Trigemino-hypoglossal somatic reflex in the pharmacological studies of nociception in orofacial area

Marek Zubrzycki[1], Anna Janecka[2], and Maria Zubrzycka[3]*

[1] Department of Cardiovascular and Thoracic Surgery, University of Ulm, Ulm, Germany; [2] Department of Biomolecular Chemistry, Faculty of Medicine, Medical University of Lodz, Lodz, Poland; [3] Department of Experimental Physiology, Chair of Experimental and Clinical Physiology, Medical University of Lodz, Lodz, Poland;
*Email: maria.pawelska-zubrzycka@umed.lodz.pl

Disorders involving the orofacial area represent a major medical and social problem. They are a consequence of central nociceptive processes associated with stimulation of the trigeminal nerve nucleus. A rat model of trigeminal pain, utilizing tongue jerks evoked by electrical tooth pulp stimulation during perfusion of the cerebral ventricles with various neuropeptide solutions, can be used in the pharmacological studies of nociception in orofacial area. The investigated neuropeptides diffuse through the cerebroventricular lining producing an analgesic effect either directly, through the trigemino-hypoglossal reflex arc neurons or indirectly through the periaqueductal central gray, raphe nuclei or locus coeruleus neurons.
The aim of this review is to present the effect of pharmacological activity of various neuropeptides affecting the transmission of the sensory information from the orofacial area on the example of trigemino-hypoglossal reflex in rats.

Key words: orofacial pain, trigemino-hypoglossal reflex, neuropeptides, perfusion of cerebral ventricles

INTRODUCTION

Although acute and chronic pain disorders involving the trigeminal system afflict literally millions of patients, the precise mechanisms for many of these pain conditions and targets for effective therapeutics remain incompletely understood (McDonough 2014, Tzabazis 2014).

Generation of afferent impulses and release of a number of neuropeptides from nerve terminals to the cerebral circulation plays a role in the etiology of orofacial region pain syndromes (Lazarov 2007, Hargreaves 2011). Within the orofacial area, the sensory fibers transmitting afferent information run within the branches of the trigeminal nerve (Heft 1992, Benoliel and Eliav 2012). Sensory fibers transmitting afferent impulsation from the face and the oral cavity include both large diameter fibers belonging to Aβ group and small diameter ones – Aδ and C. Small diameter nerve fibers Aδ – fast-conducting, as well as C – slow-conducting, are present in the tooth pulp and transmit nociceptive impulsation (Zimmermann 1977, Bender 2000).

Various pain signal transduction cascades have been elucidated in trigeminal neurons using animals models, however, the translation of these findings into diagnostic and pharmacological tools has been limited by the paucity of models which allow for evaluation of the responsiveness of nociceptors to the magnitude of nociceptive response.

Despite several controversies, it is generally accepted that in rats, tooth pulp stimulation represents a valuable pain model (Morita et al. 1977, Toda et al. 1980, Chapman et al. 1986, Sugimoto et al. 1988, Alantar et al. 1997); moreover, tooth pulp stimulation has been proposed as a model for trigeminal pain (Chapman et al. 1986). Therefore, facilitation or inhibition of bulbar somatic reflexes triggered by nociceptive impulses can be regarded as indicative of facilitation or inhibition of nociception.

Utilization of bulbar somatic reflexes in the research of nociception requires elucidation of: the neuronal organization existing between the first

Correspondence should be addressed to M. Zubrzycka
Email: maria.pawelska-zubrzycka@umed.lodz.pl

sensorineuron, whose body is located in the trigeminal ganglion and the motoneuron in the motor nuclei of the cranial nerves; the transmitters and modulators released by the neurons constituting the reflex arc; the membrane receptors binding the transmitters and modulators present between the neurons of the reflex arc and their density on the cell membrane, as well as the effect on the central element of the reflex arc of both the impulsation transmitted from the periphery and that coming from the superior nerve centers.

The aim of this review is to present the effect of pharmacological activity of various neuropeptides affecting the transmission of the sensory information from the orofacial area on the example of trigemino--hypoglossal reflex in rats.

