The Autoimmune Aetiology of Unexplained Chronic Pain

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Abstract

Chronic pain is the leading cause of life years lived with disability worldwide. The aetiology of most chronic pain conditions has remained poorly understood and there is a dearth of effective therapies. The WHO ICD-11 has categorised unexplained chronic pain states as 'chronic primary pains' (CPP), which are further defined by their association with significant distress and/or dysfunction. The new mechanistic term, 'nociplasticic pain' was developed to illustrate their presumed generation by a structurally intact, but abnormally functioning nociceptive system. Recently, researchers have unravelled the surprising, ubiquitous presence of pain-sensitising autoantibodies in four investigated CPP indicating autoimmune causation. In persistent complex regional pain syndrome, fibromyalgia syndrome, chronic post-traumatic limb pain, and non-inflammatory joint pains associated with rheumatoid arthritis, passive transfer experiments have shown that either IgG or IgM antibodies from patient-donors cause symptoms upon injection to rodents that closely resemble these clinical disorders. Targets of antibody-binding and downstream effects vary between conditions, and more research is needed to elucidate the details. The central nervous system appears largely unaffected by antibody binding suggesting that the clinically evident CNS symptoms associated with CPP might arise downstream. In this narrative review pertinent findings are described, and it is suggested that additional symptom-based disorders might be examined for the contribution of antibody-mediated autoimmune mechanisms.

Introduction

Persistent chronic pain conditions are the leading causes of life years lived with disability worldwide [1]. There are few effective treatments and even the minority of patients who experience substantial pain relief from available medications will typically lose this benefit over time as their bodies develop tolerance [2]. The great majority of patients are left without effective long-term analgesia.

This unfortunate dearth of effective measures to treat chronic pain conditions reflects our poor understanding of their aetiologies. Intuitive assumptions have not born out; for example, there is limited association between the nature of any structural lesions such as degenerative bone changes, and the presence or severity of such pains [3]. Furthermore, although psychological and social factors are consistently associated, their association is considered bidirectional [4], and persuasive brain mechanisms responsible for the translation of distress experiences into pain perception have yet to be identified [5]. Chronic pain conditions typically come without systemically elevated inflammatory markers, and most patients test negative in standard autoantibody assays. In other words, symptoms that profoundly affect billions of people across the globe have remained unexplained. New approaches to their understanding are needed.

Recently, the World Health Organisation's ICD-11 has classed the largest group of unexplained pains as 'chronic primary pain' (CPP), coded MG30.0. This new category incorporates regional conditions such as musculoskeletal back pain and complex regional pain syndrome, widespread pains such as fibromyalgia syndrome, visceral pains and several forms of facial pains and headaches [6]. The WHO diagnostic criteria for CPP are that i) the pain persist for more than 3 months, ii) the condition is not better explained by another diagnosis and iii) the pain is 'associated with significant emotional distress' (e.g., anxiety, anger, frustration, or depressed mood) and/or significant functional disability (interference in activities of daily life and participation in social roles). This definition is an elegant solution to earlier struggles to diagnose and code chronic pain which relied on separate, *either* somatic *or* psychological codes; the WHO approach integrates chronic pain's biopsychosocial dimensions and abandons those unhelpful dichotomies.

In parallel, a classification initiative under the umbrella of the International Association for the Study of Pain (IASP) has produced a new *mechanistic term* for CPP. Prior to this effort, all chronic pains had been assigned either of two mechanisms, 'nociceptive pain' (through tissue damage or inflammation) or 'neuropathic pain' (through damage or disease directly affecting the nervous system itself). It was increasingly recognised that the large group of unexplained chronic pains are poor fits for this classification [7]. The new term, '*nociplastic pain'* applies where pain is presumed to arise from an abnormal function of the pain-

processing nervous system itself, after exclusion of any nociceptive and neuropathic mechanisms. CPP are presumed predominantly nociplastic in nature. Although a welcome advance, this definition does not clarify the causes from which such abnormal nervous system function arises.

