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Osteoarthritic pain: a review of current, theoretical and emerging therapeutics

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Background: Despite exciting progress and growth in the understanding of molecular and cellular mechanisms of chronic pain, osteoarthritis (OA) pain remains a challenging clinical entity to treat. There is an emerging diversity of algogenic mechanisms suggesting heterogeneity in pain aetiology in the OA patient population. *Objective/methods*: This review article summarises key issues in existing therapies for OA pain and highlights the emerging compounds in early and late development. It also highlights where tolerability may be a concern, especially in the older populations in which treatment interactions for co-morbid conditions may further narrow therapeutic index. Importantly, the authors also examine the diversity of biology that underpins OA pain and highlight the opportunities for the future. *Results/conclusions*: Many emerging therapies are presently in proof-of-concept clinical testing for treatment of OA. A growing understanding of the heterogeneity in the OA patient population, will challenge the ability to accurately understand observed efficacy or safety signals in these relatively small trials and how they may titrate to a broader patient population. We may need to wait several more years to understand whether the need for a differentiated therapy demanded by patients, payors and physicians alike, will be met.

Keywords: analgesia, disease modification, osteoarthritis, pain

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1. Introduction

Research strategies for therapeutic modulation of osteoarthritis (OA) are focused on pain relief or modification of underlying disease. For both paradigms current treatment options are inadequate. Disease modification has primarily focused on chondroprotection, although to date no agent is registered by the FDA as disease modifying in OA. Adequate control of pain also remains a primary unmet need with particular concerns around improved efficacy, safety and tolerability, compared to presently available therapies.

Historically, separate scientific and clinical faculties have owned OA disease knowledge and the neuroscience of pain. However, the pain matrix in OA is multi-faceted (**Figure 1**) and may depend on disease status, environmental, gender, sex, genetic and personality determinants. Relative contribution of these factors varies across the OA patient population, opening opportunities for individualised, pharmacological approaches.

2. Current therapies and emerging challenges

Treatment guidelines for musculoskeletal pain include those published by the American College of Rheumatology, American Pain Society and European League