TRIGEMINO-HYPOGLOSSAL REFLEX

The reflexes used for over a decade in the research of conduction within the brainstem include the jaw-opening reflex (JOR), the trigemino-biventral reflex (Oliveras et al. 1974) used most frequently in tests on cats and rats as well as evoked tongue jerks (ETJ) due to trigemino-hypoglossal reflex, tested on rats (Leśnik and Traczyk 1978, Zubrzycka et al. 1997, Zubrzycka and Janecka 2000).

The trigemino-hypoglossal reflex has been used to study the role of neuropeptides in pain transmission through the cerebral ventricles in rats. The hypoglossal nerve nucleus is situated superficially under the floor of the fourth cerebral ventricle, which allows to suppose that chemical substances can penetrate to that nucleus from the IV ventricle lumen faster than to the motor trigeminal nerve nucleus, located deeper under the floor of the IV ventricle. The magnitude of the trigemino-hypoglossal reflex and the factor modulating the reflex depend on the branch of the trigeminal nerve, whose stimulation with electric impulses evokes contractions of the tongue muscles (Leśnik and Traczyk 1978, Zubrzycka et al. 1997). Stretching of the tongue does not cause any changes in excitability of hypoglossal nerve (n. XII) motoneurons, because no intrafusal spindles in rat (Green and Negishi 1963) have been found in the tongue muscles. Annulospiral endings in the intrafusal spindles modulate excitability of the motoneurons for other skeletal muscles via spinomuscular loop.
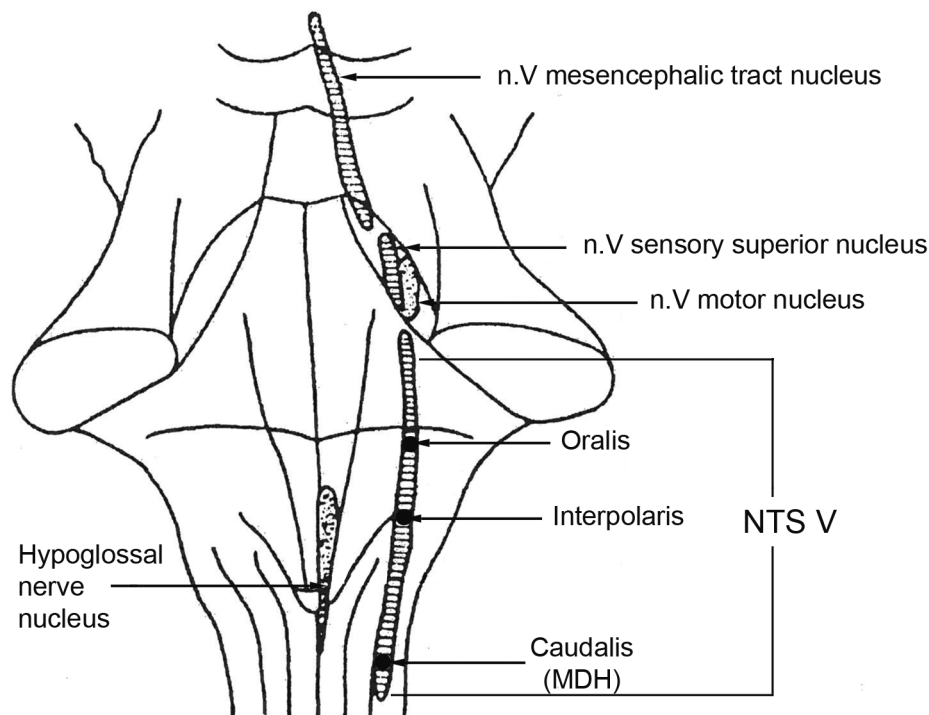

Fig. 1. Dorsal view of the brain stem with schematic drawing of the trigeminal sensory complex. The spinal nucleus is composed of oralis, interpolaris, and caudalis subnuclei. NTS V: n.V spinal tract nucleus; MDH: medullary dorsal horn.