On the background of a poorly understood aetiopathogenesis for CPP, a distinct experimental paradigm, 'passive immunoglobulin transfer' was proposed, to examine the potential causal contributions from functionally-active non-inflammatory autoantibodies [8]. The general principle of passive transfer experiments is that presumed pathogenic human serum-immunoglobulins are isolated from patients and transferred to rodents; the animals are then assessed for signs of the disease (Figure 1). It is possible to achieve success when key immune targets and downstream pathways are preserved between human and rodent; successful transfer is indicated by the reproduction of core features of the disease, highlighting autoimmune causation [9]. A prominent example of successful passive transfer are classical results in myasthenia gravis where rodents develop muscle weakness when injected with patient-derived IgG [10]. It was hypothesised that immunoglobulin passive transfer may identify a directly causative role of autoantibodies in CPP.

First experiments indicated subtle abnormalities in rodent behaviour [8, 11] but over the past decade, passive transfer experiments in four CPP models have proven more successful than anticipated. While experimental paradigms differed between conditions, materials from most or all patients, within each tested CPP diagnostic sub-group, were shown to harbour pathogenic pronociceptive antibodies whereas people without chronic pain always tested negative. These experiments have satisfied Witebsky's autoimmunity criteria for each investigated condition, and have provided a novel mechanistic direction for future drug development [9]. We present a narrative review of this emerging research field and delineate future directions.

Results

Persistent Complex Regional Pain Syndrome (CRPS)

CRPS (formerly called Reflex Sympathetic Dystrophy, RSD) is a regional CPP which typically arises after distal limb trauma [12]. Most patients (85%) will spontaneously improve within 12-18 months post trauma. However, subsequent improvement is uncommon [13]. Persistent CRPS (pCRPS), defined as CRPS lasting longer than about 18 months is considered one of the most severe pain conditions that humas experience, with a profound impact on quality of life [14]. Drugs are generally ineffective, and apart from prolonged infusions of low-dose ketamine which may cause drug highs and hallucinations [15, 16] the only pain-relieving treatment option for which sufficient RCT-derived evidence exists is implantation of a neuro-stimulator [17].

Serum-immunoglobulin G (IgG) transfer from patients with pCRPS significantly depressed mouse rearing-behaviour [8, 11], but no other CRPS signs were detected (Table). Hypothesising that trauma may be required to render transferred circulating human autoantibodies proalgesic, we combined the passive transfer with a small hind-paw incision ('Brennan incision model', Figure 1) [18]. This two-hit (circulating antibodies and limb injury) 'passive-transfer-trauma model' strikingly reproduces pertinent clinical signs including unilateral mechanical limb hyper-sensitivity and swelling. Findings were later confirmed in an independent laboratory, where additionally transfer of cold hyperalgesia, a prominent and distressing CRPS symptom was demonstrated alongside abnormal single neuron response profiles reflecting the observed behavioural hypersensitivities [19]. Transfer of IgG obtained from patients with high pain intensities caused a stronger phenotype providing a rare example of concordance between patient- and model-phenotypes [19]. Although there was no regional or systemic inflammation, augmented glial cell activation persisted along central nervous system pain pathways. Since treatment with the interleukin 1β receptor antagonist anakinra abrogated these disease signs, it is likely that antibody binding triggers immune activation in pain-relevant tissues such as dorsal root ganglia or the central nervous system [20]; the antibody binding targets are yet to be discovered.

Table. *Results of passive immunoglobulin transfer studies.*

Study	Condition	Methods[$]	Findings in rodents[#]
Goebel et al. 2005 [8]	pCRPS	8mg/day IgG ip x 5 days, 1 patient.	Reduced movement.
Goebel et al. 2011 [11]	pCRPS	8mg/day IgG ip x 5 days, 12 patients.	Reduced movement and coordination.
Tekus et al. 2014 [21]	pCRPS	12mg/day IgG ip for 2 days; on second injection day right hind-paw injection; 2 further injections 5, 6 days later.	Enhanced paw swelling and mechanical sensitivity.
Li et al. 2014 [22]	PTCLP	Tibia fracture and 3 weeks casting in both wild-type, or B-cell depleted mice, or mice deficient in producing IgM*.	Reduced paw sensitisation and swelling.
Wigerblad et al. 2016 [23]	RAJPs	0.124-4mg total IgG iv, or ACPA+/- IgG, once only; pooled preparations from ACPA+ ve or -ve patients or controls.	Enhanced paw mechanical and thermal sensitivities and reduced movement. ACPA IgG enriches most strongly in ankle joints. without causing synovitis, binds to osteoclasts in vivo, elevates Cxcl1/2 mRNA levels in joint.
Dawes et al. 2018 [24]*	CASPR2 autoantibody positive neuropathic pain	6mg-10mg IgG daily i.p., derived from 2 patients with very high CASPR2 antibody levels, over 14-22 days.	Slow development (after>10 days) of significant mechanical-without thermal hyperalgesia, no motor abnormalities. Channel-de-clustering identified as

