Autoimmunity Reviews xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Autoantibody pain

Andreas Goebel

Pain Research Institute, Department of Translational Medicine, University of Liverpool, and The Walton Centre NHS Foundation Trust, Liverpool, L9 7AL, UK

ARTICLE INFO

Article history:
Received 1 February 2016
Accepted 8 February 2016
Available online xxxx

Keywords:
Autoantibody
Pain
Neuropathic pain
Complex regional pain syndrome
CRPS
Voltage gated potassium channels
Chronic fatigue syndrome

ABSTRACT

As autoantibodies bind to target tissues, Fc-region dependent inflammation can induce pain via mediators exciting nociceptors. But recently another possibility has emerged, where autoantibody binding to nociceptors can directly cause pain, without inflammation. This is thought to occur as a result of Fab-region mediated modification of nerve transduction, transmission, or neuropeptide release. In three conditions, complex regional pain syndrome, anti-voltage gated potassium channel complex autoimmunity, and chronic fatigue syndrome, all associated with no or only little inflammation, initial laboratory-, and trial-results have suggested a potential role for autoantibody-mediated mechanisms. More research assessing the pathogenic roles of autoantibodies in these and other chronic pain conditions is required. The concept of autoantibody-mediated pain offers hope for the development of novel therapies for currently intractable pains.

Contents

1. Introduction

The objective of this review is to highlight the topic area of 'autoantibody pain'. It focuses on the emerging field of autoantibody-associated, non-inflammatory chronic pain conditions in the three examples of Complex Regional Pain Syndrome, anti-potassium channel-complex antibody associated pains, and painful chronic fatigue syndrome. (See Table 1.)

Chronic pain is a common human health condition that is associated with a poor quality of life [1]. Most patients with chronic pain will, over time develop both pain-associated dysfunction, and psychological co-morbidity, so that chronic pain conditions incur high costs to the individual, their family, healthcare systems, and society as a whole [4]. Recognition of the importance of chronic pain as a healthcare problem, and of the need to find effective management strategies has been rising [5].

An understanding of the biological mechanisms underpinning chronic pain is required to develop effective pain-therapies, yet these mechanisms are often unclear. Although we don't know how established demographic or psychosocial risk factors are translated into the development of chronic pain, these risk factors, and most structural tissue abnormalities, such as degenerative changes have in fact very little power to predict pain in an individual [6,7]. On the other hand, using rodent models to better understand chronic pain has been challenging. These models won't mimic the selective onset of chronic

E-mail address: andreasgoebel@rocketmail.com.

http://dx.doi.org/10.1016/j.autrev.2016.02.011
1568-9972/

Table 1
Mechanisms of autoantibody-mediated pain. Note, in predominantly Fc-region mediated conditions, additional Fab-mediated effects may contribute, and vice-versa.? = unconfirmed. Some pain conditions are additionally associated with muscle pains and cramps, typically arising in response to the experience of severe pain, or as a result of the inability to exercise. Fc/Fab = pain mediated by the autoantibody Fc/Fab region. 'Nociceptor' = small diameter sensory nerve cell, which responds to potentially-, or actually tissue-damaging stimuli.

Mechanism of autoantibody-pain		Pain classification	Disease example
Fc	Binding to non-neuronal, cells; Fc-region triggered inflammation leading to i) sensitization/activation of intact nociceptors by inflammatory mediators, plus possibly ii) damage to nociceptors as result of the inflammation.	i) Nociceptive, plus possibly ii) neuropathic	Bullous pemphigoid
	Binding to neurons, or glia; Fc-region triggered complement activation and (potentially minimal-) inflammation leading to neuronal damage.	Neuropathic	Guillain–Barre-syndrome [15]; Neuromyelitis optica [16]
Fab	Binding to nociceptors; Fab-region mediated modification of the bound target, including: i) binding-site blockade, ii) alteration in the target conformation, iii) target activation, iv) target-crosslinking with internalization, v) altered neuropeptide secretion from the nociceptor.	Neuropathic	? CRPS ? VGKC-associated pain ? Chronic fatigue syndrome
	Binding to cells in the nociceptors' vicinity; Fab-region mediated change in cell signaling such as increased mediator secretion consequently activating and/or sensitizing nociceptors	Nociceptive	

pain in humans, as most rodents develop significant persistent pain, but only a minority of human patients do so, after any given kind of injury [9]. Thus the variable factors determining the development of human chronic post-injury pain cannot be fully understood from these models. Similarly patients can also develop chronic pain 'out of the blue', without any obvious preceding trauma or distress, a human observation of variability, for which there is no rodent model. Analgesic compounds developed using standard-injury rodent-models have unfortunately rarely been successful in clinical practice [10,11]. Many of the drugs, which we use today to treat chronic pain, have rather small effect sizes, tolerance develops with long-term use, and their significant central side effects give much cause for concern [12].

Thus today's pain science cannot explain the development of chronic pain for an individual patient, and Pain Specialists can frequently not treat them with an effective therapy.