NEURONAL ORGANIZATION OF TRIGEMINO-HYPOGLOSSAL REFLEX ARC

The central projection of the trigeminal ganglion sensory neurons, particularly those innervating the tooth pulp, has been investigated extensively (Woda et al. 1977, Arvidsson and Gobel 1981, Hayashi et al. 1984). It turned out that, after entering the brain, a portion of afferent fibers of the trigeminal nerve extends towards the midbrain, forming the mesencephalic tract, reaching the n.V mesencephalic tract nucleus. A distinct part of afferent fibers divides into short ascending and longer descending branches. The ascending ones terminate at the pons in the n.V principal sensory nucleus, whereas the descending ones form the n.V spinal tract, extending downwards even to the cervical segment of the spinal cord. There is n.V spinal tract nucleus (NTS V) on its medial side. The nucleus consists of three parts arranged longitudinally: n.V anterior spinal tract nucleus (oralis), n.V interpolar spinal tract nucleus (interpolaris) and n.V posterior spinal tract nucleus (caudalis) (Olszewski 1950) (Fig.1). The subnucleus caudalis has several morphological and physiological similarities with the spinal dorsal horn, to the extent that it is now often termed the medullary dorsal horn (MDH) (Sessle 2005).

Stimulating the tooth pulp with simultaneous recording of the action potentials of the second sensory neuron, Woda and others (1977) and Tomita and others (2012) found that impulsation from the tooth pulp is transmitted directly to all the nuclei of the sensory trigeminal nerve complex. By labeling neurons and nerve fibers after injection of horseradish peroxidase into the pulp of maxillary and mandibular teeth in cats Arvidsson and Gobel (1981) as well as in rats Jacquin and others (1983) and Marfurt and Turner (1984) demonstrated that projections from these teeth run ipsilaterally to n.V principal sensory nucleus and predominantly to the anterior portion of n.V spinal tract nucleus.

It is conceivable that the n.V nuclei complex plays the role of double nociceptive representation for the orofacial area: n.V posterior nucleus of the spinal tract receives from the face and the oral cavity, whereas those located anteriorly to the obex – impulses from the oral cavity (Woda et al. 1977, Azerad et al. 1982, Sessle 2005). The sensory information from the tooth pulp reaching the anterior n.V spinal tract nucleus can be modulated by sensory information from n.V posterior nucleus of the spinal tract (Han et al. 2008). Moreover, it is known that the nociceptive responses mediated by C fibers are conducted to n.V posterior spinal tract nucleus, and those conducted by Aδ are
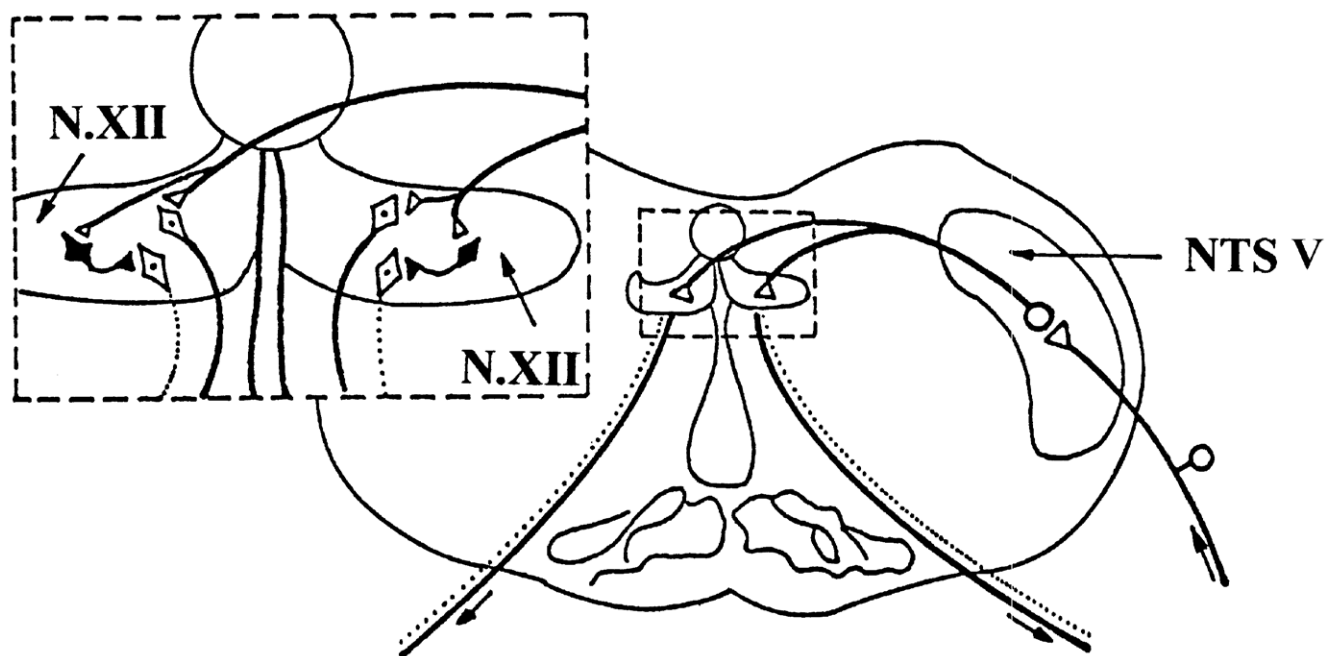

