Additional Information on Neuropeptides – VIP & NPY

Vasoactive intestinal peptide (VIP) is a polypeptide hormone that was first discovered in relation to its actions on blood flow and electrolyte secretion in the intestinal tract. It was subsequently discovered to serve as a multi-functional neurotransmitter and neuromodulator in the nervous system and organs throughout the body. VIP-containing neurons are highly concentrated in the adrenal glands, salivary glands, and pancreas. (Igarashi et al., 2011) VIP is frequently co-secreted with acetylcholine (ACh) from parasympathetic nerves, (Culp & Richardson, 1996) and it has therefore been employed as a marker of parasympathetic nervous activity. (Konttinen et al., 1997; Takenaka et al., 2006)

Neuropeptide Y (NPY) is another key peptide that has multiple functions in the central and peripheral nervous systems and in various tissues of the body. Centrally, NPY is inhibitory for sympathetic activity and it has a role in countering stress, anxiety and depression. (Heilig, 2004) Peripherally, however, NPY's actions are stimulatory, synergizing with glucocorticoids and catecholamines to enhance the stress response. (Kuo & Zukowska, 2007) In peripheral nerves NPY is often stored and co-released with noradrenaline. (Lundberg et al., 1990; Lundberg et al., 1982) Peripheral NPY is regarded largely as a marker of sympathetic nervous system activity, although some studies have examined plasma NPY specifically in relation to stress resilience and psychological conditions such as PTSD disorder. (Heilig, 2004)

VIP and NPY have been shown to be important non-adrenergic, non-cholinergic (NANC) neurotransmitters that affect saliva flow and secretion of salivary proteins. (Ekström, 1999) Immunohistochemical studies have shown dense distributions of VIP-containing nerve fibers around the acini, ducts, and blood vessels of human minor glands. (Konttinen et al., 1992; Konttinen et al., 1997; Feher et al., 1999) The nerves supplying these glands show relatively little staining for tyrosine hydroxylase (TH), an enzyme marker associated with sympathetic nerves, and they are therefore considered to be predominantly parasympathetic. (Konttinen et al., 1992) Studies using animal models have shown that both mucin secretion and sustained fluid secretion from the sublingual glands are induced primarily by parasympathetic input (ACh and VIP), while no response is seen to sympathetic stimulation. (Culp & Richardson, 1996)

The major sources of human saliva are the submandibular and parotid salivary glands. In contrast to the minor glands, these glands receive heavy innervation from both the sympathetic and parasympathetic nervous systems. In animal studies, exocrine secretion of proteins has been found to be induced primarily by sympathetic (β-adrenergic) control, with some contribution from parasympathetic (cholinergic) nerves; fluid secretion is mostly under parasympathetic control, with some minor contribution also from α_1-adrenergic activation. (Proctor & Carpenter, 2007; Ekström et al., 1996; Culp & Richardson, 1996) In human subjects, fluid secretion from the parotid glands was similarly found to be largely regulated by muscarinic-cholinergic mechanisms with smaller contributions from α_1- and β_1-adrenergic mechanisms; protein (α-amylase) secretion was observed to be affected by both cholinergic and adrenergic pathways. (Jensen et al., 1991) In addition to secreting the main neurotransmitters NAd and ACh, respectively, many sympathetic and parasympathetic nerve fibers around the acini, ducts, and blood vessels of these human glands also show immunoreactivity for VIP, NPY, and other neuropeptides, indicating that these peptides also play a role in regulation of saliva. (Heym et al., 1994; Kusakabe et al., 1998; Matsuda et al., 1997)

NPY, VIP, and various other neuropeptides have been measured in whole saliva and parotid saliva from healthy humans, (Dawidson et al., 1997; Naito et al., 2003; Satoh et al., 2009) and levels in saliva have been shown to be altered by nervous stimulation from acupuncture. (Dawidson et al., 1998) VIP has also been examined extensively in human labial gland saliva from Sjögren's syndrome patients and healthy controls. (Santavirta et al., 1997; Konttinen et al., 1997; Törnwall et al., 1994; Törnwall et al., 1995; Konttinen et al., 1992) Because of the general association of VIP and NPY with parasympathetic and sympathetic nerves, respectively, there is also some interest in exploring these peptides as non-invasive autonomic markers in saliva.

