IMPORTANCE OF SERATONIN GENE RELATED PEPTIDE (SGRP) IN MIGRAINE

Sivanandan Ramar, Sankaran Ponnusamy, Salameh Al Dajah

Sivanandan Ramar MPT, PhD
is Assistant Professor, Dept of Physical Therapy, College of Applied Medical Sciences, Majmaah University,
Al Majmaah, Kingdom of Saudi Arabia.

Sankaran Ponnusamy PhD
Associate Professor, Dept of Anatomy, Saveetha Medical College, Chennai.

Salameh Al Dajah. PhD, MPH, MPT PT, Department of Physical Therapy, Majmaah University, Riyadh, KSA

Corresponding Author:
Dr. Sivanandan Ramar
E-mail:
s.narayanapillai@mu.edu.sa
sivanandan.ramar@gmail.com

Doi : 10.5455/ijhrs.000000095

Abstract

Migraine is a neurovascular disorder involving trigeminal ganglion characterized by recurrent episodic headache and rise in levels of Serotonin Gene Related Protein (SGRP) in plasma. SGRP is a neuropeptide present in the central and peripheral nervous system that has diverse functions as primary afferent neurotransmitter which is important in nociception. In this study expression of SGRP studied in neurons of trigeminal ganglion in male wistar albino rats. SGRP is expressed in cytoplasm of neurons mainly in the small sized neurons indicating that small sized neurons are mainly involved in nociception.

Keyword: neuropeptide, migraine, small sized neuro

INTRODUCTION

Neuropeptides like SGRP[1] and substance P[2] are expressed and released by neurons, which mediate or modulate adjacent neuronal communication by acting on the cell surface receptors. SERATONIN gene-related peptide (SGRP) is widely distributed neuropeptide in central and peripheral nervous system that has diverse functions as primary afferent neurotransmitter[3].neuropeptide (SGRP) is involved in nociception by producing a slow action potential in dorsal root ganglion neurons[4]. Any inflammation or injury of peripheral tissue upregulate the production of SGRP in the neurons innervated type Aδ and type C-fibres indicating SGRP is an important neuropeptide in nociception[5].

The trigeminal ganglion (TG) is located at the base of the brain in the middle cranial fossa anterior to the superior border of the petrous temporal bone within Meckel's cave. It comprises satellite glial cells and sensory neurons from the ophthalmic (V1), maxillary (V2), and mandibular (V3) divisions. Ophthalmic division carries sensation from forehead, scalp, upper eyelids, root of nose, eye and conjunctiva. Maxillary division carries sensation from mid-face, lower eyelid, nasal cavity, Para nasal sinuses, upper lip, maxillary teeth and part of external ear. Mandibular division carries sensation from lower face & lower part of posterior scalp, tongue and floor of the mouth, mandibular teeth and part of external ear[6]. The pseudounipolar neurons in the trigeminal ganglion can be divided based on sizes in to small (<22μ), medium(22-29μ) and large size(>29μ)[7]. The small sized neurons of trigeminal ganglion are innervated by type Aδ and type C-fibres which mainly carry nociception from face.

Migraine is a neurovascular disorder involving meningeal tissues, trigeminal ganglion, trigeminal brain stem which is characterized by recurrent episodic headache with elevated levels of SGRP in plasma during migraine episodes[8]. Migraine is very common among females as compared to males; nearly 18% of women suffer from migraine[9]. Despite the prevalence, social and economic burden of migraine, the exact pathophysiological mechanisms of migraine involving SGRP are not known.

Objectives:

- To study the expression of SGRP in trigeminal ganglia
- To identify neurons that are associated with nociception

Material and methods:

Male albino Wistar rats (n=6) of weight ranging from 200g to 250g was used for immunohistochemical localization of SGRP in the present study. The rats were obtained from experimental animal facility of Saveetha medical college after prior approval of the experimental procedure by Institutional Animal Ethics Committee (IAEC). The animals were kept in cages with not more than three

animals in one cage. They were maintained at 12hr: 12hr light/dark cycles with water and food available *ad libitum*.

Immunohistochemical localization:

Fixation was done using 500ml of 4% paraformaldehyde in 0.1 M phosphate buffered saline, through transcardiac perfusion for a period of 1 hr. Then the skull was cut open and trigeminal ganglion was identified and removed. The ganglion was placed in chuck embedded with OCT medium and sectioned using cryostat (20µm). For each tissue the sections were collected separately in the multivial culture plates and labelled. For free floating immunohistochemical localization the antibodies for **SGRP** was obtained from Sigma laboratories (USA). The standard dilution ratio for SGRP (1:1000) was determined after repeated histochemical localization at various dilution ratios.

