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Review

Immunosensory signalling by carotid body chemoreceptors☆

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ABSTRACT

Injections of lipopolysaccharide (LPS) have been used to produce the signs of sepsis and study their underlying mechanisms. Intravenous (IV) injections of LPS in anesthetized cats induce tachypnea, tachycardia and hypotension, but ventilatory changes are suppressed after sectioning carotid and aortic nerves. Otherwise, LPS increases the basal frequency of carotid chemosensory discharges, but reduces ventilatory and chemosensory responses to hypoxia and nicotine injections. Increases in cytokines (IL-1β, IL-6 and TNF-α) are observed in plasma and tissues after injecting LPS. In carotid bodies perfused *in vitro*, TNF-α reduces chemosensory discharges induced by hypoxia. The rat carotid body and its sensory ganglion constitutively express LPS canonical receptor, TLR4, as well as TNF-α and its receptors (TNF-R1 and TNF-R2). Increases of TNF-α and TNF-R2 expression occur after LPS administration. The activation of peripheral and central autonomic pathways induced by LPS or IL's is partly dependent on intact vagus nerves. Thus, the carotid and vagus nerves provide routes between the immune system and CNS structures involved in systemic inflammatory responses.

1. Introduction

The "Systemic Inflammatory Response Syndrome" (SIRS) is defined by consensus as the presence of two or more of the following signs: hyperthermia, tachypnea, tachycardia and leukocytosis; a syndrome further recognized as "sepsis", in case of proven or suspected microbial etiology; if complicated by hypotension, it is named "severe sepsis" (ACCP/SCCM, 1992). The mechanisms giving way to these clinical and laboratory signs have received much attention.

Lipopolysaccharide (LPS), a constituent of the outer membrane from Gram-negative bacteria, has been assayed extensively as a potent inflammogen to induce SIRS in experimental animals, since this endotoxemia represents a model of sepsis without an actual infection focus (Freise et al., 2001). Particular attention has been paid to the roles played by pro-inflammatory cytokines, especially interleukins IL-1β and IL-6, as well as tumor necrosis factor-alpha (TNF-α). An intravenous (IV) infusion of LPS in cats rapidly increases plasma levels of TNF-α (Otto and Rawlings, 1995), a potent pro-inflammatory cytokine released by immune cells. High increases in plasma levels of TNF-α have been reported after IV administration of LPS in humans (Michie et al., 1988; Ottaway et al., 1998), IV and intraperitoneally (IP) in rats (Asari et al., 1996) and IV in adult cows (Ohtsuka et al., 1997).

The effects of LPS may result from either direct actions of pro-inflammatory cytokines on central nervous system (CNS) structures responsible for the SIRS manifestations, or they may be mediated by activation of autonomic afferent pathways (Dantzer et al., 2000). In particular, it has been reported that IP administration of LPS in rats stimulates vagal primary afferent fibers (Goehler et al., 1997, 1999), which mediate the activation of CNS structures and functions (Gaykema et al., 2007; Marvel et al., 2004; Borsody and Weiss, 2005); but, it has been also reported that efferent vagal stimulation or application of its transmitter ACh attenuates TNF-α release (Borovikova et al., 2000; van Westerloo et al., 2006). Because of its rich vascularization and abundant chemosensory innervation (see Verna, 1997), the carotid bodies are also attractive candidates to serve as peripheral detectors of immunogenic agents in the blood.

The arterial chemoreceptor system is composed of the carotid and the aortic bodies. Each carotid body is innervated by the carotid (sinus) nerve, branch of the glossopharyngeal nerve, and with the perikarya of its sensory fibers located in the petrosal ganglion. The aortic bodies are innervated by the aortic (depressor) nerves, branches from the vagus nerves, and with the perikarya of their sensory fibers located in the nodose ganglia. We assume that the observations here reported on carotid bodies also apply to the aortic bodies.

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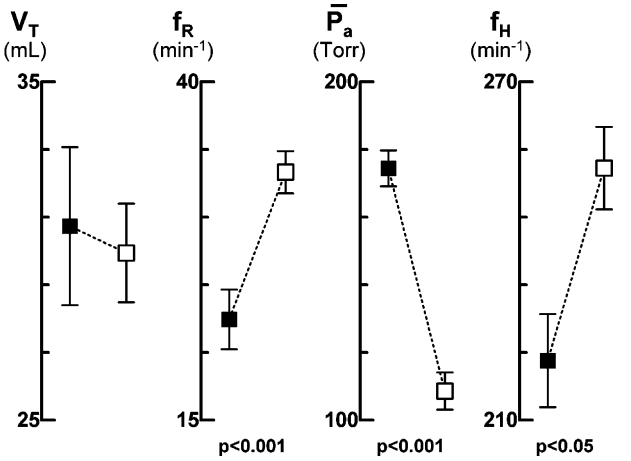

