Bioelectronic Medicine

A Stimulating Concept: Bioelectronic Medicine in Inflammatory Disease

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Recent discoveries in neuroscience and immunology have revealed that stimulation of specific neural circuits can ameliorate certain experimental inflammatory diseases. Accumulating evidence on a prototypical reflex circuit that includes the vagus nerve, termed the "inflammatory reflex," has spawned clinical trials using implanted vagus nerve stimulators to treat patients with chronic inflammatory diseases. Modulation of neural reflex activity potentially represents a groundbreaking advance in treatment options for chronic inflammation, but our understanding of the involved components and signals is still incomplete. Here, the experimental basis for use of bioelectronic medicine in treatment of inflammatory disease and future challenges in this rapidly evolving field are reviewed and discussed.

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INTRODUCTION

Inflammation is important for microbial defense and tissue healing, but it must be very carefully managed to maintain homeostasis and health. Excessive and nonresolving inflammation disrupts homeostasis and may cause inflammatory diseases. Such immune system dysregulation underlies septic shock, rheumatoid arthritis, inflammatory bowel disease, psoriasis, multiple sclerosis, atherosclerosis, certain cancers and a range of other diseases. Consequently, nonresolving inflammation contributes significantly to morbidity and mortality worldwide (1,2).

Steroidal and nonsteroidal antiinflammatory drugs, small molecule compounds and specific anticytokine drugs are widely used to treat inflammatory diseases. However, this therapy may cause serious side effects and yet fail to provide satisfactory help for a significant portion of patients. Development of effective treatment to regulate specific inflammatory processes with limited side effects has proved challenging, and conceptual innovations are greatly needed (1,2). Bioelectronic medicine, the interdisciplinary field that brings together molecular medicine, neuroscience and bioengineering, holds great promise for targeted and specific therapy in the near future and may have utility in treatment of inflammatory diseases, for example, by modulating signals in neural reflexes (3–5).

NEURAL REFLEX CIRCUITS ARE AN INTEGRAL COMPONENT OF THE IMMUNE SYSTEM

Neural reflex circuits are crucial regulators of organ function and homeostasis. For example, heart rate, blood pressure and body temperature are closely monitored and regulated by neural signals. Interestingly, a connection also between the nervous system and inflamed tissue was described when the four clinical hallmarks of inflammation redness, swelling, warmth and pain were defined by Aulus Cornelius Celsus in *De Medicina*. It has now become clear that body surfaces are equipped with a dense mesh of sensory nerves that possess similar molecular recognition systems for danger signals as immune cells do (6). Invading bacteria directly activate sensory nerves and elicit axonal signals (7). Endotoxin and proinflammatory cytokines also elicit sensory signals that result in a motor nerve response (8–10). In this way, neural reflexes can respond to microbial invasion and tissue injury.

Recent insights into these mechanisms have fundamentally changed our understanding of immune system homeostasis: The immune system can no longer be regarded fully autonomous, because it is regulated by homeostatic autonomic neural reflexes. These discoveries are now spawning novel and revolutionary ideas for support of tissue healing and treatment of chronic inflammatory diseases using electrical nerve stimulation to regulate inflammation (11–15). Furthermore, the insight that sensory nerve signals arise as a result of microbial inva-

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sion and immune activity suggest that it may be possible to monitor inflammation by measuring signals in the nervous system.

A PROTOTYPICAL IMMUNE-REGULATORY NEURAL CIRCUIT: THE INFLAMMATORY REFLEX

A particular immune-regulatory neural circuit, in which the vagus nerve plays a key role, is called the "inflammatory reflex" and has been the focus of extensive study over the last decade (11,15,16). In this reflex circuit, vagus nerve fibers report inflammatory events in its sensory domain to the brainstem, which elicits regulating motor signals to the periphery. For example, IL-1β injected intraperitoneally or in the portal vein activates sensory neurons and signals in the vagus nerve that ultimately give rise to fever (17) and triggers motor signals in the splenic nerve (8,15,18). Electrical stimulation of the vagus nerve (VNS) inhibits release of proinflammatory cytokines by activating α7 nicotinic acetylcholine receptors (α7nAChR) on leukocytes in spleen (19,20).