Fig. 2. A scheme of the trigemino-hypoglossal reflex arc. NTS V – n.V spinal tract nucleus; N.XII – hypoglossal nerve nucleus; light-colored triangle – the excitatory synapse, dark triangle – the inhibitory synapse.

processed mainly in n.V anterior nucleus of the spinal tract (Pajot et al. 2000).

The presence of fibers connecting the n.V sensory nuclei with the motor nucleus of the hypoglossal nerve has been reported. Their existence has been confirmed by electrophysiological studies (Stewart and King 1963). Sumino and Nakamura (1974), recording cellular potentials during induction of trigemino-hypoglossal reflex, found numerous inhibitory interneurons present around the hypoglossal nerve motoneurons. These authors suggested the presence of a bisynaptic connection in the brain stem on the basis of the difference between the delay of potential in the motoneurons of n.XII and conduction in the inferior alveolar nerve. The same authors hypothesized that the neurons of the reticular formation located in the vicinity of the hypoglossal nerve nucleus play the role of inhibitory interneurons in the trigemino-hypoglossal reflex.

In the trigemino-hypoglossal reflex such as tongue jerks (ETJ) evoked by tooth pulp stimulation, the impulsation from n.V sensory nuclei was transferred to the ipsi- and contralateral hypoglossal nerve nucleus where it stimulated the motoneuron of the tongue-withdrawing muscles, and by excitation of the inhibitory interneuron caused inhibition of the tongue protrusion muscles motoneuron (Fig. 2).

The trigemino-hypoglossal reflex arc extends below the floor of the IV ventricle between the sensory nucleus of the trigeminal nerve and the motor nucleus of the hypoglossal nerve. The hypoglossal nerve nucleus is situated superficially under the floor of the IV ventricle. Neuropeptides introduced into the cerebral ventricles can reach that nucleus from the lumen of the IV ventricle faster than other elements of the trigemino-hypoglossal reflex arc and can interact with the motor and sensory centers or the ETJ-mediating neurons.

NEUROPEPTIDES IN THE CEREBROSPINAL FLUID

The cerebroventricular system can play the role of a humoral information channel in the central nervous system (CNS). In view of the above, changes of cerebrospinal fluid (CSF) composition should influence the somatic reflex whose centers are located in the vicinity of the cerebral ventricles.

A concept considering neuropeptides in the extracellular fluid (ECF) of the brain rather than those in the CSF or plasma as primary signals, triggering a variety of receptor-mediated effects, has been adopted by Veening and Barendregt (2010). Movement within the ECF, following central neuropeptide release occurs primarily by diffusion according to the concentration gradient (Proescholdt et al. 2000). The ECF interconnects freely with the CSF into which neuropeptides will spill over after accomplishing their receptor-mediated actions in the brain. While not likely to contain biologically active endogenous neuropeptides, the CSF may be used as a vehicle to transport exogenous neuropeptides across the ependyma into the brain parenchyma following intracerebroventricular (i.c.v.) administration (Bittencourt and Sawchenko 2000). Thus, due to the reversed concentration gradient following administration, exogenous neuropeptides in the CSF can potentially reach numerous, even very distant, locations within the brain (Bittencourt and Sawchenko 2000). In contrast, an endogenous neuropeptide is unlikely to gain access to its receptors by first passing into the CSF and then diffusing back into the brain parenchyma against the naturally occurring concentration gradient. Hence, once arrived in the CSF following transport in the extracellular fluid, the majority of neuropeptides are probably no longer of biological significance.