Fig. 1. Effects of LPS on cardio-respiratory variables. Data obtained from recordings in cats under control conditions (filled squares) and after 30–90 min of IV infusion of LPS 750 μg/kg (open squares). V_T, tidal volume; f_R, respiratory frequency; $\overline{P_a}$, mean arterial pressure; f_H, heart frequency. Means ± SEM's; $n = 9$. Statistical differences ascertained by Mann–Whitney tests. Illustration prepared from part of the data presented as Table 2 in Fernández et al. (2008).

2. Effects of LPS administration in cats and rats

We (Fernández et al., 2008) found that a 20-min IV infusion of LPS (for a total of 750 μg/kg) in pentobarbitone-anesthetized cats induced tachypnea, tachycardia and systemic hypotension, thus reproducing characteristic elements of septic shock. This is summarized in Fig. 1. It is worth mentioning that LPS infusion did not affect ventilation in cats previously subjected to bilateral carotid and aortic neurotomies. Furthermore, topical application of 2 μg LPS to the surface of both CBs (with their innervation intact) elicited tachypnea.

When carotid nerve impulses were recorded in these animals, an increase in the basal frequency of chemosensory impulses (f_χ) occurred very shortly after the IV administration of LPS, which was maintained for several hours, as represented by the filled bars in Fig. 2.

Above results suggest that excitation of carotid body chemoreceptors may mediate some of the manifestations of severe sepsis. Although increased body temperature is a prominent element of SIRS, our cats could not exhibit such response because they were anaesthetized and externally thermoregulated.

Our results differ from those reported by Tang et al. (1998). They observed that LPS injected IV in rats produced tachypnea and tachycardia within 2 h, and hypotension after 4 h, a similar time course than that observed in our cats. However, they reported that the tachypneic response was suppressed by previous bilateral cervical vagotomy, while – on the contrary – previous denervation of peripheral chemoreceptors (by combined carotid and aortic neurotomies) accelerated the hyperventilatory response to LPS. Thus, they conclude that LPS-induced hyperventilation is mediated by excitation of lung vagal afferences and that it is restrained by arterial chemoreflexes. However, all these rats were ventilated by a mixture of air enriched in O_2 (50%) along all procedures, thus reducing arterial chemoreceptors contribution to ventilatory regulation. Otherwise, the series of previously vagotomized rats presented a permanently reduced respiratory rate and enhanced tidal volume, as expected from the elimination of Hering-Breuer's vagally mediated self-steering.

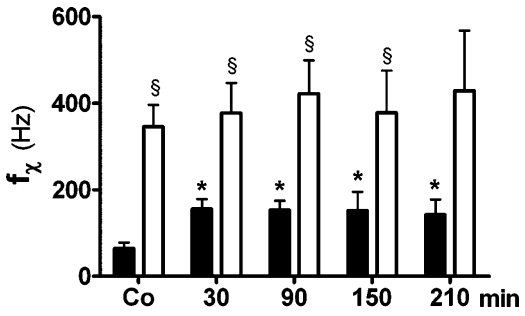

Fig. 2. Effects of LPS on carotid chemosensory activity. Frequency of chemosensory discharges (f_χ) recorded from the carotid (sinus) nerve under control conditions (Co) and after 30, 90, 150 and 210 min of IV administration of LPS 750 μg/kg. Filled bars, basal rates under resting conditions; empty bars, maximal rates obtained shortly after IV administration of nicotine bitartrate 200 μg/kg. Means + SEM's; $n = 4$. Statistical differences ascertained by repeated measures ANOVA followed by Bonferroni's multiple comparisons test ($^*p < 0.05$ *vs.* Co), and by two-ways ANOVA followed by Bonferroni post-test ($^§p < 0.05$ *vs.* basal f_χ).

Shen et al. (2004) observed lethal hypotension in rats given LPS 50 mg/kg IV, but those rats which had been subjected to sino-aortic denervation died consistently earlier than those subjected to sham operation. They attributed this shorter survival time to absence of baroreceptor function, which may indeed contribute to it, but they did not take into consideration that sino-aortic denervated rats were also deprived of arterial chemoreceptor function.