Cholinergic signals in the vagus nerve travel to the celiac ganglion and are propagated to the spleen via the adrenergic splenic nerve, which terminates in close apposition of choline acetyltransferase (ChAT)-expressing lymphocytes. A specific $ChAT^+$ lymphocyte subset, $CD4^+$ $CD44^{hi}$ $CD62L^{low}$ $ChAT^+$ T cells, responds to adrenergic signals with release of acetylcholine, the cognate ligand for the α7nAChR, and relays the splenic nerve signals to α7nAChR-expressing innate immune cells (20–27). This complex circuit of sensory and motor nerve fibers and immune cells that relay neural signals represents an autonomic reflex that senses and modulates cytokine production and inflammation (14,16,28–30).

BIOELECTRONIC INTERVENTION IN THE INFLAMMATORY REFLEX

Because mechanistic details of the inflammatory reflex are known, it has been possible to investigate whether activation of circuit components, including electrical nerve stimulation, can treat inflammatory disease. Cervical VNS improved survival and reduced organ damage in animal models of severe sepsis (23,31,32), ischemia-reperfusion (33,34), artery occlusion shock (35), ventilator-induced lung injury (36), hemorrhagic shock (37) and burn injury (38). In a model of peritonitis, signals in the vagus nerve controlled resolution and proresolving mediators of inflammation (39). VNS also reduced disease severity in experimental models of rheumatoid arthritis (40), colitis (41,42), arthritis (43) and postoperative ileus (44,45).

Based on this knowledge, implanted vagus nerve stimulators are now used in exploratory clinical trials to treat rheumatoid arthritis, colitis and postoperative ileus. Preliminary observations reported from the rheumatoid arthritis clinical trial by Frieda Koopman *et al*. indicate reduced disease scores and reduced levels of C-reactive protein in blood after a brief daily activation of an implanted vagus nerve stimulator. Reported side effects were limited and benign (46). Although definitive data is pending, these first observations of the effect of implanted vagus nerve stimulators are quite encouraging.

A MULTITUDE OF NEURAL CIRCUITS REGULATE INFLAMMATION

In addition to the inflammatory reflex, a number of other neural pathways regulate inflammation and immunity. Activation of muscarinic signaling in the central nervous system mimics the effect of direct vagus nerve stimulation on cytokine release in endotoxemia and requires an intact vagus nerve (47–49). Signals in the vagus nerve can also inhibit intestinal cytokine release independently of the spleen (44), bypassing the prototypical signaling pathway in the inflammatory reflex. Furthermore, electrical stimulation applied to the sciatic nerve regulates innate immune activation by controlling vagus nerve-dependent dopamine release from the adrenal gland (50,51). Another specific neural immune reflex acts as a gateway for entry of autoreactive T cells to the CNS. In this circuit, sensory signals that arise in the hind limb reach the spinal cord and brain stem to activate adrenergic neurons that regulate T cell extravasation by modulating the expression of chemokine receptors on vascular endothelial cells (52). Yet another neural pathway regulates hepatic invariant NKT cells (iNKT) cell activity through an adrenergic signal, and blockade of this neural conduit prevents stroke-associated pneumonia in mice (53). Endotoxin and IL-1β trigger activity in the hypothalamus–pituitary–adrenal axis with a resulting increase in blood levels of glucocorticoids (54), which have anti-inflammatory properties. This list of immune-regulatory neural circuitry is not exhaustive, and it is very likely that many similar and related autonomic reflex circuits remain to be discovered. Presently, there is sufficient data to conclude that neural signals exert significant control over the immune response to trauma and microbial invasion. Modulation of nervous signals can alter the course of inflammation, but much remains to be discovered on the details of the intricate signals involved and how to modulate the neural circuitry to achieve optimal control.

