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The Neurochemical Anatomy of Trigeminal Primary Afferent Neurons

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1. Introduction

Somatic sensations of the head and orofacial region are transmitted by trigeminal primary afferent neurons, a group of neural-crest derived sensory neurons. Most of their cell bodies are located outside the central nervous system, residing in the trigeminal ganglion (TG) but some of them lie centrally within the brainstem, in the mesencephalic trigeminal nucleus (MTN).

The TG represents a cranial analog of the dorsal root ganglia in the peripheral nervous system (Darian-Smith, 1973). TG neurons have a unique morphology and are classified as pseudounipolar (Krastev, 2009). Their centripetal processes, usually called trigeminal primary afferents, carry somatosensory information from mechanoreceptors, thermoreceptors and nociceptors in the face, the oral and nasal cavities, and through the portio major of the trigeminal nerve reach their main target neurons in the trigeminal sensory nuclei (Fig. 1), where they establish synaptic contacts with their perikarya (for reviews, see Darian-Smith, 1973; Dubner et al., 1978; Kruger & Young, 1981).

Mesencephalic trigeminal neurons are considered centrally displaced ganglion cells but in spite of their curious central location they maintain some characteristics of neural crest cell derivates. The great majority of MTN cells are large pseudounipolar neurons which provide the innervation of the masticatory muscle spindles and periodontal ligament pressoreceptors. Their central branches enter the trigeminal motor nucleus and several other brainstem nuclei around it (Fig. 1), where they make excitatory synaptic connections with jaw-closing motor or premotor (last-order interneurons) neurons, respectively (see Capra & Dessem, 1992 for a review). Unlike the TG cells however, MTN neurons receive synaptic inputs that potentially modify their output (reviewed in Lazarov, 2000). MTN neurons are also remarkable insofar as they, without an exception, constitute one distinct functional class of trigeminal sensory neurons, i.e. proprioceptive neurons (Jerge, 1963; Cody et al., 1972). Due to their ectopic location within the brain, in addition to this classical function, some mesencephalic trigeminal neurons may act as interneurons capable of integrating peripheral and central information prior to reaching the trigeminal motor nucleus (Kolta et al., 1995). The functional segregation between peripheral and central primary afferent neurons is a further striking feature of the mammalian trigeminal sensory system (reviewed in Waite, 2004).

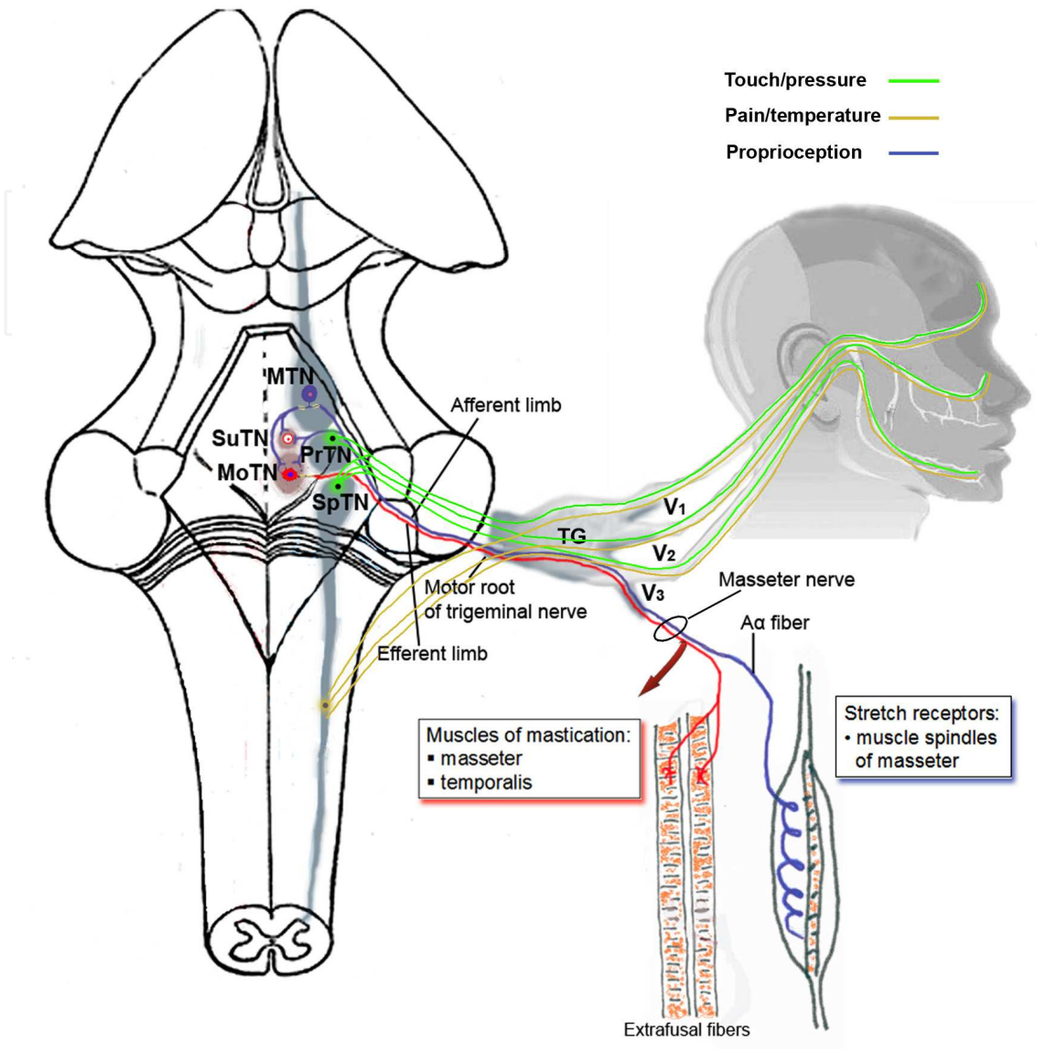

Fig. 1. Schematic illustration of the trigeminal pathways for orofacial somatic sensation. Tactile (touch and pressure) sensibility of the face and mouth is relayed through the large diameter Aβ axons of the trigeminal ganglion (TG) neurons to the principal sensory trigeminal nucleus (PrTN) and rostral part (subnucleus oralis and interpolaris) of the spinal trigeminal nucleus (SpTN), while pain and thermal sensations from the orofacial structures are conveyed by the thin Aδ and C trigeminal primary afferents to the subnucleus caudalis of the SpTN. Proprioceptive sensation from the face and oral cavity is transmitted directly or through premotor neurons in the supratrigeminal nucleus (SuTN) to the motor trigeminal nucleus (MoTN) via the central processes of primary afferent neurons whose pseudounipolar cell bodies are mainly located in the mesencephalic trigeminal nucleus (MTN). The efferent limb (depicted in red) of the reflex arc producing jaw closure (jaw jerk or masseteric reflex) is formed by the axons of trigeminal motoneurons traveling through the motor root of the trigeminal nerve to the muscles of mastication. V_1, V_2, V_3, ophthalmic, maxillary and mandibular divisions of the trigeminal nerve, respectively.

