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Acute Inhibition of Inflammation Mediated by Sympathetic Nerves: The Inflammatory Reflex

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Abstract
In this review, we will try to convince the readers that the immune system is controlled by an endogenous neural reflex, termed inflammatory reflex, that inhibits the acute immune response during the course of a systemic immune challenge. We will analyse here the contribution of different sympathetic nerves as possible efferent arms of the inflammatory reflex. We will discuss the evidence that demonstrates that neither the splenic sympathetic nerves nor the hepatic sympathetic nerves are necessary for the endogenous neural reflex inhibition of inflammation. We will discuss the contribution of the adrenal glands to the reflex control of inflammation, noting that the neurally mediated release of catecholamines in the systemic circulation is responsible for the enhancement of the anti-inflammatory cytokine interleukin 10 (IL-10) but not of the inhibition of the pro-inflammatory cytokine tumour necrosis factor α (TNF). We will conclude by reviewing the evidence that demonstrates that the splanchnic anti-inflammatory pathway, composed by preganglionic and postganglionic sympathetic splanchnic fibres with different target organs, including the spleen and the adrenal glands, is the efferent arm of the inflammatory reflex. During the course of a systemic immune challenge, the splanchnic anti-inflammatory pathway is endogenously activated to inhibit the TNF and enhance the IL-10 response, independently, presumably acting on separate populations of leukocytes.

Introduction

Our body is able to defeat and overcome infections and injuries thanks to the ability of the immune system to activate humoral and cell-mediated responses starting with the development of an inflammatory response [1]. An impaired immune function means that the body cannot respond to the immune challenge causing, therefore, distress to all the other systems of the body and, in extreme cases, compromising their ability to support basic life functions. On the other hand, an exaggerated inflammatory response is also dangerous because it has

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the potential to damage the body, producing life-threatening multi-organ failure, as described during the initial phases of sepsis [2]. It is therefore not surprising that our body has developed a series of physiological strategies to keep the immune system under control.

In this short review, we will try to convince the readers that the nervous system, and in particular the sympathetic branch of the autonomic nervous system is a key player amongst the check and balance mechanisms that characterize the acute immune response to an immune challenge. All leukocytes, belonging to both innate and adaptive immunity, express adrenergic receptors and are, therefore, subjected to the influence of sympathetic nerves (see [3] for a comprehensive review on this matter). As a matter of fact, sympathetic nerves exert a fundamental role in regulating leucocyte trafficking, immune cell recruitment and activation, and subsequent cytokine release, all essential factors for determining the outcome of the immune response [4, 5].

Hugo Besedovsky and colleagues were the first to propose the nervous system as part of the regulatory mechanism acting in a negative feedback manner to maintain an immune homeostasis [6]. In particular, they demonstrated that, during an immune challenge, the immune system talks to the central nervous system that, in turn, engages two different inhibitory pathways: the hypothalamic-pituitary-adrenal (HPA) axis, which is responsible of the systemic release of glucocorticoids [7], and the sympathetic nervous system [6]. Are sympathetic nerves, therefore, part of an endogenous nervous reflex that acutely inhibits the inflammatory response to an immune challenge? Several lines of evidence seem to support this theory: (1) sympathetic nerves extensively innervate primary and secondary lymphoid organs [8] as well as the adrenal gland, which can release catecholamines into the bloodstream when preganglionic splanchnic sympathetic fibres are activated; (2) all leukocytes express adrenergic receptors [9], broadening the scope of how sympathetic nerves could modulate immune function; (3) several in vitro studies strongly support an anti-inflammatory role for [3] catecholamines mediated by β2-adrenergic receptors expressed on different leukocytes [10–12]; (4) a large literature describes how exogenous activation of different sympathetic nerves has anti-inflammatory properties [13–16], demonstrating that sympathetic nerves can inhibit inflammation also in vivo.

