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Review Article

Brain-derived neurotrophic factor is related to stress and chewing in saliva and salivary glands

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SUMMARY

Chewing is one of the most important orofacial functions. During this process, food is reduced in size, while saliva moistens the food and binds it into a bolus that can be easily swallowed. Characteristics of the oral system, including the number of teeth, bite force, and salivary flow, influence the masticatory process. In addition, salivary glands produce several cell growth factors and play an important role in human health. The nerve growth factor (NGF) family consists of NGF, brain-derived neurotrophic factor (BDNF), and neurotrophins-3 to 7. BDNF is a well-studied neurotrophin involved in the neurogenesis, differentiation, and maintenance of select peripheral and central neuronal cell populations during development and adulthood. However, there has been no detailed description of the expression of neurotrophins other than NGF in the salivary gland. We previously studied the effect of immobilization stress + chewing on BDNF secretion and its receptor, tyrosine receptor kinase B, in rat submandibular glands and found increased BDNF expression in duct cells under these conditions. In this review, we describe recent advances in understanding the role of stress and chewing-related BDNF in the saliva and salivary glands.

1. Introduction

Chewing is the process in which teeth crush and grind food into smaller pieces. It is the first step of digestion and increases the surface area of foods to facilitate more efficient breakdown by enzymes. During the chewing process, the cheek and tongue position the food between the teeth for grinding. As chewing continues, the food softens and warms, and enzymes in the saliva begin to break down carbohydrates in the food. After chewing, the bolus of food is swallowed and it enters the esophagus and continues to the stomach, where the next step of digestion occurs [1].

The whole saliva in the mouth, which is in contact with the teeth and oral mucosa, is derived predominantly from three major paired salivary glands, namely the parotid, submandibular, and sublingual glands, and from minor salivary glands in the oral mucosa including the tissue of the buccal, labial, and lingual mucosa, the soft palate, the lateral regions of the hard palate, and the floor of the mouth or between the muscle fibers of the tongue [2]. The main role of the salivary glands is to secrete saliva, which assists in food digestion and swallowing and promotes chewing and antimicrobial activities [3,4]. The salivary glands are predicted to also have other important roles since they produce a variety of substances; moreover, because acinar cells produce saliva from blood plasma, saliva includes many components derived from blood [5]. In addition, the volume and quality of salivary products are associated with the maintenance of oral health, which is linked to systemic health including that of the respiratory tract [6]. Therefore, the identification of salivary products might reflect the status of systemic health or disease.

Salivary glands produce several cell growth factors and play an important role in human health [7]. Accordingly, the discovery that growth factors such as epidermal growth factor (EGF) and nerve growth factor (NGF) in the rat submandibular gland led to the acknowledgment of new salivary gland functions [8,9]. The NGF family comprises NGF, brain-derived neurotrophic factor (BDNF), and neurotrophins (NTs)-3 to 7, all of which are collectively referred to as NTs [10]. The mouse salivary gland expresses a high level of NGF [11]. However, few reports have described the expression of NTs other than NGF in the salivary gland [12].

NTs interact with the tyrosine receptor kinase (Trk) family of high-affinity protein kinase receptors. BDNF specifically interacts with the TrkB receptor [10] to promote the survival and differentiation of neurons and is involved in the modification

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of neurotransmission and synaptic plasticity of the central and peripheral nervous systems [13]. BDNF is predominantly found in the hippocampus and is associated with episodic memory [14]. Immobilization stress reduces mRNA levels of NTs such as *NGF*, *BDNF*, and *NT-3* in the rat brain, and especially in the hippocampus [15]. In contrast, NGF expression is increased in response to stress in the mouse salivary gland [11]. The production of various cell growth factors is often increased during episodes of stress to maintain homeostasis in the salivary gland [11,16].

In this review, we describe the role of stress and chewing-related BDNF in the salivary glands and elaborate on its significance in the saliva and salivary glands. We also summarize evidence that suggests a relationship between immobilization stress + chewing and BDNF expression within the salivary gland and describe the effect of immobilization stress on BDNF and TrkB expression in male rat submandibular glands.