A commonly held hypothesis in neurobiology is that neuronal morphology frequently mirrors chemical neuroanatomy and also neurons in different functional pathways, within which they lie, can be characterized by their neurochemical profiles. In this respect, the various neuronal populations that constitute the TG and MTN can be identified not only on the basis of their morphological characteristics and electrophysiological properties but also by their neurochemical content. This issue is of key importance since the transmitter content of different neuronal populations often correlates well with their target projections. It is assumed that trigeminal primary afferent neurons exhibit pathway-specific patterns of neurochemical expression, a concept that has been called chemical coding (Costa et al., 1986). It has also been proposed that the differently fated embryonic migration, synaptogenesis, and peripheral and central target field innervation could affect the individual neurochemical phenotype of TG and MTN neurons. Trigeminal primary afferent neurons utilize a wide variety of chemical neuromessengers for synaptic transmission and possess the ability to produce relevant adaptive changes in their neurochemical phenotype in response to environmental cues (for recent reviews, see Lazarov, 2002, 2007).

This chapter therefore focuses on the chemical neuroanatomy of the TG and MTN neuronal populations under normal conditions, the role and relationship of neurotransmitters and their corresponding receptors in relaying orofacial sensations and also refers to the interactions with other atypical neuromessengers and neurotrophic factors. We have also surveyed the chemical plasticity of developing and mature TG and MTN neurons to gain insight into their structural and functional properties in an altered neurochemical balance, with special reference to trigeminal nerve degeneration and regeneration, and clinical implications.

2. Neurotransmitters and their known receptors in trigeminal primary afferent neurons

Using immunohistochemistry and *in situ* hybridization histochemistry we have identified distinct neuronal, partly chemically coded, subpopulations in the intact TG and MTN. Our findings suggest that trigeminal primary afferent neurons are chemically heterogeneous and appear to use various chemical neuromediator candidates for synaptic transmitters. These include classical and peptide transmitters, calcium-binding proteins as neuronal markers and other neuroactive molecules (Table 1). In addition, we have demonstrated that TG and MTN neurons receive inputs from different groups of neurons that contain multiple transmitter substances. Indeed, both the TG and MTN receive catecholaminergic, nitrergic and peptidergic innervation in the form of perineuronal arborizations encircling in a basket-like manner the perikarya of large unstained neurons. It is assumed that the pericellular baskets can function as a key communication medium between immunopositive projections and immunonegative neuronal somata in the orofacial somatosensory information processing. Last but not least, it is now well established that the cell bodies of TG and MTN neurons are richly endowed with postsynaptic receptors for a huge array of neurotransmitters and neuroactive substances.

2.1 Classical transmitters

In recent years, a variety of 'classical' transmitter substances and their receptors have been associated with subsets of trigeminal primary afferent neurons. Among them are amino acids (both excitatory and inhibitory) and monoamines. On the other hand, our studies

Neuroactive substance	Trigeminal ganglion	Mesencephalic trigeminal nucleus	Effect of activation
Neurotransmitters and their known receptors			
Glutamate (GLU)	+	+IC, F/T	Membrane depolarization: fast and/or slow excitation
AMPA receptors	-	+IC	Postsynaptic rapid excitation
KA receptors	+	+IC	Presynaptic modulation of transmitter release
NMDA receptors	-	+IC	Presynaptic auto- or postsynaptic heteroreceptors
metabotropic receptors	mGluR5	mGluR1α, mGluR2/3	Heteroreceptors and/or autoreceptors: neuronal excitability and transmission regulation
Aspartate	+	±IC, F/T	Membrane depolarization
Gamma aminobutyric acid (GABA)	+	±IC, F/T	Membrane hyperpolarization: inhibition Membrane depolarization: excitation
$GABA_A$ receptor	+ (γ1, γ2 subunits)	+IC	Postsynaptic fast inhibition
$GABA_B$ receptor	+ ($GABA_{B2}$ subunit)	+IC	Presynaptic regulation of K^+, Ca^{2+}channels: long-term inhibition of synaptic transmission
Glycine	-	-	Postsynaptic facilitation of ATP, SER and DA release
Dopamine (DA)	-	+F/T	Membrane hyperpolarization
D_1 receptor	-	+IC	Masseter muscle proprioceptive processing
D_2 receptor	+	+P	Periodontal ligament proprioceptive processing
Serotonin (SER)	-	+F/T	Membrane depolarization: modulation of sodium currents
$5\text{-}HT_{1B}$ receptor	+	ND	

Neuroactive substance	Trigeminal ganglion	Mesencephalic trigeminal nucleus	Effect of activation
5-HT_{1D} receptor	+	ND	
5-HT_{1F} receptor	+	ND	
5-HT_2 receptor	ND	+IC	Intracellular transduction pathways activation
5-HT_3 receptor	ND	+IC	Postsynaptic slow excitation
5-HT_7 receptor	+	ND	
Histamine (HIS)	ND	+F/T	Membrane depolarization
H_1 receptor	+	+IC	Postsynaptic excitation
H_3 receptor	-	+P	Presynaptic inhibition
Adenosine 5ˡ-triphosphate (ATP)	ND	+F/T	Membrane depolarization Facilitation of neuronal discharge
$P2X_2$ receptor	+	+	Postsynaptic fast excitation
$P2X_3$ receptor	-	+	Presynaptic modulation of neurotransmitter release
$P2X_4$ receptor	+	+	
$P2X_5$ receptor	+	+	
$P2X_6$ receptor	+	+	
P2Y receptor	-	-	
Nitric oxide (NO)	+	+IC	Membrane depolarization: promotion of intracellular cGMP synthesis;
Carbon monoxide (CO)			
Neuropeptides and their known receptors	+	+	tonic background stimulation
Substance P (SP)	+	-	Neuromodulation
SP receptor	-	-	Neuromodulation
SOM ss2(b) receptor	-	+	
Neuropeptide Y (NPY)	+	-	
NPY Y_1 receptor	+	-	
NPY Y_2 receptor	+	-	
NPY Y_5 receptor	-	+	
Enkephalin (ENK)	+	-	Neuromodulation
Preprodynorphin	+	ND	
μ-opioid receptor	+	-	
δ-opioid receptor	+	-	
κ-opioid receptor	+	-	
Orexin (hypocretin) A	-	+F/T	Neuromodulation
Orexin receptor-1	ND	+	Induction of calcium currents