We will now try to present what we consider the most crucial pieces of evidence that support Besedovsky's original theory: that sympathetic nerves are the motor arm of an endogenous neural reflex, now usually termed the inflammatory reflex [6], that acutely inhibits the inflammatory response to a systemic immune challenge. We will base our discussion mainly on studies where the sympathetic influence on immune function is investigated by comparing the effects on animals where selective sympathetic nerves have been surgically ablated prior to the immune challenge. In particular, we will focus our review mainly on the knowledge developed studying animals made endotoxemic by systemic injection of lipopolysaccharide (LPS, a component of the wall of gram-negative bacteria).

The Spleen: Where Sympathetic Nerves Modulate Immune Function?

The spleen is a major secondary lymphoid organ, and is anatomically separated into white pulp, marginal zone and red pulp. The white pulp contains the periarteriolar lymphoid sheaths, rich in T cells (the vast majority of leukocytes present in the white pulp), and the lymph follicles, with dividing B lymphocytes and macrophages [17, 18]. The marginal zone, located between the white and the red pulp, is rich in specialized macrophages (also known as metallophilic macrophages) and dendritic cells [17, 18]. The red pulp, instead, contains platelets, granulocytes, and a large population of monocytes [17, 18].

The spleen has always been considered the principal target organ where the sympathetic control of immunity takes place, for several reasons. First of all, in response to an immune challenge, the leukocytes located in the spleen are major producers of cytokines, including the sufficient and necessary mediator of inflammation, tumour necrosis factor α (TNF; [19]). The spleen is exclusively innervated by sympathetic nerves [20, 21]. Two major splenic sympathetic nerves run along the splenic artery, separate in several sympathetic nerves composing the splenic neurovascular bundle and enter the splenic parenchyma. Splenic sympathetic innervation is mostly present around vascular structures and to a lesser extent as discrete nerves in the white pulp (mostly in the periarteriolar lymphoid sheaths) and the red pulp, where sympathetic fibres may closely contact T cells and macrophages [22]. The cell bodies of these postganglionic sympathetic fibres are mainly located in the suprarenal (splanchnic) and coeliac ganglia [23, 24].

Are splenic sympathetic nerves able to modulate immunity? The answer to this question is straightforward: yes, they can! Katafuchi and colleagues showed that the medial preoptic area (MPO) in the brain has a role in the control of the splenic natural killer (NK) cells. Ablation of the MPO in rats suppressed the functional activity of splenic NK cells, and this effect was prevented by prior

ablation of the splenic sympathetic nerves [25]. Nance and colleagues also showed that intracerebroventricular injection of prostaglandin E2 reduced the systemic production of pro-inflammatory cytokines in response to systemic LPS treatment. This reduction was also abrogated by prior splenic nerve ablation [26]. One of the most convincing pieces of evidence that splenic sympathetic nerves have the potential to influence immunity comes from the studies where the cholinergic anti-inflammatory pathway was described [27, 28]. According to the extensive literature on this topic, electrical stimulation of the vagus nerve inhibits the release of TNF from the spleen, an effect that also depends on the splenic nerves (for a detailed description of the cholinergic anti-inflammatory pathway mechanism see [29]). The anti-inflammatory potential of stimulating the vagus nerve, or other autonomic nerves, to treat chronic inflammatory conditions has attracted much interest in the last decades [30, 31].

