Review Article

Sensory Integration: Cross-Modal Communication Between the Olfactory and Visual Systems in Zebrafish

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Abstract

Cross-modal sensory communication is an innate biological process that refers to the combination and/or interpretation of different types of sensory input in the brain. Often, this process conjugates with neural modulation, by which the neural signals that convey sensory information are adjusted, such as intensity, frequency, complexity, and/or novelty. Although the anatomic pathways involved in cross-modal sensory integration have been previously described, the course of development and the physiological roles of multisensory signaling integration in brain functions remain to be elucidated. In this article, I review some of the recent findings in sensory integration from research using the zebrafish models. In zebrafish, cross-modal sensory integration occurs between the olfactory and visual systems. It is mediated by the olfacto-retinal centrifugal (ORC) pathway, which originates from the terminalis nerve (TN) in the olfactory bulb and terminates in the neural retina. In the retina, the TNs synapse with the inner nuclear layer dopaminergic interplexiform cells (DA-IPCs). Through the ORC pathway, stimulation of the olfactory neurons alters the cellular activity of TNs and DA-IPCs, which in turn modulates retinal neural function and increases behavioral visual sensitivity.

Key words: olfacto-retinal pathway, sensory integration, vision, zebrafish

Introduction

Cross-modal sensory integration occurs in all vertebrate species including humans (Brooke et al. 1965; Demski and Northcutt 1983; Zucker and Dowling 1987; Gire et al. 2013). Defects in this process may lead to serious neurological malfunctions, such as difficulties in position (proprioception), movement (vestibular system), or response to classic sensory stimulation (e.g., vision, olfaction, hearing, and taste) (Gleiss and Kayser 2012; Heinzle et al. 2012; Kent et al. 2012).

Studies that investigate cross-modal sensory integration particularly those involved in the visual system have been previously reported (Behrens and Wagner 2004). In all vertebrate species examined thus far (e.g., teleost, reptiles, birds, rodents, and primates), the neural retinas receive centrifugal signals from the brain. Depending on the species, the centrifugal input may originate from different

parts of the brain, such as the isthmo-optic nucleus, pretectal cortex, thalamus, or olfactory bulb. In birds, for example, their retinas receive centrifugal inputs from the midbrain isthmo-optic nucleus (Uchiyama et al. 1995). Lesion of the isthmo-optic nucleus results in alterations in the pattern of retinal ganglion cell firing. In rats, the retinas receive serotonergic feedback from the diencephalon and mesencephalon (Gastinger et al. 2004). Yet, the roles of serotonergic signaling transduction in retinal functions remain to be studied. In monkeys, cortex projections to lateral geniculate nucleus have been identified (Briggs et al. 2011). It is believed that the cortex signals sharpen the receptive fields of lateral geniculate nucleus neurons, enhance the transmission of neural signals relayed through the brain, and augment directed attentions. Also, in monkeys, the retinas receive histamine input that is originated from the hypothalamus

(Gastinger et al. 1999). In isolated retinas, the application of histamine alters the membrane potentials of retinal bipolar cells and the firing patterns of retinal ganglion cells (Gastinger et al. 2004; Yu et al. 2009; Akimov et al. 2010).

In humans, sensory signaling interactions between the olfactory and visual systems have been reported (Gottfried and Dolan 2003; Gire et al. 2013). Imaging and psychological analyses revealed that the interactions take place in the forebrain, somewhere between the anterior hippocampus and rostromedial orbitofrontal cortex. A theory arising from these studies is that following cross-modal sensory integrations, measures of performance or behavior in response to sensory stimulation are enhanced, particularly when a stimulus in one modality is ambiguous or underdetermined. The molecular and cellular pathways involved in such types of sensory integrations, however, remain to be investigated.

Recently, zebrafish become a model system for studying neurobiology and physiology (Dodd et al. 2000; McGonnell and Fowkes 2006; Mauri et al. 2018). Zebrafish also provide a tool for characterizing the molecular and cellular basis of sensory integration and brain function. Because zebrafish maintain high evolutionary proximity to mammals, the findings from zebrafish research may be readily applied to studies of the mechanisms of sensory integration in other vertebrate species including humans.

A centrifugal pathway between the olfactory and visual systems

Zebrafish possess a prominent anatomic pathway, known as the olfacto-retinal centrifugal (ORC) pathway, that connects the olfactory and visual systems (Li and Dowling 2000; Maaswinkel and Li 2003; Wang et al. 2011). The ORC pathway originates from the terminalis nerve (TN) that is embedded in the olfactory bulb. Each olfactory bulb contains approximately 20–30 TNs (Figure 1A,B). The TNs project axons to large brain areas, and through the optic nerve, some of the TN axons enter the retina where they extend in the interplexiform layer (IPL) along the board of inner plexiform layer (INL). While propagating in the IPL, the TN axons are branched. They project to the INL and synapse with a class of inner retinal neurons, known as dopaminergic interplexiform cells (DA-IPCs) (Figure 1C). The TN axons may also synapse with other retinal cell types, such as retinal ganglion cells (Stell et al. 1984). The TNs synthesize and release several types of neuropeptides, which include gonadotropin hormone-releasing hormone-like hormone (GnRH) (Appelbaum et al. 2006; Ramakrishnan et al. 2010; Wang et al. 2011).

