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# **Transient-Receptor Potential (TRP) and Acid-Sensing Ion Channels (ASICs) in the Sensory Organs of Adult Zebrafish**

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## **Abstract**

Sensory information from the aquatic environment is required for life and survival of zebrafish. Changes in the environment are detected by specialized sensory cells that convert different types of stimuli into electric energy, thus originating an organ-specific transduction. Ion channels are at the basis of each sensory modality and are responsible or are required for detecting thermal, chemical, or mechanical stimuli but also for more complex sensory processes as hearing, olfaction, taste, or vision. The capacity of the sensory cells to preferentially detect a specific stimulus is the result of a characteristic combination of different ion channels. This chapter summarizes the current knowledge about the occurrence and localization of ion channels in sensory organs of zebrafish belonging to the superfamilies of transient-receptor potential and acid-sensing ion channels that are involved in different qualities of sensibility superfamilies in the sensory organs of zebrafish. This animal model is currently used to study some human pathologies in which ion channels are involved. Furthermore, zebrafish is regarded as an ideal model to study in vivo the transient-receptor potential ion channels.

**Keywords:** sensory organs, sensibility, transient-receptor potential ion channels, acid-sensing ion channels, zebrafish

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## **1. Introduction**

Sensory information from the environment is required for life and survival, and it is detected by specialized cells which together make up the sensory system. In fishes the sensory system

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consists of specialized sensory organs (SO) able to detect light, mechanical and chemical environmental stimuli [1]. SO contain differentiated and specialized sensory cells that convert different types of stimuli into electric energy, thus originating an organ-specific transduction. Actually it is accepted that ion channels are at the basis of each sensory modality and are responsible or are required for detecting thermal, chemical, or mechanical stimuli [2–4].

The identification of ion channels selectively activated by specific stimuli supported the concept that the expression of a particular ion channel confers selectivity to respond to a unique stimulus. Nevertheless, the ion channels originally proposed as specific transducers are not selectively associated with the distinct types of sensibility. In fact, it has been observed that ion channels originally associated with one particular stimulus can be activated by different stimuli and are expressed in sensory cells functionally specific for other sensitivities. In other words, a specific ion channel can be expressed in more than a sensory cell type, and each cell type may express more than one type of ion channel. Thus, the capacity of the sensory cells of a SO to preferentially detect a specific stimulus is the result of a characteristic combination of different ion channels [5–7]. On the other hand, to be a reasonable candidate for sensing and/or transducing a stimulus, an ion channel must be expressed in the right place. Thus, the sensory cells of SO are thought to express ion channels that can act as sensors/transducers of the sensibility they are deputy. For example, some acid-sensing ion channels (ASICs) are presumably involved in mechanosensation and therefore are expressed in the mechanoreceptor cells. Also, in detecting chemical properties of food, ASICs participate, and consistently they are present in sensory cells of taste buds.

The interest for the presence of ion channels in the zebrafish SO is because it is a model to study some human pathologies in which ion channels are involved, related to vision [8–10], hearing and balance [11–13], taste [14], or olfaction [15]. Furthermore, zebrafish is regarded as an ideal model to study *in vivo* the transient-receptor potential (TRP) ion channels [16, 17].

Thus, this chapter summarizes the current knowledge about the occurrence and localization in SO of zebrafish of ion channels belonging to the superfamilies of TRP and ASICs that are involved in different qualities of sensibility.

## 2. The superfamily of transient-receptor potential (TRP) ion channels

TRPs are nonselective cation channels, of which few are highly  $\text{Ca}^{2+}$  selective and some are permeable for highly hydrated  $\text{Mg}^{2+}$ . The TRP superfamily is subdivided into seven subfamilies: TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPP (polycystin), TRPML (muco-lipin), TRPA (ankyrin), and TRPN (NOMPC-like); the latter one is found only in invertebrates and fishes [18]. In yeast, the eighth TRP family was recently identified and named as TRPY [19].

At least 28 different TRP proteins have been identified in mammals. Structurally, a typical TRP protein contains six putative transmembrane domains (S1–S6) with a pore-forming reentrant loop between S5 and S6. Intracellular N- and C-termini are variable in length and consist of a variety of domains [3, 20, 21]. This ion channel superfamily shows a variety of gating mechanisms with modes of activation ranging from ligand binding, voltage, and changes in temperature to covalent modifications of nucleophilic residues (see for a review [3, 22, 23]).