2. Development and evolution of masticatory organ

The masticatory organ, originally derived from a component of the branchial system, has evolved over a long period into an organ for emotional management after passing through stages in which the organ was used predominantly as a tool or weapon to express aggression [17]. During the process of evolution, as species adapted from life in the sea to life on land, the original branchial visceral organ evolved to form the face, pharynx, and masticatory organ [18]. Phylogenetic relationships have been preserved, and the human orofacial system thus retains the basic topography and function of that of its progenitor species, which is evident from the underlying nervous system [19].

As a derivative of the first branchial arch, the masticatory organ has functionally changed from its original autonomic pumping role to an organ to express emotion [20]. The trigeminal nerve supplies signals for both efferent and afferent pathways. During these processes, the masticatory organ is mainly used for expressing emotion, particularly aggression, and for instinctive purposes such as predation [21,22]. Evidence suggests that the masticatory organ is directly related to the limbic system [23]. Modern humans retain this connection, and therefore this organ is also used to express some aggression in the form of sleep bruxism as well as mastication [24].

Many animal species grind their teeth as a component of their response to a threatening or stressful situation. During the evolutionary process, animals have long used the masticatory organ as an emotional outlet in addition to a tool for chewing food [1]. It has been suggested that modern humans continue to use the masticatory organ to express aggression if they are overwhelmed psychologically (e.g. chewing gum) [25]. Several studies have shown that psychic stress and occlusal disharmony are related to bruxism [26,27]. From a psychosomatic point of view, unresolved psychic problems are transferred to the organ level. Utilizing chewing as a stress outlet is an efficient, risk-free solution to the problem of stress management [28]. Many lines of evidence using animal models have demonstrated in recent years that chewing can help attenuate stress-induced neurophysiological events (see Section 6).

3. Relationship between chewing and saliva

Chewing assists in several functions including food intake, bolus formation, and digestion [29]. The masticatory central pattern generator (CPG) is located in the brainstem and involves mostly neurons in the vicinity of the trigeminal system [30,31]. Although this has been known since the early 1970s, the precise organization of the trigeminal circuits that are involved and the basic mechanisms governing interactions between the cellular components remain largely unknown [32]. Although there is still discussion regarding the location of the masticatory CPG, it has been reported that basic chewing rhythms are controlled by a CPG located in the medial bulbar reticular formation in close association with inputs from peripheral sense organs that have a modifying effect on the pattern generator [33]. In contrast, rhythmic neurons are also known to exist in the posterior medial portion of the bulbous network, including giant reticular nuclei [30,32]. Chewing involves the actions and effects of the masticatory muscles, saliva, teeth, temporomandibular joint, and tongue [34]. The quality of chewing can be evaluated as the chewing performance, or the capacity to reduce the food particle size when chewing peanuts for a standardized period [35]. Chewing performance has also been defined as the number of chews necessary to render food ready for swallowing [36]. Chewing performance is dependent on the number of teeth in functional occlusion [37] and the maximal chewing force [38], and it deteriorates with tooth loss [39]. The chewing force is positively correlated with the surrounding periodontal tissue, among other factors [40]. Consequently, complete or partial denture wearers have a low chewing force and a lower chewing performance [41]. The salivary flow rate also influences the chewing performance, which declines with reduced salivary secretion [42]. Furthermore, during head and neck cancer treatment with high-dose chemoradiation-induced xerostomia, the number of chewing cycles before initiating a swallow increases [43]. The mechanism of increased salivation is more complicated. Naturally, increased salivation also occurs in other salivary glands [44]. The posterior area of the insular cortex is known to induce salivation in response to chewing in rats [45]. There has also been a report that the lateral hypothalamus affects salivary secretion during feeding in the rat submandibular gland [46]. Increased salivary secretion in response to chewing is also the result of a masticatory–salivary reflex, which is primarily unilateral and dependent on the applied stimulus intensity [47]. Variations in the frequency of the chewing cycles do not seem to influence the salivary flow rate [48].