BIOELECTRONIC MEDICINE BEYOND INFLAMMATION

The scope of bioelectronic medicine is not limited to treatment of chronic inflammation. For example, electrical VNS reduces bleeding time and blood loss in experimental traumatic injury (55). Burn injury victims often suffer from fluid leakage from blood vessels and complications from severe tissue edema. Electrical VNS reduced vascular permeability in the skin and lung in an animal model of burn injury, significantly reducing tissue edema in treated animals (56). VNS had beneficial effects in experimental heart failure and is currently under investigation for treatment of heart failure in humans (57,58). Stimulation of peripheral nerves, including VNS, is also used in treatment of intractable epilepsy and certain forms of headaches and migraine (59). Application of a local DC current may be helpful in rehabilitation after

stroke and in other diseases with damage to the central nervous system (60). Moreover, bioelectronic medicine is used experimentally to restore damaged vision (61). In light of this, a number of diseases considered to primarily be of noninflammatory origin may significantly benefit from targeted nerve stimulation using bioelectronic devices. Furthermore, as discussed elsewhere in this issue of *Bioelectronic Medicine*, implantable sensors for a range of physiological variables are being developed (62). Coupled with active bioelectronic devices, these technologies have the potential to revolutionize diagnosis and treatment by recording and modulating signals in real time. Currently available devices have, however, not yet been deemed sufficiently reliable for patient use without human supervision (63).

CURRENT CHALLENGES IN BIOELECTRONIC MEDICINE

The optimal signaling in the inflammatory reflex (and other reflex circuits) for maximum effect on the immune response is not known. The precise identity of the involved neurons remains unclear and the effects on inflammation and immune cell activity of specific stimulation modalities have not been determined. To study this in detail, new stimulation techniques with better signal control, ideally connecting to individual nerve fibers, would be of great utility.

The role of the sensory portion of the inflammatory reflex for immune system regulation is not well understood. It is possible that select afferent signals in the vagus nerve activate motor centers in the brain that in turn regulate immune cell behavior through signals in the efferent vagus nerve, and through other efferent neural and hormonal mechanisms. The recent discovery that sensory nerves can directly detect presence of pathogens and regulate local immune responses (6,7,10) inspires a range of new opportunities. Decoding the afferent signals elicited by tissue injury, pathogen invasion, cytokines and inflammation will be an important step in understanding the reflex control of immune homeostasis. This may be significant, because it is conceivable that sensory signals can be interpreted and used to guide real-time diagnosis and bioelectronic modulation of ongoing inflammation.

Input to bioelectronic devices need not be limited to neural signals. As a multitude of measurements become accessible in real time, it will be a challenge to integrate the complex sets of information in a meaningful way to make it useful for improving therapy.

High biocompatibililty is naturally vital for maintaining the integrity of the tissue–machine interface (63–66) and necessary to reduce the risk for undesirable side effects from implanted devices. An alternative is development of external devices that use other methods to activate neural circuits, for example magnetic fields. If the future clinical trials show efficacy of nerve stimulation in treatment of inflammatory diseases, such noninvasive approaches may be well worth intense pursuit.

CONCLUSION

We are just beginning to understand some of the molecular mechanisms that govern the multidirectional communication between damaged tissue, microbes, immune cells and the nervous system. Sensory nerves detect microbial invasion and report on immune system activity. Motor nerves regulate cytokine release and inflammation. The discovery of the inflammatory reflex in the control of immune homeostasis and the promising, yet preliminary, results from studies of implanted devices for treatment of inflammatory disease are truly of breakthrough character. Although bioelectronic medicine is in its infancy, it has the potential to revolutionize diagnosis and treatment of a wide range of inflammatory diseases.

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DISCLOSURE

The author declares that he has no competing interests as defined by *Bioelectronic Medicine*, or other interests that might be perceived to influence the results and discussion reported in this paper.

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