Neuroactive substance	Trigeminal ganglion	Mesencephalic trigeminal nucleus	Effect of activation
Orexin (hypocretin) B	-	+F/T	Neuromodulation
Orexin receptor-2	ND	+	Induction of calcium currents
Calcium-binding proteins			
Parvalbumin (PV)	+	+IC	Intracellular Ca buffering
			Selective marker for orofacial proprioceptors
Calbindin D-28 (CB)	+	+IC	Selective neuronal marker
Calretinin (CR)	+	+IC	NA
S-100	+	-	Selective glial marker
Neurocalcin	+	-	
Osteocalcin	+	+IC	Selective marker
Osteopontin	+	+IC	Selective marker
Peptide 19	+	+IC	Selective marker
Nerotrophic factors and their receptors			
Pan-neurotrophin receptor $P75^{NTR}$	+	+IC	Increase in mature neuronal excitability
Nerve growth factor (NGF)	+	+IC,F	Trophic support
TrkA	+	+IC	NA
Brain derived neurotrophin factor (BDNF)	+	+IC	Trophic support Neuronal phenotype maintenance
Neurotrophin 4-5 (NT-4/5)	+	-	NA
TrkB	+	+IC	Neuronal survival
Neurotrophin 3 (NT-3)	+	+IC	Trophic support
			Modulation of neuronal electric activity
TrkC	+	+IC	Neuronal survival
Glial cell line-derived neurotrophic factor (GDNF)			Trophic support
GFRalpha-1 receptor	+	+IC	NA
Ret receptor	+	+IC	NA

IC, intracellular; F/T, fibers and/or terminals; ND, no data; NA, not analyzed; P, pontine portion of MTN

Table 1. Overview of the established and putative neuromessengers, specific markers, neurotrophic factors and their known receptors and major functions in orofacial somatosensory signaling under normal conditions

clearly show that other classical neurotransmitters, such as acetylcholine, and purines like adenosine 5[1]-triphosphate (ATP) and its metabolite adenosine are not present in TG and MTN neurons.

2.1.1 Amino acids

There are three major amino acid neurotransmitters in the nervous system: glutamic acid (L-glutamate), gamma-amino butyric acid (GABA) and glycine. Glutamate (Glu) is considered a promising excitatory transmitter of the trigeminal primary afferent neurons in rats and cats. It is stored in both the large and small TG cells (Wanaka et al., 1987; Azérad et al., 1992; Stoyanova et al., 1998), and, in addition, all five known kainate (KA) ionotropic receptor subtypes are expressed in a majority of them, occasionally combined with metabotropic mGluR5 subunits (Sahara et al., 1997). Experimental results indicate that the metabotropic Glu receptors play an important role in the somatic sensation of TG neurons together with the ionotropic ones (Araki et al., 1993). Functional contribution of peripherally localized Glu receptors in acute and chronic pain processing is amply documented (Carlton, 2001) and further discussed in Section 5. Similarly, most mammalian MTN neurons contain glutaminase, a major enzyme involved in the biosynthesis of Glu (Kaneko et al., 1989; Turman & Chandler, 1994b) and receive glutamatergic synaptic input (Chandler, 1989; Copray et al., 1990). Further, recent research has revealed that vesicular glutamate transporter 1 is expressed in the cell bodies as well as both in the central axon terminals and peripheral sensory endings of MTN neurons in newborn and adult rats (Pang et al., 2006). Finally, all ionotropic receptor subtypes, AMPA (Mineff et al., 1998; Pelkey & Marshall, 1998; Petralia & Wenthold, 1992; Turman et al., 2000), KA and NMDA (Pelkey & Marshall, 1998; Petralia et al., 1994a,b,c; Turman et al., 2002) and some metabotropic subtypes, mGluR1α, mGluR5 and mGluR2/3 (Turman et al., 2001) have been localized on mesencephalic trigeminal neurons. Iontophoretic studies have also suggested that monosynaptic transmission between jaw-closing primary afferents and jaw-closing motoneurons is mediated primarily by non-NMDA receptors (Chandler, 1989), whereas both NMDA and non-NMDA receptors have been involved in the transmission from premotoneurons to jaw-opening motoneurons (Katakura & Chandler, 1990). The identification of mGluR subunits in mesencephalic trigeminal neurons which receive, as already noted, axosomatic input and/or synthesize mGluRs in the soma and then translocate the proteins to central terminals suggests that these, along with NMDA but not AMPA receptors, may function as either auto- or heteroreceptors in central MTN terminals (Turman et al., 2001).

GABA and glycine are both known to participate in the control of masticatory rhythms (Chandler et al., 1985). The presence of glycine, however, has been reported neither in TG nor in MTN neurons (Copray et al., 1990; Lazarov, 2002). On the other hand, GABA is localized in a substantial number of TG cells in rats (Szabat et al., 1992) and cats (Stoyanova et al., 1998). In addition, TG cells express two distinct GABA receptors, ionotropic $GABA_A$ γ1 and γ2 subunits, mostly co-localized in the same neuron (Kondo et al., 1994), and metabotropic $GABA_{B2}$ (Durkin et al., 1999). Our experiments have also pointed out that a subpopulation of smaller MTN cells, presumably interneurons, which are apposed to large mesencephalic trigeminal neurons, may be of a GABAergic nature (Lazarov & Chouchkov,

1995b; Lazarov, 2000, 2002). Besides, molecular biological studies have shown that pseudounipolar MTN neurons respond to GABA and accordingly express $GABA_A$ receptor α2, β2 and γ2 subunit mRNAs (Hayar et al., 1997; Ishii & Kang, 2002), and $GABA_{B1}$ (Margeta-Mitrovic et al., 1999) and $GABA_{B2}$ (Li et al., 2001) receptor proteins. In line with this evidence, several research groups have consequently reported GABAergic innervation of the MTN in rats (Copray et al., 1990; Ginestal & Matute, 1993), guinea pigs (Turman & Chandler, 1994a), rabbits (Kolta et al., 1991a,b) and cats (Lazarov & Chouchkov, 1995b; Lazarov, 2000, 2002). Ultrastructural and confocal laser-scanning studies have additionally revealed the existence of GABAergic synapses upon the cell bodies of MTN neurons in the rat (Chen et al., 2001). Taken together, these results suggest that excitability of jaw muscle spindle afferents is presynaptically controlled by interneurons containing GABA and these play an important role in modulating the jaw-jerk reflex.