In addition, there is some evidence indicating a relationship between chewing and saliva in humans and animals and suggesting that increased chewing might increase salivary output, whereas reductions in chewing have the opposite effect. For example, parotid gland atrophy and reduced proline-rich protein concentrations in the parotid saliva follow the initiation of a liquefied diet in rats [49,50], whereas parotid gland enlargement and an increase in the salivary flow rate follow the implementation of a diet that requires more chewing [51]. In humans, liquid diet initiation leads to reduction in the salivary flow rate from stimulated parotid glands and subsequently, to the increase in both stimulated and unstimulated whole saliva [52]. Further, for institutionalized children, diet modification, to make it less acidogenic, less retentive, and of firmer texture, resulted in an increased flow rate of stimulated parotid saliva and increased plaque pH [53]. Moreover, salivary flow rates were significantly correlated with maximal chewing force [54]. Moreover, the flow rate of unstimulated whole saliva was determined to significantly increase in human subjects after chewing four sticks of sugar-free gum per day for 8 weeks [55]. In addition, the frequent consumption of sugar-free chewing gum for 2 weeks results in increased stimulated parotid saliva flow rates and reduced plaque acidogenicity [56]. However, electromyographic assessments of masseter muscle activity during eating and gum chewing suggest that diet alterations alone are probably insufficient to produce the extent of chewing stimulus required to achieve a measurable increase in salivary gland function in community-dwelling adults [57]. The use of sugar-free gum to enhance remineralization by stimulating salivary flow is now an accepted preventive therapy [58].

During chewing, food mixes with saliva to form a bolus, which is a smooth, rounded, and lubricated portion of mechanically broken

down food [29]. The water in saliva moistens the food particles, whereas the salivary mucins bind masticated food into a coherent and slippery bolus that can easily slide through the esophagus without damaging the mucosa [59]. The enzymatic digestion of carbohydrates is also initiated in the food bolus [60]. The water content of the food bolus does not seem to be the main factor to initiate swallowing [61]; it is more likely that the cohesive forces between the food particles in the food bolus determine when the bolus is ready to be swallowed. Thus, the optimal moment for swallowing appears to occur when the cohesive forces among the food particles in the bolus are strongest. The cohesive forces are a product of both particle size reduction and saliva secretion [62].

4. Salivary secretion related to stress

The salivary glands are exocrine glands characterized by the presence of numerous excretory units (acini) and a distinctive duct system. Acini are formed by groups of acinar cells and form a sac-like lumen, which drains into small ducts. The acinar cells are categorized as mucous and serous cells based on whether they can or cannot secrete mucins, respectively. The ducts consist of excretory, intercalated, and striated types, and duct cells secrete a characteristic set of proteins [12]. Thus, saliva secreted by one type of gland is a composite of the secretions of various groups of glandular cells. A composite of the secretions of all different salivary glands forms "whole" saliva.

Saliva has various important roles in maintaining oral health [63], including cleaning the oral cavity, solubilizing food substances, forming boluses, facilitating mastication and swallowing, clearing food and bacteria, buffering pH, diluting detritus, lubricating the mucosa, and facilitating speech [64]. Moreover, specific components of saliva protect the teeth by neutralizing acid through buffering actions, maintaining supersaturated calcium phosphate concentrations with regard to hydroxyapatite, and participating in enamel pellicle formation [63]. Saliva components also contribute to the mucosal coating and exert antimicrobial activities and provide defense, in addition to digestive actions. Antimicrobial proteins and peptides in saliva comprise a first line of defense that prevents infection and disease by interfering with microbial entry and multiplication. Most of these protective proteins including mucins, cystatins, lysozyme, lactoferrin, and immunoglobulin A (IgA) belong to the innate immune system [64]. Accordingly, saliva helps to maintain oral health, and changes affecting salivary function can compromise the integrity of soft and hard tissues in the oral cavity.