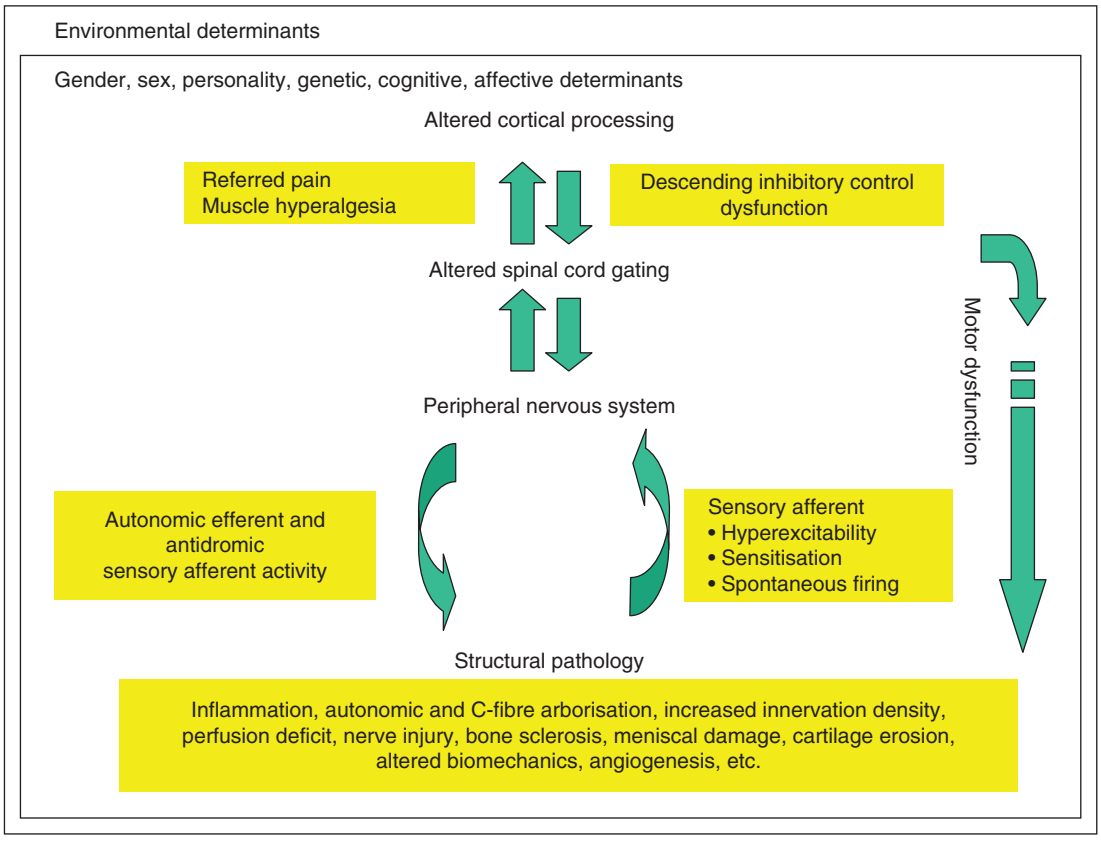

Figure 1. The osteoarthritis pain matrix. In total, the osteoarthritis pain matrix constitutes an interaction between structural pathology, innervation of the joint (sensory, motor, autonomic), dysfunction of pain processing at spinal and cortical levels and various environmental and individual determinants. Relative contribution of each may vary over time and also between patients giving rise to multiple pharmacological intervention points and a segmented patient population.

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Against Rheumatism. At the core of these recommendations is the management of patient exposure to safety concerns with anti-inflammatory drugs. These concerns are similarly shared by OA patients, particularly the elderly, who may be willing to forgo efficacy, in favour of a lower perceived safety burden [1]. Therefore, common across these recommendations is the first-line treatment of OA pain with paracetamol, reflecting an improved safety profile relative to anti-inflammatory drugs, in particular non-selective COX and COX-2-selective drugs. This appears paradoxical, as therapeutic doses of paracetamol (1 g) inhibit COX-1 and -2 by ~ 50% [2,3].

NSAIDs, both non-selective and COX-2 selective, generally exhibit an improved pain relief compared with paracetamol, although efficacy within this class is considered to be clinically poor and maximum effect size is at the threshold of a 'minimal perceptible improvement' for patients [4,5]. The differentiated safety profile of non-selective and selective COX-2 inhibitors is a well-covered subject area. Generally, increased COX-1 selectivity is associated with elevated gastrointestinal risk and selectivity for COX-2 is associated with increased cardiovascular risk, predominantly myocardial infarction, stroke, hypertension and congestive heart failure [6]. Studies comparing COX-2 inhibitors with placebo and observational studies/meta-analyses comparing COX-2 inhibitors with non-selective NSAIDs are cited as evidence of a differentiated cardiovascular risk [7-12]. Although, regulatory authority attention in this area has been well documented, drug development activity in this area continues. Some of the more recent activity and issues are exemplified by etoricoxib (Arcoxia™; Merck) and lumiracoxib (Prexige®; Novartis).

Lumiracoxib is weakly acidic (pK_a: 4.7), it is mildly differentiated from other COX-2 selective drugs by demonstrating a short elimination half-life (4 h), but sustained pharmacokinetics and pharmacodynamics in target tissue (e.g., synovial fluid) [13]. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) indicated a significantly lowered rate of ulcer complications compared with non-selective NSAIDs, although no benefit was observed in patients taking low-dose aspirin. A numerical,

but non-significant, increase in myocardial infarction with lumiracoxib compared to naproxen was observed and the hazard ratio increased further in patients not taking aspirin [14]. Whether this constitutes a signal for increased myocardial infarction risk with lumiracoxib or a cardioprotective profile for naproxen has been extensively debated. Some of the more salient points are that the trial was conducted at relatively high doses of lumiracoxib (400 mg/day) (for OA recommended dose is 100 mg/day), although this needs to be balanced against trial exclusion of high-risk patients with a history of myocardial infarction, stroke, coronary artery bypass surgery, angina, congestive heart failure or evidence of silent myocardial infarction on electrocardiogram. Furthermore, discussion around whether the trial was underpowered for this particular variable has also been raised [3,15]. Novartis have now successfully launched lumiracoxib (Prexige) in the UK and completed a Mutual Recognition Procedure in the EU. Resubmission in the US and a 'not approvable' letter was received in September 2007, with a requirement for more data on a potential liver signal.