			pertinent molecular mechanism.
Cuhadar et al. 2019 [19]	pCRPS	8mg IgG daily ip for four consecutive days, paw incision on day 2.	Mechanical and thermal hyperalgesia, IgG from patients with higher pain intensities have stronger effects; sensitisation demonstrated in single pain-nerve fibres.
Helyes et al. 2019 [20]	pCRPS	8mg IgG daily ip for 2-14 consecutive days, paw incision on second injection day.	Stable hyperalgesia over 14 days, normal resolution of paw inflammation but persistent activation of glia cells along central pain pathways, reversible by anakinra treatment.
Guo et al. 2020 [25]	PTCLP/eCRPS	Serum (0.5ml), or purified immunoglobulin (5mg IgG or 500ug IgM) from both patients with either eCRPS, or pCRPS injected ip once, to mice deficient in producing IgM, 3 weeks after tibia fracture and casting.	eCRPS sera and IgM, but not eCRPS IgG elicits allodynia and unweighting in injured hindpaws. pCRPS sera typically not pro-nociceptive.
Goebel et al. 2021 [26]	FMS	8mg purified IgG from patients with FMS (8x individual UK, 3x pooled Swedish) injected daily over 1-4 days ip.	IgG elicits mechanical and thermal hyperalgesia, reduced muscle strength/ movement, small fibre pathology. Human IgG enriches in DRGs, not detected in CNS.
Ishikura et al. 2021 [27]*	Neuromyelitis optica spectrum disorder (NMOSD)	4ul of monoclonal anti-aquaporin IgG antibody (AQP4, prepared from patient-plasmablasts), or 3ul of anti-AQP4 positive NMOSD patient serum infused into T10 spinal cord.	Larger spinal cord lesions and astrocyte activation, increased bilateral mechanical hyperalgesia.
Jurczak et al 2021 [28]	RAJPs	2 mg monoclonal IgG i.v., once only, IgG generated from single memory B cells and antibody secreting cells isolated from synovial fluid mononuclear cells from RA patients.	Enhanced paw mechanical sensitivity, reversed with osteoclast and ASIC3 inhibitors.

Table. [$]Models use mice excepting the NMOSD model which uses rats, experiments involving injuries were conducted under general anaesthesia; [#]all findings are against healthy controls, in some studies additionally against disease controls; pCRPS = persistent complex regional pain syndrome >18 months duration; IgG = immunoglobulin G; ip = intraperitoneally; PTCLP = post-traumatic chronic limb pain; IgM = immunoglobulin M; RAJPs = non-inflammatory joint pains associated with rheumatoid arthritis; ACPA = anti-citrullinated protein antibody; CLCX-1 = murine cytokine homolog to human Interleukin- 8; *neuropathic pain model; CASPR2 = Contactin-associated protein-like 2; eCRPS = early CRPS <18 months duration; DRGs = dorsal root ganglia; CNS = central nervous system; aab = autoantibody;