Salivary gland function is largely under autonomic neuronal (sympathetic nervous and parasympathetic nervous) control. The parasympathetic nerves generally govern salivary fluid secretion, whereas the sympathetic nerves regulate protein secretion [65]. However, the parasympathetic nerves also affect salivary protein secretion, and the protein secretion of some glands including the sublingual and some of the minor glands might be entirely under parasympathetic control. Sympathetic stimulation can also stimulate the salivary flow rate [64]. Sympathetic activation during stress does not inhibit salivary flow (rather, the familiar sensation of a dry mouth is related to a concomitant parasympathetic withdrawal). Moreover, the sympathetic and parasympathetic branches are not antagonistic but exert relatively independent effects in which the activity of one branch might synergistically augment the effect of the other [66].

Two primary neuroendocrine systems have received particular interest in the study of human stress, including the hypothalamus–pituitary–adrenocortical (HPA) system, which controls the secretion of cortisol, and the sympathetic adrenomedullary (SAM) system, which controls secretion of catecholamine [67,68]. In the HPA system, cortisol secretion is regulated by the adrenocorticotropic hormone (ACTH) from the pituitary gland [67,68]. Salivary cortisol levels are closely correlated with blood cortisol levels and therefore reliably reflect HPA activity [69]. Many reports have shown that various types of psychological and social stress activate the HPA system and consequently induce significant increases in salivary cortisol levels [70,71]. In the SAM system, direct measurements of salivary catecholamine do not reflect SAM activity [72]. Recent reports have identified various saliva stress markers such as α-amylase, IgA, BDNF, NT-3, and chromogranin A (CgA) [73–78]. In previous studies, we demonstrated that human submandibular glands produce BDNF and CgA [79,80]. Using immunoelectron microscopy, we showed that immunoreactivity for CgA is localized to the secretory granules and the saliva matrix of ductal cavities and that CgA is produced predominantly by serous cells before being secreted into the saliva [79]. In addition, we showed that the immunoreactivity for BDNF is localized to serous cells and is also observed in the saliva matrix of ductal cavities [80]. Currently, the measurement of these salivary proteins is thought to be a useful tool to evaluate activation of the SAM system [81–85].

5. BDNF in the salivary glands

BDNF was purified in 1982, approximately 30 years after the discovery of NGF, from pig brain as a cell survival-promoting factor for sensory neurons [86,87]. BDNF is the most well-studied and highly characterized NT in the central nervous system (CNS) and has received remarkable attention from clinicians because of its importance in the development and maintenance of normal brain functions. Furthermore, growing evidence suggests a role for BDNF in the pathophysiology of brain-associated illnesses including both neurodegenerative and psychiatric diseases [88,89]. At the synapse, BDNF plays an important role in long-term potentiation [90]. In the hippocampus in particular, BDNF expression varies depending on stress [91], stress + chewing behavior [92], exercise [93], and learning [94]. In addition, it plays an important role in facilitating the formation of neural networks. BDNF is also found in the lachrymal glands [95], lymphocytes [96], vascular endothelial cells [97], and the salivary glands of rats [98,99] and humans [80]. As an activity-dependent NT with receptors densely distributed throughout the CNS including the limbic system and midbrain, BDNF has clearly emerged as a major regulator of synaptic plasticity [89].

To examine the role of BDNF in regulating stress, we immobilized male Sprague-Dawley rats aged 7–9 weeks using a stress model according to an established protocol that rapidly induces ACTH and corticosterone production [100,101]. Using multiple techniques that combined the microdissection of BDNF immunofluorescence-positive cells and quantitative RT-PCR, we demonstrated increased expression of BDNF mRNA and protein in rat submandibular gland tissue localized to the ductal epithelium following the application of stress [73]. Further, using *in situ* hybridization (ISH) with an oligonucleotide probe, Ernfors et al. described for the first time that *BDNF* mRNA is not expressed in the rat submandibular gland in the absence of stress [102]. Our findings were consistent with these results in non-stress conditions. In general, a high level of BDNF expression has been observed in the central and peripheral nervous systems since BDNF mediates the cell survival and differentiation of neurons [10]. However, BDNF has also been reported in non-neural tissues of rats, such as the heart [103], lung [104], platelets [105], lymphocytes [96], and lacrimal glands [95].

