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Review Article

Neuropeptides and ATP signaling in the trigeminal ganglion

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Summary Peripheral nociceptive stimuli from orofacial structures are largely transmitted by the trigeminal nerve. According to the peripheral noxious stimuli, neurons in the trigeminal ganglion (TG) produce neuropeptides such as substance P, and calcitonin-gene-related peptide, etc. Beside the production of neuropeptides, there exists unique non-synaptic interaction system between maxillary and mandibular neurons in the TG. Neurons in the TG are surrounded by satellite glial cells (SGCs), which initially receive the signal from TG neurons. These activated SGCs secrete a transmitter to activate adjacent SGCs or TG neurons, thereby amplifying the signal, for example, from mandibular neurons to maxillary neurons in the TG. Similar to the dorsal root ganglion, in the TG, microglia/macrophage-like cells (MLCs) are activated by uptake of a transmitter from TG neurons or SGCs. This communication between neurons, SGCs, and MLCs results in responses such as ectopic pain, hyperesthesia, or allodynia. The focus of this review is the cooperative interaction of the maxillary and mandibular nerves in the TG by neuropeptides, and adenosine 3′-phosphate (ATP) signaling from neurons to SGCs and MLCs. Stimulated neurons either secrete ATP by means of vesicular nucleotide transporters, or secrete neuropeptides from the neuronal cell body to mediate signal transmission.

Abbreviations: TG, trigeminal ganglion; DRG, dorsal root ganglion; SGC, satellite glial cell; MLC, microglia/macrophage-like cell; ATP, adenosine 3′-phosphate; VNUT, vesicular nucleotide transporter; SP, substance P; CGRP, calcitonin-gene-related peptide; VIP, vasoactive intestinal peptide; PACAP, pituitary adenylate-cyclase-activating polypeptide receptor type 1.

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Contents

1. Introduction

Peripheral nociceptive stimuli from intra- and extra-oral structures are largely transmitted by the trigeminal nerve. The primary afferent neurons of the trigeminal nerve are mainly located in the trigeminal ganglion (TG) and partially localized in the mesencephalic trigeminal nucleus in the brain stem. The trigeminal nerve consists of three main branches: the ophthalmic (V1), maxillary (V2), and mandibular (V3) nerves, each of which provides somatosensory innervation of a specific region of the head. Trigeminal nerve neurons are pseudounipolar and are distributed within distinct areas of the TG. In the rat, the neuronal distribution is evident in the rostral and caudal regions of the TG [1].

Neuropathic pain caused by peripheral nerve injury is common following procedures such as tooth extraction and often leads to ectopic orofacial pain [2] via two possible mechanisms. The first is related to the coincidental cross-migration of V2 and V3 neurons such that they are found outside their respective regions. In fact, some V2 neurons are located in the region of V3 neurons and vice versa. Alternatively, neurotransmitters secreted by damaged neuron affect not only adjacent neurons but also neurons in other regions.

The signal from TG neurons is initially transmitted to the surrounding satellite glial cells (SGCs) via the gap junctions between them [3]. Neurotransmitters secreted in TG neurons may also act on SGCs through the latter's surface receptors. SGCs activated by TG neurons secrete transmitters, which act on adjacent SGCs or TG neurons and result in signal amplification, including from the region of V3 neurons to that of V2 neurons. In addition, as in the dorsal root ganglion (DRG), responses such as hyperesthesia or allodynia are enhanced by microglia distributed in the TG that are activated by neurotransmitters released by TG neurons or SGCs.

The focus of this review is the molecular signaling from TG neurons to SGCs and from SGCs to other cells, including other TG neurons, SGCs, and microglia/macrophage-like cells (MLCs). We also discuss the signaling molecules used by these cells, particularly neuropeptides and adenosine 3′-phosphate (ATP), and the possible role of the non-synaptic interaction system between maxillary and mandibular neurons in TG.

2. Neuropeptides in TG neurons

Neurons of the TG secrete several different neuropeptides, including substance P (SP), calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), pituitary adenylate-cyclase-activating polypeptide receptor type 1 (PACAP), neuropeptide Y (NPY), and somatostatin (SS). These neuropeptides are present in neurons, and by acting as neuromediators or neuromodulators, are involved in signal transmission. The neuropeptides in the TG were previously well reviewed by Lazarov [4]; here we present several recent findings on this group of signaling molecules.

2.1. Substance P

As a member of the tachykinin family of neuropeptides, SP is distributed not only in neurons but also in the cells of peripheral tissues [5,6]. Accordingly, its effects are not limited to the nervous system but are more extensive. In the TG, >99% of the nerve fibers that store SP are unmyelinated, and most are small and medium-sized neurons (cross-sectional area <800 m^2) [7]. In untreated animals, SP-containing cells with diameters of 15—50 μm are distributed throughout the TG and comprise 10—30% of all TG cells [8]. SP-containing afferents are unmyelinated C-fibers in which SP is secreted from both central and peripheral nerve terminals [9]. Although SP can be released from terminals within the brain stem and peripheral tissues, its transport is mostly to the latter [10]. SP in TG neurons may be associated with neurogenic inflammation, a tissue reaction that develops in acute conditions such as wound repair, in which damaged TG neurons release SP, resulting in a temporal decrease in SP-immunoreactive (IR) neurons. The injury of peripheral neurons induces an increase in SP production; however, the increase in the proportion of SP-IR neurons occurs not only in the maxillary nerve but also in mandibular nerves (Fig. 1). Because primary afferent neurons in TG are anatomically isolated from one another and not synaptically interconnected, other means of interaction must exist between maxillary and

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