Post Traumatic Chronic Limb Pain (PTCLP) / early CRPS

In the 'tibia-fracture-cast model' for post-fracture limb pain, both pharmacological B-cell depletion and B-cell knockout (muMT mice) reduce persistent pain whereas acute post-traumatic pain is not affected [22, 29]. These results indicate that prolonged limb pain after trauma in the context of limb-immobilisation is at least in part sustained by IgM-mediated autoimmunity. The model is also proposed to resemble the relatively common, transient form of CRPS; in keeping, when muMT mice were subjected to this model, the normal pain phenotype was reconstituted by intraperitoneal transfer at 3 weeks post fracture of either wild-type fracture mouse serum-IgM, or CRPS-patient serum-IgM; neither CRPS *serum-IgG* transfer, nor serum-IgM transfer from patients after uncomplicated limb fracture had this effect [25]. Interestingly, IgM transfer was only pathogenic if the immunoglobulin was obtained from patients with early CRPS (<12 months) rather than the less common persistent CRPS. These results are therefore the first to indicate that distinct or evolving (e.g., through isotype switch), autoimmune-related mechanisms may underpin these two ('early' and 'persistent') CRPS types, an idea which has separately emerged from clinical studies [30]. Since the model is strictly dependent on limb cast immobilisation, the results also highlight that the well-established benefit of early *mobilisation* after fracture [31] may be arbitrated by the prevention of regional autoimmune activation.

Additional experimentation has begun to reveal targets for PTCLP/eCRPS-related autoantibodies. For example, IgM directed against keratin type 16 was identified in both patients with CRPS of duration less than one year and in mice with fracture-casted limbs [32]. The generation of murine autoantibodies after tibial fracture relies on both neuropeptide signalling [33] and activation of the sympathetic nervous system [34], and the formation of germinal centres in regional lymph nodes is reliant on IL-6 activation which appears to underpin autoantibody formation [35].

Rheumatoid Arthritis associated non-inflammatory joint pains (RAJP)

RA is a common autoimmune disease affecting 0.1-1% of the total population. The disease can be sub-classified into at least two different subsets referred to as seropositive (60-80%) and seronegative, depending on the presence/absence of rheumatoid factor (antibodies reactive with the Fc-part of IgG), and/or anti-citrullinated protein antibodies (ACPA), commonly detected using anti-cyclic citrullinated peptide (CCP) assays. RA is also associated with other autoantibodies, including antibodies against proteins that have undergone other types of post-translational modifications such as carbamylation and acetylation; these types of antibodies are jointly referred to as anti-modified protein antibodies (AMPA). It is now well established from retrospective studies that individuals may be seropositive for AMPAs many years before developing symptoms of inflammatory arthritis [36, 37]. Changes in the repertoire of AMPAs are paralleled by changes in the clinical picture, with a "pre-RA" development of pain and fatigue and signs of bone loss and subclinical inflammation most

often in those individuals who later develop RA [38]. In fact, joint pain often develops before signs of joint inflammation and is thus one of the first indicators of an emerging RA.

In established RA, disease-modifying anti-rheumatic drugs (DMARDS) and glucocorticoids often reduce disease activity and joint inflammation and can also reduce pain. However, even if improved with introduction or change of DMARDs non-resolved pain remains a problem for a substantial proportion of individuals with RA [39]. In some patients such pain appears focused around joints. This indicates that synovitis is not the only reason for joint pain in RA, however the mechanisms that are responsible for the inflammation-independent joint pain that occurs both in the very early phase of the disease and in periods of medically controlled disease activity had remained unknown.

The possibility that certain RA-associated autoantibodies drive such “non-inflammatory” joint pain in RA was tested by transfer of IgG from RA patients to mice. One injection of IgG from ACPA-positive, but not ACPA-negative RA patients or healthy controls, significantly reduced withdrawal thresholds to mechanical stimulation without generating visual signs of joint inflammation, indicating that IgG in seropositive individuals has strong pronociceptive properties [23]. This observation was substantiated by the finding that injection of purified ACPA (polyclonal ACPA), but not the non-ACPA IgG from the same individuals, also induced mechanical and thermal hypersensitivities and reduced locomotion, absent any sign of local or systemic inflammation (Figure 1) [23].

Using monoclonal antibodies generated from RA patients can be informative when elucidating potential pain mechanisms even when the binding specificity of the antibodies remain unknown. In recent work two different RA patient-derived monoclonal antibodies induced transient mechanical hypersensitivity, still in the absence of edema, synovitis, and analgesic effect of naproxen [28]. It is likely that several mechanisms, including both Fab and Fc mediated, work in parallel to produce these ‘non-inflammatory’ joint pain effects, and further studies to delineate the pronociceptive role of autoantibodies in RA are needed [40].