Our findings now permit definitive conclusions that both TG and MTN neurons contain a stable concentration of Glu and GABA as possible transmitters. It still remains to clarify the possible synaptic relationships between Glu- and GABA-immunoreactive profiles in the TG and MTN, and their related functional implications. We have observed that both amino acid neurotransmitters are present in separate subpopulations of trigeminal neurons, e.g. most large neurons are glutamatergic while certain small neurons are GABAergic (Lazarov, 2002). Thus, it seems likely that excitatory amino acid(s) may be the transmitter(s) of large myelinated non-nociceptive primary afferents whereas GABA is probably the mediator of smaller trigeminal neurons, as suggested by Salt & Hill (1983).

2.1.2 Monoamines

Out of the six different types of monoamines, catecholamines [dopamine (DA), noradrenaline (NA) and adrenaline (A)] are the most important group. The earliest evidence for the catecholaminergic innervation of the TG sprang from the works of Santini (1966) and Lukás et al. (1970). In these initial studies by using immunocytochemistry with antiserum against tyrosine hydroxylase (TH), the rate-limiting enzyme of catecholamine synthesis, the immunostained neurons within the ganglion were proposed to be DAergic. Applying an antibody against the DA molecule itself, it is now inferred that TH-containing neurons in the TG do not synthesize DA but they are enveloped by DAergic pericellular arborizations (Kummer et al., 1990). A similar pattern has been observed for NA within the ganglion: TG cells are immunonegative to the NA-synthesizing enzyme, dopamine-β-hydroxylase (Katz et al., 1983) but receive dense NAergic innervation from postganglionic sympathetic neurons (Kummer et al., 1990). Hence, immunohistochemical evidence has suggested that TG neurons do not utilize catecholamines as possible transmitters but are under the influence of catecholaminergic afferent fibers of presumable sympathetic origin. Clinical observations imply that primary afferent neurons whose cell bodies reside in the TG express receptors for DA of the D_2 subtype, although these receptors do not function as autoreceptors but rather have a role in pain syndromes involving the head and the neck (Peterfreund et al., 1995).

In the same way, none of the MTN neurons in rats (Copray et al., 1990; Liem et al., 1997), cats (Lazarov & Chouchkov, 1995b) and humans (Usunoff et al., 1997) exhibits immunoreactivity for DA or NA but their perikarya are closely surrounded by fine DAergic

and NAergic baskets originating from the A9 and A10 cell groups, the substantia nigra and ventral tegmental area, and the neighboring locus coeruleus, respectively. Our immunohistochemical and *in situ* hybridization experiments have further shown that MTN neurons express the two principal subtypes of DA receptors, though they are unequally distributed within the nucleus: as in muscle spindle afferents, D_1 receptors are found throughout the MTN of the rat, whereas D_2 receptors and periodontal afferent neurons are confined to the caudal part of the nucleus (Lazarov & Pilgrim, 1997). This suggests that the two types of primary afferents may be modulated differentially by DA. The DA input to the MTN may modulate neuronal excitability, rates of transmitter synthesis, transport and release, as well as the number of pre- and postsynaptic receptors (Liem et al., 1997).

In addition to the catecholaminergic input, the TG and MTN are under the influence of another monoaminergic system, namely the serotoninergic system, one of the oldest amine systems in the brain. Indeed, several immunohistochemical studies have revealed the serotoninergic supply of the mammalian TG and MTN. In fact, we have found that the TG lacks intrinsic serotonin (SER)-containing cells but a plexus of varicose nerve fibers of extraganglionic origin covers the immunonegative neurons in a basket-like manner (Chouchkov et al., 1988). Likewise, SER is present neither in the cell bodies nor in neuronal processes of MTN neurons (Lazarov & Chouchkov, 1995a). However, SERergic axonal varicosities reaching the MTN from the mesopontine and medullary raphe nuclei form a pericellular basket-like network around immunonegative mesencephalic trigeminal neurons (Tashiro et al., 1989). Electron microscopic studies show direct synaptic contacts between SER-containing terminals and MTN perikarya in rats (Copray et al., 1991; Liem et al., 1993; Liem & Copray, 1996; Li et al., 2000), cats (Lazarov & Chouchkov, 1995a) and rabbits (Kolta et al., 1993). Out of the large group of the serotonin receptors, also known as 5-hydroxytryptamine receptors or 5-HT receptors, the presence of high affinity 5-HT_{1B} and 5-HT_{1D} receptors is demonstrated at protein and mRNA levels in TG neurons of the rat (Bruinvels et al., 1992; Wotherspoon & Priestley, 2000), guinea pig (Bonaventure et al., 1998) and human (Longmore et al., 1997). The mRNA encoding the 5-HT_7 receptor is also found to be expressed in the human TG (Terrón et al., 2001). At the same time, in the rat MTN an abundant number of the 5-HT_2 (Cornea-Hébert et al., 1999), 5-HT_3 (Morales et al., 1998) and 5-HT_4 receptor (Lazarov, 2007) have been established. SER has been hypothesized to be involved in trigeminal pain (Moskowitz et al., 1979) and SER antagonists have important clinical implications for antimigraine drug development (discussed later in Section 5). Recent data indicate that SER plays a significant role in the control of oral-motor activity as well (Li et al., 2000) and various oral-motor disorders, either drug induced or occurring as a consequence of injury, might result from altered modulation of sodium channels by SER (Tanaka & Chandler, 2006).

As in the case of catecholamines, both peripheral and central trigeminal primary afferent neurons do not contain histamine in their cell bodies but MTN neuronal perikarya receive a direct histaminergic input by hypothalamic descending fibers (Inagaki et al., 1987). In particular, neuronal somata throughout the whole rostrocaudal length of the nucleus are encircled by histaminergic fibers and their terminals, many of the latter forming axo-somatic synapses on them. Our laboratory has provided immunohistochemical evidence for the presence of two distinct histamine receptor subtypes, H_1 and H_3, in the rat MTN, albeit in

different neuronal subpopulations (Lazarov & Gratzl, 2006). Overlapping with muscle spindle afferents, histamine H_1 receptors are scattered throughout the full extent of the MTN, whereas H_3 receptors and periodontal afferent neurons are restricted to its caudal region. Since H_1 receptors are excitatory, histamine may act in this way on MTN neurons via the axo-somatic synapses, as suggested by Inagaki et al. (1987). Conversely, the H_3 receptors do not function only as autoreceptors but also as heteroreceptors, modulating MTN neuronal activity and release of other neurotransmitters from them. Therefore, it seems that the majority of MTN neurons respond to central histamine via the activation of H_1 and inhibition of H_3 receptors, thus participating in the control of feeding behavior.