Neuropeptide which is administered i.c.v. is first diluted in the CSF, and then diffuses through the whole area of the ventricular and cerebellomedullary cistern walls into the ECF of the brain. From the ECF, it diffuses into the vicinity of structures responsible for the trigemino-hypoglossal reflex. Hence, the ultimate concentration of the neuropeptide following i.c.v. administration, which is effective in the specific structures, is significantly lower than the initial concentration.

EFFECT OF NEUROPEPTIDES PERFUSED THROUGH THE CEREBRAL VENTRICLES ON THE TRIGEMINO-HYPOGLOSSAL REFLEX ARC NEURONS

The magnitude of ETJ evoked by tooth pulp stimulation was the measure of the effect of neuropeptides on neural structures. The reflex undoubtedly occurs with significant involvement of substance P (SP)-, oxytocin (OT)-, vasopressin (AVP)-, galanin (GAL)-, enkephalin (ENK)-, vasoactive intestinal peptide (VIP)-, and somatostatin (SOM)-ergic neurons and its magnitude is proportional to SP-, OT-, AVP-, GAL-,

ENK-, VIP-, SOM-ergic transmission (Zubrzycka and Janecka 2005, 2007a, 2008, Zubrzycka et al. 2002, 2005).

The reflex is enhanced during perfusion of the cerebral ventricles with SP and VIP because the cell receptors of the neurons conducting impulsation in this reflex arc are probably not completely saturated with endogenous SP and VIP molecules (Zubrzycka and Janecka 2007a).

The first sensorineuron of the trigemino-hupoglossal reflex arc evoked by tooth pulp stimulation has been determined to be SP-ergic (Brodin et al. 1981, Gazelius et al. 1981). The second neuron located in the principal sensory nucleus n.V and NTS V is characterized by a low number of SP-ergic neurons, but, particularly in NTS V, there are numerous SP-ergic fibers and high density of SP-ergic receptors. Similarly, the hypoglossal nerve nucleus (n. XII) contains many SP-ergic receptors, a moderate number of SP-ergic fibers and no SP-ergic neuron bodies (Shults et al. 1984). Various evidence suggests interaction of SP with ENK, VIP, SOM, GAL, OT, AVP in transmission of nociceptive information in the gelatinous substance of the spinal cord and NTS V (Skofitsch et al. 1985, Xu et al. 1990, Yang et al. 2007). The above areas are rich in mu-opioid receptors (MOR), inhibiting pain transmission evoled by stimulation of Aδ and C fibers (Mansour 1994, Heinke et al. 2011, Lesniak and Lipkowski 2011). Considering the similarities in the distribution of SP and opioid receptors, Jessel and Iversen (1977) proposed a hypothesis that activation of opioid receptors is responsible for the analgesic effect of SP. However, SP did not bind to opioid receptors in the brain, and therefore it was suggested that the analgesic effect of SP was due to the release of endogenous opioids (Kondo et al. 2005).

It was demonstrated that AVP, OT, GAL, EM-2, ENK-Met, and morphiceptin moderately inhibit ETJ via their own and opioid receptors. AVP, OT, GAL analogs, competing for the binding sites with OT-, AVP-, GAL-, SP-ergic receptors, inhibit ETJ effectively (Zubrzycka and Janecka 2005, 2007a, 2008, Zubrzycka et al. 2002, 2005). GAL exerts its inhibitory effect by blocking the excitatory action of SP and calcitonin gene-related peptide (CGRP) (Hua et al. 2005, Xu et al. 1990) and enhancing the opioid analgesia (Hua et al. 2004, Wiesenfeld-Hallin et al. 1990). Other authors confirm that these neuropeptides enhance the synthesis and release of ENK in periaque-

ductal central gray (PAG) and exert an analgesic effect mediated by opioids (Martin and Voigt 1981, Yang et al. 2006).

The role of opioid receptors in neuropeptide-induced modulation of the trigemino-hypoglossal reflex was confirmed by blocking of these receptors with naloxone (NAL) or a selective MOR antagonist – β-funaltrexamine (β-FNA) (Zubrzycka and Janecka 2005, 2008, 2011, Zubrzycka et al. 2002, 2005). Blocking with NAL the opioid receptors located in the centers adjacent to the cerebral ventricles abolished to a considerable extent the inhibition of nociceptive trigemino-hypoglossal reflex due to PAG stimulation, which evidences the role of opioid receptors in modulation of the reflex magnitude (Zubrzycka and Janecka 2001, 2011).

