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MINI-REVIEW

Role of BDNF in the taste system

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Abstract **Neurotrophins are a family of proteins that regulate neural survival, development, function and plasticity in the central and the peripheral nervous system. There are four neurotrophins: NGF, BDNF, NT-3 and NT-4. Among them, BDNF is mostly studied in the taste system due to its high expression. Recent studies have shown BDNF play an important role in the developmental and mature taste system, by regulating survival of taste cells and geniculate ganglion neurons, and maintaining and guiding taste nerve innervations. These studies imply BDNF has great potentialities for therapeutic usage to enhance sensory regeneration following nerve injury, with aging, and in some neurodegenerative diseases.**

Keywords brain-derived neurotrophic factor (BDNF), taste bud, geniculate ganglion, chorda tympani nerve

Introduction

In the central and the peripheral nervous system, neurotrophins are major regulators of multiple processes including neuron differentiation, survival, dendritic pruning, patterning of innervation, synaptic function and plasticity (Bibel and Barde, 2000; Huang and Reichardt, 2001). There are four neurotrophins: nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4). And, there are two classes of receptors for these four neurotrophins: the p75 neurotrophin receptor and Trk receptor tyrosine kinases (Huang and Reichardt, 2001) . P75 binds all four neurotrophins; NGF binds TrkA; BDNF and NT-4 bind TrkB; and NT-3 mainly binds TrkC (Huang and Reichardt, 2001). Among the 4 neurotrophins, BDNF is the most abundant growth factors in the brain. It is indicated that BDNF plays an important role in sustaining physiological processes of the normal, intact adult brain. For example, BDNF modulates dendritic branching and dendritic spine morphology (Horch and Katz, 2002; Tanaka et al., 2008), as well as synaptic plasticity and long-term potentiation (LTP) (Figurov et al., 1996). Besides, BDNF has a role in regulating hypothalamic metabolic function, further reflecting the diversity of its role in the adult brain (Xu et al., 2003; Cao et al., 2009).

Taste system is a perfect model to study neurotrophins' function. Taste buds arise in discrete, specific locations, and nerves that innervate them can easily be quantified. Besides, neurotrophins and their receptors can also be examined in transgenic overexpressing, or knockout mice. Among all the neurotrophins, BDNF and its receptors have been shown to be continuously expressed in the developmental and adult taste system (Ganchrow et al., 2003; Yee et al., 2003; Huang and Stähler, 2009; Nosrat et al., 2012). This review will summarize how BDNF regulates taste neuron survival, taste nerve outgrowth and target innervation during development and in the mature taste system.

The peripheral taste system

Taste buds

In the taste system, taste buds are used to detect five essential taste qualities: sweet, bitter, sour, salty and umami (amino acid). In mammals, taste buds are located on the tongue, soft palate, pharynx, and epiglottis. On the tongue, taste buds are housed in specialized epithelial organs called papillae. There are three types of papillae: fungiform papillae (scattered

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throughout the front two-thirds of the tongue), foliate papillae (short vertical folds found on the lateral margins of the tongue) and circumvallate papillae (situated at the very back of the tongue) (Hill, 2004; Krimm, 2007).

All taste buds regardless of their location, are composed of anywhere from 50 to 100 taste cells, depending on the species (Finger, 2005). Taste cells can be grouped into different cell types based on their function, ultrastructure or light microscope markers (Farbman, 1965; Murray et al., 1969; Kinnamon et al., 1985). The presence or absence of specific proteins can also be used to differentiate subsets of taste cells. For example, there is one type of taste cells termed as Phospholipase C β2 taste cells since they contain Phospholipase C β2 (PLC β2), a principal GPCR effector, involved in intracellular signaling for transducing sweet, bitter or umami (Hoon et al., 1999; Miyoshi et al., 2001; Finger, 2005). Another type of taste cell possesses specialized chemical synapses and co-expresses some synaptic proteins like SNAP-25 (Yang et al., 2000).