Fibromyalgia Syndrome (FMS)

FMS is a common, widespread CPP that affects more than 2% of the global population; it arises often following a period of suffering from regional CPP)[41-43]. As in many autoimmune rheumatic diseases, FMS is more prevalent among women [44-47]. Several other medical conditions, and overlapping pain disorders display dramatically increased rates of *comorbid* FMS [48]. FMS is defined by widespread pain, fatigue, emotional distress, and patients characteristically display a markedly increased sensitivity to pressure [49, 50]. Other sensory abnormalities, such as paraesthesias and an enhanced cold sensitivity are common [50, 51].

A wealth of evidence from different brain imaging modalities demonstrate that FMS is associated with structural and functional aberrations in the brain [52], including signs of reduced inhibitory pain processing [53, 54]. Such 'central sensitization' has long been thought to be the cause of FMS symptoms, but increasingly, peripheral sensory afferent abnormalities have received more attention. Fourty-50% of patients have small-fibre pathology, with loss of epidermal and corneal innervation [51, 55]; microneurography has revealed increased excitability of peripheral C-nociceptors in a subset of patients [51, 56], and quantitative sensory testing reliably detects sensory abnormalities [50, 57]. Together this indicates that sensory afferents are structurally and functionally abnormal [56, 58].

The first investigation of IgG transfer from patients to mice provided a potentially transformational advance in our understanding of FMS [59]. FMS IgG produces painful mechanical and cold hypersensitivities, reduced activity, reduced paw grip strength, and small-fibre pathology in mice. The sensory hypersensitivities are associated with reduced activation thresholds in nociceptors. Patient IgG thus recapitulates sensory, motor, and anatomical symptoms of FMS [26]. Patient IgG labels cells in the dorsal root ganglia where the cell bodies of somatosensory afferent neurons reside, particularly satellite glial cells (SGCs) that enwrap the soma of DRG neurons. Importantly, patient IgG also displays an increased binding to sections of *human* DRG, thus demonstrating autoreactivity and strengthening the case for IgG autoantibodies in causing FMS [26]. The transfer of symptoms from patients to mice with each investigated IgG preparation (derived from either UK or Swedish donors), and their reversibility after stop of IgG transfer suggests that therapeutic interventions that reduce circulating IgG levels may be effective treatments for many patients with FMS.

The mechanisms of autoantibody related CPP - regional immune activation or changes in channel function

While there is comprehensive evidence for pathological behavioural effects of CPP patient-derived IgG or IgM autoantibodies, i.e. rodents become hyper-sensitive, there is yet little known about the underpinning molecular mechanisms. In all four investigated CPP regionally confined inflammatory effects were demonstrated in proximity to sensory neurons. This suggest that these conditions are neither prototypical inflammatory autoimmune conditions such as lupus or pemphigus, nor pure autoimmune channelopathies where antibody binding solely affects receptor or channel function on sensory neurons; the latter mechanism appears to underpin antibody-medicated pain in voltage gated potassium channel autoimmunity [24].

Neuropathic pain conditions: autoimmunity involving voltage gated potassium channels (CASPR2) and aquaporins

In two rare neurological conditions that are known to be caused by autoantibodies and which can be associated with neuropathic pain, pathogenic autoantibodies have been

shown to cause pain sensitivity in passive transfer experiments [24, 27]. Lessons learned from this research may enhance future investigations in CPPs; autoantibody binding to nerves in CASPR2 conditions is not associated with any discernible inflammatory response; sensitivity in the rodents is instead caused by a direct antibody effect on receptor integrity and function ('autoimmune channelopathy'), whereas in the aquaporin model it may be due to antibody-induced destructive CNS effects.

Discussion

Research studies over the past decade have demonstrated the ubiquitous presence of pronociceptive autoantibodies in the serum of patients with 'unexplained' chronic primary pain conditions (CPP). These antibodies produce the respective donors' pain phenotypes after injection into rodents, indicating a contribution from autoimmune mechanisms. In the process this research instigates a paradigm shift for our understanding of chronic pain aetiologies. The results suggest that effective diagnostic and immune-treatment technologies for these patients should be attainable. The consistency of results across all four investigated CPP also suggests the value of performing assessments in additional patient groups.