Most recently, the 'Multinational Etoricoxib and Diclofenac Arthritis Long-term' (MEDAL) programme data [16,17] showed that of 34,701 patients studied, thrombotic cardiovascular events and complicated gastrointestinal events were approximately similar in patients dosed with diclofenac and etoricoxib. However, limited differentiation might have been expected, as the ratio of COX selectivity of etoricoxib (Arcoxia) compared to the ratio of COX selectivity of diclofenac is relatively narrow [3]. Although, in April 2007, the FDA voted (20:1) against approval of etoricoxib citing a requirement to be demonstrably different to existing marketed medications in risk/benefit profile.

Overall, the recent trial data confirm in general the modest effect size of NSAIDs in OA and a narrow therapeutic benefit of selective COX-2 inhibitors over the non-selective NSAIDs. Improvements in gastrointestinal tolerability using a COX-2 inhibitor can be negated in patients taking aspirin for cardio-protection, as many OA patients do. With differentiation increasingly important to regulatory authorities (as exemplified by etoricoxib's failure to gain FDA approval) and drug safety high on patient's agenda [1], other therapeutic interventions for pain management in OA are still extensively employed.

Although a detailed analysis of randomised, placebo-controlled trials of other existing pharmacological treatments of OA knee pain is beyond the scope of this review, a recent meta-analysis of 63 trials and 14,060 patients by Bjordal *et al.* [5] indicates that pharmacological interventions are generally poor in short-term pain relief in OA. Of the assessed treatments, intra-articular steroid injections or topical use of NSAIDs offered the maximum efficacy at any time point over the first 4 weeks of therapy compared to oral NSAIDs, paracetamol, glucosamine sulfate, chondrotin sulfate or opioids. Overall, effect size was small, with evidence only supporting a clinically slight improvement in pain scores with intra-articular steroids or topical NSAIDs [5].

In contrast, the efficacy of some physical interventions in OA knee pain are generally more robust than existing pharmacological treatments. Transcutaneous electrical nerve stimulation, electro-acupuncture, and low level laser therapy all induce statistically significant, clinically relevant short-term pain relief [18]. Evidence for improved efficacy over drug intervention and a 'perception' among patients of improved safety versus systemic drug therapy continues to ensure the use of physical agents in the treatment of OA pain [18].

In summary, current pharmacological treatment of OA pain is generally unsatisfactory. Safety concerns remain a priority to patients and regulators alike. The opportunity to deliver drugs directly to the joint and 'circumnavigate' at least some safety liabilities from systemic drug exposure is a growing area. Finally, efficacy of most pharmacological treatments appears to be poor. However, the concern is that the OA population is highly heterogeneous, and delivering patient benefit may require a portfolio of approaches with a greater diversity of mechanisms than available at present. Some of these mechanisms may develop from progress in disease understanding and learnings from a decade of investigation into structural modification in the clinic.

3. Progress in structural modification – a route to pain?

There is a strongly emerging view that OA can no longer be considered as predominantly a cartilage disease, but as a complex pathology caused by mechanical injury leading to progressive joint destruction. There is some evidence for an association between specific joint pathology and the presence of joint pain. Thus, disease modification strategies for arresting or reversing the progression of joint degeneration have been hypothesised to impact on pain generation. An important driver for this has been the developing understanding of the neuroanatomy of the diarthroidal joint and its relationship with underlying pathology.

Joints are supplied by a combination of thick myelinated Aβ (Group II), thinly myelinated Aδ (Group III), unmyelinated C-(Group IV) and postganglionic sympathetic nerve fibres. Aβ fibres of the joint terminate in the capsule, fat pad, ligaments, menisci and periosteum, whereas Aδ and C-fibres innervate the capsule, ligaments, menisci, periosteum and mineralised bone, in particular in regions of high mechanical load [19-22]. Under disease conditions, these innervation territories are highly plastic. An example of such plasticity is the innervation of normally aneural tissues such as cartilage with substance P and calcitonin-gene-related peptide (CGRP) positive nerves in patients with OA [23]. Therefore, a 'normally' insensate structure potentially becomes a candidate for pain in OA and,

furthermore, may also accelerate disease status via localised neurogenic inflammation.