Geniculate ganglion and petrosal ganglion

In the taste system, geniculate ganglion is made up of sensory neurons and innervate taste buds in the front two-thirds of the tongue (fungiform papillae), the soft palate and the nasoincisor ducts of the hard palate (Hill, 2004; Krimm, 2007). Geniculate neurons deliver information from chemosensory cells in taste bud to the central nervous system (Mistretta and Hill, 1994). Three sensory nerve bundles originate from the ganglion to innervate different fields (Mistretta and Hill, 1994; Krimm, 2007): the chorda tympani (CT) innervating taste buds in the fungiform papillae and anterior foliate papillae; the greater superficial petrosal nerve (GSP) innervating taste buds in the incisive papilla and soft palate; and the posterior auricular nerve innervating the skin of the external ear. The number of neurons in the geniculate ganglion innervating the tongue is roughly the same as the number of neurons innervating the palate (Patel et al., 2010).

Additional taste axons are supplied by neurons of the petrosal ganglion; these neurons innervate taste buds in the circumvallate papillae and most of the taste buds in the foliate papillae via the glossopharyngeal nerve. Geniculate and petrosal ganglia neurons relay taste signals to nucleus of the solitary tract (NST). Taste information is transmitted through the parabrachial nucleus (in rodents) into the thalamus, then thalamus deliver the information to primary gustatory cortex in the insula (Carleton et al., 2010).

Communication between taste cells and nerve fibers

Several neurotransmitters have been proposed for communication between taste cells and nerve fibers, including acetylcholine, ATP, glutamate, serotonin (5-HT), γ-aminobutyric acid (GABA) (Huang et al., 2007; Murata et al., 2010; Starostik et al., 2010; Ji et al., 2014a). However, adenosine 5′-triphosphate (ATP) is the key neurotransmitter in this system. Most (98.4%) geniculate neurons express the ATP receptor, P2X3; while 52.6% of geniculate neurons can be labeled with anti-P2X2 (Ishida et al., 2009). Most P2X2- and P2X3-immunoreactive nerve fibers in the taste buds in anterior two-thirds of tongue are derived from the chorda tympani nerve (Ishida et al., 2009). In response to gustatory stimulation, taste bud cells release ATP to activate P2X2 and P2X3 receptors on gustatory nerve fibers (Finger et al., 2005). Combined mutations in these two ATP receptors eliminated taste responses in gustatory nerves, while the responses to cool saliva and touch remains (Finger et al., 2005). Thus, ATP is an important chemical signal connecting taste buds to taste nerve fibers (Finger et al., 2005; Huang et al., 2007; Ishida et al., 2009; Chen et al., 2010; Murata et al., 2010; Ji et al., 2014c).

Taste bud cells are very plastic and have a limited life-span (Beidler and Smallman, 1965). Therefore they are constantly renewed (Beidler and Smallman, 1965). As a result of taste cell turnover, taste cells need to constantly be reinnervated by gustatory nerve fibers. Some of these taste cells synapse with gustatory nerves (Yee et al., 2003), the constant turnover of taste cells necessitates continuing support for synaptogenesis throughout an animal's life time. While it is unclear what controls this constant reinnervation of new taste cells by gustatory afferents, it is easy to envision that neurotrophins (which have this role during development) could continue to orchestrate taste cell-nerve fiber connections in adulthood.

Development of geniculate ganglion and the role of neurotrophins

Development of geniculate ganglion

During geniculate ganglion genesis, the number of geniculate neurons is determined by a balance between neuron proliferation, differentiation, and apoptosis. In the geniculate ganglion, neuron production peaks at around E10 followed by loss of neuron cell number and ganglion volume from E12.5 to E14.5 in mice (Patel and Krimm, 2010). Therefore, the geniculate ganglion overproduces neurons first and then reduces these numbers through programed cell death (Carr et al., 2005).

As taste neurons of the geniculate ganglion differentiate they send out axons that follow spatially restricted pathways from geniculate neurons to the tongue surface (Mbiene and Mistretta, 1997), indicating that molecular cues guide them to these locations. At E14.5, chorda tympani nerves reach the tongue epithelium, penetrate the epithelium and form a distinctive nerve ending called neural bud (Lopez and Krimm, 2006). Both attractive and repulsive cues have been found for axon guidance, including: semaphorins, ephrins, and netrins (Yu and Bargmann, 2001). In the taste system,

Sema3A is one of these guidance molecules regulating axon guidance of geniculate neurons (Vilbig et al., 2004). Sema3A is expressed in the tongue and is required for both trigeminal and geniculate axon guidance (Vilbig et al., 2004). It prevents premature and aberrant growth of axons into the mid-region of the tongue (Vilbig et al., 2004).