Gaykema et al. (1998) observed that the IP administration of LPS in rats induced rapid activation of vagal sensory fibers perikarya located in nodose ganglia, as shown by the expression of the marker c-Fos, but that such immunolabelling was absent if rats had been subjected to subdiafragmatic vagotomy before LPS injection. They also studied the increased c-Fos activity in rats treated with LPS IV, an increase which was reduced but not eliminated by previous subdiafragmatic vagotomy. But, in this case, vagal nodose ganglion cells should still be connected through the aortic nerve to the aortic bodies, another site of activation accessible to IV LPS.

Hermann et al. (2001) observed that c-Fos activation of solitary tract nuclei (STN) increased by 4.2 times after administering LPS 1 mg/kg IV in rats, but that increase was only by 2.7 times when LPS was given after ipsilateral cervical vagotomy. These observations lessen the importance of vagal afferences for activation of STN and further propose that these nuclei themselves were a primary central nervous detector of cytokines. Our observations may offer another explanation: that the carotid bodies chemoreceptor input to the CNS provides an alternative route for the access of inflammatory signals from the periphery to the CNS centers involved in the production of the manifestations of severe sepsis.

In spite of the increased basal carotid chemosensory activity induced by LPS, animals showed decreased ventilatory reflex responses to IV injections of nicotine and brief hypoxic (100% N_2 for 10 s) exposures (Fernández et al., 2008). As represented by the empty bars in Fig. 2, maximal frequencies in carotid chemosensory discharges induced by injections of high doses of nicotine (or hypoxic exposures) were not significantly different from those attained under control conditions, meaning that chemosensory responses (maximal f_χ – basal f_χ) to these stimulants were reduced (Fernández et al., 2008). This may indicate that animals subjected to endotoxemia – while maintaining an enhanced chemosensory discharge level and tonic state of chemoreflex ventilation – are liable to reduced transient chemosensory and chemoreflex ventilatory responses to excitatory stimuli.

An analysis of the frequency of spontaneous gasps (sighs) occurring in our cats before and after LPS administration (not included in our previous report) reveals that such frequency was enhanced in 4 cats, reduced in 2 and not significantly changed in 3 cats, when carotid nerves were intact along the procedure. However, 5 out of 6 cats – in which one or both carotid nerves had been sectioned – showed an increased frequency of gasps. It is well known that gasps are reflex responses originated from excitation of rapidly adapting pulmonary mechanoreceptors and conveyed via vagal afferences

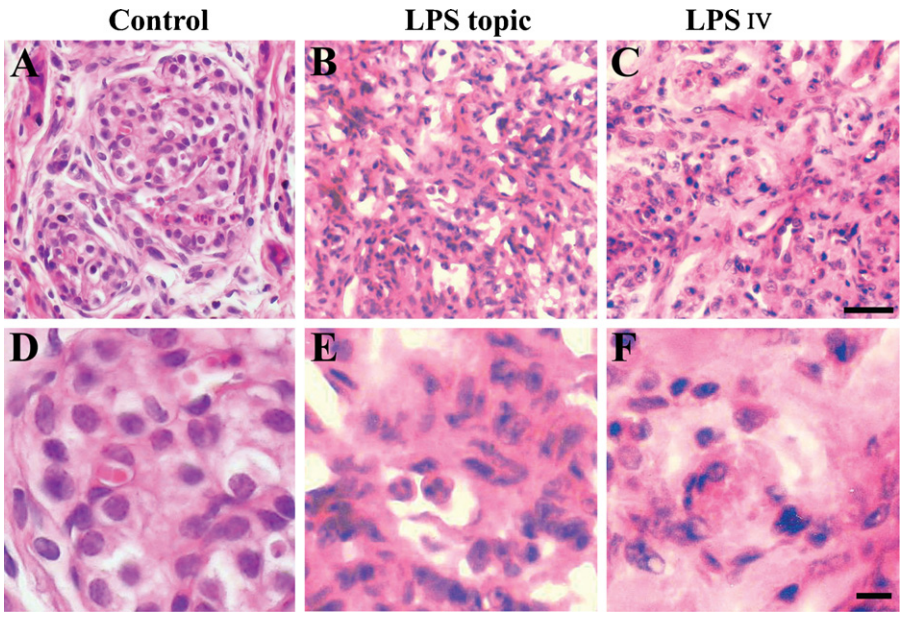

Fig. 3. Effects of LPS on carotid body structure. Histological sections from cat carotid bodies obtained in control condition (A and D), excised after 5 h of topical application of 2 μg LPS upon carotid body surface (B and E), and excised 5 h after IV infusion of 750 μg/kg LPS (C and F). Scale bar, 60 μm in A, B and C, and 10 μm in D, E and F. Haematoxylin and Eosin staining. Photomicrographs kindly provided by Prof Sergio González, Dept. Pathology, Faculty of Medicine, P. Catholic University of Chile.