Sympathetic innervation of the joint is generally associated with blood vessels, controlling local vascular tone. In a diseased joint, sympathetic innervation is highly dynamic with examples of both ingress into novel territories [23] and also reduced nerve fibre density in other tissues [24,25]. An interaction with the immune system has also been observed, with sympathetic nerve fibres acting in both a pro-inflammatory (low-fibre density) and anti-inflammatory (high-fibre density) conditions via local release of noradrenaline and modulation of immune cell function. This is controlled in part, by local leukocyte release of growth promoters and repellents (e.g., semaphorin3C). The imbalance of this interplay and loss of local sympathetic regulation may exacerbate and sustain chronic joint inflammation [24,25].

In population studies there is a significant discordance between radiographically diagnosed OA and knee pain [26]. However, using other imaging modalities such as MRI, significant structural associations such as bone marrow lesions, subarticular bone attrition and synovitis/effusion [27,28] have been related to knee pain. Relative contribution of these processes in the OA population appears to be strongly segmented. Intra-articular anaesthetic studies in hip and knee OA support a peripheral drive to pain in ~ 60 – 80% of patients, depending on the affected joint [29,30]. In others, spinal or supraspinal mechanisms, for example, central sensitization, dysfunction of descending inhibitory control [31] or altered cortical processing of noxious information, may play a greater role (**Figure 1**) [32].

3.1 Chondroprotection and pain

Disease modification in OA has primarily focused on factors that affect cartilage matrix or chondrocyte metabolism either to prevent further loss or promote regrowth or healing. These approaches have been explored in the clinic for additional pain relief as a secondary, downstream effect [33-41]. Disease-modifying approaches have included: the tetracycline antibiotic, doxycycline; oral glucosamine sulfate; chondroitin sulfate; the bisphosphonate risedronate [42,43]; diacerein and direct intra-articular administration of hyluronan.

Efficacy end points in these trials have primarily used standardised protocols for radiographic joint space narrowing (JSN) as a surrogate measure of articular cartilage thickness [44]. Some form of patient evaluation of severity of joint pain, prompted by the Western Ontario and McMaster Universities OA Index (WOMAC) 5-item pain subscale, or pain questionnaires following disease flares or forced activity were also used (see [45] for review of these trials). Both chondroitin sulfate and glucosamine demonstrated some evidence for arrest of JSN [34,35,37,39], although effects on symptom relief were relatively minor [45]. Further studies sponsored by the National Institute of Health examined both glucosamine and chondroitin sulfate alone and in combination versus placebo in a blinded 6-month, multi-centre study. In isolation, neither treatment exhibited significant improvements in knee pain versus placebo [46]. Furthermore, recent Cochrane Database updates on glucosamine including pooled results from 20 studies with 2570 patients, failed to show benefit in pain and WOMAC function [47]. In contrast to chondroitin and glucosamine, doxycycline only provided a slowing of JSN rather than frank arrest. Unfortunately, the patients selected for this trial had low mean baseline pain score and therefore an assessment of symptomatic relief under treatment was not possible [40]. Risedronate in OA has been explored in three studies. A 285-patient study focused on symptom relief in knee OA [41], whereas two further Phase III studies powered for structural modification investigation in a total of 2483 patients with knee OA [48]. In all studies risedronate (compared with placebo) did not improve pain or alter progression of OA. However, recent work indicates potentially beneficial effects on trabecular bone loss and structure [49]. Finally, diacerein has been explored in several studies in both hip OA [33] and knee OA [38]. Cochrane analysis of a total of seven studies in over 2000 patients indicates that diacerein exhibits a statistically significant slowing of structural progression in hip OA, but not knee OA [50]. Furthermore, this analysis also concluded that diacerein showed a small, but significant, improvement in pain versus placebo [50].

Overall, chondroprotective strategies in OA have demonstrated that pharmacological slowing of disease is feasible, although there is limited evidence for meaningful symptom improvement. As discussed previously, significant tolerability concerns with NSAIDs and opiates make long-term use of these treatments a concern. In the future, disease modification *per se* may yet occupy a position in the OA treatment regimen for long-term chronic dosing and prevention of further joint destruction and (if a relationship exists) pain. However, safety and tolerability concerns of manipulating connective tissue metabolism will be a priority [51]. Despite these caveats therapeutic approaches to chondroprotection continue to be progressed.