The evidence referred to in the paragraph above shows that experimental interventions into the brain or peripheral nerves can indeed activate anti-inflammatory responses mediated by the splenic nerves. But the important question that we should ask, at least for the purpose of this review, is: are splenic sympathetic nerves the motor arm of the inflammatory reflex? In other words, are the splenic nerves the pathway for the anti-inflammatory response that is driven from CNS *endogenously*, without experimental interventions? The answer to this question is more complex (see also the paragraph below on the splanchnic sympathetic nerve). To the best of our knowledge, only three studies have directly investigated the effects on the endogenous inflammatory response of surgical splenic denervation prior to LPS challenge [32–34]. Meltzer and colleagues showed that rats with cut splenic nerves respond to systemic LPS treatment with the same amount of TNF as sham-operated rats [32]. We recently replicated this finding, showing also that levels of the anti-inflammatory cytokine interleukin (IL) 10 were similarly unaffected by splenic denervation [34]. Torres-Rosas and colleagues actually found that prior splenic denervation produced an inhibition, rather than an enhancement, of the TNF response to LPS in mice [33]. The consistent finding that surgical ablation of splenic sympathetic nerves does not enhance the inflammatory response to LPS means that the splenic sympathetic nerves are not the efferent arm, or at least not the only efferent arm, of the endogenous inflammatory reflex.

This argument has further implications. It is commonly stated that the cholinergic anti-inflammatory pathway is the motor arm of the inflammatory reflex [35]. This well-studied pathway is activated by electrical or pharmacological stimulation of vagal efferent nerve fibres, whose anti-inflammatory action depends, inter alia, on the spleen and the splenic sympathetic nerves [35]. We have two reasons not to accept the cholinergic anti-inflammatory pathway as the motor arm of the endogenous inflammatory reflex. First, the cholinergic anti-inflammatory pathway does not work without intact splenic nerves [36] yet, as discussed above, splenic neurectomy does not prevent the endogenous inflammatory reflex. Second, we have reported that cutting the vagus nerves, on which the cholinergic anti-inflammatory response depends [35], does not influence the TNF response to systemic LPS [34, 37]. These arguments are developed further elsewhere [28, 38, 39].

Adrenal Glands: Humoral Control of Immunity

Adrenal glands have the potential to modulate immunity. They are anatomically and functionally divided in a cortex and a medulla, with different embryonic origins and functions. The cortex is responsible for the release of glucocorticoids that occurs when the HPA axis is reflexly activated in response to an immune challenge [7]. The adrenal medulla is considered analogous to a sympathetic prevertebral ganglion since preganglionic sympathetic fibres from within the greater splanchnic nerves synapse directly with, and drive, the chromaffin cells responsible for secreting adrenaline, noradrenaline and to a lesser extent, dopamine into the bloodstream. Both glucocorticoids and catecholamines are anti-inflammatory [6, 40].

A demonstration of the anti-inflammatory potential of neurally driven release of adrenal catecholamines by chromaffin cells comes from the elegant studies that describe the acute effects of electroacupuncture on inflammatory responses to systemic LPS in mice [33, 41]. These studies showed that electroacupuncture, performed at the ST36 Zusanli acupuncture point, was able to activate a neuronal network that caused an increase in plasma catecholamine levels, which attenuated the TNF and IL-6 response to systemic LPS [33, 41].

Surgical and pharmacological adrenalectomies have been shown to dramatically increase the mortality rate to a moderately high dose of LPS in mice [42]. This was associated with an exaggerated TNF response, compared to that of control animals. Both the elevated TNF response and the subsequent lethality of that dose of LPS in adrenalectomized mice could be avoided by exogenous administration of glucocorticoids [42]. This shows that the adrenal glands are involved in the anti-inflammatory

neurohormonal response to endotoxemia. However, Meltzer and colleagues were not able to replicate the same finding to lower doses of LPS in rats. These authors showed that adrenalectomy, with or without concomitant splenic denervation, did not enhance the inflammatory response to LPS, raising some doubts on the actual involvement of the adrenal glands in the reflex control of inflammation [32]. The reason for this discrepancy between these apparently similar studies is unknown. We recently replicated a similar experiment in rats and, at least in our experimental procedure, the adrenalectomy was associated with a dramatic enhancement of TNF plasma levels in response to a medium dose of LPS [43], confirming Ramachandra's original findings [42]. Is this reflex anti-inflammatory response mediated by glucocorticoids or catecholamines released in the bloodstream? We recently tested this by severing the adrenal nerves prior to the systemic immune challenge. This procedure allowed us to maintain an intact HPA axis and corticosterone response to LPS, while the sympathetic preganglionic input to the catecholaminergic cells was removed. Our results showed that this procedure did not have any major effect on the TNF response to systemic LPS, but it strongly reduced the resultant levels of the anti-inflammatory cytokine IL-10. Evidently, circulating catecholamines differentially affect these two key cytokine components of the anti-inflammatory reflex response to systemic LPS [34].