The study of human genetic variants holds promise for both understanding the causes of pain variability, and developing novel analgesic treatments for chronic pain [13]. But another recent approach to identify biological risk factors in chronic pain is the study of autoantibodies. An overview of the mechanisms by which autoantibodies may cause pain is given in the Table.

Some autoantibodies are recognized as causing pain by inducing an inflammatory reaction, triggered by binding of complement to their Fc-region (Fig. 1A, [14]). Inflammatory mediators excite nearby intact nerve-afferents sensing actual or potential tissue damage, 'nociceptors' (Box 1). These nociceptors are the peripheral components of the pain pathway. The ensuing pain is termed 'nociceptive' (Box 1). Where such an inflammatory reaction also causes nerve cell damage,[1] 'neuropathic' pain, defined as pain arising from a pathogenic process that directly affects the somatic nervous system (Box 1) may additionally arise (Fig. 1A) [2,17]. In contrast, where autoantibodies bind directly to nociceptors, causing either nerve-cell damage including as a consequence of complement binding, or causing a change in nerve-function, the resulting pain is primarily neuropathic.

Recent results have highlighted, that there is a group of chronic painful conditions, which are associated with α) no, or only minimal regional immune cell infiltration and tissue damage, β) normal systemic inflammatory markers, and γ) specific peripherally binding serum-autoantibodies that activate cells in tissue culture. In these conditions, a minimal form of autoantibody-induced, complement-dependent inflammation may cause damage only to the bound cell-membrane structures [18]; alternatively, these autoantibodies' pertinent pathophysiological action may include autoantibody-Fab-region-mediated change of the function of the bound target (Table) [18,19], such as:

i) direct modification of either function, or expression of receptors, or channels on nociceptors; the bound target may undergo conformational change, may be activated, or blocked, or cross-linked and internalized [18]. In consequence, the nociceptor alters its transduction- or translation properties, or its pattern of neuropeptide secretion, so that it becomes spontaneously active, and/or more sensitive to noxious or non-noxious activation (Fig. 1B). Inflammation is not required for these changes to occur. If channels are involved, then the disease-mechanism is termed an 'autoimmune channelopathy', paralleling known channelopathies with the lead symptom pain, such as erythromelalgia [20]

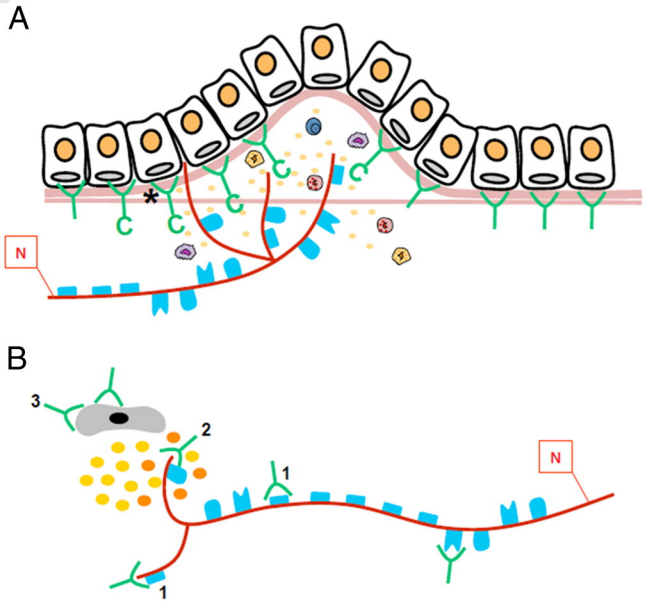

Fig. 1. *Mechanisms of autoantibody-mediated pain.* 'N' = nociceptor; A. In pemphigoid disease, autoantibody-binding to epitopes at the dermal–epidermal junction is followed by complement binding ('C') to the autoantibody Fc-region, which then induces inflammation leading to dermal–epidermal splitting (*, only one epidermal layer shown). Inflammatory mediators (yellow dots) painfully excite intact nociceptors ('nociceptive' pain). Secondary 'neuropathic' pain may arise from inflammation-induced nerve cell damage, including mechanical stretch between epidermal-, and dermal layers. B. An alternative kind of autoantibody-mediated pain depends upon Fab-region-mediated modification of the bound target. When binding to nociceptor surface receptors or channels (light blue), the autoantibody Fab-region directly alters neuronal transduction/translation ('1'), or neuropeptide release (orange dots) ('2'). Alternatively ('3') autoantibody Fab-region binding to peri-neuronal cells can trigger subtle release of inflammatory mediators (yellow dots), that can excite nociceptors.

[1] 'Damage' is the concept of an alteration of nerve function which is not dependent on the ongoing presence of a pathogenic element; for example nerve exposure to inflammatory-, or metabolic stress may induce lasting changes in nerve receptor expression, which continue even if the stressor has stopped.

Please cite this article as: Goebel A, Autoantibody pain, Autoimmun Rev (2016), http://dx.doi.org/10.1016/j.autrev.2016.02.011