Enhanced activity of MMP-2, -7, -8, -9, -13 and -14, as well as a disintegrin-like MMP with thrombospondin-type motifs (ADAMTS)-4 and -5 have been associated with increased matrix degradation in osteoarthritic cartilage. In keeping with this, Wyeth are in Phase I development with Agg-523, an inhibitor of ADAMTS-4 and -5. MMP-13 is also a prime target, co-localised in human OA cartilage tissue, with cleaved type II collagen. Non-selective MMP inhibition has been associated with musculoskeletal syndrome (MSS), characterised by stiffening of joints [52]. Pfizer have published improved selectivity with pyrimidinetrione-based inhibitors of MMP-13 [53], similarly Wyeth [54] and Amgen (Alantos) [55] are also pursuing MMP-13 inhibitors. Of particular note, Alantos were pursuing an intra-articular approach that may potentially mitigate systemic MSS liability [55]. Whether these (and other) approaches deliver disease modification and pain resolution will therefore be

further prosecuted in the clinic. While preclinical models suggest that MMP inhibition is associated with improvements in behavioural surrogates of pain [56], validation of this will require clinical evaluation.

3.2 Changes in bone and association with pain

As outlined above, the neuroanatomy of mineralised bone, bone marrow and periosteum is well defined. Aβ, Aδ, C-fibres and sympathetic fibres distribute densely throughout the periosteum, entering bone in close association with blood vessels [20]. Of these tissues, the periosteum has the greatest density of sensory and sympathetic innervation, which may be further enhanced during joint inflammation. For example, preclinical models of arthritis show dynamic periosteal neurovascular plasticity and evidence of nerve fibre sprouting [57]. Interestingly, neuromediators released from sensory or sympathetic nerves such as noradrenaline, serotonin and glutamate as well as a number of neuropeptides (vasoactive intestinal peptide, CGRP, pituitary adenylyl cyclase-activating peptide, neuropeptide Y and substance P) have been identified in bone. Furthermore, their receptors are found on osteoblasts and osteoclasts, where they modulate cellular activity [58-60], suggesting neuromodulation of bone modelling.

Electrophysiological studies of the mechano-sensitivity of joint innervation indicate that generally Aβ fibres are activated by non-noxious normal working range joint movement, whereas ~ 50% of Aδ and 70% of C-fibres are classified as high threshold units [61]. During inflammation, Aδ and C-fibres show increased mechano-sensitivity. Low threshold populations exhibit exaggerated responses, whereas high threshold populations and units that were initially mechano-insensitive are sensitized and respond to movements in the normal working ranges of the joint [62]. So far, no specific investigation of functional properties of bone sensory afferents have been made, in particular in animal models that more closely resemble OA pathology.

MRI imaging studies in OA indicate an association of pain with a hyper-intense signal on T2-weighted fat-suppressed images in the subchondral bone [27]. What may underpin these MRI signals and hence structural association with pain is still under debate. Zanetti *et al.* [63] reported that although approximately half of the lesion was normal tissue, abnormalities were observed including bone marrow necrosis, abnormal (necrotic or remodelled) trabeculae, bone marrow fibrosis and a small percentage of bone marrow oedema and bone marrow bleeding. So far, the local milieu within these lesions is unknown, although the observed oedema and bleeding may indicate inflammatory mediator release. The subsequent sensitisation of innervating subchondral Aδ and C-fibres and altered bone mechanics due to remodelled trabeculae, may be sufficient to cause activation and sensitisation of high and low threshold sensory afferents following joint use.

