Best Practice & Research Clinical Rheumatology 28 (2014) 625–635

Contents lists available at ScienceDirect

Best Practice & Research Clinical Rheumatology

journal homepage: www.elsevierhealth.com/berh

7

Vagus nerve stimulation: A new bioelectronics approach to treat rheumatoid arthritis?

F.A. Koopman [a], P.R. Schuurman [b], M.J. Vervoordeldonk [a], P.P. Tak [a, c, d, *]

[a] Department of Clinical Immunology and Rheumatology, Amsterdam Rheumatology and Immunology Center, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
[b] Department of Neurosurgery, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
[c] GlaxoSmithKline, Stevenage, United Kingdom
[d] University of Cambridge, Cambridge, United Kingdom

Keywords:
Rheumatoid arthritis
Cholinergic anti-inflammatory pathway
Vagus nerve stimulation

A B S T R A C T

There has been a marked improvement in the treatment of rheumatoid arthritis (RA), but most patients do not achieve disease remission. Therefore, there is still a need for new treatments. By screening an adenoviral short hairpin RNA library, we discovered that knockdown of the nicotinic acetylcholine receptor type 7 (α7nAChR) in RA fibroblast-like synoviocytes results in an increased production of mediators of inflammation and degradation. The α7nAChR is intimately involved in the cholinergic anti-inflammatory pathway (CAP). This led us to study the effects of α7nAChR activation in an animal model of RA, and we could show that this resulted in reduced arthritis activity. Accordingly, stimulation of the CAP by vagus nerve stimulation improved experimental arthritis. Conversely, we found aggravation of arthritis activity after unilateral cervical vagotomy as well as in α7nAChR-knockout mice. Together, these data provided the basis for exploration of vagus nerve stimulation in RA patients as a novel anti-inflammatory approach.

* Corresponding author. Department of Clinical Immunology and Rheumatology, Room F4-105, Academic Medical Center, University of Amsterdam, PO Box 22700, 1100 DE Amsterdam, The Netherlands. Tel.: +31 20 566 7765; fax: +31 20 691 9658.
E-mail address: p.p.tak@amc.uva.nl (P.P. Tak).

http://dx.doi.org/10.1016/j.berh.2014.10.015

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease, which is characterized by pain, swelling, and stiffness of joints, due to synovial inflammation. During active disease, the joints are limited in motion and function, and persistence of synovial inflammation leads to the development of bone erosions and, finally, joint deformities [1]. The signs and symptoms of this condition can be reduced by treatment with synthetic and biological disease-modifying antirheumatic drugs (sDMARDs and bDMARDs, respectively). Treatment of RA is usually initiated with methotrexate, a sDMARD, and can be combined with corticosteroids and other sDMARDs. Biological DMARDs are indicated if there is insufficient response to the initial sDMARD treatment or if there are unfavorable prognostic factors present, such as very active disease, early joint damage, or presence of (high levels) of autoantibodies, immunoglobulin M (IgM) rheumatoid factor (RF), and/or anti-citrullinated protein antibodies (ACPAs) [2]. Despite the fact that there are many types of DMARDs available, there are still many RA patients who do not improve sufficiently. Besides the lack of response to therapy as a reason for the discontinuation of treatment, there are also patients who discontinue medication because of side effects, or because they do not want to take chronic medication. As a result, the need for the development of new therapeutic strategies remains.

Cholinergic anti-inflammatory pathway

Inflammation in peripheral tissues, as observed in RA, can be detected by the afferent vagus nerve and this information is signaled towards the brain. Peripheral administration of the pro-inflammatory mediators lipopolysaccharide (LPS) or interleukin-1-beta (IL1-beta) in rats normally elicits fever, but after bilateral subdiaphragmatic vagotomy the fever response is abated [3,4]. Later, there was the surprising finding that the vagus nerve could not only sense inflammation but also influence it. Activation of the vagus nerve, which is a part of the parasympathetic nervous system, was found to dampen inflammatory processes. Rats with carrageenan-induced hind paw edema (acute inflammation model) were injected intracerebroventricularly (i.c.v) with a very low dose (noneffective if given systemically [3]) of the anti-inflammatory drug CNI-1493, and there was a significant decrease in paw edema. The anti-inflammatory mechanism of action of i.c.v. CNI-1493 was, at the time, unknown, but after bilateral cervical vagotomy the drug was no longer able to reduce paw edema. In combination with the finding that an i.c.v. injection of CNI-1493, but not saline, could increase efferent vagus nerve activity, this led to the conclusion that activation of the vagus nerve by i.c.v. CNI-1493 treatment had an anti-inflammatory effect [5]. These were the first indications that efferent vagus nerve activation could inhibit inflammation in an animal model. The combination of sensing peripheral inflammation by the afferent vagus nerve and the subsequent anti-inflammatory response of the efferent vagus nerve is currently known as the cholinergic anti-inflammatory pathway (CAP) [6].

The CAP can also be activated by electrical vagus nerve stimulation (VNS) or stimulation of the nicotinic acetylcholine receptor type 7 (α7nAChR) [7,8]. The parasympathetic neurotransmitter acetylcholine is the anti-inflammatory mediator of the CAP, which activates the α7nAChR. Acetylcholine can be produced by the vagus nerve, but it can also be produced by nonneuronal cells, for instance, in the spleen. Several studies have shown that the spleen is essential for the anti-inflammatory effect of the vagus nerve, because after splenectomy VNS is no longer capable of reducing inflammation [9–12]. After VNS, the anti-inflammatory reflex appears to travel through the sympathetic splenic nerve towards the spleen. The splenic nerve produces norepinephrine, which triggers choline acetyltransferase-positive (CHAT+) T cells in the spleen to produce acetylcholine (Fig. 1) [13,14]. CHAT-positive cells are also found in the synovium of the RA joint [15,16], which suggests that acetylcholine can also be produced locally in the joint. Joints are not known to be innervated by the vagus nerve, but there appear to be sympathetic fibers in the RA synovium [17]. It is, therefore, conceivable that norepinephrine-producing sympathetic fibers in the joint activate CHAT+ T cells to produce acetylcholine, but this has not been studied yet.

CAP in experimental arthritis

In the past decade, the anti-inflammatory effect of the vagus nerve has been shown in animal models for sepsis, acute pancreatitis, colitis, postoperative ileus, and acute respiratory distress