The purine nucleosides adenosine and ATP can function as neurotransmitters or neuromodulators in both the CNS and PNS by signaling through specific receptors termed adenosine (also known as P1) and P2 receptors, respectively. Our attempts fail to identify purines in the TG and MTN neurons, though the latter are innervated by adenosine deaminase-containing projections from the hypothalamus (Nagy et al., 1986). Inasmuch as their terminals contacting MTN perikarya also express immunoreactivity to histamine, it seems that the two substances may coexist there, as noted by Yamamoto et al. (1988). In the TG, an abundant expression of the adenosine A1 receptor protein (Schindler et al., 2001) and the six P2X receptor subtypes (Xiang et al., 1998; Dunn et al., 2001) has been shown in a large number of small nociceptive neurons, which may be suggestive of a role of these receptors in analgesia. The existence of excitatory adenosine $A2_A$ receptors (Rosin et al., 1998) and $P2X_2$, $P2X_3$, $P2X_4$, $P2X_5$ and $P2X_6$ purinoceptors (Khakh et al., 1997; Patel et al., 2001; Lazarov, 2007) has been shown in populations of large proprioceptive mesencephalic trigeminal neurons. P2X receptors, which are ATP-gated cation channels, have been shown to be responsible for mediating both fast excitatory responses in central and peripheral neurons and the presynaptic modulation of neurotransmitter release (reviewed by Ralevic & Burnstock, 1998). It is likely that certain ionotropic P2X purinoceptors may be involved in the processing of proprioceptive information, thus suggesting a potentially important physiological role of ATP at sites where it is released extracellularly (Khakh et al., 1997).

2.2 Neuropeptides

Neuropeptides are a heterogeneous group of several hundred biologically active peptides, present in neurons of both the mammalian CNS and PNS, and involved in the transmission of signals as pure neuromediators or neuromodulators. In general, a large number of putative peptide transmitters have been identified in neurons and/or neuronal processes in the TG, but none of them has been found in mammalian MTN neuronal somata under normal conditions (see reviews by Lazarov, 1994, 2002, 2007). In particular, two subpopulations of primary afferent neurons, containing neuroactive peptides are distinguished in the TG: a number of substance P (SP)-, neurokinin A (NKA)-, calcitonin gene-related peptide (CGRP)-, cholecystokinin (CCK)-, somatostatin (SOM)-, vasoactive intestinal polypeptide (VIP)- and galanin (GAL)-immunoreactive ganglion cells with small- and medium-sized somata, and relatively fewer in number larger-sized neuropeptide Y (NPY)- and peptide 19 (PEP 19)-immunoreactive trigeminal neurons. It is noteworthy that SP, CGRP, SOM and GAL are found in small-diameter TG cells with conduction velocities in

the C-fiber range, PEP 19 and NPY are usually expressed in the large ones, and opioid peptides, CCK, VIP and pituitary adenylate cyclase activating polypeptide (PACAP) are observed in both small and large trigeminal neurons (Kummer & Heym, 1986; Weihe, 1990). Our previous studies have also revealed that although devoid of synaptic contacts, TG neurons express an array of peptide receptors for SP, CGRP, CCK, opioid peptides and NPY (see Lazarov, 2002, and references therein). The occurrence of peptidergic arborizations of extrinsic origin around the perikarya of some TG neurons suggests that these are under the influence of multiple biologically active peptides.

Several lines of physiological evidence indicate that SP and CGRP have excitatory effects and depolarize TG neurons (Otsuka & Konishi, 1976; Spigelman & Puil, 1991) while SOM and opioids appear to be inhibitory in nature (Randic & Miletic, 1978). Considering the important functional segregation of TG cells into large (mostly mechanoreceptive) and small (mainly nociceptive) neurons, it is not surprising that the neuropeptides SP and CGRP have been associated with the transmission of nociceptive impulses. However, small-diameter primary afferent neurons not only transmit noxious messages to central neurons but are also active in the periphery in mediating axon-reflex mechanisms and an inflammation response (Couture & Cuello, 1984; Foreman, 1987). Therefore, it is more reasonable to consider the role of SP and CGRP both in the transmission of sensory information from the periphery and in the peripheral effector functions such as neurogenic vasodilatation (McCarthy & Lawson, 1989, 1990), thus implicating them into the pathophysiology of migraine. Moreover, SOM can interact with SP causing inhibition of its release and consequent neurogenic vasodilatation (Brodin et al., 1981). Several lines of evidence indicate that sensory opioids could act synergistically with SP to induce histamine release (Foreman, 1987) and GAL may have an inhibitory effect on the nociceptive transmission (see Xu et al., 1990, and references therein). Therefore, all these peptides play a co-transmitter role and may have significant functions in disease mechanisms associated with head pain in humans (for a recent review, see Edvinsson & Uddman, 2005).

In view of the presence of a large number of neuropeptides in the TG cells, their absence in the morphologically homologous MTN neurons is rather surprising. Obviously, the absence of a peptide in two distinct populations of trigeminal primary afferent neurons indicates that different peptides subserve diverse sensory modalities, at least under normal conditions. In extension of previous inferences, we are confident that there exists a complex coexistent relationship between the chemoanatomical constellation of trigeminal primary afferent neurons and sensory modality transmission (Lazarov, 2002). Notwithstanding that intact mesencephalic trigeminal neurons do not express neuropeptides in their perikarya they are largely influenced by various synaptic inputs. Relevant to the dense peptidergic innervation of the nucleus, receptors for certain peptides have been localized on MTN neuronal somata (reviewed in Lazarov, 2002, 2007). According to Copray et al. (1990) it is likely that the synaptic input on MTN cells only affects the neuronal activity expressed at the central and peripheral terminals, in a more indirect mode and after a longer interval. The authors claim that this points to the presence and involvement of receptor systems that are not directly linked to ion channels but to a much slower secondary-messenger-induced biochemical effector cascade. As argued in the Introduction section, MTN neurons may operate under some circumstances like traditional “integrate and fire” neurons in addition

to typically sensory neurons, which generally do not receive synaptic contacts at their somata and do not discharge repetitively (Del Negro & Chandler, 1997).