Bone remodelling may also have a direct effect on joint pain. Bone density studies indicate that these lesions can also be associated with increased bone density as well as osteopenic bone [64,65]. Catastrophic skeletal remodelling and association with pain has been studied in models of osteoblastic and osteoclastic bone cancer models [65]. In mouse primary osteolytic models (2472 sarcoma), tumour cells contact and injure distal processes of sensory fibres. In contrast, damaged afferent nerves in mouse bone exhibit a net increase in density due to sprouting following injection of primary osteoblastic (ACE-1) tumour cells [65]. Models of OA (rat mono-iodoacetate and rat menisectomy) also show that a similar elevation of nerve injury markers (e.g., activating transcription factor-3) occurs during bone remodelling [66,67]. These models also demonstrate a pharmacological sensitivity to drugs known to effectively ameliorate neuropathic pain (e.g., gabapentin, amytriptyline) [66,68]. However, clinical support for using such drugs in OA pain treatment is limited at present.

Interventional therapy targeting bone resorption has been explored in OA. There is a broadening scope for the use of calcitonin in OA pain. Thus, Novartis and Nordic Bioscience have initiated a Phase III trial of their oral salmon calcitonin tablet, formulated using Emisphere's eligen delivery technology, for OA [69]. Interestingly, Phase II trials of oral salmon calcitonin, have also shown significant improvements in OA pain [70]. Calcitonin-induced pain relief is likely caused by a number of mechanisms. Calcitonin has been demonstrated to have anti-inflammatory effects via inhibition of prostaglandin E2 synthesis, and also elevate endogenous β-endorphin levels. Furthermore, exogenous calcitonin may cross the blood–brain barrier to modify pain end points in rodent models, possibly via direct interaction with receptors in the brain stem or by stimulation of descending spinal serotonergic pathways [71].

Other antiresorptive agents (e.g., the bisphosphonate risedronate) induce osteoclast apoptosis and also ameliorate pain in patients with osteolytic bone metastases and other painful skeletal syndromes (e.g., reflex sympathetic dystrophy associated with increased bone turnover). Interestingly, risedronate had no effect on OA signs and symptoms despite evidence of improvements in trabecular bone loss and structure [41,48,49]. Furthermore, preclinical data also indicate that risedronate has an additional intrinsic antihyperalgesic activity associated with reduced cell infiltration and inhibition of TNF-α and leukotriene B4 (LTB4) [72]. It is thus surprising that no effect has been noted on OA signs and symptoms, possibly reflecting inadequate exposure in OA clinical trials [41,48,49].

Chemoreception in bone and bone lesions may also serve as a stimulus for prolonged activation of skeletal sensory nerves. Haematopoietic and immune cells within bone marrow or infiltrating inflammatory cells secrete prostaglandins, cytokines, neurotrophins, chemokines, serotonin and so on, which directly excite or sensitise primary afferents (see Section 4). Furthermore, in diseases with significant bone remodelling, skeletal pain is often reported in advance

of radiological evidence of bone destruction, suggesting that early skeletal pain may be driven via local inflammation rather than by frank bone degradation. During bone remodelling, osteoclasts secrete protons, which will activate transient receptor potential vanilloid 1 (TRPV1) channel, acid-sensing ion channels (ASICs) or augment/stimulate sensory afferent firing via inhibition of K^+ channels [73]. The relative contribution of TRPV1 and ASICs to proton activation of sensory afferents is only just emerging and may be species and nerve-fibre-type specific (isolectin $B4^{-/+}$) [74].

ASICs are members of the degenerin/epithelial amiloride-sensitive Na^+ channel (EnaC) superfamily. Several subunits have been identified, 1a, 1b, 2a, 2b, 3 and 4, but there has been little progress in developing selective pharmacological tools. Amiloride has been shown to be a nonselective blocker of ASICs with low potency, but improved blockers of peripheral ASIC 1, 2 and 3 channels, such as A-317567, with IC_{50} values for ASIC1a-, ASIC2a- and ASIC3-like currents of 2.0, 29.1 and 9.5 μM [75], respectively, have been reported but not validated in clinical development. However, PainCeptor have announced the intention to take PPC-5650, an ASIC modulator, into Phase I trials this year [76].

No discussion of the origins of bone pain in OA would be complete without consideration of intra-osseous hypertension. The pathophysiology remains unclear, although phlebographic studies in OA indicate impaired vascular clearance from bone and raised intra-osseous pressure in the bone marrow near the painful joint [77]. What may subsequently cause pain is as yet unknown. Increased trabecular bone pressure, ischaemia and inflammation are all possible stimuli [78]. As such, mechanically sensitised primary afferents or indeed development of a localised ischaemic neuropathy may drive pain. Interestingly, intra-osseous hypertension is observed in patients with pain at rest/night pain [77]. Night pain in particular, has been difficult to treat with existing anti-inflammatory therapies. Therefore, greater understanding in the underlying drivers may offer novel differentiated therapeutic opportunities.