Dopamine-related neural signals induce TN projection to the retina

Several lines of transgenic zebrafish that express protein markers in the TNs and their axons have been reported (Appelbaum et al. 2006; Ramakrishnan et al. 2010; Wang et al. 2011). These fish provide excellent tools for characterization of the development and function of the ORC pathway. Using Tg(GnRH-3::GFP) transgenic fish, Pfister et al. (2015) examined the courses of TN axonal projection to the retina. In developing embryos, soon after the neurogenesis of TNs at approximately 1.5 days postfertilization, TN axons are observed in the brain. However, in the retina, the first TN axons are not detected until 2.5 days postfertilization, when the first DA-IPCs are differentiated (Gao et al. 2005). Upon entering the retina, the TN axons extend in the IPL and project to the INL. Most dramatically,

Figure 1. The ORC pathway in zebrafish (lateral view, anterior is to the left). (A) A schematic representation of TNs and axons in the olfactory bulb and brain. Red circles and lines represent TN cell bodies and axons. Note the TN axons in the optic nerve and eye. Abbreviations: OB, olfactory bulb; RE, retina; TC, tectum; TE, telencephalon. (B) A confocal image of immunostaining of whole-mount olfactory bulb that shows TNs and axons. Scale bar: 35 μ m. (C) A confocal image of retinal section colabeled with antibodies that recognize TN axons (red) and DA-IPCs (green). Scale bar: 20 μ m (modified from Maaswinkel and Li 2003).

they directly project to areas where the DA-IPCs are located (Figure 2A,B).

In the retina, DA-IPCs are the only cell types that synthesize and release dopamine (Dowling 1991; Yazulla et al. 1996). To study the possible roles of dopamine on TN axonal projection, Pfister et al. (2015) examined the distribution of TN axons in adult zebrafish retinas in which DA-IPCs are degenerated and subsequently regenerated (Figure 2C–F). DA-IPCs can be destroyed by intraocular injection of neurotoxin 6-hydroxydopamine (6-OHDA; Lin and Yazulla 1994; Li and Dowling 2000). In the absence of DA-IPCs, TN axons are reduced in number and eventually disappeared from the retina. After 4 weeks of 6-OHDA treatment, regeneration of DA-IPCs becomes evident. During the course of DA-IPC regeneration, TN axons reappear in the retina and recontact with newly generated DA-IPCs. Together, the data suggest that DA-IPCs or DA-IPC-related dopaminergic signaling transductions may play important roles for the development and maintenance of the TN networks in the neural retina.

Property of TNs

Using Tg(GnRH-3::GFP) zebrafish, Huang and Li (2011) and Wang et al. (2011) characterized the TNs, such as resting and firing potentials, spontaneous firing patterns, and the expression of neurotransmitter receptors. On average, the resting potential of TNs is

Figure 2. Fluorescent images of Tg(GnRH-3::GFP) retinas that show the projection and distribution of TN axons. TN axons (green) were detected by the expression of GFP. DA-IPCs (red) were labeled by antibodies against tyrosine hydroxylase. **(A,B)** Images of retinal sections from embryos that show the projection of TN axons. At 2 days postfertilization, the first DA-IPCs (arrows with solid tail) are found in the retina. At 2.5 days postfertilization, the TN axons (arrows with dashed tail) enter the retina through the optic nerve (indicated by asterisks) and project toward DA-IPCs. Dashed lines outline the lens and retina. Scale bar: 50 μ m. **(C–F)** Images of whole-mount adult retinas that show TN axons (green) in the presence or absence of DA-IPCs (red). In control retinas, TN axons are present (C). DA-IPCs are degenerated after treatment with 6-OHDA (D), but they can be regenerated (E,F). Note that the TN axons are disappeared after DA-IPC degeneration (D) and reappeared after DA-IPC regeneration (E,F). Abbreviations: d, day; dpi, days post injection; GFP, green fluorescent protein. Scale bar: 50 μ m (modified from Pfister et al. 2015).

approximately -69 mV, and the threshold potential for firing evoked spikes is -45 mV. Based on their spontaneous firing patterns, four different types of TNs are identified, which are characterized by rhythmic firing, burst firing, irregular firing, and rare firing (Figure 3). Among the TNs recorded ($n = 145$), approximately 40% show rhythmic firing patterns. The rest can be equally divided into burst, irregular, and rare firing groups. In all cases, the firing of TNs can be inhibited by tetrodotoxin, indicating that the function of TNs is largely mediated by voltage-gated sodium channels.