2.3 Gaseous neuromessengers

In addition to the classical and peptide transmitters, several second messenger systems may be involved in orofacial signal processing. During the last decade the free radical gases nitric oxide (NO) and carbon monoxide (CO) have been found to function as putative messenger molecules both in central and peripheral trigeminal primary afferent neurons. Indeed, recent research in animals and humans has shown that the neurons in the MTN, along with TG cells, contain heme oxygenase, the CO-synthesizing enzyme (Uddman et al., 2004; Fan et al., 2008). The enzyme responsible for the synthesis of NO, nitric oxide synthase (NOS), and its histochemical marker, NADPH-diaphorase are expressed both in TG and MTN neurons in rats (Stoyanova & Lazarov, 2005), rabbits (Kolesar et al., 2006) and cats (Lazarov & Dandov, 1998) as well. The nerve cell bodies containing NOS are predominantly of small to medium size and they also express SP and CGRP (Edvinsson et al., 1998). Moreover, all these studies demonstrate that large unstained trigeminal neurons are innervated by nitrergic fibers and that NO increases the excitability and modifies other electrophysiological properties of these cells. Rather than acting via traditional receptors on the postsynaptic membrane, NO exerts its effect by diffusion into the adjacent neurons to activate soluble guanylyl cyclase, leading to an increase in intracellular cGMP. Furthermore, NO possibly produces an increase in MTN neuronal electrotonic coupling and therefore is involved in the synchronization of their activity too. Finally, there is functional evidence to support the involvement of NO in the development and maintenance of inflammation and pain (Yun et al., 1996). It has been suggested that as in other regions, both gaseous messengers possibly interact in a complex, dynamic way in the orofacial sensory processing where CO, being a more stable gas, may be responsible for basal activity and provide tonic background stimulation, whereas surges of NO transiently amplify or deliver phasic signaling (Fan et al., 2008).

2.4 Calcium-binding proteins

The calcium-binding proteins (CaBPs) represent one of the physiological systems for maintaining calcium ion intracellular homeostasis (reviewed in Baimbridge et al., 1992). In the last two decades they have received increased attention due to their implementation as specific markers for large-sized primary afferent subpopulations and their involvement in many calcium-dependent phenomena in the nervous system both under normal and abnormal conditions (Anderssen et al., 1993). Neuron-specific CaBPs, parvalbumin (PV), calbindin D-28k (CB) and calretinin (CR), are observed to be expressed predominantly in the large-sized TG and MTN neurons (Ichikawa et al., 1994; Lazarov et al., 1998), a subpopulation with inward calcium current. Interestingly, a typical glial cell-specific protein, S-100, is also localized, mostly co-expressed with CB, in TG neurons of epibranchial placode origin (Ichikawa et al., 1997). In addition, immunoreactivity to neurocalcin, a newly identified member of the neuronal CaBP family, has been shown in large or medium in size TG cells (Iino et al., 1998). Two additional newly discovered bone matrix CaBPs, osteocalcin and osteopontin, have recently been co-localized with PV in the cell bodies of both TG and

MTN neurons (Ichikawa et al., 1999; 2000). Data from ongoing experiments have provided compelling evidence that CaBPs might function as intracellular calcium transporters or as a buffering system for cell protection during neuronal activity in normal circumstances. They may also affect calcium-dependent neuronal properties such as excitability, release of neurotransmitters and resistance to excitotoxicity in mammals (see Baimbridge et al., 1992). Additionally to intracellular roles, S-100 may be involved in the neurotrophic functions of trigeminal primary afferent neurons.

3. Neurotrophic factors and neurotrophin receptors

Neurotrophic factors or neurotrophins are a family of structurally and functionally related polypeptides that promote neuronal differentiation, survival and neurochemical plasticity during development by signaling via both a low-affinity p75 receptor and high-affinity transmembrane receptors belonging to the Trk proto-oncogene family. It has been proposed that neurotrophins and their receptors play an essential role in long-term neural trophics and trophic mechanisms during adult life, and may also regulate phenotypic expression. Recent advances in neuroscience have shown that in addition to their trophic support actions, neurotrophins share many functional properties with classical neurotransmitters as well and may function as neuromodulators in neuronal signaling.

In fact, the concepts of neurotrophin-dependent survival, neurotrophin switching and neurotrophin co-operativity have largely arisen from works on the trigeminal system (Davies, 1997). Indeed, it is now well documented that developing trigeminal afferent neurons respond to all four known neurotropic factors, albeit in different capacities. Specifically, the localization of the nerve growth factor (NGF), brain-derived neurotrophin factor (BDNF), neurotrophin-3 (NT-3) and NT-4/5 has been demonstrated in discrete neuronal subsets of the human TG at an age ranging from 23 weeks of gestation to adulthood (Quartu et al., 1997). In early development, embryonic TG neurons depend for their survival on the action of the BDNF, NT-3 or NT-4/5 but not on NGF (Buchmann & Davies, 1993). Accordingly, within the developing TG neurotrophin receptor expression is high around the time of target innervation (Ernfors et al., 1992) and, moreover, two or more Trk receptor isoforms are co-expressed in embryonic rat TG neurons (Moshnyakov et al., 1996). Similarly, MTN neurons display modality specific neurotrophin dependence in their development (Davies, 1997). For instance, during the earliest stages of neurogenesis the developing MTN neurons are transiently supported by BDNF and NT-3, but not by NGF (Copray & Liem, 1993; Davies et al., 1987). Recent work on the human MTN also suggests an active role for the glial cell line-derived neurotrophic factor and possibly other cognate ligands in the trophism from prenatal life to adulthood of the cells subserving the proprioceptive sensory transmission (Quartu et al., 2006). Studies on the neurotrophin receptor expression indicate the presence of p75 (Henry et al., 1993) and all the Trk receptor types within the adult (Yamuy et al., 2000) and developing MTN (Williams et al., 1995). Besides, most MTN neurons express multiple Trk isoforms (Jacobs & Miller, 1999). These results conclusively support the notion that MTN neurons are sensitive to the direct effects of more than one neurotrophin. Recent studies provide some of the initial evidence that the neurotrophin requirements of trigeminal primary afferent neurons are related to a specific sensory modality. For example, the high-affinity NGF receptor, TrkA, is considered a

marker for peptide-containing nociceptors. Interestingly, Trk receptors appear to be co-expressed with SP and CGRP in a population of small trigeminal primary afferent neurons (Quartu et al., 1996).