TRP channels serve diverse functions. The members of the TRP superfamily with potential capability for mediating mechanosensing include TRPC1, TRPC3, TRPC5, TRPC6, TRPV4, TRPM3, TRPM7, TRPP1, and TRPP2 [3, 23–27]. Some of them have been suggested as candidates for the mechanotransduction channel in the inner ear vertebrate hair cells, thus involved in hearing and balance. Nevertheless, Wu et al. [28] informed that the available results argue against the participation of any of the mouse TRP channels in hair cell transduction. Conversely, other studies suggest that TRPC3 and TRPC6 are required for the normal function of cells involved in hearing and are potential components of mechanotransducing complexes [29]. TRPC1, TRPC3, TRPC5, and TRPC6 channels contribute to auditory mechanosensation in a combinatorial manner but have no direct role in cochlear mechanotransduction [30].

Six members of this superfamily, TRPA1, TRPM8, TRPV1, TRPV2, TRPV3, and TRPV4, seem to participate in temperature sensing and TRPV1, TRPV2, TRPV3, and TRPV4 have incompletely overlapping functions over a broad thermal range from warm to hot [3, 7, 23, 31]. TRPA1 and TRPM8 respond to cool and cold, TRPV1 and TRPV2 are activated by painful levels of heat ( $>43^{\circ}\text{C}$  and  $>52^{\circ}\text{C}$ , respectively), TRPV3 and TRPV4 respond to non-painful warmth ( $33\text{--}39^{\circ}\text{C}$ ), TRPM8 is activated by non-painful cool temperatures ( $<25^{\circ}\text{C}$ ), and TRPA1 is activated by painful cold ( $<18^{\circ}\text{C}$ ; [32]). As a poikilotherm that lives in water, the detection of small fluctuations in the temperature can be of capital importance in zebrafish for survival.

Most of the authors suggest that chemosensation is determined primarily by the chemical activation of nociceptors and thermoreceptors and that activation by chemicals involves the direct activity of an ion channel by chemical stimuli: the so-called ionotropic transduction [33, 34]. TRP channels play integral roles in transducing chemical stimuli, giving rise to sensations of taste, irritation, warmth, coolness, and pungency. Among them are TRPM5, TRPV1, TRPA1, TRPM8, TRPV3, and TRPV4 [35, 36]. In this regard, TRPV1 is responsive to noxious stimuli and various chemical agents [31, 37–40].

### 3. The superfamily of acid-sensing ion channels (ASICs)

ASICs are voltage-insensitive, amiloride-sensitive  $\text{Na}^{+}$ -selective cation channels that monitor moderate deviations from the physiological values of extracellular pH [24, 41, 42]. In mammals six ASIC proteins encoded by four genes have been identified: ASIC1a, ASIC1b, ASIC2a, ASIC2b, ASIC3, and ASIC4 which differ in their kinetics, external pH sensitivity, tissue distribution, and pharmacological properties [43, 44]. The pH values required for half-maximal activation are 6.2–6.8 for ASIC1a, 5.9–6.2 for ASIC1b, 4.9 for ASIC2a, and 6.5–6.7 for ASIC3 [45, 46]. This capability of respond to minimal variation in pH might be of capital importance for survival in the aquatic environment. Structurally, ASICs consist of two transmembrane domains and a large extracellular loop [47], and in addition to their roles as detectors of pH variations, some ASICs may work as mechanosensors (or are required for mechanosensation) and nociceptors [47–53].

The members of these two families of ion channels that exhibit mechanosensitivity, thermosensitivity, and chemosensitivity are summarized in **Table 1**.

Mechanosensitivity	Thermosensitivity	Chemosensitivity
TRPA1, TRPC1, TRPC3, TRPC5, TRPC6, TRPV1, TRPV2, TRPV4, TRPM3, TRPM4, TRPM7, TRPM8, TRPP1, TRPP2	TRPA1, TRPM8, TRPV1, TRPV2, TRPV3, TRPV4	TRPM5, TRPV1, TRPA1, TRPM8, TRPV3, TRPV4
ASIC1, ASIC2, ASIC3	ASIC1, ASIC2, ASIC3	ASIC1, ASIC2, ASIC3

**Table 1.** Members of the transient-receptor potential (TRP) ion channel and acid-sensing ion channel (ASIC) superfamilies that exhibit mechanosensitivity, thermosensitivity, and chemosensitivity.