(Reynolds, 1962). Therefore, it is possible that an increased rate of spontaneous gasps would result from excitation of these lung receptors by the cytokines involved in LPS-induced inflammation.

Otherwise, it has been previously reported that the section of carotid nerve afferences reduces consistently the incidence of spontaneous gasps (Zuazo and Zapata, 1980). But, the important increase in gasp frequency observed after LPS administration in carotid denervated cats (here reported) indicates that this restraint is overcome by the enhancement of the pulmonary reflex responsible for spontaneous gasps.

Our post-mortem histological studies of the carotid bodies revealed disorganization of glomic lobules and increased intralobular connective tissue (see Fig. 3), as well as marked increase in polymorphonuclear cells, mainly attached to blood vessels (Fernández et al., 2008). This histological picture resembles that of carotid body inflammation (glomitis) described in humans (Heath and Smith, 1992).

3. Pro-inflammatory receptors in carotid body tissue

With regard to pro-inflammatory cytokines, it has been shown that IL-1β injections depolarize glomus cells and increase their $[Ca^{2+}]_i$ (Shu et al., 2007), and increase the expression of tyrosine-hydroxylase (TH), the rate limiting enzyme for catecholamine synthesis, in rat carotid bodies (Zhang et al., 2007). Increased $[Ca^{2+}]_i$ in cultured glomus cells and catecholamine release have been also reported in response to IL-6 application (Fan et al., 2009).

Responses described above may be explained by the observations that glomus cells from rat carotid body express interleukin-1 (IL-1) receptor type I (IL-1RI) (Wang et al., 2002; Zhang et al., 2007), and IL-6 receptor α (Wang et al., 2006). The expression of IL-1RI in rat carotid body is up-regulated after IP injection of IL-1β (Zhang et al., 2007). Cell elements between glomus cells clusters, probably sustentacular cells, were also weakly stained for IL-1RI (Zhang et al., 2007). It has also been reported that well characterized sustentacular cells of adrenal medulla and paragangliomas show immunostaining for TNF-α and IL-6 (Kontogeorgos et al., 2002).

We (Fernández et al., 2008) reported that the cat carotid body expresses both messenger RNA's for TNF-R1 and TNF-R2 receptors. Furthermore, positive immunoreactivity for TNF-α protein and TNF-R1 was found in glomus cells cytoplasm, and in capillary endothelial cells of the carotid body. These observations suggest that TNF-α and TNF-R1 proteins are constitutively expressed in the cat carotid body.

More recently, Fernández et al. (2011) determined that the rat carotid body and nodose-petrosal-jugular ganglion complex express LPS canonical receptor, Toll-like receptor 4 (TLR4), as well as TNF-α and its receptors (TNF-R1 and TNF-R2). LPS administration (15 mg/kg IP) evoked myeloid differentiation gene 88 (MyD88)-dependent pathway activation of nuclear factor (NF)-κB p65 and mitogen-activated protein kinases (p38 MAPK and ERK) in both structures. Furthermore, LPS consistently increased TNF-α and TNF-R2 at these sites. Double-labeling studies showed that the aforementioned increases occurred in TH(+) cells of carotid body and nodose-petrosal-jugular ganglion complex, corresponding to the dopaminergic chemosensitive pathway. It had previously been reported that rat nodose ganglion expresses TLR4 mRNA and protein (Hosoi et al., 2005). Thus, the increased TNF-α and TNF-R2 expression in arterial chemoreceptor pathways results from LPS acting directly through TLR4/MyD88-dependent mechanisms. Therefore, it is possible that LPS (and other immunogens) may induce the release of TNF-α, locally synthesized in carotid body cells, which – acting as autocrine or paracrine factor – may in turn modify chemoreceptor function.

Fig. 4 summarizes data available on cytokines effective upon carotid body glomus cells, identified pro-inflammatory receptors, and well-known synaptic transmitters in the carotid chemoreceptor complex.