The sympathetic and parasympathetic origins of the peptide-containing nerves associated with the human salivary glands have not been well studied, however. Dual staining for tyrosine hydroxylase (TH) in the VIP-containing nerves around the parotid glands found only sparse TH reactivity, suggesting that these nerves are predominantly parasympathetic in nature. (Heym et al., 1994)   This agrees with the strong presence of VIP-reactive nerves in the predominantly parasympathetic innervation of the human minor and sublingual glands. (Kontinnen et al., 1992; Kontinnen et al., 1997; Rossoni et al., 1979) Unfortunately, however, we are unaware of any study of the sympathetic/parasympathetic nature of the nerves supplying the human submandibular glands. In the human parotid gland, TH staining of NPY-containing nerves indicated that they were both sympathetic and parasympathetic in nature. (Heym et al., 1994) This finding agrees with studies of the innervation of rat salivary glands, where NPY-positive *sympathetic* nerves were associated with blood vessels, while NPY-positive *parasympathetic* nerves were associated with the glandular acini. (Leblanc & Landis, 1988; Schultz et al., 1994)

It is therefore possible that the general association of NPY with sympathetic activity may not hold true for human salivary glands. Further research is needed, however, in order to understand more fully the roles of neuropeptide transmitters in human salivary glands and to assess their utility as markers of autonomic nervous activity. Since the submandibular glands are estimated to supply 65% of resting whole saliva, (Humphrey & Williamson, 2001) a better understanding of the involvement of the neuropeptides in the control of these glands would be especially helpful.

References

Culp, D.J. & Richardson, L.A. (1996). Regulation of mucous acinar exocrine secretion with age. *J Dent Res, 75*(1), 575-80.

Dawidson, I., Angmar-Månsson, B., Blom, M., Theodorsson, E., & Lundeberg, T. (1998). The influence of sensory stimulation (acupuncture) on the release of neuropeptides in the saliva of healthy subjects. *Life Sci, 63*(8), 659-74.

Dawidson, I., Blom, M., Lundeberg, T., Theodorsson, E., & Angmar-Månsson, B. (1997). Neuropeptides in the saliva of healthy subjects. *Life Sci, 60*(4-5), 269-78.

Ekström, J. (1999). Role of nonadrenergic, noncholinergic autonomic transmitters in salivary glandular activities in vivo. In: J.R. Garrett, J. Ekström, L.C. Anderson, (Eds.), *Neural Mechanisms of Salivary Secretion* (pp. 94-130). Basel: Karger.

Ekström, J., Asztély, A., & Tobin, G. (1996). Non-adrenergic, non-cholinergic influences on parotid acinar degranulation in response to stimulation of the parasympathetic innervation in the anaesthetized rat. *Exp Physiol, 81*(6), 935-42.

Fehér, E., Zelles, T., & Nagy, G. (1999). Immunocytochemical localisation of neuropeptide-containing nerve fibres in human labial glands. *Arch Oral Biol, 44*(Suppl 1), S33-37.

Heilig, M. (2004). The NPY system in stress, anxiety and depression. *Neuropeptides, 38*(4), 213-24.

Heym, C., Webber, R., & Adler, D. (1994). Immunocytochemical correlation of peptides and tyrosine hydroxylase in nerve fibres of the human parotid gland. *Arch Oral Biol, 39*(3), 213-21.

Humphrey, S.P. & Williamson, R.T. (2001). A review of saliva: Normal composition, flow, and function. *J Prosthet Dent, 85*(2), 162-9.

Igarashi, H., Fujimori, N., Ito, T., Nakamura, T., Oono, T., Nakamura, K., Suzuki, K., et al. (2011). Vasoactive intestinal peptide (VIP) and VIP receptors: Elucidation of structure and function for therapeutic applications. *Int J Clin Med, 2*(4), 500-08.

Jensen, J.L., Brodin, P., Berg, T., & Aars, H. (1991). Parotid secretion of fluid, amylase and kallikrein during reflex stimulation under normal conditions and after acute administration of autonomic blocking agents in man. *Acta Physiol Scand, 143*(3), 321-29.