In summary, bone remodelling via osteoblastic and clastic activity has been associated with modification of sensory afferent innervation of bone in oncology. Similar mechanisms may also play a role in OA. Activation of bone sensory afferents through chemoreception or interactions with bone vasculature may act in synergy to establish a chronic bone pain in OA.

4. Joint inflammation and inflammatory mediators of pain

Most cases of clinically significant OA are accompanied by significant inflammation. Often cited as evidence of joint inflammation in OA, is a synovial reaction including synovial hyperplasia, fibrosis, thickening of synovial capsule, activated synoviocytes and in some cases lymphocytic infiltrate (B and T cells, as well as plasma cells) [79]. Other innervated structures of the joint such as the white adipose tissue of the fat pad also show evidence of inflammation and can act as a rich source of inflammatory adipokines [80,81]. As a broad indicator of inflammatory status of the joint, synovial fluid has been extensively profiled for mediator concentrations in several arthropathies. Key mediators in OA versus RA are exemplified in **Table 1**. Broadly, excitatory amino acids, neuropeptides and cytokines are consistently elevated in RA when compared to OA, with a particular exacerbation of IL-6 concentrations in RA relative to OA (**Table 1**).

4.1 Opioids and their receptors

In patients who do not respond or have contraindications to selective and non-selective NSAIDs, opiate analgesia is frequently employed to treat OA pain. Early in the 1990s, the opiate G-protein-coupled receptor family was identified together with a variety of endogenous ligands derived from proenkephalin gene products. An additional orphan opioid-like receptor ORL1 was identified with a corresponding ligand nociceptin/orphanin FQ. ORL-1 has a distinct ligand recognition pattern and different anatomical distribution to opiate receptors [82].

Opiates act at peripheral, spinal and supraspinal sites [83]. In the periphery, inflammation enhances the apparent potency of opioid agonists, in particular agonists at the μ-receptor. This may be due to a combination of peripheral and central changes in receptor density, affinity and recruitment of endogenous opioid-expressing leukocytes to the site of injury. Opioid receptor activation in the periphery hyperpolarises sensory neurons and attenuates nerve hyperexcitability caused by inflammation or injury [84,85]. Localised, intra-articular delivery of morphine support the concept that peripherally restricted opiate analgesia is plausible in OA and may overcome the common adverse events of centrally penetrating opiates [86]. Several pharma are investigating peripheral restricted μ-opioid agonists. Purdue are investigating DiPOA, (8-[3,3-diphenyl-propyl]-4-oxo-1-phenyl-1,3,8-triaza spiro[4.5]dec-3-yl)-acetic acid, a selective μ-receptor agonist with a brain:blood ratio of 0.019 ± 0.014 [87]. Furthermore, the antidiarrhoea drug loperamide, which also does not penetrate the blood–brain barrier, has shown efficacy in a number of post-operative, inflammatory, bone cancer and neuropathic pain models [88,89]. Adolor is developing ADL-2-1294, a topical and intra-articular formulation of loperamide for local delivery. Reformulation of existing μ-opiate agonists and fixed-dose combinations comprise the majority of other pharma activity in this area.

Delta opioid receptor (DOR) agonists have the potential for analgesic efficacy without the confounding side effects of proteotypic μ-opioid receptor agonists such as morphine [90]. The first moderately selective, non-peptidergic delta opioid agonist was BW373U86, closely followed by the selective

Table 1. Knee synovial fluid inflammatory mediator, neuropeptide, neurotransmitter and excitatory amino acid concentrations in OA and RA.