Single or repeated immobilization stress stimuli markedly reduce *BDNF* mRNA expression in the rat hippocampus [106]. However, increased levels of BDNF mRNA and protein occur in the

pituitary glands of rats stressed for 60 min, whereas decreased levels occur following stress for 180 or 300 min [107]. In our study, significant increases in BDNF mRNA and protein in the submandibular gland and sustained increases in BDNF expression were observed in immobilization-stressed rats compared to those in non-stressed rats. Of note, a marked increase in *BDNF* mRNA was observed in rats following immobilization stress for 30 min. Moreover, BDNF levels were decreased after 180 min of post-immobilization stress compared to levels in non-stressed rats. These findings suggest that the salivary gland is sensitive to stress; in particular, BDNF expression increases within submandibular gland tissue in response to stress. An earlier study showed that BDNF expression is not expressed in human or murine submandibular gland tissue in non-stress conditions [108]; however, a variation of BDNF expression might be induced in stress conditions. We previously reported that BDNF expression in the submandibular gland is upregulated by a chronic stressor [98], and increased BDNF mRNA and protein expression were observed in salivary duct cells as a result of immobilization stress and chewing behavior [99]. Whereas the localization of BDNF in the salivary gland has been demonstrated in rats, the expression of BDNF in humans is poorly understood [73]. Therefore, in our study, we investigated the expression and localization of BDNF in the human submandibular gland (HSG) using various methods. BDNF was consistently localized to serous and ductal cells in the HSG, as detected by immunohistochemistry (IHC) and ISH [80], with stronger reactivity in serous cells than in ductal cells. Western blotting also showed one significant immunoreactive band at 14 kDa in the HSG and saliva [80]. Thus, in humans, BDNF is produced by the HSG and secreted into saliva.

6. Functional roles of released BDNF in the salivary gland

Interestingly, during non-stress and time-course stress treatments, *TrkB* mRNA was not detected in submandibular gland tissue or oral/esophageal mucosa by RT-PCR despite observed increases in BDNF mRNA and protein levels [73]. Previous reports failed to demonstrate TrkB expression in the human salivary gland [108] or esophageal mucosa [109] in the absence of stress, and BDNF derived from the submandibular gland is suggested to act at distant sites following secretion into the bloodstream. We found that acute immobilization stress for 60 min did not affect *TrkB* mRNA expression in the cerebral cortex, hippocampus, lung, stomach, liver, pancreas, and kidney. However, compared to its expression in the absence of stress, *TrkB* mRNA expression in the pituitary and adrenal glands was modified, and expression of the TrkB receptor was maximally increased at 60 min of stress in the adrenal medulla [110]. Our data indicated that TrkB expression in the adrenal medulla following acute stress might be important within the first 60 min of stress, but not at later times, because these levels had returned to control levels following 180 min of stress [110]. Indeed, the time of maximal TrkB expression following a stress stimulus corresponds to the period of time when plasma BDNF levels are highest following stress for 60 min [111]. NGF is released from salivary glands into the bloodstream following stress induced by fighting [11]. Further, exogenous NGF administration results in marked adrenal gland hypertrophy [112], and blood NGF might target the adrenal gland [11]. Since substances produced by the adrenal cortex pass from the cortical artery into the adrenal medulla, BDNF produced by the adrenal cortex might also interact with TrkB expressed in the adrenal medulla. Thus, it is possible that blood BDNF, in a similar manner to blood NGF, activates TrkB in the adrenal medulla during acute stress. Moreover, BDNF induces the release of catecholamines from PC12 cells derived from the chromaffin cells of the rat adrenal medulla [113]. This BDNF-evoked release is completely blocked by the tyrosine kinase inhibitor K252a. Ultimately, the BDNF-evoked release of catecholamine could be explained by TrkB activation [113]. Thus, BDNF–TrkB interactions might modulate catecholamine release from adrenal chromaffin cells in conditions of acute stress. In addition, there is a positive correlation between serum and brain BDNF protein levels [114]. However, serum BDNF is unlikely to affect the CNS since it is derived from platelets [115], which are a rich source of BDNF outside of the CNS [115] and represent a major storage site of this factor in peripheral blood, resulting in serum levels that are higher than plasma levels [116]. Therefore, it is necessary to investigate whether plasma BDNF levels affect brain function or the development of psychiatric diseases such as schizophrenia, depression, and bipolar disorder. Interestingly, low levels of free BDNF exist in rat plasma [117] and since BDNF can cross the blood-brain barrier [118], it might have more significant effects on the CNS than serum BDNF. Recently, we used transgenic mice overexpressing BDNF in the salivary gland and found that salivary BDNF has anxiolytic-like effects that mediate the activation of GABAergic neurotransmission through BDNF signaling in the hippocampus [119]. Although it is generally believed that trauma-induced alterations in NTs and their receptors within the CNS might protect against neuronal damage [120], free plasma BDNF could contribute to recovery with a decrease in BDNF. However, the source and role of plasma BDNF remains poorly understood. The results of our study indicate that the rat submandibular gland might be an important source of plasma BDNF.