	Neuromast	Inner ear	Olfactory epithelium	Taste buds	Retina
<i>trpc1</i>			+		INL, GCL
<i>trpc2a</i>			+		
<i>trpc2b</i>			+		
<i>trpc3</i>					+
<i>trpc5a</i>					INL, GCL
<i>trpc5b</i>					INL
<i>trpc7a</i>			+		
<i>trpm1a</i>					INL
<i>trpm4b</i>	+		+		
<i>trpm5</i> /TRPM5			+	+	
TRPA1	+	+			
TRPV4	HC, MC	NEC	CON, nsc	SC	AC
ASIC1	HC				
ASIC2	HC, nerves		nsc (cilia)	SC, nerves	INL, IPL, GCL
ASIC4	HC, MC			SC	PhR, GCL

AC, amacrine cells; CON, ciliated olfactory neurons; FR, photoreceptors; GCL, ganglion cell layer; HC, hair cells; INL, inner nuclear layer; IPL, inner plexiform layer; MC, mantle cells; NEC, neuroepithelial cells; SC, sensory cells; nsc, non-sensory (nonolfactory) cells.

**Table 2.** Detection of transient-receptor potential (TRP) ion channels and acid-sensing ion channels (ASICs) in the sensory organs of zebrafish in larval state and adults.

4. TRP and ASICs in zebrafish

Expression of individual TRP ion channels has been observed in many tissues evidencing their roles as multifunctional cellular sensor proteins and functional analysis revealed their participation in all kinds of sensory detection: thermodetection, mechanodetection, chemodetection, nociception, and light perception.

In zebrafish, TRP channel genes belonging to the melastatin (TRPM [54–56]) vanilloid [57], canonical (TRPC [58, 59]) ankyrin [60, 61] and TRPN (also known as NOMPC [62]) have been detected. But based on their distribution, not all these ion channels are expressed in SO and therefore are involved in sensory detection.

Phylogenetic analysis has revealed 11 *trpm* genes and 12 *trpc* genes in the zebrafish genome: simple genes were identified for *trmp2*, *trmp3*, *trpm5*, *trmp6*, and *trmp7*, duplicate orthologs were found for *trpm1* (*trpm1a* and *trpm1b*), and quadruplicate orthologs were found for *trpm4* (*trpm4a*, *trpm4b1*, *trpm4b2*, *trpm4b3*) [56]. Regarding the TRPC family, simple genes were identified for *trpc1* and *trpc3* and duplicate for *trpc2* (*trpc2a* and *trpc2b*), *trpc4* (*trpc4a* and *trpc4b*), *trpc5* (*trpc5a* and *trpc5b*), *trpc6* (*trpc6a* and *trpc6b*), and *trpc7* (*trpc7a* and *trpc7b*) [58, 59, 63, 64].

In zebrafish the orthologs and paralogs of the six ASIC proteins detected in mammals have been identified and are denominated zASICs: zASIC1.1, zASIC1.2, zASIC1.3, zASIC2, zASIC4.1, and zASIC4.2. The six proteins encoded by these genes have similar predicted molecular masses (~60 kDa) and share 60–75% amino acid sequence with rat and human ASICs [65].

## 5. TRP and ASICs in the sensory organs of zebrafish

Whole-mount in situ hybridization experiments as well as immunohistochemistry revealed the occurrence of TRPs and ASICs in SO of zebrafish as well as changes in the pattern of expression between developing and adult animals. Furthermore, functional analyses have demonstrated the involvement of some ion channels in different modalities of sensitivity.

### 5.1. Lateral line, superficial neuromasts, and ear

The mechanosensory cells in zebrafish are grouped into superficial and deep neuromasts that form the lateral line system (LLS [66, 67]) and in the sensory epithelia of the inner ear [68, 69]. The neuromasts and the neuroepithelium of the inner ear are filled with specific hair sensory cells that sense water flow and movement and endolymph movement, respectively. Thus, hair sensory cells are functionally mechanoreceptors where the conversion of mechanical stimuli into electrochemical signals, i.e., mechanotransduction, takes place, presumably because of the presence of mechanotransducer ion channels.

The role of TRPA1 in zebrafish mechanotransduction is still unclear. Using morpholino anti-sense oligonucleotides, it was observed that TRPA1 is required for inner ear and LLS hair cell function since these animals showed deafness [60]. In contrast, *trpa1a;trpa1b* doubly homozygous mutant zebrafish larvae have normal hair cell function [61]. The mechanosensory roles of TRPA1 in zebrafish are not supported by results obtained in TRPA1 knockout mice in which inner ear hair cell function was normal [70, 71]. A preliminary study of our group failed to demonstrate TRPM8 in sensory cells of the inner ear (**Figure 1e**).