The Gastro-Intestinal Tract a Key Physiological System for Innate Immunity: Focus on the Liver

For its anatomical position and its physiological function, the gastro-intestinal (GI) tract is a unique system that has to deal, on a daily basis, with a heavy load of antigens. It continuously interacts with harmless food, commensal bacteria and, not infrequently, with harmful molecules or microorganisms, which might be ingested with the diet or leak through the mucosal barrier [44]. The intestinal mucosal is home to a large population of immune cells, which may be modulated by the autonomic nerves that extensively innervate the GI tract [20]. In this review, we are focusing on the acute aspects of sympathetic immunomodulation, and therefore will not cover the neural control of immunity in the gut in the context of chronic inflammatory conditions such as inflammatory bowel diseases [45–47].

Closely associated with the GI tract is the liver, a fundamental mediator of local and systemic immunity [48]. The liver is home of an important population of resident macrophages, the Kupffer cells, which can detect immune challenges and release early inflammatory markers in response [49]. Given its anatomical position, the liver is the first organ that gets exposed to toxins or pathogens escaping from the GI tract, via the portal system: therefore, it is not surprising that it is one of the most important organs involved in innate immunity. Recently, it was shown that, in response to intravenous LPS, the liver is the dominant source of TNF production [50]. The liver also contains dendritic cells, CD4+ and CD8+ T cells, NK cells, B cells, and NK-T cells [48]. Sympathetic nerves innervate the liver in rats, monkeys, and humans, especially the hepatic blood vessels rather than the parenchyma [51, 52], and their activation has immune repercussions.

Connie Wong and colleagues showed that the sympathetically mediated inhibition of the hepatic invariant NK T cells was responsible for the lethal immunosuppression that follows stroke in mice [53]. This indicates that hepatic sympathetic nerves, when activated, have the potential to strongly influence the immune status of the body. We recently tested whether hepatic sympathetic nerves are reflexly activated during an acute immune challenge (intravenous LPS) to influence the ensuing acute inflammatory response. Our data showed that rats with the hepatic sympathetic nerves severed responded to intravenous LPS with IL-10 and TNF levels no different to those of sham-operated animals [34], indicating that these nerves are not necessary for the acute reflex control of systemic inflammation. These results deviated from those reported by Soto-Tinoco and colleagues, where animals with denervated livers responded to LPS with an exaggerated TNF release [54]. It is likely that several differences in experimental approach underlie these discrepancies. Of note, however, Soto-Tinoco and colleagues applied peri-portal capsaicin with their surgical denervation and found that intraperitoneal capsaicin had a similar effect. These observations therefore implicate the involvement of afferent fibres in the responses they saw, rather than the sympathetic efferent supply to the liver.

The Splanchnic Anti-Inflammatory Pathway: The Motor Arm of the Inflammatory Reflex

On the basis of the evidence stated so far, it is possible to say that prior section of either the splenic, adrenal, or hepatic sympathetic nerves does not acutely disinhibit the TNF response to LPS and that only adrenal nerve section produces an inhibition of the anti-inflammatory cytokine IL-10. In simple words, there is not a single