Pronociceptive autoimmunity differs between specific types of CPP (Table). Pathogenic antibodies may be either IgG or IgM types and there are pharmacodynamic differences between the CPP models; in CRPS and PTCLP trauma is required to render antibodies pathogenic – their simple presence in the circulation causes no harm. Common to all these conditions is that painful changes are fully reversible when the serum-antibody concentration diminishes.

In CRPS it is unknown how the triggering injury and autoimmune response causatively interact. Injury factors may either reveal cryptic antigens leading to *de novo* stimulation of the adaptive immune system, or they might allow already existing circulating autoantibodies to gain access to pertinent antigens [60]; in the prolonged limb-pain (PTCLP) model the injury triggers an adaptive immune response leading to increased pain-sensitivity. In these models, antibody-mediated symptoms are strictly regional, consistent with the respective clinical conditions, despite systemic circulation of the abnormal immune factors. These findings corroborate the validity of 2-hit autoimmunity models - both antibodies and trauma are required - for regional antibody-mediated autoimmune disorders in medicine [61, 62]. CRPS should now perhaps not be considered 'unexplained', however, target cells and molecular structures are yet to be identified.

In FMS several distinct immune trigger pathways appear possible. One potential pathway is suggested by the well-established link between FMS and the past experience of

psychosocial stressors (Figure 2) [63]. Whether and how such an experience can trigger an immune response in susceptible people requires further study but the possibility that prevention of psychosocial distress might avert chronic pain through modification of an immune pathway is a tantalising emerging paradigm. A separate immune activation pathway is suggested by the high FMS prevalence in patients with established autoimmune conditions, which might be mediated through shared genetic and environmental risk factors [41].

Antibody-mediated immune processes in CPPs have been 'hiding in plain sight', invisible to measurements of inflammatory markers, peripheral blood cell inflammatory profiles, proteomic, microbiome or genetic investigations [64]. Passive transfer approaches have proven powerful tools to elucidate the pivotal role of non/minimal-inflammatory, functionally active autoantibodies.

The reviewed studies into non-destructive immune processes call for scrutiny about assumed correlations between the degree of tissue destruction caused by a certain pathophysiological mechanism and the relevance of this factor for patients' quality of life. The summarized experiments reconfirm that solely functional, non-destructive biological factors can cause exquisite hypersensitivities which severely affect daily living.

Future Directions

More research is required to understand how pronociceptive antibodies cause disease. Few targets for CPP-related autoantibodies have been discovered. However, some cellular binding targets are already established such as dorsal root ganglion satellite glia cells and neurons. Identification of epitopes will enable the development of diagnostic tests and targeted therapies, but the goal of reducing antibody serum titres can already be addressed in clinical trials. Plasma exchange, high-dose IVIG treatment, and recently- developed biologic drugs that target the FcRn receptor [65] or B-cells and plasma cells [66] are effective in other autoantibody-mediated conditions and might be promising treatment technologies for CPP; a note of caution may apply in regards to B-cell ablation approaches - no efficacy signal on concomitant FMS has been reported, to our knowledge from trials conducted in RA or Lupus; similar as with some established antibody-mediated conditions available B-cell ablation methods may not effectively reduce pertinent pathogenic antibodies which will continue to be produce by plasma cells or by B-cells residing in privileged environments [66] - immune treatments for FMS-concomitant conditions may not improve FMS, and separate types of immune treatments may be needed [67].

Patients can perceive disabling ongoing symptoms from 'successfully' treated disorders; the recent recognition of long-COVID symptoms has heightened our awareness about these issues: although tissue destruction is halted, a different biological process ensues from which many patients may still feel very much disabled [68]. We would like to suggest that the results described here might sharpen our focus for similar research in the field of

unexplained symptoms or symptom-based disorders, such as primary fatigue, tinnitus or postural tachycardia syndrome (POTS) [69].