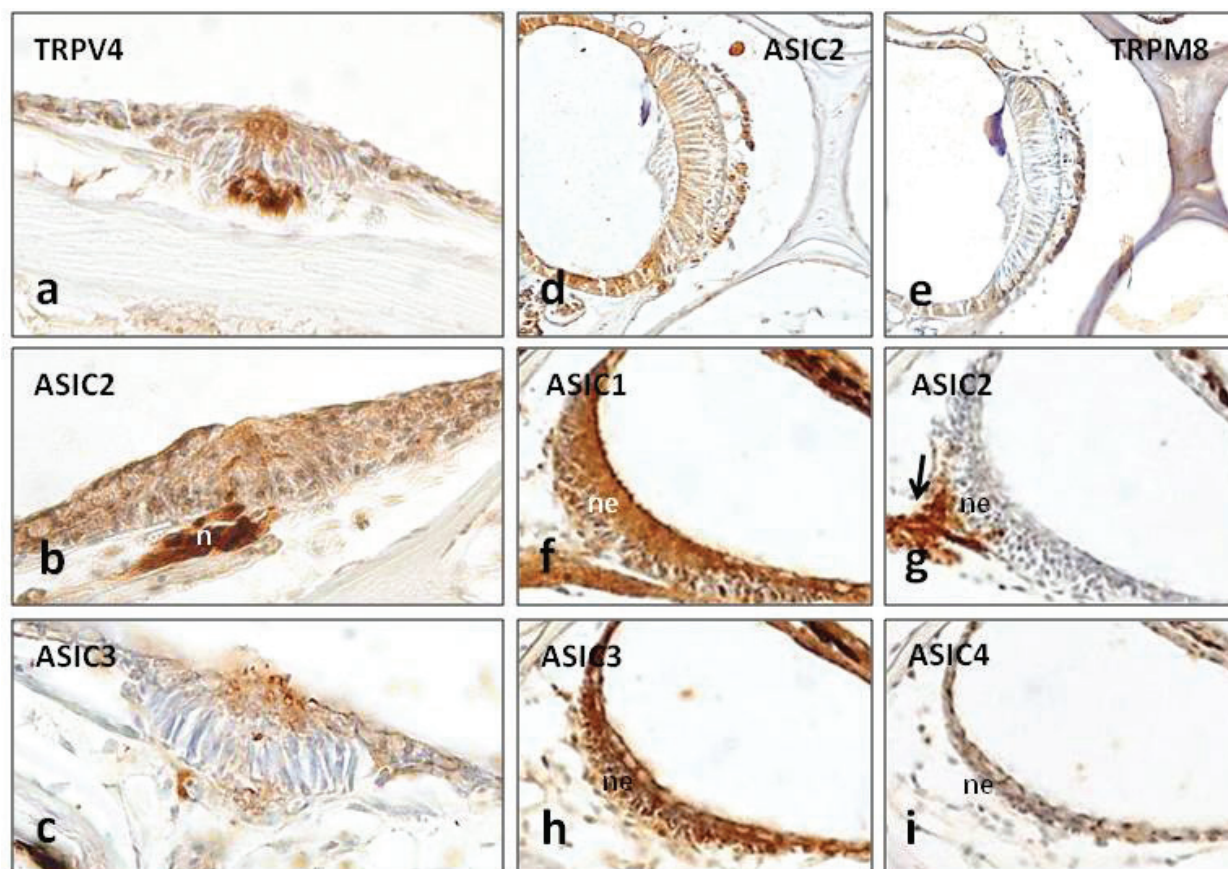
TRPV4 is involved in mechanic and chemical sensation but also responds to warm temperatures and acidic pH (see [72]). Whole-mount in situ hybridization in zebrafish embryos showed



expression of *trpv4* in neuromasts of LLS at 24 hours post fertilization (hpf), which decreases at 3 days post-fecundation (dpf) but remains at residual levels [57]. Using immunohistochemistry, TRPV4 was detected in neuromasts showing two patterns of distribution: in mantle cells alone or in a subset of hair sensory cells in addition to the mantle cells; the superficial neuromasts (pit organs) also displayed TRPV4 immunostaining in both mantle and hair cells [73] (**Figure 1a**). In the inner ear, TRPV4 immunoreactivity was observed in some hair cells of the macula and in a subpopulation of hair cells in the cristae ampullaris of the three semicircular canals [73].