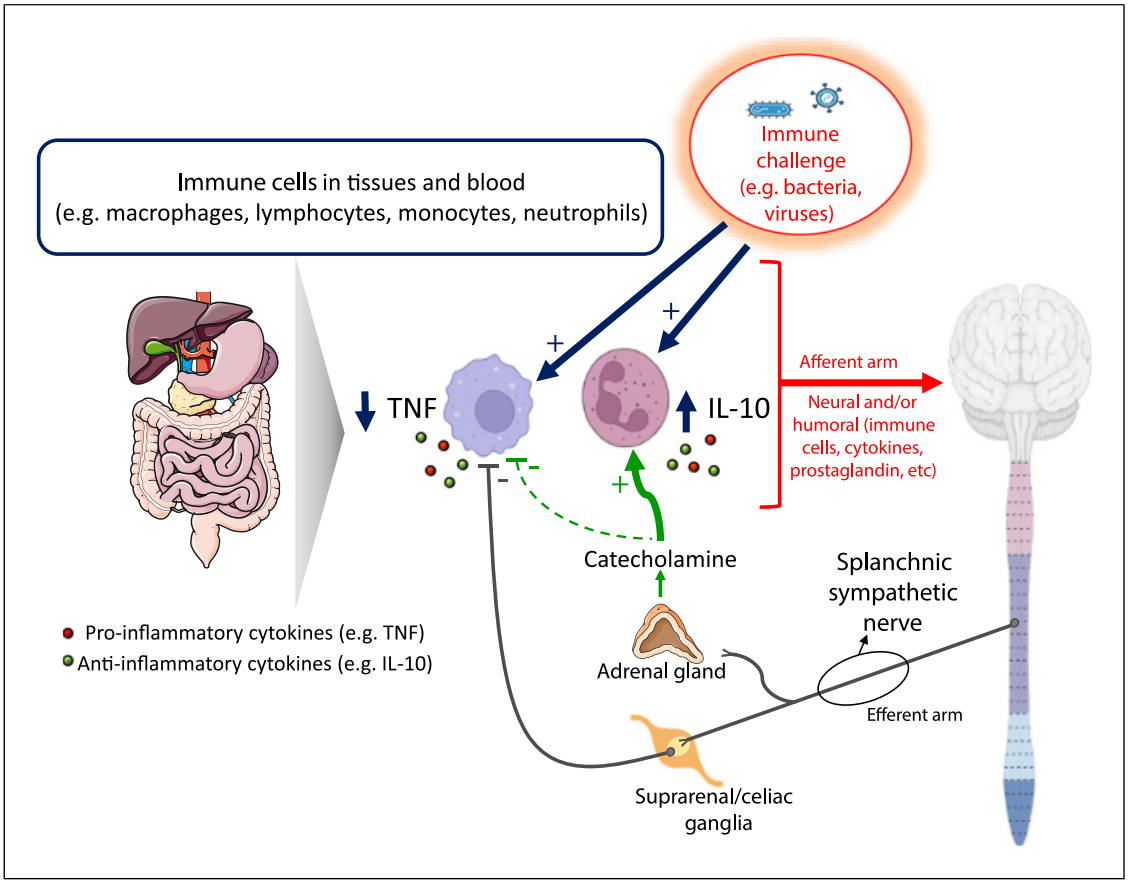

Fig. 1. Diagram showing current concepts of the inflammatory reflex. In response to an immune challenge, leukocytes release inflammatory mediators. The immune system talks to the central nervous system through a neural and/or humoral sensory arm (in red). In response, the brain activates the splanchnic anti-inflammatory pathway. The adrenal glands release catecholamines in the bloodstream (in green), while sympathetic nerves release noradrenaline and other co-transmitters locally in the spleen and other abdominal organs. Systemic catecholamines are responsible for the enhancement of IL-10; local sympathetic nerves are primarily responsible for the inhibition of TNF. IL-10, interleukin 10; TNF, tumour necrosis factor α.