4. Trigeminal response to injury and neurochemical plasticity of trigeminal primary afferent neurons

Research on putative neuromessengers in the trigeminal sensory system has reached another peak of interest over the last decade since it was shown that primary afferent neurons possess the ability to make adaptive changes in their transmitter phenotype in response to environmental cues (Table 2). It is now well known that injury to the peripheral trigeminal nerve results in nerve cell degeneration and that peripheral nerve damage evokes dynamic alterations in the levels of expressions of neurotrophins, neuropeptides and their receptors in the projection areas of injured axons, a phenomenon called chemical plasticity (Hökfelt et al., 1994). Indeed, after axotomy of the inferior alveolar nerve, there is a marked reduction in the total SP and CGRP expression in TG neurons (Elcock et al., 2001) and their release is largely enhanced by peripheral inflammation (Neubert et al., 2000). Conversely, the NPY and VIP levels are dramatically increased in axotomized TG neurons (Sasaki et al., 1994; Fristad et al., 1998). It is generally presumed that neuropeptides repressed after axotomy participate normally in sensory transmission while those induced may function as neurotrophic factors involved in the response to injury and in axonal regeneration (Nielsch & Keen, 1989). The axonal signals induced in response to nerve injury activate several signaling pathways of genes in the neuronal cell bodies that may lead to two opposing outcomes: cell death or regenerative response. In effect, peripheral nerve injury causes the surviving neurons to shift their activity away from normal maintenance and neurotransmission toward a regenerative state (Navarro, 2009). It is thought that changes in gene expression after axonal injury are due to a blockage of NGF retrograde axonal flow from the periphery to the cell body. This may explain why both high (TrkA) and low (p75) affinity neurotrophin receptor transcripts in the TG neurons increase after tooth injury (Wheeler et al., 1998)

As it can be inferred from Table 2, axotomy-induced alterations in the expression of neuroactive substances in MTN neurons include a long-lasting decrease (down-regulation) in the content of CaBPs, up-regulation of NO and some neurotrophins, and a *de novo* synthesis of certain neuropeptides, such as GAL, NPY and CGRP (see Lazarov, 2002, 2007, and references therein). A commonly shared view is that a characteristic of neuropeptides is the plasticity in their expression, reflecting the fact that release has to be compensated by *de novo* synthesis in the neuronal body (Navarro et al., 2007). It may be postulated that the newly synthesized neuropeptides can enhance MTN neuronal survival and neurite regeneration in the adaptive processes following nerve injury. Therefore, a peptide involvement in the proprioceptive function develops mainly in abnormal conditions. Navarro and co-workers (2007) also state that injured neurons respond by up-regulation of neurotrophins, either by autocrine or paracrine sources, and that additional exogenous supply of neurotrophic factors may further enhance the regenerative response of peripherally axotomized neurons. It should be noted that the survival of proprioceptors during the early postnatal period is probably dependent upon BDNF since its application to

the proximal stump of the transected masseteric nerve delays the loss of MTN neurons after the cut (Ichikawa et al., 2007). On the other hand, altered levels of CaBPs may be related to adequate cell body response since the sensitivity of damaged neurons to the intracellular

Neuroactive substance	Trigeminal ganglion Injury consequence	Mesencephalic trigeminal nucleus	Effect
Neurotransmitters			
NO	Upregulation	Upregulation	Cell death or defenc
Neuropeptides			
SP	Downregulation		
CGRP	Downregulation	De novo synthesis	Supportive role in
NPY	Upregulation	De novo synthesis	Cell protection
GAL	Upregulation	De novo synthesis	Cell regeneration
PACAP	Upregulation	De novo synthesis Increase in neurotrophin responsiveness	Increase in neurotrophin responsiveness
Calcium-binding proteins			
Parvalbumin (PV)	Downregulation	Downregulation	Cell defence
Calbindin D-28 (CB)	Downregulation	Downregulation	Cell survival
Neurotrophic factors and their receptors			
NGF	Upregulation	Upregulation	Peptide synthesis induction Enhancement membrane Enhancement of membrane potential oscillations
TrkA	Upregulation	Upregulation	Enhanced neuronal survival and maintenance
BDNF	Upregulation	Upregulation	Cell protection

Table 2. Summary of the injury-induced alterations in the expression of neuroactive substances and their effects on mammalian trigeminal primary afferent neurons

calcium concentration is different from that of intact ones. A logical explanation for the reported down-regulation in CaBP expression may be the actual reduction of the MTN cell number following periphery axotomy (Ichikawa et al., 2007). This would be in line with the suggestion that persistently increased levels of NOS in mesencephalic trigeminal neurons may be involved in slowly progressive nerve cell death following nerve damage because they may lead to an augmented vulnerability of the neurons to calcium-mediated

neurotoxicity. Alternatively, it is reasonable to speculate that the possible endogenous production of NO might underlie a defense mechanism of the neurons against nerve injury and, thus, improve survival and active regeneration of MTN neurons.

In summary, these findings provide compelling evidence that the content of the neurochemicals in both central and peripheral trigeminal primary afferent neurons is not static and their level may vary in case of marked changes in the environmental conditions, thus implying neuroplasticity as another major attribute of theirs.

5. Clinical relevance

Trigeminal primary afferent neurons have been the focus of intense research also because of their contribution to acute and chronic pain states, and the important role played by trigeminal nociceptive pathways in most clinically significant pain disorders. In response to trigeminal nerve activation, craniofacial pain symptoms can manifest as transient pain conditions as reported with toothaches and headaches, or can transform into more chronic pain conditions such as migraine, temporomandibular joint disorders or trigeminal neuralgia (Durham & Garrett, 2010). Apart from electrical activation, chemical activation of the trigeminal nerve leads to an afferent and efferent release of certain neuropeptides that facilitate peripheral inflammatory responses and causes activation of second-order neurons involved in pain transmission (Buzzi, 2001). Accumulating evidence suggests that CGRP and NO are involved in the underlying pathophysiology of all vascular headaches, the vast majority of which are associated with an inflammatory process. In particular, CGRP, a potent vasodilator and pro-inflammatory agent which is expressed by trigeminal nociceptors, has been identified as a key player in the pathomechanism of migraine headache (McCulloch et al., 1986). Clinical studies have also shown a clear association between the head pain and the release of CGRP, from the trigeminovascular system (for a review, see Edvinsson & Uddman, 2005). For example, during migraine attacks there is a marked increase in the plasma levels of CGRP and the administration of a recently developed CGRP blocker, BIBN4096BS, causes the headache to subside and the neuropeptide levels to normalize (Olesen et al., 2004). On the other hand, the efficacy of SER agonists for migraine therapy is known, and this amine, probably along with CGRP, has been hypothesized to be involved in trigeminal pain (Moskowitz et al., 1979) by activating 5-HT_{1B}, 5-HT_{1D} (Bonaventure et al., 1998; Wotherspoon & Priestly, 2000) and 5-HT_7 (Terrón et al., 2001; see also Classey et al., 2010) receptors. Indeed, the systemic administration of sumatriptan, the most-studied of the serotonergic drugs now collectively known as the triptans, lowers CGRP levels to nearly normal levels coincident with headache relief (Goadsby & Edvinsson, 1991). NO, an inflammatory mediator, is also currently thought of as a key molecule in migraine pain, possibly in concert with CGRP (Thomsen & Olesen, 1996). Results from animal studies have provided evidence for the involvement of NO in sensitation and/or activation of the trigeminovascular system and repressed release of CGRP from trigeminal neurons in response to treatment with NO donors or application of the anti-migraine drug sumatriptan, which has affinity for 5-HT_{1B}, 5-HT_{1D} and 5-HT_{1F} receptors (Bellamy et al., 2006). It seems likely that NO production and neuropeptide release are functionally linked in severe vascular headaches. Conversely, SP, which along with CGRP is the most definitely characterized peptide in the TG, is not released in the cranial blood flow in migraine suggesting that SP does not take part in vascular nociception in man