It was demonstrated that GAL, OT and AVP potentiate the analgesic effect of opioids and that GAL causes analgesia by modulating SP-ergic transmission, both at the presynaptic level by inhibition of SP release and at the postsynaptic one by blocking the SP-ergic receptor (Zubrzycka and Janecka 2007a, 2008), whereas the serotonin (5-HT) receptor antagonist methysergide blocks the analgesic effect of AVP (Zubrzycka and Janecka 2005).

The various effects of neuropeptides perfused through the cerebral ventricles on the trigemino-hypoglossal reflex can be explained by their different effect on n.V sensory nuclei neurons, interneurons, n.XII motoneurons, as well as the structures modulating transmission via the elements of the investigated reflex arc.

THE EFFECT OF ELECTRIC TOOTH PULP AND PAG STIMULATION ON RELEASE OF THE SELECTED NEUROPEPTIDES INTO THE CSF

The neuromodulators and neurohormones produced in the neural tissue and released into the CSF may participate in modulation of the activity of the nerve centers located in the vicinity of the cerebral ventricles, in the area containing the sensory and motor centers of the studied trigemino-hypoglossal reflex (Black 1982, Bloom and Segal 1980, Jackson 1980). Nociceptive stimuli cause the release of neuropeptides into the CSF and the ECF. The endogenous neuropeptides present in the CSF and released into it as a result of afferent nociceptive transmission also under physiological condi-

tions, can be considered to modulate somatic bulbar reflexes. Therefore, it was important to investigate the effect of electric stimulation of nociceptive terminals and PAG on the level of release of neuropeptides involved in modulation of pain transmission processes. It seems that stimulation of tooth pulp and nociceptive fibers causes significantly increased release of immunoreactive SP and β-endorphin (β-EP) without any effect on the release of AVP and OT into the CSF (Bach and Yaksh 1995, Lu et al. 2009, Orlowska et al. 1994, Zubrzycka and Janecka 2002, 2007b, 2011).

The fibers containing SP, AVP, OT and β-EP are widely distributed in the brain and terminate in PAG, but their main projections extend along the cerebral ventricles, where they are in close contact with the ependyma of the third ventricle and the CSF – containing neurons (Veening and Barendregt 2010, Vigh--Teichmann and Vigh 1989, Vigh et al. 2004). Therefore, active transport of neuropeptides into the CSF might be effected via specialized ependymal cells – tanycytes, extending from the third ventricle (Bjelke and Fuxe 1993, Guerra et al. 2010, Langlet et al. 2013). Bach and Yaksh (1995), Landgraf and Neuman (2004) found continuous exchange between the CSF and ECF, which means that the endogenous neuropeptides present in the CSF compartment can migrate from their release site. Some peptides can reach the CSF also through the periventricular structures, Virchow-Robin perivascular spaces and through blood-brain-barier (BBB) (Proescholdt et al. 2000).

The lack of effect exerted by stimulation of the trigeminal nerve sensory branches on the immunoreactive AVP and OT content in the CSF (Zubrzycka and Janecka 2007b, Orłowska et al. 1994) can be explained by the fact that nociceptive stimulation causes the release of considerable amounts of AVP and OT from the dendrites into the ECF without altering the concentration of these neuropeptides in the CSF. It does not mean that AVP and OT released into the ECF do not reach the cerebral ventricles, but it may suggest the loss of many molecules of these neuropeptides on the long way to the ventricles due to receptor binding and degradation by enzymes.

On the other hand, PAG stimulation caused a decrease of immunoreactive SP release without any effect on β-EP release into the CSF (Zubrzycka and Janecka 2002, 2011), which suggests that PAG stimulation must not cause depolarization of a sufficient number of terminals of the fibers extending close to the

ependyma, probably due to too small volume of release of these neuropeptides from the brain nuclei as well as different proportions of distribution of their receptors in functional PAG columns.