Conclusions:

Take Home Messages

- Unexplained chronic pain conditions are now coded in ICD-11 as 'chronic primary pain' (MG30.0). Their mechanism has been described as 'nociplastic', characterised by abnormal function of the pain nervous system itself, absent either painful peripheral stimuli or direct nerve damage.
- Immunoglobulin transfer experiments from patients with unexplained chronic pain conditions to rodents have uncovered the surprising, ubiquitous presence of pronociceptive autoantibodies which can explain pertinent clinical symptoms. Treatments reducing autoantibody levels may provide promising therapeutic approaches.

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Figures

Figure 1

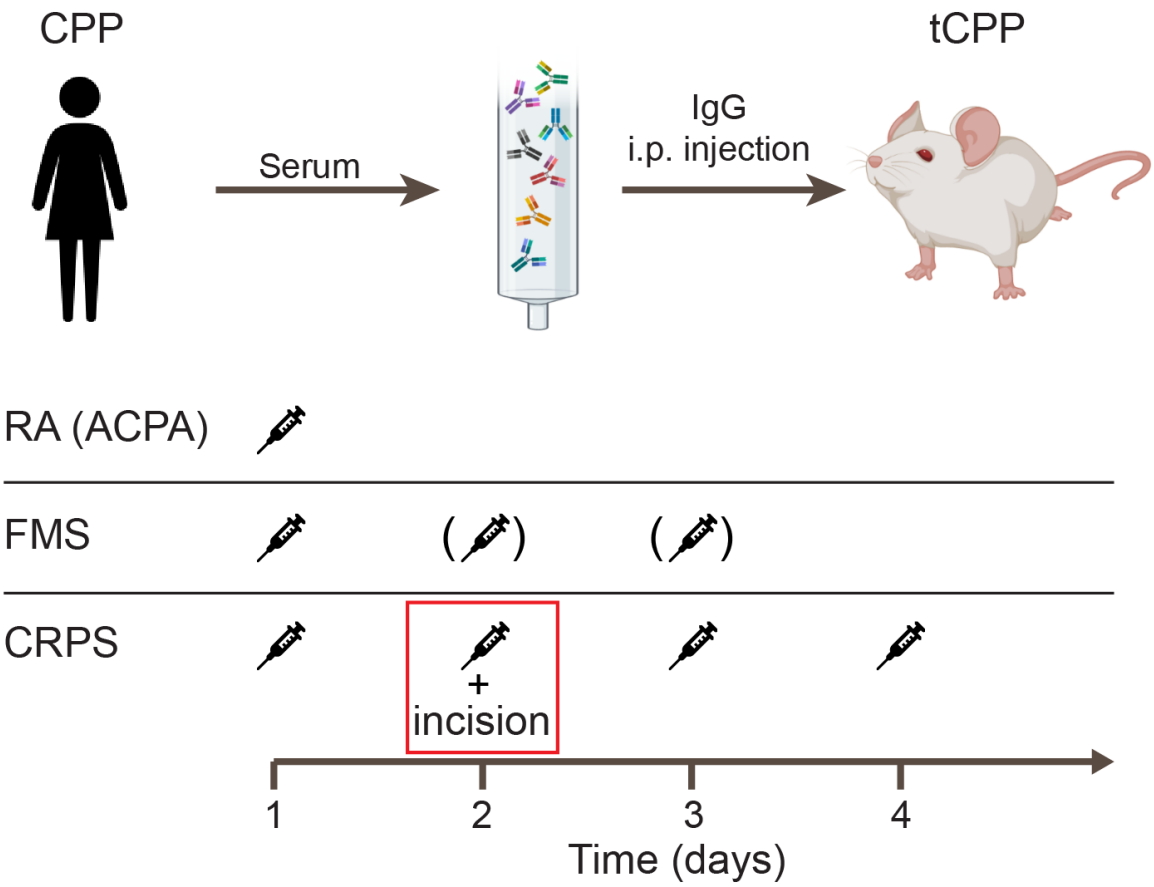

Figure 1. *Experimental passive transfer models*. CPP = patient suffering from chronic primary pain; tCPP = transferred chronic primary pain condition; RA(ACPA) = rodent model for rheumatoid arthritis associated non-inflammatory joint pains: injection of either total IgG from ACPA positive patients, or of purified ACPA causes non-inflammatory joint pains; ACPA = anti citrullinated protein antibodies; syringe symbol = intra-peritoneal IgG injection; FMS = model for fibromyalgia syndrome; syringe symbol in brackets = one injection causes pertinent abnormalities but to produce the full phenotype additional injections are probably required; pCRPS = model for persistent Complex Regional Pain Syndrome over 18 months duration;; incision = hind-paw skin and superficial muscle incision in the CRPS model under general anaesthesia. (*colour reproduction preferred*)