4. Effects of TNF-α on carotid body chemosensory activity

Because of above considerations, we (Fernández et al., 2008) tested the effects of TNF-α on chemosensory activity recorded from cat's carotid bodies perfused-superfused *in vitro*. Increasing doses of TNF-α injected through the perfusing line failed to modify the chemosensory activity recorded under normoxic conditions (PO_2 *ca.* 100 Torr). However, when high frequencies of chemosensory responses were maintained by perfusing the preparation with a

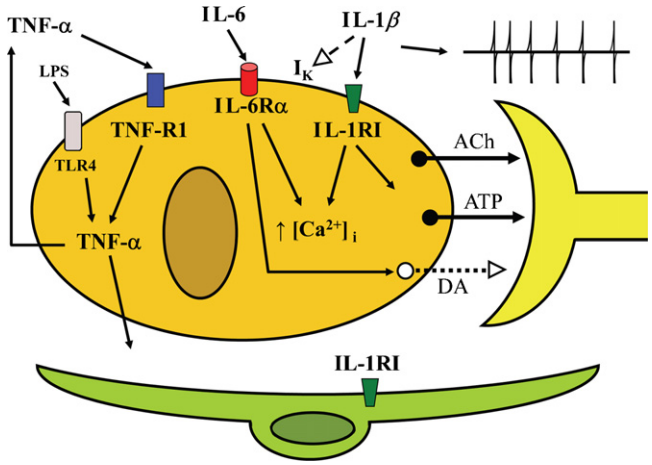

Fig. 4. Sites of action of immunogen and cytokines on arterial chemoreceptor complex. Schematic drawing of carotid body elements: glomus cell (in orange), sustentacular cell (in green) and carotid chemosensory nerve ending (in yellow). To the right, well accepted synaptic transmitters between glomus cell and nerve ending: acetylcholine (ACh), ATP and dopamine (DA), the first two excitatory and the last one inhibitory. In upper part, cytokines confirmed to be effective upon glomus cells and/or chemosensory activity: interleukin 1-beta, interleukin 6, and tumor necrosis factor alpha. Cytokines receptors known to be present in glomus cells are also shown. Chemosensory nerve discharge, in upper right corner. For abbreviations, see text.

hypoxic solution (PO_2 *ca.* 30 Torr), intrastream injections of TNF-α induced transient falls in the (enhanced) frequency of carotid nerve chemosensory impulses. These reductions in nerve discharges were dose-dependent on the range 0.2 pg to 100 ng of TNF-α, as illustrated in Fig. 5.

The depressant effects of TNF-α on carotid chemosensory activity enhanced by hypoxic conditions, described above, may result from direct effects of TNF-α on glomus cells (endowed with TNF-α receptors) or from indirect effects mediated by release of dopamine from glomus cells, an effective inhibitory transmitter between these cells and chemosensory nerve endings (Zapata, 1975; Zapata et al., 2000). In this respect, it is known that TNF-α increases both basal and K^+-induced dopamine release in the dopaminergic hypothalamic-pituitary axis (De Laurentis et al., 2002). The rapid enhancement of TH expression in carotid body tissues after IP injection of IL-1β (Zhang et al., 2007) suggests that pro-inflammatory cytokines promote dopamine release from gloms cells, thus reducing or eliminating the increases in carotid chemosensory nerve activity in response to chemoreceptor stimulants.

Clusters of glomus cells are also observed at the superior laryngeal nerve bifurcation from the vagus nerve, immediately below the nodose ganglion. MacGrory et al. (2010) recorded isolated vagal fibers innervating those cells and observed that IL-1β and TNF-α had no statistically significant effect on the frequency of action potentials, while NaCN was a highly effective stimulant. However, they did not study the effect of TNF-α on the preparation subjected to hypoxic stimulation.

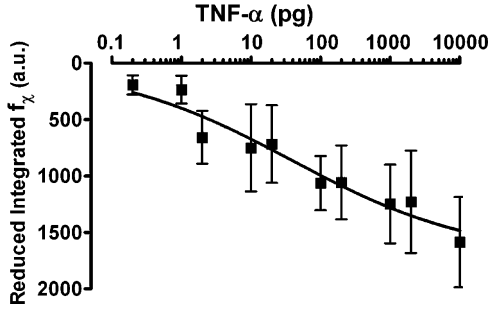

Fig. 5. Depressant action of TNF-α on carotid chemoreceptor activity excited by hypoxia. Carotid bodies perfused-superfused *in vitro*. Effects of increasing doses of TNF-α (abscissa in logarithmic scale) applied through perfusion line during hypoxic stimulation of preparations (PO_2 30 Torr). Reductions of chemosensory discharge (ordinate) expressed as arbitrary units (a.u.) of integrated area under the curve of hypoxic f_χ level. Values, means ± SEM's; $n = 5$. Curve fitted to sigmoid function.

5. Concluding remarks

Most of the observations presented above indicate that carotid bodies not only serve as detectors of the levels of normal constituents of the blood, but that they also are capable of recognizing the presence of immunogens and cytokines in the blood. Thus, they provide an alternative route to vagal afferences for signalling between the immune system and the central nervous system structures involved in the organization of the systemic inflammatory response syndrome (SIRS).

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