Regarding ASICs specific immunoreactivity for ASIC1 and ASIC3 (**Figure 1c**) was detected in the hair cells of LLS, while ASIC2 was restricted to the nerves supplying neuromasts (**Figure 1b**). Moreover, supporting and mantle cells, i.e., the non-sensory cells of the neuromasts, also displayed ASIC4 [74]. In the inner ear sensory cells, ASIC1 and ASIC3, but not ASIC4, were found in neurosensory cells (**Figure 1f, h, and i**), while ASIC2 was only found in the nerves supplying them (**Figure 1g**).

It is possible that these ion channels could account for the transduction of mechanical stimuli as specialized hair cells in the LLS neuromasts are able to detect water movements and vibrations comparable to hair cells in the mammalian inner ear. Moreover the occurrence of TRPV4 in the ear neuroepithelia claims for an involvement of this ion channel in hearing and balance.

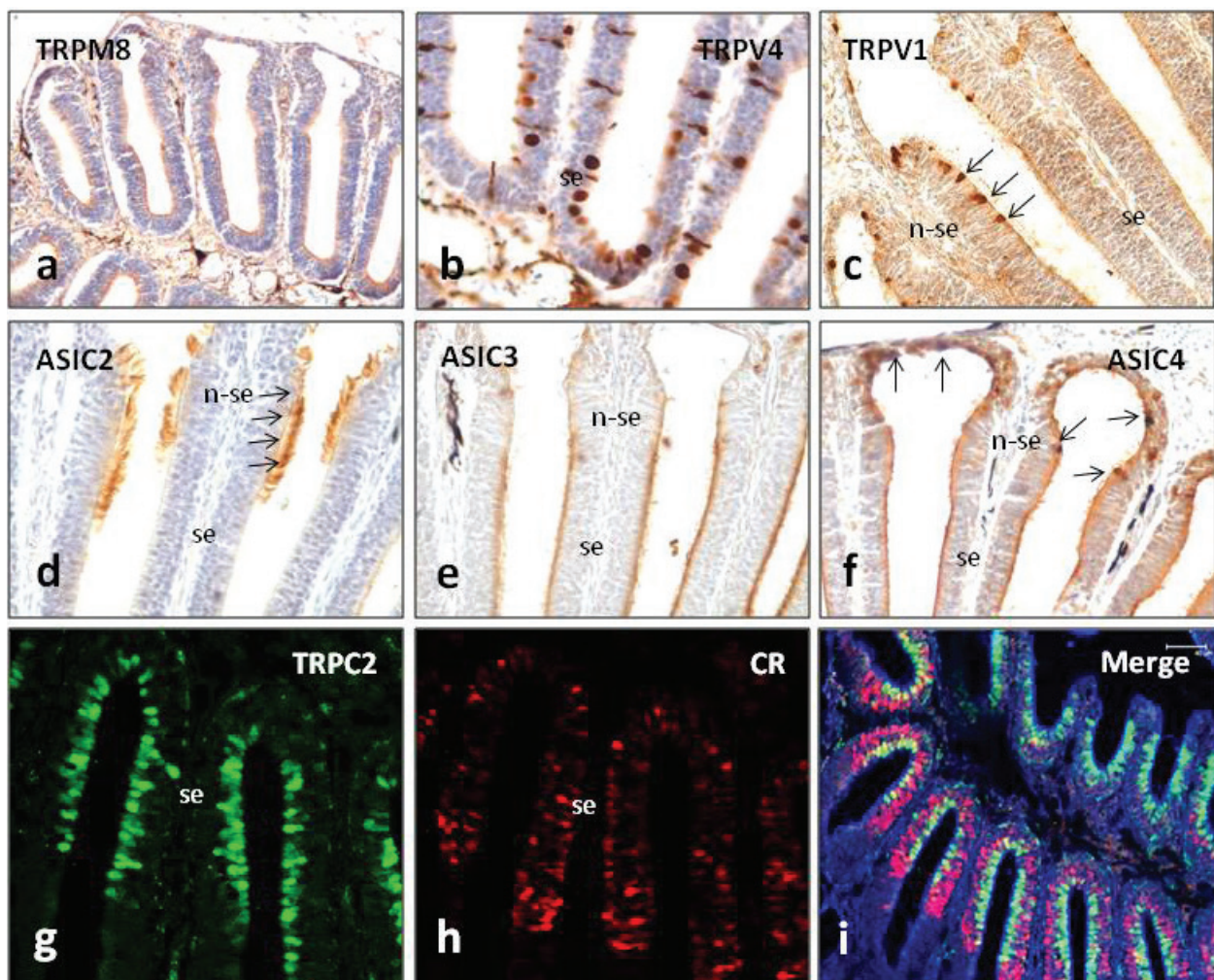


**Figure 1.** Immunohistochemical localization of ASICs and TRPV4 in the canal neuromasts (a–c) and inner ear neuroepithelia (ne) of adult zebrafish. N: nerve.

