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Review

Signal processing at mammalian carotid body chemoreceptors

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ABSTRACT

Mammalian carotid bodies are richly vascularized chemosensory organs that sense blood levels of O_2, CO_2/H^+, and glucose and maintain homeostatic regulation of these levels via the reflex control of ventilation. Carotid bodies consist of innervated clusters of type I (or glomus) cells in intimate association with glial-like type II cells. Carotid bodies make afferent connections with fibers from sensory neurons in the petrosal ganglia and receive efferent inhibitory innervation from parasympathetic neurons located in the carotid sinus and glossopharyngeal nerves. There are synapses between type I (chemosensory) cells and petrosal afferent terminals, as well as between neighboring type I cells. There is a broad array of neurotransmitters and neuromodulators and their ionotropic and metabotropic receptors in the carotid body. This allows for complex processing of sensory stimuli (e.g., hypoxia and acid hypercapnia) involving both autocrine and paracrine signaling pathways. This review summarizes and evaluates current knowledge of these pathways and presents an integrated working model on information processing in carotid bodies. Included in this model is a novel hypothesis for a potential role of type II cells as an amplifier for the release of a key excitatory carotid body neurotransmitter, ATP, via P2Y purinoceptors and pannexin-1 channels.

Contents

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1. Introduction

Peripheral arterial chemoreceptors, located principally in the carotid bodies play an important role in the maintenance of homeostasis in the respiratory and cardiovascular systems. The paired carotid bodies are located at the bifurcation of the common carotid artery where they sample the chemical composition of arterial blood [1]. These organs act as polymodal chemoreceptors that detect a variety of blood-borne chemicals, including low oxygen (hypoxia), high CO_2/H^+ (acid hypercapnia), and low glucose (hypoglycemia). During chemoexcitation, afferent nerve impulses travel along the carotid sinus nerve and are relayed to the nucleus tractus solitarius in the brainstem. Here, afferent signals from carotid bodies are integrated with neural circuitry that regulates breathing. Thus, during hypoxemia the resulting increase in carotid sinus nerve afferent discharge leads to corrective changes in ventilation and restores normal blood oxygen levels [1,2].

The output from the carotid body, i.e., the frequency and pattern of the carotid sinus nerve discharge, is shaped by the actions of several neurotransmitters and neuromodulators that act on ionotropic and metabotropic receptors in the carotid body [3–6]. It is generally agreed that the carotid body consists of aggregates of several functional units or "glomoids". Each aggregate comprises convoluted blood vessels closely associated with innervated clusters of chemoreceptor cells (i.e., glomus, or type I cells). Glomus cells are enveloped by glia-like, sheath cells (i.e., sustentacular, or type II cells) [7]. Chemical and electrical synapses among these elements, together with the presence of several neurochemicals and their receptors in type I cells and/or sensory terminals, allow for complex sensory processing in the carotid body. This processing involves synaptic as well as autocrine–paracrine signaling pathways.

The first part of this review will highlight our current understanding of some of these signaling pathways, gaps in knowledge, and controversies surrounding the actions of some neurochemicals. The participation of neuropeptides in carotid body signaling, including endothelin-1 (ET-1), substance P, angiotensin II, and pituitary adenylate cyclase-activating polypeptide (PACAP), is becoming increasingly important, as discussed elsewhere [6,8–10]. However, in this review, our emphasis will be mainly on interactions involving small molecule neurochemicals. We will consider fast synaptic transmission mediated via ligand-gated receptors, autocrine–paracrine signaling via G-protein coupled receptors, and the inhibitory role of the gasotransmitter nitric oxide (NO) that is released by autonomic efferent nerves. Finally, we will re-visit a topic that has received comparatively little attention, namely the physiological role of the glia-like type II cells in carotid body function. In particular, we consider the novel hypothesis that type II cells may be active participants during paracrine signaling and contribute to excitatory purinergic neurotransmission by amplifying ATP release via pannexin-1 channels.

2. Anatomy and histology of the carotid body

As illustrated schematically in Fig. 1A, the mammalian carotid body consists of clusters of parenchymal chemoreceptor type I (glomus) cells interdigitated by glia-like type II cells. Type I cells are innervated via the carotid sinus nerve by sensory afferent nerve terminals whose cell bodies lie in the petrosal ganglion. Penetrating

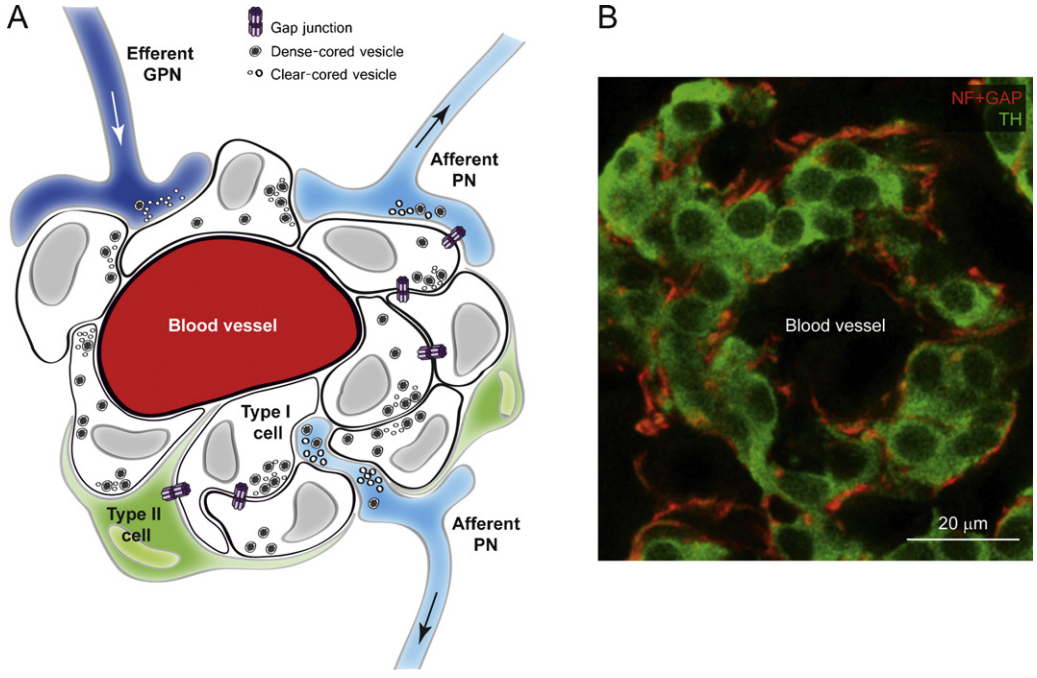

Fig. 1. Anatomical organization and innervation of the carotid body. (A) Schematic representation showing the innervation of chemoreceptor (type I) cell clusters by afferent fibers from petrosal neurons (PNs) and efferent fibers from the glossopharyngeal nerve (GPN). Note the intimate association of type I cells with type II cells and their close proximity to blood vessels. Gap junctions may occur between neighboring cells. (B) Confocal section of a 2 week-old rat carotid body immunostained for neurofilament (NF)/GAP-43 that labels sensory nerve fibers and terminals (red), and tyrosine hydroxylase (TH) that labels mainly type I cells (green).
Adapted from [5].