Because the TNs are embedded in the olfactory bulb, it has been speculated that the function of TNs is influenced by glutamatergic

Figure 3. Current-clamp traces showing the firing of TNs isolated from Tg(GnRH-3::GFP) fish. The firing can be classified as **(A)** rhythmic firing, **(B)** burst firing, **(C)** irregular firing, and **(D)** rare firing. Scale bar: 1 s (modified from Wang et al. 2011).

olfactory input. To test this hypothesis, Wang et al. (2011) examined the expression of glutamate receptors on the TNs and the roles of glutamate on TN firing using isolated TNs from transgenic Tg(GnRH-3::GFP) fish. They found that the application of glutamate, as well as its receptor agonist kainic acid (KA) or N-methyl-D-aspartate (NMDA) depolarizes TN membrane potentials and increases the frequency of spontaneous firings. The effects of KA and NMDA can be blocked by bath application of cyanquinoxaline (CNQX, non-NMDA ionotropic receptor antagonists) or D-2-amino-7-phosphonoheptanoic acid (D-AP-7, NMDA receptor antagonists), suggesting that both non-NMDA and NMDA receptors are expressed on TNs (Figure 4).

Effects of olfactory stimulation on visual sensitivity

Dopamine is an important neural modulator in visual system functions (Dowling 1991; Yazulla et al. 1996; Weiler et al. 1997). In fish retinas, for example, the application of dopamine reduces the receptive field of horizontal cells (Umino et al. 1991) and decreases the current flow of bipolar cells (Yu and Li, 2005). Thus, dopamine is sometimes regarded as an inhibitory factor in retinal functions. Because the TNs express glutamate receptors, it is conceivable that the firing of TNs will be changed in response to increases of glutamate after olfactory stimulation, and because the TN axons synapse with DA-IPCs, it is possible that stimulation of olfactory neurons alters the dynamics of dopamine release by DA-IPCs. Using microdialysis and high-performance liquid chromatography assays, Puppala et al. (2004) and Huang et al. (2005) demonstrated that in zebrafish, stimulation of olfactory neurons decreases the content of dopamine in the retina. Based on these findings, it is conceivable that in response to olfactory stimulation, some of the dopamine-mediated inhibition of neural activity will be lifted and, as such, retinal functions such as visual sensitivity will be increased.

Figure 4. Effects of glutamate, KA, and NMDA on TN membrane potential and spontaneous firing. (A–C) Current-clamp traces showing the increase in membrane potentials in response to glutamate (300 μ M), KA (50 μ M), and NMDA (100 μ M). (D–F) Loose-patch recording traces showing the increase in firing frequency of spontaneous action potentials in response to bath application of glutamate, KA, and NMDA. The effects of KA and NMDA can be blocked by CNQX (10 μ M) and D-AP-7 (100 μ M), respectively. Horizontal and vertical bars on the right side of the trace indicate the time scale and response amplitude, respectively (modified from Wang et al. 2011).

To test this hypothesis, Li and coworkers (Maaswinkel and Li 2003; Huang et al. 2005; Li et al. 2017) measured the visual sensitivity of zebrafish in response to olfactory stimulation using a behavioral assay based on visually mediated escape responses (Li 2001). In those studies, amino acids (e.g., alanine, arginine, aspartate, and methionine) were chosen to stimulate olfactory neurons, because they are among the most effective odors for zebrafish (Edwards and Michel 2002). It is found that in early morning, stimulation of olfactory neurons increases visual sensitivity (Figure 5). Blockage of the olfactory input to the retina (e.g., bulbectomy or ablation of olfactory sensory neurons) or inhibition of dopaminergic signaling transduction in the retina (e.g., destroy DA-IPCs or inject dopamine receptor antagonists to the retina) eliminates the effect of olfactory stimulation on visual sensitivity. Together, the results from those studies demonstrate the roles of cross-modal sensory integration in retinal sensitivity.

Influential factors that may affect the development and function of the ORC pathway

Previously, a zebrafish mutation *night blindness b* (*nbb*) that causes visual defects has been identified (Li and Dowling 2000). Under normal illumination conditions, the visual threshold of *nbb* fish is indistinguishable from wild-type animals. However, after prolonged dark adaptation (e.g., >2 h), the visual sensitivity of *nbb* fish is decreased. Using conventional histological and immunolabeling methods, Li and Dowling (2000) found that in *nbb* retinas, the distribution of TN axons is disorganized and the number of DA-IPCs is reduced. Molecular cloning and sequencing analyses of *nbb* mutation revealed that *nbb* is a homolog of mammalian *SCL/TAL1*