THE ROLE OF BRAIN STEM STRUCTURES IN NEUROMODULATION OF PAIN FROM THE OROFACIAL AREA

The brainstem has been considered to contain an extensive, multineuronal network responsible for inhibition of nociceptive impulses and polysynaptic sensory reflexes at the level of dorsal horns of the spinal cord and NTS V. The network comprises the neurons of PAG, dorsal raphe nucleus (NDR), nucleus raphe magnus (NRM) and the surrounding reticular formation including magnocellular reticular nucleus, gigantocellular reticular nucleus (NRG) and paragigantocellular reticular nucleus (NRPG) (Beitz et al. 1983) (Fig. 3).

The PAG effects are mediated mainly by rostral ventromedial medulla (RVM). The PAG/RVM system exerts bidirectional control in pain transmission processes (Heinricher et al. 2009), the neuronal background of which can be attributed to the presence of a heterogenous cell population in the RVM: the OFF cells, characterized by cessation of electric discharges during nociceptive reflexes and the ON cells, whose discharges cease suddenly immediately before the nociceptive reflexes. These cells are sensitive to the effect of opioids (Reichling et al. 1988).

The electric stimulation of PAG caused reduction or complete abolition of the ETJ amplitude and that effect was reversible with NAL (Zubrzycka and Janecka 2000, 2001). Electric stimulation of PAG proved to be more effective than AVP, OT, GAL, ENK, EM-2, and morphiceptin perfused through the cerebral ventricles (Zubrzycka and Janecka 2005, 2008, Zubrzycka et al. 2002, 2005). It was also demonstrated that the electric stimulation of tooth pulp and PAG changes the expression level of mRNA for neuropeptides such as: SP, AVP, OT, GAL, VIP, SOM, EM-2 and opioid receptors in mesencephalic, hypothalamic and thalamic tissues as a result of excitation or inhibition of the cerebral structures involved in transmission and modulation of nociceptive information (Zubrzycka et al. 2011). The higher expression level of mRNA for many neuropeptides and opioid receptors enhances their synthesis and causes more potent analgesic effect. The mechanism of

such changes has not been completely elucidated so far. It seems that the estimation of mRNA levels for the aforementioned neuropeptides can facilitate the understanding of the role of these neuropeptides in the trigemino-hypoglossal reflex.

Thus, it is conceivable that the investigated neuropeptides selectively excited the neurons activated by nociceptive stimuli in the spinal cord and NTS V, and exerted their effect on the mesencephalon, hypothalamus and thalamus, modulating the ETJ amplitude via these structures. The perfusion of the cerebral ventricles with neuropeptides could affect the excitability mainly of the neurons in PAG, NDR and locus coeruleus (LC), the structures located in the vicinity of the ventricular system, and influence the neurons of the sensory center, motor center and interneurons of the investigated reflex arc. The facilitating or inhibitory effect was dependent on the binding site of the investigated neuropeptide to the membrane receptor, time, in which it is released from the receptor and the rate of its degradation. It allows to conclude that synergistic combinations of many of the investigated neuropeptides enhance the analgesic effect of opioids and that these neuropeptides alone, or in appropriate combinations, inhibit ETJ and increase analgesia in the orofacial area.

The scheme illustrating the central control of negative impulses in NTS V neurons, effected by negative feedback is shown in Fig. 3.

Nociceptive impulsation from the orofacial area excites (bright triangle – the excitatory synapse) the nociceptive neuron (P) of the n.V spinal tract nucleus (NTS V). Then, via ascending pathways, it reaches PAG, NRM and NDR. PAG excitation is transmitted to the raphe nuclei – NRG and NRPG. Impulses from PAG and raphe nuclei (dark triangle – the inhibitory synapse) the nociceptive neurons in NTS V directly and indirectly by excitation of ENK-ergic neurons (E) and non-nociceptive ones (NP). Impulsation from the LC inhibits pre- and postsynaptically the activity of NTS V nociceptive neurons. The common characteristics of the spinal dorsal horns and NTS V allow to suppose that the physiological mechanisms in these structures are similar.

The mechanism of excitation of PAG projections by endogenous opioids has not been elucidated completely yet. The ENK-ergic neurons or β-EP-containing terminals of axons projecting there from the hypothalamus seem to exert an inhibitory effect on another, e.g.