BDNF support geniculate neuron survival during development

During development of many sensory systems, neurotrophins support neuron survival (Crowley et al., 1994; Smeyne et al., 1994). In the taste system, BDNF and NT-4 are important regulators of geniculate neuron number (Patel and Krimm, 2010, 2012). In mice overexpressing BDNF or NT-4 driven by a keratin promoter K14, geniculate neuron numbers are increased during development (Lopez and Krimm, 2006). *Bdnf*$^{-/-}$ and *Ntf4*$^{-/-}$ mice lose about half of their geniculate neurons during development (Patel and Krimm, 2010), while *Bdnf*$^{-/-}$/*Ntf4*$^{-/-}$ mice lose around 90% of their geniculate neurons from E13.5- E18.5 (Patel et al., 2010). As we know, Bax is a member of the Bcl-2 family of proteins that play key roles in programmed cell death, which may contribute to neuron loss (White et al., 1998). In BDNF null mice, Bax removal rescues neuron losses, demonstrating BDNF may promote survival of ganglion neuron by suppressing the Bax-dependent cell death pathway (Patel et al., 2010). Together, these findings indicate that geniculate ganglion neurons are very dependent on BDNF during development.

BDNF regulate geniculate nerve (taste nerve) outgrowth and innervation

In addition to promoting neuronal survival, BDNF regulate axon elongation, target innervation, and synapse formation in many sensory systems (Campenot, 1977; Fundin et al., 1997; Huang and Reichardt, 2001; Yan et al., 2007). In the gustatory system, BDNF regulates taste nerve outgrowth and guidance to the final target (i.e. taste buds) during taste system development (Lopez and Krimm, 2006; Ma et al., 2009). *Bdnf* mRNA is found in fungiform papilla epithelium when geniculate axon growth cones are arriving there (Nosrat and Olson, 1995; Nosrat et al., 1996). In addition, BDNF has been shown to promote outgrowth and attract geniculate ganglion neurites in vitro (Hoshino et al., 2010). When BDNF is overexpressed in non-taste epithelium *in-vivo,* non-taste filiform papillae were innervated by gustatory fibers, indicating that BDNF attracted the chorda tympani nerves to incorrect locations in the tongue (Lopez and Krimm, 2006). Following BDNF removal, gustatory axons fail to correctly locate and innervate fungiform papillae, indicating that BDNF is necessary for normal targeting (Ma et al., 2009). In conclusion, BDNF is important for taste nerve outgrowth and guidance to the taste bud during development.

Development of taste buds and the role of BDNF

Development of taste buds

The initial formation of fungiform papillae occurs without innervation; however, the maintenance of fungiform papillae and taste buds is dependent on gustatory innervation (Farbman and Mbiene, 1991; Sollars and Bernstein, 2000; Sollars, 2005). Specifically, fungiform papillae are present at the tongue as early as E13.5 in mice (Kim et al., 2003). By E14.5, the chorda tympani has reached the developing fungiform papillae and penetrated the epithelium (Lopez and Krimm, 2006). Gustatory nerve innervation is necessary for maintaining the taste bud in later development. For example, when the chorda tympani nerve is sectioned during postnatal development, the effects on the structural integrity of fungiform papillae and taste buds were more severe at younger than at older ages (Sollars, 2005). Nerve section at the earliest ages results in a complete and permanent loss of both taste buds and fungiform papillae (Sollars, 2005). Therefore, postnatal taste bud development is very dependent on innervation.