specific target organ where sympathetic nerves inhibit inflammation during a systemic immune challenge [43]. It is therefore difficult to confirm Besedovsky's theory from this series of studies. However, almost 10 years ago we tested whether the splanchnic nerves, composed by preganglionic sympathetic fibres, projecting to the adrenal medulla and prevertebral sympathetic ganglia as well as postganglionic sympathetic fibres projecting to several abdominal organs, could serve as the efferent arm of the inflammatory reflex. We confirmed that LPS given i.v. produces an increase of the splanchnic sympathetic nerve activity [37]. Rats subjected to bilateral splanchnic denervation responded to LPS with an exaggerated inflammatory response, compared to sham-operated animals [37]. This exaggerated inflammatory response consisted of an enhanced release of plasma TNF, IL-6, and interferon gamma, with a reduction of the anti-inflammatory cytokine IL-10 (surprisingly, also the pro-inflammatory cytokine IL-1β was inhibited by splanchnic denervation) [55]. We also proved that splanchnic denervation disinhibited inflammation similarly in other species, namely, mice and sheep [56, 57]. Furthermore, we found that the reflex can be initiated not only by LPS, a toll-like receptor (TLR) 4 agonist, but also by Pam2Cys, a TLR2 and 9 agonist, and by Poly I:C, a TLR3 agonist [57].

It seems that the splanchnic sympathetic nerves are both necessary and sufficient to mediate the endogenous inflammatory reflex. Administration of the ganglion blocker pentolinium tartrate adds no further enhancement of TNF or reduction of IL-10 responses to LPS than bilateral denervation of the splanchnic nerves, while combined

denervation of the lumbar and cervical sympathetic nerves was without effect [34]. This clearly demonstrates that what we termed the splanchnic anti-inflammatory pathway, consisting of preganglionic and postganglionic sympathetic fibres running in the splanchnic nerves, represents the efferent arm of the inflammatory reflex [38, 39]. The importance of the splanchnic sympathetic nerves in the reflex control of systemic inflammation was also confirmed by other researchers [58]. In unpacking the splanchnic anti-inflammatory pathway, we recently found that its control of pro- and anti-inflammatory cytokines (TNF, IL-10) was mediated by distinct sympathetic efferent nerve fibres. It turns out that the nerve fibres supplying the adrenal medulla to cause adrenaline release into the bloodstream are responsible for the enhanced expression of IL-10, while sympathetic nerves innervating the spleen and other abdominal organs are primarily responsible for the inhibition of TNF (Fig. 1). Thus, the sympathetic influence of pro- and anti-inflammatory cytokine responses is presumably mediated by a divergent neural control, presumably acting on separate populations of leukocytes [34].

Conclusions

We believe that the initial theory of Besedovsky, which stated that sympathetic nerves are reflexly activated during an immune challenge to inhibit the ensuing immune response, has been confirmed. In particular, we and others showed that the inflammatory reflex exists and its efferent arm is what we termed the splanchnic anti-inflammatory pathway [39]. The splanchnic anti-inflammatory pathway is important since it is active in different species and responds to systemic immune challenges mimicking viral, gram-negative, and gram-positive bacterial infections [39, 57]. The splanchnic anti-inflammatory pathway does not need any exogenous intervention but is endogenously activated by the immune challenge itself. Its inhibitory action on innate immune function is powerful: animals with the splanchnic anti-inflammatory pathway surgically ablated were able to clear an *E. coli* systemic infection in less than 90 min, while animals with the splanchnic nerves intact were not [56].

While extensive research work has been done on the pathways composing the efferent arm of the inflammatory reflex, much less is known about the afferent arm and the central integrative pathways. Recent studies have described the important contributions of the carotid body and of a liver-spinal axis as possible sensory arms of the inflammatory reflex [54, 58]; however, the contributions from the vagus nerve and circulating humoral factors, including immune cells and their by-products, also need to be considered. Further, studies are necessary to delineate the inflammatory reflex and understand how the sympathetic nervous system is involved in the check and balance mechanisms that characterize immune responses, acute and chronic, involving innate and adaptive immunity.

Conflict of Interest Statement

No conflict of interest, financial or otherwise, is declared by the authors.

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Author Contributions

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