(Holthusen et al., 1997). It has recently been demonstrated that SP release in the TG is predominantly increased after orofacial inflammation (Neubert et al. 2000) and such a release may play an important role in determining the trigeminal inflammatory alloying concerning the temporomandibular joint disorder (Takeda et al., 2005). The authors point out that NK1 receptor antagonists may be useful as therapeutic agents to prevent the mechanical allodynia. $P2X_3$ receptors may be another therapeutic target for treating temporomandibular joint disorder pain (Shinoda et al., 2005).

Another common clinical concern regarding the trigeminal nerve is trigeminal neuralgia. Evidence for the role of SP and CGRP in trigeminal neuralgia pain is clearly apparent (Stoyanova & Lazarov, 2001). Inhibitory neurotransmitters, such as GABA, are thought to have a role in analgesia and many GABAergic drugs, acting through metabotropic $GABA_B$ receptors, are useful in the treatment of migraine and trigeminal neuralgia. With regard to the latter, a GABA analogue, gabapentin, has been reported to be effective in the management of migraine and trigeminal neuralgia, and also displays anti-nociceptive activity in various animal pain models. In addition, a selective $GABA_B$ receptor agonist, baclofen, has been shown to elicit pain relief and, thus, it might play a therapeutic role in the inhibition of nociceptive hypersensitivity in trigeminal neuralgia (Fromm, 1994).

Clinically relevant is also pain, caused by a central or peripheral nerve lesion which is commonly termed neuropathic pain, and the concomitant neurogenic inflammation. Orofacial neuropathic pain, like anywhere in the body, may occur as a result of tissue damage and the activation of nociceptors, which transmit a noxious stimulus to the brain (Vickers & Cousins, 2000). The abnormal facial pain involves regeneration of damaged nerve fibers and may account for chemical changes in injured neuronal cell bodies. As mentioned above, a variety of neuropeptides, such as SP, CGRP, GAL and NPY, are up-regulated following peripheral axotomy (see Table 2) and craniofacial muscle inflammation (Ambalavanar et al., 2006). Results from studies on animal pain models have suggested that NPY and its receptors are potential targets for treatment of pain, especially neuropathic pain (Silva et al., 2002). The efficacy of opioid receptor agonists in modulation of nociceptive inputs in a wide range of orofacial pain models, including neuropathic pain (Catheline et al., 1998) and inflammatory pain (Ko et al., 1998) is also acknowledged. Given that NGF is responsible for the increased expression of SP and CGRP during neurogenic inflammation (Lundy & Linden, 2004), it is not much surprising that the systemic administration of anti-NGF neutralizing antibodies prevents the up-regulation of neuropeptides in primary afferent neurons innervating the inflamed skin (Woolf et al., 1994). Changes in the injured neurons can also influence the ability of the surrounding glial cells to release neuromodulators such as NO and ATP, thus implicating satellite glial cells in the TG as a determinant of orofacial neuropathic pain. This fits well with the notion that the $P2X_3$ receptor is transiently up-regulated and anterogradely transported in trigeminal primary afferent neurons after neuropathic injury (Eriksson et al., 1998). Purinergic receptors on TG neurons are thus likely to be a legitimate target for therapeutic intervention in neuropathic pain and orofacial inflammation (Ambalavanar et al., 2005). Recent findings further demonstrate that masseter inflammation differentially modulates Glu receptor subunits and that the induced changes in them may contribute to functionally different aspects of craniofacial muscle pain processing under inflammatory conditions (Lee and Ro, 2007).

6. Concluding remarks

Based on the information now available, it has become evident that miscellaneous transmitter candidates are associated with a subset of trigeminal primary afferent neurons and, besides, these are well-innervated by aminergic, peptidergic and nitrergic fibers of a probable extrinsic origin. The data also suggest that some classical neurotransmitters and neuropeptides not only mediate trans-synaptic information coding but can also act as long-term morphogenetic signals and trophic factors. Progressive discovery of the multiplicity of chemical messengers, of coexistent transmitters (or transmitter candidates), their receptors and transducing mechanisms, and of local mechanisms for transmitter release, has reinforced the view that chemical coding in trigeminal primary afferent neurons, either peripherally or centrally, is multiple, heterogeneous, plastically varying and characterized by a wide spectrum of co-existing messenger substances. In line with similar morphological features and trophic factor requirements, as well as diverse central and peripheral targets, and physiological properties, we show that TG and MTN neurons have both similarities and differences in their neurochemical content. On the one hand, the most important similarity relates to the fact that both central and peripheral trigeminal primary afferent neurons express, indeed to a varying degree, classical transmitters and neuronal markers, such as calcium-binding proteins. On the other hand, the most marked spatial difference is the presence of certain neuropeptides in the TG cell bodies and their absence in the MTN neuronal somata under normal conditions. As argued before, we believe that the differently fated embryonic migration, synaptogenesis, and peripheral and central target field innervation can possibly affect the individual neurochemical phenotypes of trigeminal primary afferent neurons.

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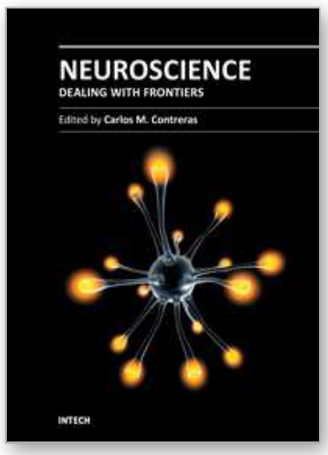

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The Neuronal Doctrine recently reached its 100th year and together with the development of psychopharmacology by the middle of 20th century promoted spectacular developments in the knowledge of the biological bases of behavior. The overwhelming amount of data accumulated, forced the division of neuroscience into several subdisciplines, but this division needs to dissolve in the 21st century and focus on specific processes that involve diverse methodological and theoretical approaches. The chapters contained in this book illustrate that neuroscience converges in the search for sound answers to several questions, including the pathways followed by cells, how individuals communicate with each other, inflammation, learning and memory, the development of drug dependence, and approaches to explaining the processes that underlie two highly incapacitating chronic degenerative illnesses.

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