## 5.2. Olfactory epithelium and taste buds

The taste buds and the olfactory epithelium detect chemical changes in the aquatic environment. In zebrafish the chemosensory cells are grouped into taste buds [75] and in the lamellae of the olfactory epithelium [76]. Moreover, scattered solitary chemosensory cells are present in the skin [77].

The occurrence of *trpv4* mRNA in the olfactory pit of zebrafish was observed during the embryonic period [57]. Thereafter, TRPV4 immunoreactivity was observed in ciliated olfactory neurons and in unidentified cells placed in the non-sensory olfactory epithelium but not the crypt neurons [73, 78] (**Figure 2b**). On the other hand, ASIC2 mRNA and protein were detected in the olfactory rosette of adult zebrafish. Specific ASIC2 hybridization was observed in the luminal pole of the non-sensory epithelium, especially in the cilia basal bodies, and immunoreactivity for ASIC2 was restricted to the cilia of the non-sensory cells; ASIC2 expression was always absent in the olfactory cells [79] (**Figure 2d**).



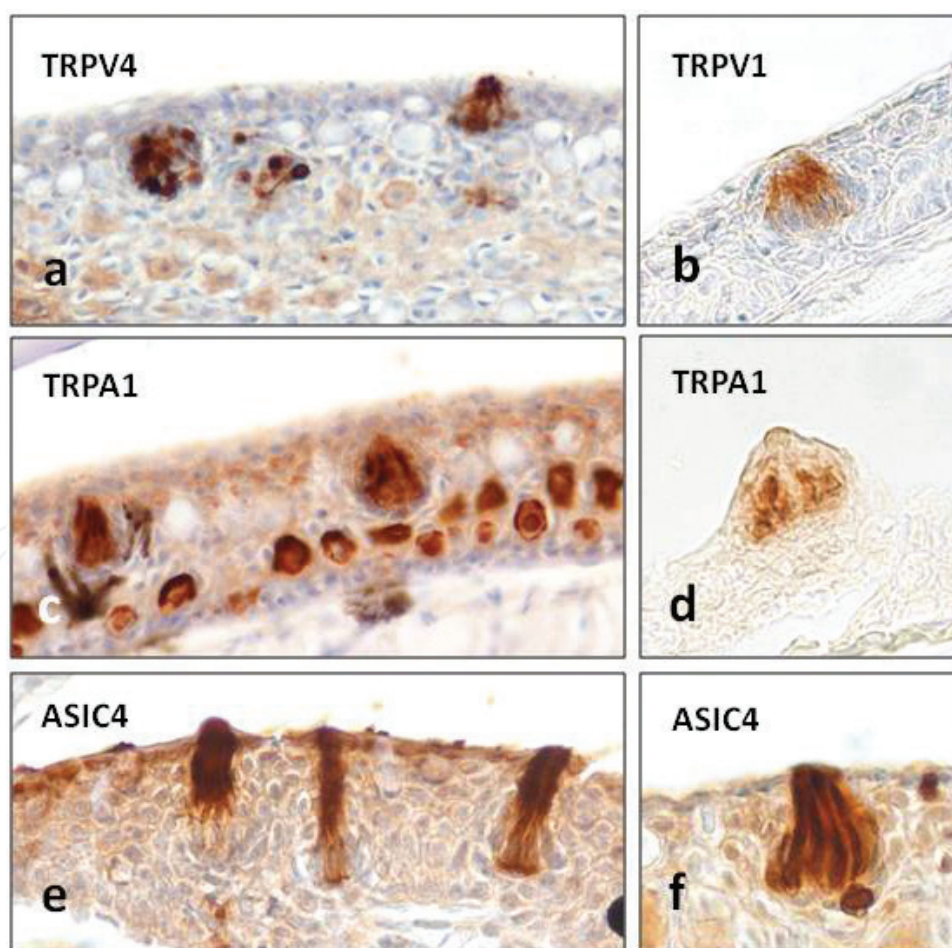
**Figure 2.** Immunohistochemical localization of TRP and ASICs in the olfactory epithelium of adult zebrafish. se, sensory epithelium; n-se, non-sensory epithelium.