Figure 5. Behavioral visual threshold of control and experimental zebrafish in response to olfactory stimulation. When tested in early morning hours, the visual threshold of control fish is approximately log I = -3.8 (black bars). Note the decrease of visual threshold (increase of visual sensitivity) in response to olfactory stimulation with amino acids (hatched bars). The effects of olfactory stimulation on visual sensitivity are not evident in surgically or drug-treated animals (gray bars). Abbreviations: OB, olfactory bulb; OE, olfactory epithelium; DA, dopaminergic neuron; DR, dopamine receptor. * $P < 0.01$ (modified from Li and Dowling 2000; Maaswinkel and Li 2003; Li et al. 2017).

interrupting locus (*Stil*) (Li et al. 2013). *Stil* is highly conserved in vertebrate species and is expressed in many cell types, including neurons (Izraeli et al. 1999; Erez et al. 2004; Arquint et al. 2012). Thus, it is possible that the development and function of ORC-mediated sensory integration are influenced by genetic factors.

Previous studies have suggested that the function of retinal neurons is affected by GnRH (Grens et al. 2005; Tello et al. 2008). Because the TNs synthesize and release GnRH, it is likely that the function of ORC signaling transduction is directly regulated by GnRH. Considering the time-dependent effects of olfactory input in retinal function (Maaswinkel and Li 2003) and the day-night fluctuation of behavioral visual sensitivity in zebrafish (Li and Dowling 1998; Ren and Li 2004; Yu et al. 2007; Li et al. 2005; 2012), it is possible that the function of the ORC pathway may also be influenced by other factors that are involved in regulation of the day-night rhythms of animal behavior and physiology, such as melatonin (Reppert 1997; Stewart 2001). In zebrafish, melatonin is mainly synthesized and released from the pineal gland (Pevet and Challet 2011), and the roles of melatonin on retinal cellular functions are antagonistic to dopamine (Behrens et al. 2000; Ribelayga et al. 2002). Although the expression of melatonin receptors in the TN remains to be determined, it is possible that melatonin may directly modulate TN output in the retina, for example, by decrease of TN-induced dopamine release from the DA-IPCs (Exposito et al. 1995).

Concluding remarks

This paper provides a brief review of the current knowledge of cross-modal sensory information integration between the olfactory and visual systems in zebrafish. The integration is mediated by the ORC pathway, which is formed during early embryonic stages (Pfister

et al. 2015). The development of the ORC pathway is mediated by neural signals related to the neurogenesis and/or function of retinal DA-IPCs (Pfister et al. 2015). In zebrafish, stimulation of the olfactory neurons alters the firing of TNs, which in turn decreases the release of dopamine from DA-IPCs and thereby increases retinal sensitivity (Maaswinkel and Li 2003; Huang et al. 2005; Wang et al. 2011).

Although the ORC-mediated olfactory TN inputs are incorporated into visual system functions in the retina, the integration of TN signals may also occur in other areas of the brain, such as the hypothalamus. Alterations in hypothalamus neural activity in response to sensory information integration will likely change the dynamics of hormone synthesis and release and thereby alter animal behavior and physiology. In zebrafish, stimulation of the olfactory neurons with amino acids results in alterations in male's sexual behaviors, for example, mating-like chasing behaviors are observed between males (Li et al. 2017). Although the underlying mechanisms remain to be elucidated, it is speculated that the change of animal's sexual behavior is likely mediated by one of the following pathways, both of which are involved in TN signaling integration in the hypothalamus: 1) Stimulation of the olfactory neurons activates the TNs, and the TN signals are projected to the hypothalamus via TN axons (in zebrafish, the TNs project axons to most of the brain areas, including the hypothalamus; Appelbaum et al. 2006; Wang et al. 2011). 2) Stimulation of the olfactory neurons activates the TNs; the TN signals are first incorporated into retinal ganglion cells (Stell et al. 1984), then they are propagated to the hypothalamus via retinal ganglion cell axons (Springer and Mednick 1985). The effects of TN inputs on zebrafish sexual behaviors, however, are only observed in early morning (before sun rise, during which time mating normally takes place). Stimulation of the olfactory neurons in the afternoon or evening hours produced no effect on animals' sexual behaviors. Similar time-dependent sensory integration and modulation of brain functions have also been described in other vertebrate species. In monkeys, for example, histamine-containing axons from the hypothalamus are found in the fovea of the retina (Gasteringer et al. 1999). The integration of histaminergic signals is required for maintaining the activity of retinal ganglion cells, but only during the day time (Gasteringer et al. 2004).

In summary, cross-modal sensory integration is an important procedure for brain function. It has been studied in different model systems. Yet, there are still a lot of unknowns in regard to the underlying pathways. It is hoped that the results from zebrafish research may provide hints for further studies of sensory integration in other vertebrate species, including primates and/or humans.

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Conflict of interest

The author declares no conflict of interest.

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