BDNF maintain taste bud number and size during development

Taste bud number and size are lost in mice that lack neurotrophins during development (Nosrat et al., 1997; Patel et al., 2010). Specifically, mice lacking BDNF lose more than half of their fungiform taste buds (Nosrat et al., 1997; Mistretta et al., 1999), and have a 59% reduction in the volume of taste buds (Patel et al., 2010). Since most geniculate neurons are lost and fail to innervate taste buds during development of mice lacking BDNF and taste buds require innervation to develop, taste buds could be lost because innervation is lost. In addition, taste buds are more sensitive to BDNF than NT-4 deletion during development (Patel et al., 2010). Absence of BDNF in mice leads to a more malformed taste bud and greater reduction in number of taste buds on the tongue; compared to NT4 knockout mice (Patel et al., 2010). This is because in addition to regulating neuron survival, BDNF is required for innervation to reach and successfully innervate taste buds. Thus, disruption in targeting means that fewer taste buds are innervated in BDNF compared with NT4 knockouts. Therefore, unlike gustatory neurons, which are equally dependent on BDNF and NT-4, more taste buds in the tongue are lost in *Bdnf*$^{-/-}$ mice.

Expression of BDNF and its potential roles in the adult taste system

BDNF continues to be expressed highly in the adult

geniculate ganglion, fungiform, foliate, and circumvallate taste buds. (Ganchrow et al., 2003; Yee et al., 2003; Huang and Stähler, 2009; Nosrat et al., 2012). In particular, BDNF and the synaptic protein, SNAP-25, are co-expressed in the adult taste cells (Yee et al., 2003), suggesting that BDNF may function to encourage synaptic contacts between taste cell and nerve fibers. Moreover, BDNF's major receptor, TrkB, is also expressed in the geniculate ganglion and taste cells of adult mice (Matsumoto et al., 2001; Huang and Stähler, 2009; Nosrat et al., 2012). Since BDNF and its receptor both continue to be expressed in adult geniculate ganglion and taste cells, it is possible BDNF may continue to regulate the adult taste system. In the adult taste system, taste cells are constantly renewed and form new connections with nerve fibers (Beidler and Smallman, 1965). Therefore, developmental factors like BDNF might continue to regulate innervation of new taste cells or synapse formation between taste cells and nerve fibers as they did in development.

Consistent with this idea, there is a correlation between loss of neurotrophins and loss of peripheral innervation in aging and neurodegenerative diseases (Bergman et al., 2000; Gardiner et al., 2008; Ji et al., 2013; Ola et al., 2013; Meng et al., 2014). In aging, reduction of NT3 and NT4 in the root sheath of ringwulst (mesenchymal sheath of the follicle) was accompanied with a loss of sensory axons into peripheral receptive fields on skin (Bergman et al., 2000). In some neurodegenerative diseases, neurotrophin factors are also reduced. In diabetes, the taste bud was impaired (Le Floch et al., 1989) accompanied with a decrease neurotrophin support (Jakobsen et al., 1981). In addition, dermal innervation is lost in diabetic mice (Greene et al., 1999) accompanied by reduced NGF support to peripheral nerve (Jakobsen et al., 1981). More importantly, when neurotrophin (NGF) was supplied, it induced increases in dermal innervation in adult diabetic mice (Christianson et al., 2007). In general, these experiments are correlative (both neurotrophins and innervation are reduced) therefore, it is still unclear whether it is the loss of neurotrophins that results in the loss of sensory innervation. However, together these studies would predict that loss of neurotrophin would cause loss of innervation in the adult.

Effects of gustatory nerve cut on the adult taste system and BDNF's potential role in the process

Degeneration and regeneration following gustatory nerve cut

After gustatory nerve section, nerve fibers within the taste bud disappear and taste evoked responses from nerve are lost (Cain et al., 1996; Guagliardo and Hill, 2007; Ishida et al., 2009). P2X3 positive fibers and taste buds both disappear from fungiform papillae by 7 days after chorda tympani nerve section in rat (Ishida et al., 2009) and within 14 days after chorda tympani and lingual nerve section in mice (Guagliardo and Hill, 2007). Electrophysiological responses were absent 2 weeks after chorda tympani nerve crush in hamster (Cain et al., 1996). Besides, taste bud number, taste bud size, and taste cell number also have a significant decrease (Farbman, 1969; Ganchrow and Ganchrow, 1989; Segerstad et al., 1989; Guagliardo and Hill, 2007; Chen et al., 2013) due to the loss of taste nerve innervation.