Konttinen, Y.T., Hukkanen, M., Kemppinen, P., Segerberg, M., Sorsa, T., Malmström, M., Rose, S., et al. (1992). Peptide-containing nerves in labial salivary glands in Sjögren's syndrome. *Arthritis Rheum, 35*(7), 815-20.

Konttinen, Y.T., Platts, L.A., Tuominen, S., Eklund, K.K., Santavirta, N., Törnwall, J., Sorsa, T., et al. (1997). Role of nitric oxide in Sjögrens's syndrome. *Arthritis Rheum, 40*(5), 875-83.

Kuo, L.E., Abe, K., & Zukowska, Z. (2007). Stress, NPY and vascular remodeling: Implications for stress-related diseases. *Peptides, 28*(2), 435-440.

Kusakabe, T., Matsuda, H., Gono, Y., Kawakami, T., Kurihara, K., Tsukuda, M., & Takenaka, T. (1998). Distribution of VIP receptors in the human submandibular gland: An immunohistochemical study. *Histol Histopathol, 13*(2), 373-8.

Leblanc, G.G. & Landis, S.C. (1988). Target specificity of neuropeptide Y-immunoreactive cranial parasympathetic neurons. *J Neurosci, 8*(1), 146-55.

Lundberg, J.M., Franco-Cereceda, A., Hemsén, A., Lacroix, J.S., & Pernow, J. (1990). Pharmacology of noradrenaline and neuropeptide tyrosine (NPY)-mediated sympathetic cotransmission. *Fundam Clin Pharmacol, 4*(4), 373-91.

Lundberg, J.M., Terenius, L., Hökfelt, T., Martling, C.R., Tatemoto, K., Mutt, V., Polak, J., et al. (1982). Neuropeptide Y (NPY)-like immunoreactivity in peripheral noradrenergic neurons and effects of NPY on sympathetic function. *Acta Physiol Scand, 116*(4), 477-80.

Matsuda, H., Kusakabe, T., Kawakami, T., Nagahara, T., Takenaka, T., & Tsukuda, M. (1997). Neuropeptide-containing nerve fibres in the human parotid gland: A semiquantitative analysis using an antibody against protein gene product 9.5. *Histochem J, 29*(7), 539-44.

Naito, T., Itoh, H., & Takeyama, M. (2003). Effects of hange-koboku-to (banxia-houpo-tang) on neuropeptide levels in human plasma and saliva. *Biol Pharm Bull, 26*(11), 1609-1613.

Rossoni, R.B., Machado, A.B., & Machado, C.R. (1979). A histochemical study of catecholamines and cholinesterases in the autonomic nerves of the human minor salivary glands. *Histochem J, 11*(6), 661-68.

Santavirta, N., Kontinnen, Y.T., & Törnwall, J., Segerberg, M., Santavirta, S., Matucci-Cerinic, M., & Björvell, H. (1997). Neuropeptides of the autonomic nervous system in Sjögren's syndrome. *Ann Rheum Dis, 56*(12), 737-40.

Satoh, Y., Itoh, H., & Takeyama, M. (2009). Effects of bakumondoto on neuropeptide levels in human saliva and plasma. *J Trad Med, 26*(3), 122-30.

Schultz, T., Soinila, J., Tolonen, R., Häppölä, O., Uusitalo, H., & Salo, A. (1994). The sympathetic and parasympathetic nature of neuropeptide Y-immunoreactive nerve fibres in the major salivary glands of the rat. *Histochem J, 26*(7), 563-70.

Takenaka, A., Leung, R.A., Fujisawa, M., & Tewari, A.K. (2006). Anatomy of autonomic nerve component in the male pelvis: The new concept from a perspective for robotic nerve sparing radical prostatectomy. *World J Urol, 24*(2), 136-43.

Törnwall, J., Konttinen, Y.T., Hietanen, J., Sorsa, T., Hukkanen, M., & Uusitalo, H. (1995). VIP in salivary glands in Sjögren's Syndrome. *Brit J Rheumatol, 34*(9), 891-93.

Törnwall, J., Uusitalo, H., Hukkanen, M., Sorsa, T., & Konttinen, Y.T. (1994). Distribution of vasoactive intestinal peptide (VIP) and its binding sites in labial salivary glands in Sjögren's syndrome and in normal controls. *Clin Exp Rheumatol, 12*(3), 287-92.