Journal of Oral and Maxillofacial Surgery, Medicine, and Pathology 26 (2014) 379–389

Contents lists available at ScienceDirect

Journal of Oral and Maxillofacial Surgery, Medicine, and Pathology

journal homepage: www.elsevier.com/locate/jomsmp

Oral Pathology/Review article

Relationship between brain-derived neurotrophic factor and stress in saliva and salivary glands

Juri Saruta[a], Masahiro To[a], Takashi Hayashi[a], Rie Kawashima[b], Tomoko Shimizu[a,c], Yohei Kamata[a,c], Momoko Kato[d], Mifumi Takeuchi[d], Keiichi Tsukinoki[a,*]

[a] Department of Oral Sciences and Research Institute of Salivary Gland and Health Medicine, Graduate School of Kanagawa Dental University, 82 Inaoka-cho, Yokosuka, Kanagawa 238-8580, Japan
[b] Department of Dentistry, Oral and Maxillofacial Surgery, Graduate School of Jichi Medical University, 3311-1 Yakusiji, Simotsuke, Tochigi 329-0498, Japan
[c] Department of Comprehensive Dentistry, Yokohama Clinic, Kanagawa Dental University, 3-31-6 Tsuruya-cho, Yokohama, Kanagawa 221-0835, Japan
[d] Department of Craniofacial Growth and Development Dentistry, Division of Orthodontics, Graduate School of Kanagawa Dental University, 82 Inaoka-cho, Yokosuka, Kanagawa 238-8580, Japan

ARTICLE INFO

Article history:
Received 11 July 2013
Received in revised form
10 December 2013
Accepted 24 December 2013
Available online 24 January 2014

Keywords:
Brain-derived neurotrophic factor (BDNF)
Saliva
Salivary gland
Stress
Tyrosine receptor kinase B (TrkB)

ABSTRACT

Objective: The nerve growth factor (NGF) family comprises of NGF, brain-derived neurotrophic factor (BDNF) and neurotrophins (NTs)-3 to -7, all of which are collectively referred to as NTs. However, the expression of NTs other than NGF in the salivary gland has not been described in detail. BDNF is a well-studied NT involved in the neurogenesis, differentiation, and maintenance of select peripheral and central populations of neuronal cells during development and adulthood. NTs, in concert with the hypothalamic–pituitary–adrenal (HPA) axis, play key roles in modulating brain plasticity and behavioral coping, especially during ontogenetically critical periods, when the developing brain is particularly sensitive to external stimuli. Early life events, such as psychophysical stress, affect BDNF levels, and induce dysregulation of the HPA axis, thereby affecting brain development and contributing to inter-individual differences in vulnerability to stress or psychiatric disorders. Immobilization stress modifies BDNF mRNA expression in some organs.
Results: We studied the effect of immobilization stress on BDNF and its receptor, tyrosine receptor kinase B (TrkB), in rat submandibular glands, and found increased BDNF expression in duct cells under immobilization stress. In addition, stress increases the amount of plasma BDNF derived from the submandibular gland, and the amount of TrkB receptor mRNA in the adrenal medulla.
Conclusions: Plasma BDNF might therefore activate TrkB receptors in the adrenal medulla during acute stress. The salivary glands are also likely to influence not only oral health, but also systemic organs. This review addresses the relationship between BDNF and stress in the saliva and salivary glands.

Contents

Abbreviations: BDNF, brain-derived neurotrophic factor; CgA, chromogranin A; CNS, central nervous system; EGF, epidermal growth factor; HPA, hypothalamic–pituitary–adrenal; HSG, human submandibular gland; IgA, immunoglobulin A; IHC, immunohistochemistry; ISH, *in situ* hybridization; NGF, nerve growth factor; NT, neurotrophin; NTs, neurotrophins; PRPs, proline-rich proteins; SAM, sympathetic adrenomedullary; TrkB, tyrosine receptor kinase B.

☆ AsianAOMS: Asian Association of Oral and Maxillofacial Surgeons; ASOMP: Asian Society of Oral and Maxillofacial Pathology; JSOP: Japanese Society of Oral Pathology; JSOMS: Japanese Society of Oral and Maxillofacial Surgeons; JSOM: Japanese Society of Oral Medicine; JAMI: Japanese Academy of Maxillofacial Implants.

* Corresponding author. Tel.: +81 46 822 8866; fax: +81 46 822 8866.
E-mail addresses: saruta@kdu.ac.jp (J. Saruta), m.tou@kdu.ac.jp (M. To), hayashi-t@plum.plala.or.jp (T. Hayashi), eternal.wish@jichi.ac.jp (R. Kawashima), shimizu@kdu.ac.jp (T. Shimizu), kamata@kdu.ac.jp (Y. Kamata), m.kato@kdu.ac.jp (M. Kato), takeuchi@kdu.ac.jp (M. Takeuchi), tsukinoki@kdu.ac.jp (K. Tsukinoki).

2212-5558/$ – see front matter
http://dx.doi.org/10.1016/j.ajoms.2013.12.013

1. Introduction

The salivary glands consist of the major salivary glands, including the parotid, submandibular, and sublingual glands, and numerous minor salivary glands scattered throughout the oral cavity [1]. The main role of the salivary glands is to secrete saliva, which assists in food digestion while promoting mastication and antimicrobial activities [2,3]. The salivary glands are predicted to have other important roles as well, since they produce a variety of substances. Saliva also includes many components that are derived from blood, because acinar cells produce saliva from blood plasma [4]. In addition, salivary products are associated with the maintenance of oral health, which is associated with systemic health, including that of the respiratory tract [5]. Moreover, in addition to the volume, the quality of saliva is also considered important for good oral health. Therefore, identification of salivary products might reflect the status of systemic health or disease.