After gustatory nerve sectioning, nerve fibers will eventually regenerate and their functional responses to taste stimuli recover (Cheal and Oakley, 1977; Robinson, 1989; Hill and Phillips, 1994; Cain et al., 1996;). Most taste buds regain their anatomical integrity during regeneration. The gustatory nerve returns by following the original pathways in the tongue. When taste axons arrive at the lingual epithelium, taste bud regeneration is initiated, and both taste bud and cell number increase (Cheal et al., 1977; Cheal and Oakley, 1977; Robinson, 1989; Guagliardo and Hill, 2007). Although some neurons are lost permanently following nerve section (Shuler et al., 2004), regeneration in the gustatory system is in general fairly robust (Guth, 1957; Oakley et al., 1993). The reason might be that the taste system is extremely plastic in adulthood. Taste cells turn over and are constantly reinnervated by nerve fibers (Beidler and Smallman, 1965). The continued presence of BDNF in adult taste system may contribute to this process.

Potential role of BDNF in gustatory nerve regeneration

BDNF expression increased in the cell bodies of the neurons that were sectioned in many sensory systems (Popper et al., 1999; Zhou et al., 1999; Hirsch et al., 2000; Ji et al., 2014b). For example, in the somatosensory system, BDNF expression in the dorsal root ganglion had a significant increase 1 day after nerve lesion and lasted for 2 weeks (Zhou et al., 1999). This indicates that BDNF might be essential to promote nerve regeneration after nerve section. In a recent study, the tibia nerve of *thy-1-YFP-H* mice (mice have normal BDNF expression) was cut bilaterally, and then grafted with the same nerve from mice lacking BDNF in Schwann cells or wild-type mice (Wilhelm et al., 2012). Two weeks later, axonal regeneration into nerve grafts without BDNF was markedly less than wild type grafts (Wilhelm et al., 2012). This study demonstrated that BDNF play an important role in motor nerve regeneration.

Unfortunately, very little is known about the influence of BDNF on nerve regeneration in the gustatory system. Cutting the glossopharyngeal nerves leads to a loss of BDNF in both nerve fibers and taste buds (Yee et al., 2005). During regeneration, nerve fibers exhibited weak BDNF immunostaining in the taste buds, implying that BDNF may be involved in taste nerve regeneration (Yee et al., 2005).

Conclusion and discussion

BDNF is produced by geniculate ganglion neurons and taste placodes (Nosrat and Olson, 1995; Nosrat et al., 1996; Huang and Krimm, 2010) and is required for their survival during development (Conover et al., 1995; Liu et al., 1995; Ernfors, 2001). Besides, BDNF produced in taste epithelium, regulates the ability of gustatory neurons to locate and innervate their correct targets during development (Ma et al., 2009; Hoshino et al., 2010). In addition, BDNF may also play an important role in the adult taste system because it is highly expressed in adult mouse geniculate ganglion, hamster fungiform, foliate, and circumvallate taste buds (Nosrat et al., 1997; Ganchrow et al., 2003; Uchida et al., 2003; Yee et al., 2003). Consistent with this idea, there is a correlation between loss of neurotrophins and loss of peripheral innervation in aging and neurodegenerative diseases (Bergman et al., 2000; Gardiner et al., 2008; Ola et al., 2013). Finally, BDNF might be required for regeneration in the gustatory system following chorda tympani nerve section since BDNF plays such an important role in the continuing reinnervation of renewing taste cells.

Considering it plays such an important role in neuronal survival and function during development and in adulthood, BDNF has a big therapeutic potential for various neurological disease. However, when it is given to patients with amyotrophic lateral sclerosis (ALS), peripheral neuropathy, Parkinson's disease and Alzheimer's disease, the results are disappointing (Apfel et al., 1998; Kordower et al., 1999; Ochs et al., 2000). The reason is due to the delivery difficulty to central nervous system. BDNF is a moderately sized and charged protein, and can't easily cross the blood–brain barrier via peripheral administration. To reach neurons of the brain or spinal cord, BDNF must be administered directly into the CNS. Two potential approaches could solve the delivery problem: intraparenchymal protein infusion and gene delivery using viral vectors. With these new delivery methods, further examination of BDNF on neurological diseases is needed.

Compliance with ethics guidelines

The authors declare no conflict of interest. This article does not contain any studies with human or animal subjects performed by any of the authors.

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