The localization of TRPV4 in the olfactory epithelium suggests that it participates in the detection of chemical stimuli, including the odorant ones. Conversely the localization of ASIC2 suggests that it is not involved in olfaction. Since the cilia sense and transduce mechanical and chemical stimuli, ASIC2 expression in this location might be related to detection of aquatic environment, pH variations, or water movement through the nasal cavity.

Unpublished results for our laboratory also demonstrated the occurrence of TRPM8, ASIC3, and ASIC4 in the microvilli of the sensory epithelium and of TRPV1 in some unidentified cells of the non-sensory epithelium (**Figure 2a, c, e, and f**). Furthermore, we detected TRPC2 in a subpopulation of olfactory neurons different to the calretinin-positive ones (**Figure 2g–i**).

In fish taste receptor cells, different classes of ion channels have been detected which, like in mammals, presumably participate in the detection and/or transduction of chemical gustatory signals. The zebrafish homolog of TRPM5 (zfTRPM5) is expressed in cells of the taste buds [55]. TRPV4 has been also detected in the sensory cells of the cutaneous taste buds and in a subset of sensory cells in the oropharyngeal ones [73, 80] (**Figure 3a**). In addition TRPV4 was detected in the cutaneous solitary chemosensory cells [73]. Preliminary results of our group

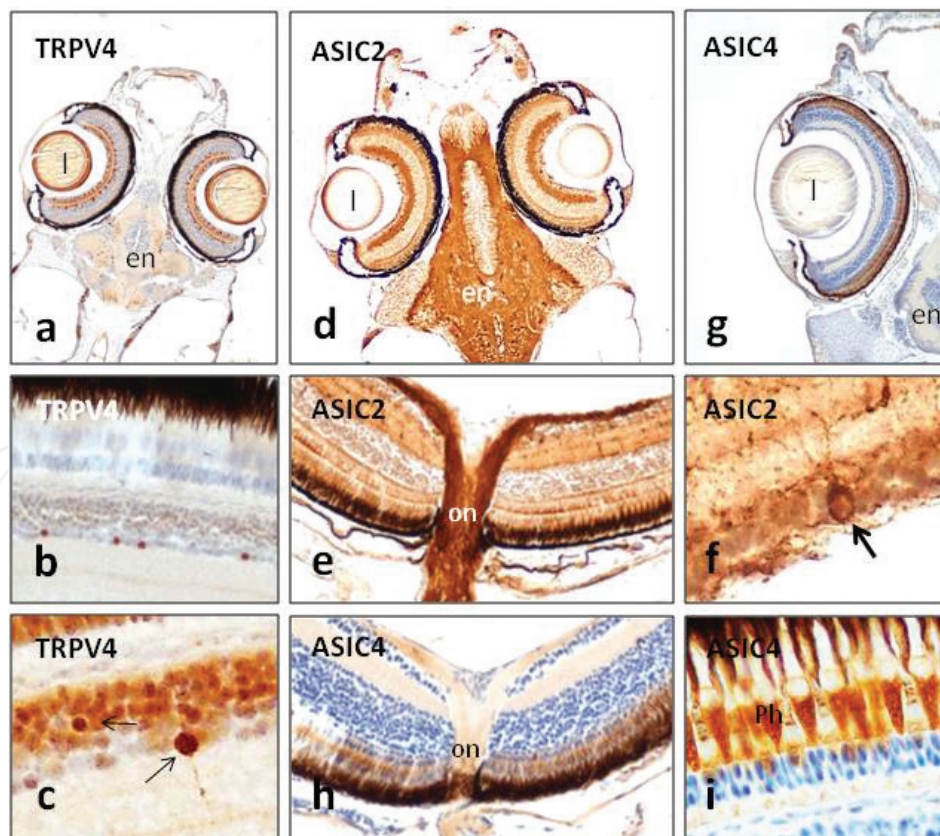


**Figure 3.** Immunohistochemical localization of TRP and ASICs in the taste buds of adult zebrafish.

have also detected TRPM1 in taste buds (**Figure 3b–d**). On the other hand, ASIC1 and ASIC3 were regularly absent from taste buds, whereas faint ASIC2 and robust ASIC4 immunoreactivities were detected in sensory cells (**Figure 3e and f**). Moreover, ASIC2 immunoreactivity was found in nerves supplying taste [81]. Since these ion channels are involved in the detection of sensory modalities other than olfaction, it can be hypothesized that taste cells sense stimuli other than those specific for taste.