Figure 2

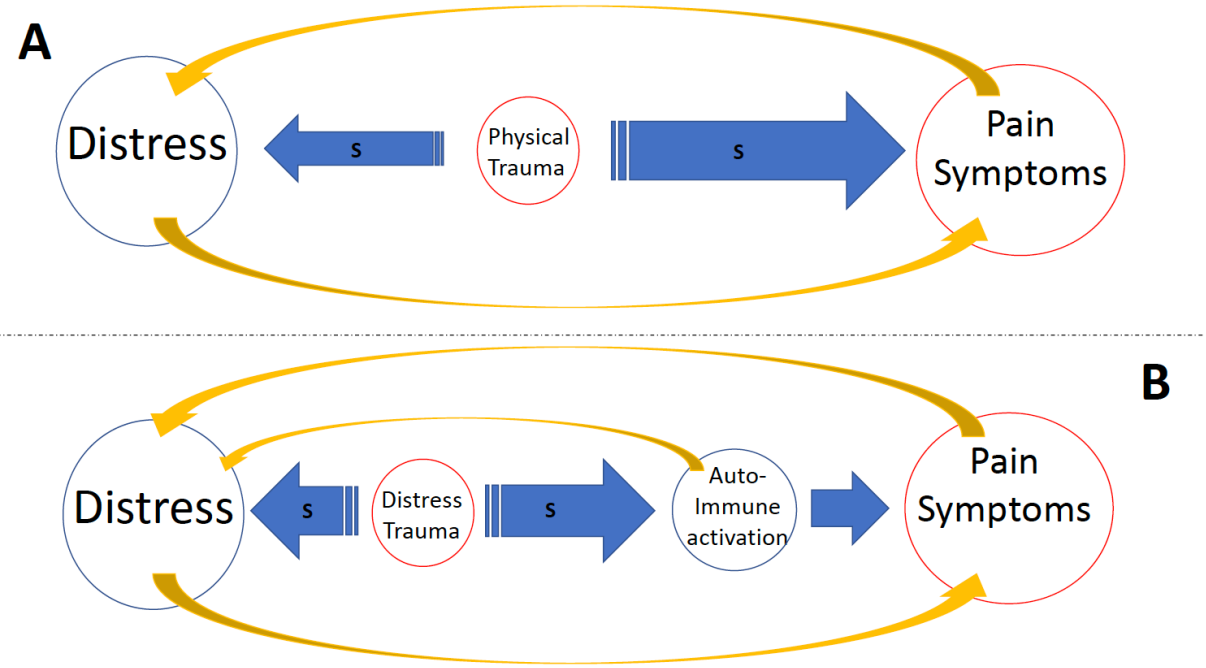

Figure 2. *The inter-relation between psychological distress and chronic primary pain.* To explain the observed frequent association of chronic primary pain with psychological distress, some conceptual models (A) have emphasised the role of physical trauma. The contribution of a self - augmenting cycle (brown arrows) has been proposed between the experiences of post-traumatic pain and distress in vulnerable people – which may persist even if tissue-effects of the original trauma have dissipated, and in some cases may even be purely activated by actual distress experiences without any tissue damage at all (not depicted).
The discovery of pronociceptive autoantibodies suggests an alternative hypothetical pronociceptive pathway (B). Triggered by patients' experience of distress from either physical or emotional trauma autoimmune mechanisms are activated resulting in production of with pronociceptive; autoantibody production sustains the relationship between pain and distress (right blue arrow); these antibodies might also directly exert a distressing effect (small brown arrow). Distress-independent triggers for the production of pronociceptive autoantibodies also exist (not shown, see text). S=susceptibility. (*colour reproduction optional*)

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