GABA inhibitory interneuron, unknown to date, which consequently leads to disinhibition, i.e. excitation of the neurons projecting to the inferior centers regulating nociception. The ENK-ergic PAG neurons are innervated by terminals containing SP (Commons at al. 2002).

Thus, a hypothetical PAG neuronal pathway would include SP-releasing axons terminating on ENK-ergic interneurons, inhibiting in turn the next inhibitory interneurons, whose short axons terminate on 5-HT, or GAL, OT, AVP projections.

Schul and Frenk (1991) present a scheme of hypothetical configuration of neurotransmitters and their effects in the PAG, from which it follows that the anal-
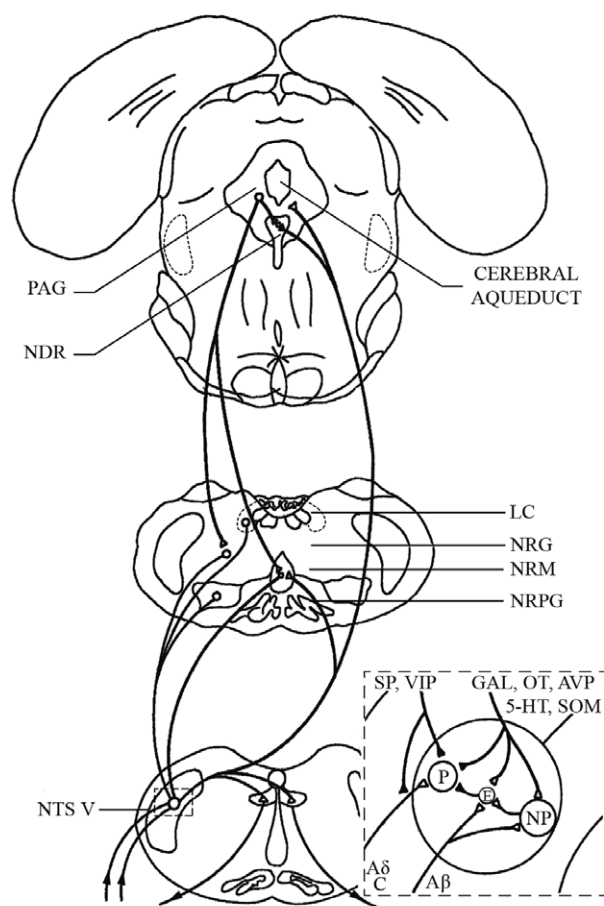

Fig. 3. A scheme of inhibition of central nociceptive impulsation control in NTS V. Nociceptive impulsation from the orofacial area stimulates a nociceptive NTS V neuron (P). From there, it reaches PAG through ascending pathways. Impulses from PAG inhibit nociceptive NTS V neurons directly and indirectly by stimulating enkephalinergic neurons (E) and non-nociceptive neurons (NP). Description in the text.

gesic action of opioids in PAG is associated with tonic release of 5-HT. The authors suggest that opioid exert an analgesic effect when a GABA-ergic neuron is inhibited by 5-HT.

Some papers concerning the role of various neurotransmitter systems involved in the nociception process have been published recently. They have demonstrated that trigeminal ganglion cell bodies and their counterparts in the spinal dorsal root ganglia synthesize a vast array of chemicals that help define the role that the primary afferent nociceptive neurons play in encoding pain in orofacial area (Lazarov 2007, Sessle 2005, 2015).

Important gaps still remain in our knowledge of these processes and further experimental studies are necessary to fully understand the mechanisms underlying the normal and pathophysiological processing of nociceptive information from the orofacial region.

CONCLUSIONS

Significant advances have been made toward elucidation of the nociceptive processes in acute and chronic orofacial pain and in characterization of changes that occur in nociceptive pathways, especially at the spinal cord. Recent findings related to peripheral and central sensitization have provided some important insights into how orofacial pain arises. Also, the possible role of sensory neuropeptides and numerous other factors in the modulation of excitability was intensively studied. This information has opened new perspectives for pain therapy. There are many processes, receptors, transmitters or modulators, among which the new drug strategies are primarily focused and can be exploited to develop therapeutically valuable drugs with novel mechanisms of action in orofacial pain.

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