### 5.3. Retina

Some TRP channels are present in the vertebrate retina. *trpC1* expression was observed in the ganglion cells as well as the inner nuclear layer of the eye, while *trpC6* was absent from SO [63]. Viña et al. [82] have investigated the expression and distribution of TRPV4 in the retina of zebrafish from 3 until 100 days post fertilization (dpf). Immunohistochemistry revealed the presence of TRPV4 in amacrine cells, localized in the inner nuclear layer and ganglion cell layers [73, 83] (**Figure 4a–c**). At 24 and 48 hpf, *trpm1a* was found expressed in different cells of the retina; thereafter at 3 dpf, it was expressed in the inner nuclear layer. On the other hand, *trpm1b* was initially expressed in cells of the outer retinal neuroepithelium and then in the inner nuclear layer [56].



**Figure 4.** Immunohistochemical localization of TRP and ASICs in the retina of larvae (a, d, g) and adult zebrafish. en, encephalon; l, lens; on, optic nerve; Ph, photoreceptors.

Regarding ASICs, in the retina of zebrafish larvae, ASIC2 and ASIC4 were detected in the retinal ganglion cells [65]. *asic1* mRNA and protein expressions were observed in the adult zebrafish retina using whole-mount *in situ* hybridization and immunohistochemistry study [84]. Viña et al. [82] in adult animals detected mRNA encoding ASIC2 and ASIC4.2 but not zASIC4.1. ASIC2 was found in the outer nuclear layer, the outer plexiform layer, the inner plexiform layer, the retinal ganglion cell layer, and the optic nerve. ASIC4 was expressed in the photoreceptor layer and to a lesser extent in the retinal ganglion cell layer (**Figure 4d-i**). Furthermore, the expression of both ASIC2 and ASIC4.2 was downregulated by light and darkness [82].

## 6. Concluding remarks

The sensory organs of zebrafish express multifunctional TRP and ASICs, most of them related to sensory modalities other than those expected for the sensory cells in which they are expressed. Based on the distribution of these multifunctional ion channels in SO, it seems they participate in multiple physiological functions as in mammals (mechanosensation, hearing, and temperature sensing) but furthermore have potential roles in olfaction, taste, and vision.

The ability to detect fluctuations in the aquatic temperature is critical to maintaining body temperature and avoiding injury in diverse animals from insects to mammals. In zebrafish ion channels are required for the sensation of heat [85]. Also of special importance for zebrafish is the detection of water movement. This function is classically attributed to the neuromast hair cells of the LLS. The occurrence of mechanosensitive ion channels in these cells supports this idea. But because the role of ASIC2 in mechanosensing and its presence in the cilia of the nonolfactory epithelium it is plausible suggest also a role of these cells in detecting water movement (see [79]). On the other hand, the presence of TRPV4 in sensory cells of the neuromasts and of the inner ear claims for an involvement of TRPV4 in mechanotransduction as suggested before [2, 72, 86] and is of particular importance since it potentially plays significant roles in human hearing [87].

Different TRP and ASICs have been observed in olfactory neurons and sensory taste cells of zebrafish, but its functions remain to be elucidated. However, in supporting a role of TRPV4 in olfaction in zebrafish, Ahmed et al. [88] and Nakashimo et al. [89] have detected TRPV1, TRPV2, TRPV3, and TRPV4 immunoreactivity in the olfactory epithelium of mice, and they suggest that TRPV channels may contribute to olfactory chemosensation. Of particular interest are the preliminary data presented here about the occurrence of TRPC2 in the olfactory epithelium of adult zebrafish. This ion channel is related to the detection of pheromones and sexual behavior in mammals [90, 91] and since zebrafish lack of a true vomeronasal organ age, sex, seasonal changes in TRPC2 must be analyzed in depth. Regarding the taste, and differently to mammals [35], the involvement of TRP ion channels has been poorly studied, while no great differences seem to exist with respect to ASICs (see [80]).

The expression of multiple TRP ion channels and ASICs in the developing and adult retina suggests they participate in vision. Fluctuations in pH play an important role in the retina, and for that reason, ASICs, and presumably also some TRPs, are thought to be involved in the fine-tuning of visual perception, adaptation to different light intensities, and phototransduction



[92]. As pH variations are also associated with pathological conditions, ASICs are likely to be involved in the pathogenesis of retinal diseases [93, 94], and its blockade may have a potential neuroprotective effect in ocular ischemic diseases [95].

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