Although the hormone-like effects of salivary gland products, such as cell growth factors, were investigated during the late 1980s and early 1990s [6,7], little is understood about the influence of the salivary glands on the entire body, and the *in vivo* functions of growth factors produced by the salivary glands have not yet been determined. Nevertheless, since components produced by salivary glands are likely to enter the bloodstream by reabsorption from the salivary gland ducts and sublingual mucosa [8], salivary glands might contribute to both oral and total health. Thus, the potential hormone-like effects of such components on the whole body should be re-examined.

Recently, the number of publications using proteomic analysis to characterize the expression of salivary proteins has increased [9–11]. Three American groups from UCSF, UCLA, and the Scripps Research Institute/University of Rochester have developed a salivary proteome consortium to build a human salivary protein catalog known as the Salivary Proteome Knowledge Base, which is funded by the National Institute of Dental and Craniofacial Research [12,13]. Several reports have demonstrated that proteomic analysis of saliva can be used to identify biomarkers as putative peptides for the diagnosis of several diseases [14–18]. Whole saliva contains proteins that can be informative when detecting diseases related to oral health [14], in particular, oral cancer [15], head and neck squamous cell carcinoma [16], Sjögren's syndrome [17], and diabetes [18]. The potential clinical roles of factors produced by the salivary glands should also be investigated in detail.

Salivary glands produce several cell growth factors and play an important role in human health [19]. Discovering that cell growth factors, such as epidermal growth factor (EGF) and nerve growth factor (NGF), are found in the rat submandibular gland has led to the acknowledgment of new salivary gland functions [20,21]. The mouse salivary gland expresses a high level of NGF [8], which is a member of the NGF family, along with brain-derived neurotrophic factor (BDNF), and neurotrophin (NT)-3, -4/5, -6, and -7, all of which are collectively referred to as neurotrophins (NTs) [22]. However, few reports have described the expression of NTs other than NGF in the salivary gland.

NTs interact with the tyrosine receptor kinase (Trk) family of high-affinity protein kinase receptors. BDNF, specifically, interacts with the TrkB receptor [22] to promote the survival and differentiation of neurons, and is involved in the modification of neurotransmission and synaptic plasticity of the central and peripheral nervous systems [23]. BDNF is predominantly found in the hippocampus and is associated with episodic memory [24]. Immobilization stress reduces mRNA levels of NTs such as NGF, BDNF, and NT-3 in the rat brain, especially in the hippocampus [25]. In contrast, NGF expression is increased in response to stress in the mouse salivary gland [8]. The production of various cell growth factors is often increased during episodes of stress to maintain homeostasis in the salivary gland [8,26].

In this review, we describe the role of BDNF in the salivary glands, and elaborate on the significance of BDNF in saliva and the salivary glands. We also summarize evidence that indicates the relationship between immobilization stress and BDNF expression within the salivary gland. The effect of immobilization stress on BDNF and TrkB expression in male rat submandibular glands is also reported.

2. Structure of the salivary glands and production of saliva

Human salivary glands basically consist of a secretory portion and ductal system [27]. The secretory portion of the glands consists of serous and mucous cells, and, depending on the composition of these cells, the glands can be classified into serous, mucous, or mixed glands [27]. The ductal system consists of ductal epithelia and is classified into intercalated, striated, and interlobular ducts according to morphology. Intercalated ducts have been considered to be the site of origin of many salivary gland tumors [28]. Functionally and histologically, the striated ducts resemble the distal renal tubules of the kidneys [29]. In addition to contributing to the characteristics of saliva, the ductal system functions as a discharge route for saliva as well [29]. Myoepithelial cells form stacks in the peripheries of acinar cells and intercalated ducts [27]. In rats and mice, on the other hand, granular ducts are found between the intercalated and striated ducts [30]. Granular ducts are not found in human salivary gland tissue, but are remarkably well developed in rodent males [30,31]. The granular ducts are androgen-dependent tissues, and, unlike human salivary glands, the salivary glands in rodents are regarded distinctly as sex hormone-dependent organs [32]. Human salivary glands are regulated by the autonomic nervous system, rather than hormonal factors. The major salivary glands are found in anatomically different locations in rodents and humans. Therefore, we emphasize the need to consider the differences from humans when analyzing rodent salivary glands.

Saliva is a complex secretion: about 90% by volume is secreted by the major salivary glands and the remaining 10% by the minor glands. These glands are located in every region of the mouth except for the gums and the anterior part of the hard palate. Saliva is sterile when it leaves the salivary glands but ceases to be so as soon as it mixes with the crevicular fluid, remains of food, microorganisms, and desquamated oral mucous cells [33]. Saliva is first produced by acinar cells, which are largely divided into two types: serous and mucous cells. The serous acinar cells of the parotid gland produce a largely serous secretion, consisting of much of the alpha-amylase found in saliva and some calcium, although they produce less calcium than is produced in the submandibular gland. The mucins are mainly produced by the submandibular and