7. Effects of chewing based on animal studies

Previous studies reported that chewing modulates the hormonal stress response [73,92,121,122]. The expression of corticotropin-releasing hormone significantly increased in the paraventricular nucleus (PVN) neurons of the hypothalamus following acute immobilization stress, and this increase is suppressed by chewing [121]. Nitric oxide modulates the activity of the endocrine system during behavioral responses to stress, and an increase in neuronal nitric oxide synthase (*nNOS*) mRNA expression under acute immobilization stress has been observed in the PVN, whereas chewing a wooden stick during immobilization decreases *nNOS* mRNA expression in the hypothalamus [100]. Fos protein, which is induced by acute immobilization stress, is generally used as a marker of neuronal activity in the PVN, and chewing behavior during stress reduces the expression of this protein [122]. ACTH and corticosterone circulating concentrations are markedly elevated in stressed animals, but this elevation is also suppressed by chewing [92]. Additionally, we previously reported that the decrease in *BDNF* mRNA expression in rat hippocampus induced by acute immobilization stress is recovered by chewing [92]. As chewing might attenuate systemic stress responses, the changes in plasma BDNF concentrations under chewing conditions could be of interest.

In our previous study, a stress + chewing model allowing 1 h of chewing during the second half of 2-h immobilization stress exposure was used to investigate changes in BDNF concentrations under stress and chewing conditions [99]. We demonstrated the increased expression of BDNF mRNA and protein in rat submandibular gland tissue following stress with or without a chewing period, with a greater increase in the stress + chewing rats [99]. Chewing involves the movement of masticatory muscles including the masseter muscles, which contributes to the development of major salivary glands [123]. In addition, chewing accelerates the production of saliva, and the salivary glands produce various growth factors [11,124,125]. Whereas exercise leads to increases in blood flow and glucose utilization [126], it also induces changes in several salivary components such as electrolytes, hormones, immunoglobulins, lac-

tate, and proteins [127]. Although the physiological mechanisms responsible for the increase in salivary BDNF under chewing conditions are not understood, the chewing-induced upregulation of salivary tissue BDNF might directly affect the salivary glands. The effect of chewing on the response to acute immobilization stress in rats is important and leads to relaxation of the stress response, which might provide protective effects for general health. Our results demonstrate that chewing influences the expression of BDNF in the salivary glands and indicate that the BDNF response to incremental levels of exercise might be of particular interest.

8. Conclusion

This review shows that oral characteristics such as chewing, saliva, and BDNF in salivary glands are related to stress. The studies described suggest that chewing plays a major role in restraining stress-induced psychosomatic disorders by downregulating activities of the limbic system, the HPA axis, the autonomic nervous system, and the immune system. Of particular interest is chewing-induced modulation of the HPA axis that controls stress hormones. The direct and indirect neuronal pathways through which chewing interferes with the HPA axis should be clarified in future studies. Chewing is complex since it involves interactions of saliva, the number of teeth, muscles, and nerves. Furthermore, because stress-related BDNF in the saliva and chewing affect each other, future studies should investigate how this connection affects general health.

Conflict of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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