as for example, the crest-derived mesodermal elements (ectomesenchyme; Noden 1984, 1991). Thus, individual embryonic tissues and their combinations may constitute the source cells for early-developing taste buds. Disrupted areas of the basal lamina could permit access to epithelium for superficial mesoderm cells as observed electron microscopically (Witt and Reutter 1996). Later, during migration into the bud's center, marginal taste bud cells loose their mesenchymal "fingerprint", i.e., vimentin filaments, as reflected by their immunohistochemical phenotype. On the other hand, vimentin expression may also be a sign of dedifferentiation of old taste cells that might migrate to the margins of the taste bud. A similar association of dedifferentiating kidney tubule cells with the expression of vimentin has been described by Ward et al. (1992). It remains unclear how aged taste bud cells are discarded, especially before the taste pore opens (at approximately week 12–14; Witt and Reutter 1996).

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