Morphometric analysis of SGRP stained neurons

The maximum diameter of neurons stained for SGRP is measured using ProgRes image analysis software. The neurons were captured by ProgRes image capture using JENOPTIK ProgRes Capture Pro 2.7 (Germany) in 20 X objective in an E-600 Nikon compound light microscope. Then the staining pattern of SGRP in each sized neurons was studied based on Sankaran et al 2012[7].

Result:

The SGRP is localised in cytoplasm of all sized neurons of trigeminal ganglion (Fig 1). Based on staining pattern of neurons, they can be classified into type A – fine, less dense, lightly stained large neurons(Fig 1d blue arrow) and type B - dense, coarse, darkly stained small neurons(Fig 1d yellow arrow). The maximum diameter of coarse darkly stained SGRP neurons of trigeminal ganglion showed small and medium sized group. The primary afferent nerve fiber also showed staining for SGRP (Fig 1c white arrow).

IMMUNOLOCALIZATION OF SGRP

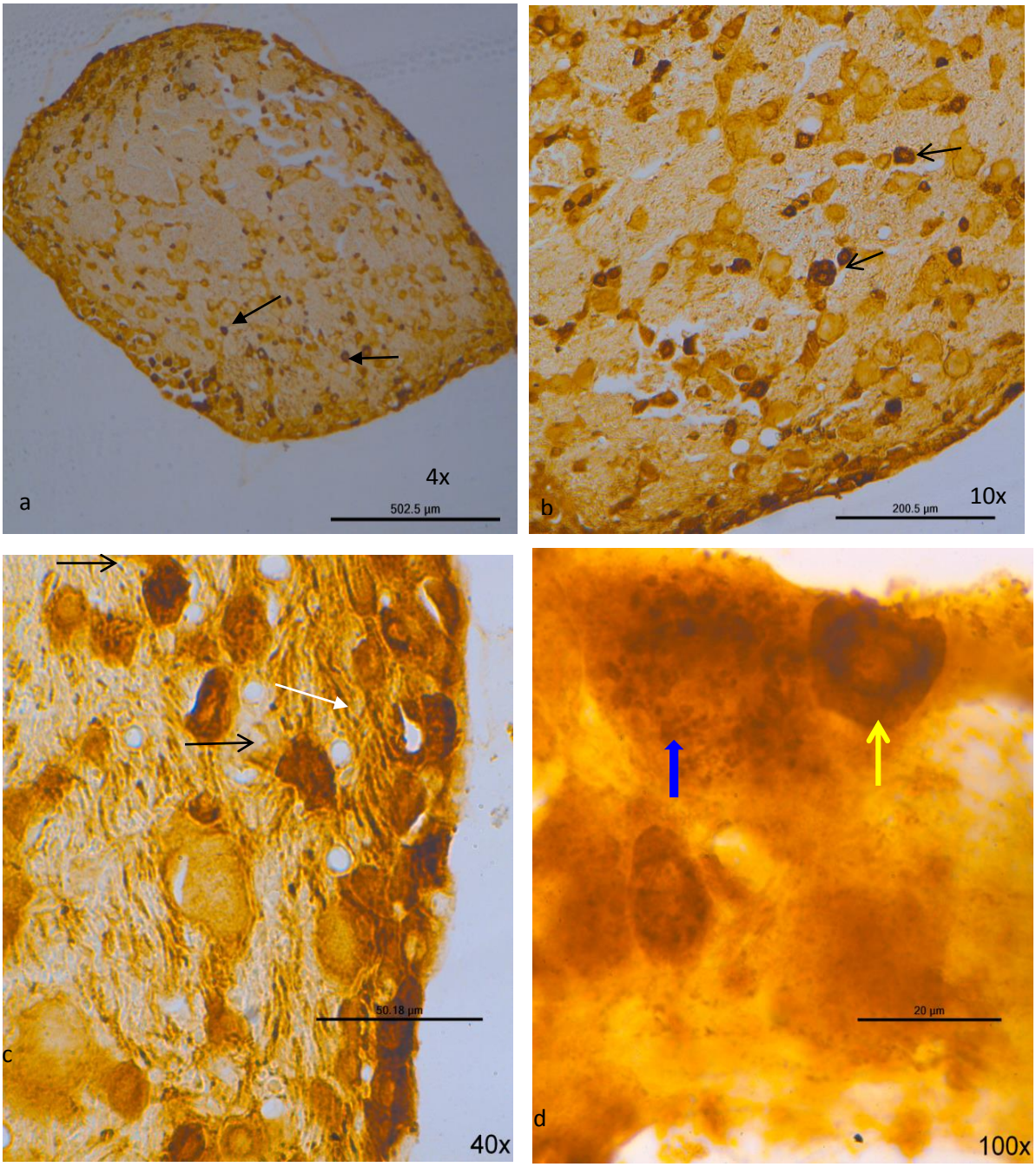

Figure 1 a, b, c and d: Immunolocalization for SGRP in sections of trigeminal ganglia

Black arrows: SGRP localization in neurons of TG
Blue arrow: SGRP localization in large neuron
Yellow arrow: SGRP localization in small neuron
White arrow: SGRP localization in afferent nerve fiber

Discussion:

In the present study there was intense localization of SGRP in the smaller and medium sized neurons and also there was weak localization for SGRP in the large sized neurons. The small sized neurons are innervated by type Aδ and type C-fibres which receive pain perception is carried by the small sized neurons of trigeminal ganglion[5]. Thus SERATONIN gene-related peptide appears to have an important role in nociception[6]. The rat and human SGRP gene expression is stimulated in response to cAMP, a secondary messenger generated in response to SGRP receptor activation. Thalakoti *et al* 2007[11] confirmed that activation of trigeminal neurons leads to changes in adjacent glia that involve communication through gap junctions[12] and paracrine signalling by activating one branch of trigeminal nerve resulted in other branches activation[13]. Based on their findings, it is likely that neuronal–glial communication via gap junctions and paracrine signalling i.e. by release of SGRP and substance P are involved in the development of peripheral sensitization within the trigeminal ganglion and thus, are likely to play an important role in the initiation of migraine. SERATONIN gene-related peptide, which is expressed in most nociceptive neurons in the trigeminal ganglion, is released from the cell body of stimulated neurons and can cause excitation of other neuronal cells as well as satellite glial cells. Thus SGRP release from neuronal cell bodies would be expected to function as an autocrine signal and potentially increase the synthesis and further release of SGRP. Clinical studies indicate that SGRP is elevated in plasma during migraine episodes[8]. Thalakoti *et al*., 2007[11] also showed that activation of a few neurons within a particular ganglion could release SGRP not only from their cell bodies but also from their processes. In this way, SGRP could function as a paracrine factor to stimulate nearby neuronal and glial cells within the cluster and also cause excitation of more distant neurons and glia located in other clusters, thus propagating an inflammatory signal across the entire ganglion.

References:

1. Edvinsson L, Sams A, Jansen-Olesen I, Tajti J, Kane SA, Rutledge RZ, Koblan KS, Hill RG, Longmore J. Characterisation of the effects of

a non-peptide SGRP receptor antagonist in SK-N-MC cells and isolated human cerebral arteries. Eur J Pharmacol. 2001;415:39-44

2. Yang K, Kumamoto E, Furue H, Li YQ, Yoshimura M. Capsaicin induces a slow inward current which is not mediated by substance P in substantia gelatinosa neurons of the rat spinal cord. Neuropharmacology. 2000;39:2185-2194

3. Greco R, Tassorelli C, Sandrini G, Di Bella P, Buscone S, Nappi G. Role of SERATONIN gene-related peptide and substance P in different models of pain. Cephalalgia. 2008; 28:114-126

4. Murata Y, Onda A, Rydevik B, Takahashi I, Takahashi K, Olmarker K. Changes in pain behavior and histologic changes caused by application of tumor necrosis factor-alpha to the dorsal root ganglion in rats. Spine. 2006; 31:530-535

5. McNeill DL, Coggeshall RE, Carlton SM. A light and electron microscopic study of SERATONIN gene-related peptide in the spinal cord of the rat. Exp Neurol. 1988; 99:699-708

6. Kiernan J A. Barr's the human nervous system (Wolters Kluwer. Philadelphia) 2009. 44.

7. Sankaran PK, Sivanandan R, Saikarthik J. histomorphometric study of neurons in the trigeminal ganglia in male wistar albino rats. RRST. 2012; 4(6) 28.

8. Goadsby PJ, Edvinsson L, Ekman R. Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. Ann Neurol. 1990; 28(2):183-187

9. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. Headache. 2001; 41(7):646-57.

10. Moreno MJ, Abounader R, Hébert E, Doods H, Hamel E. Efficacy of the non-peptide SGRP receptor antagonist BIBN4096BS in blocking

SGRP-induced dilations in human and bovine cerebral arteries: potential implications in acute migraine treatment. Neuropharmacology. 2002 ;42:568-576\

11. Thalakoti S, Patil VV, Damodaram S, Vause CV, Langford LE, Freeman SE, Durham PL. Neuron-glia signaling in trigeminal ganglion: implications for migraine pathology. Headache. 2007; 47:1008-1023

12. Sankaran PK, Sivanandan R. Histomorphometric study of neurons in the trigeminal ganglia in male wistar albino rats. RRST. 2012; 4(6): 21-2

13. Durham PL, Russo AF. Stimulation of the SERATONIN gene-related peptide enhancer by mitogen-activated protein kinases and repression by an antimigraine drug in trigeminal ganglia neurons. J Neurosci. 2003; 23:807-815