Mediator	Patient population	Concentration (pg/ml)	Fold difference	Ref.
TNF-α	OA	39 ± 6 69 ± 32		McNearney *et al.* [210] Schumacher *et al.* [127]
	RA	95 ± 25	× 2.4	
IL-6	OA	89 ± 120 398 ± 113		Bertazzolo *et al.* [211] Schumacher *et al.* [127]
	RA	1610 ± 1781	× 18	
IL-1β	OA	27.8 ± 4.5		Westacott *et al.* [212]
	RA	130.3 ± 22	× 4.6	
CGRP	OA	70 ± 48		Arnalich *et al.* [195]
	RA RA (early) (late)	134 ± 86 580 450	× 1.9	Arnalich *et al.* [195] Grimsholm *et al.* [213]
Substance P	OA	71 ± 18		Arnalich *et al.* [195]
	RA	115 ± 21	× 1.6	
VIP	OA	10 ± 4		Arnalich *et al.* [195]
	RA	19 ± 13	× 1.9	
NGF	OA	6.5 + 19.7		Dicou *et al.* [214]
	RA	12.5 + 19.2	× 1.9	
PGE2	OA	4200 ± 300		Schumacher *et al.* [127]
	RA			
Glutamate	OA	240 ± 38 μM		McNearney *et al.* [210]
	RA	332 ± 29 μM	× 1.4	
5-HT	OA	0.49 + 0.13 ug/ml		Igari *et al.* [215]
	RA	0.53 + 0.26 ug/ml	× 1	

5-HT: 5-Hydroxytryptamine; CGRP: Calcitonin-gene-related peptide; NGF: Nerve growth factor; OA: Osteoarthritis; PGE: Prostaglandin E; RA: Rheumatoid arthritis; VIP: .

SNC-80; both agonists are based on a diarylmethylpiperazine structure. These structures, and also that of the delta antagonist naltrindole, have subsequently formed the basis for extensive development of selective delta agonists. Delta opioid analgesia has been shown in primate and non-primate pain models with several ligands (e.g., [D-Pen2,D-Pen5] enkephalin, SNC-80, ARM-390). Stimulus-dependent trafficking of DOR from cytoplasm to cell surface appears to modulate apparent efficacy of agonists. This depends on the pain stimulus, the type of injury, the duration and the influence of the local neurochemical environment. Thus, delta ligands have low analgesic efficacy in acute pain models, but show robust analgesia efficacy in a variety of chronic pain conditions accompanied by inflammation [91]. Adolor has begun a Phase II trial of its delta opioid agonist ADL-5859 for pain following third molar tooth extraction in comparison to placebo and ibuprofen. The company expects to complete the study in early 2008 and to begin further trials in additional indications in the fourth quarter of 2007. A further IND filing for ADL-5747, is also expected by the end of 2007 [92].

4.2 Kinins and their receptors

Bradykinin is an important mediator of inflammatory pain causing nociceptor activation and sensitisation via B2 receptors [93]. The abundant metabolite of bradykinin, des Arg^9 bradykinin (kallidin), activates B1 receptors, which occur in low abundance in the periphery and CNS [94-96].

B2 receptors undergo desensitisation following prolonged kinin exposure, whereas B1 receptors do not desensitise rapidly and are dramatically upregulated in many tissues following injury [97-100] or exposure to IL-1β or the neurotrophin glial-derived neurotrophic factor [98,101]. Importantly, kinins cause a cascade of secondary changes, including prostanoid and nitric oxide production, phosphorylation of signalling proteins such as PKC, and the sensitisation of sensory

transducers such as the TRPV1 receptor [102]. These events are linked with heat and mechanical hyperalgesia [103,104]. In keeping with this, B2 (e.g., icatibant, bradyzide) and B1 (des Arg^{10} HOE-140; SSR240612) antagonists produce robust antihyperanalgesic effects in models of nerve injury-induced pain [105-108]. Importantly, intra-articular administration of icatibant (HOE 140) in OA patients was shown to reduce pain intensity at rest and during activity [109]. Although icatibant was on sanofi-aventis internal medicine portfolio in 2006, it is no longer listed and it is assumed that development has ceased. Other bradykinin antagonists in development include Amgen's AMG-379 and sanofi-aventis' SSR-240612, both antagonists of the B1 receptor.

4.3 Cannabinoids and their receptors

The two G-protein-coupled receptors that mediate the effects of cannabinoids are CB1 and CB2. The receptors are 44% identical and couple to Gi/o proteins inhibiting cellular adenylyl cyclase and MAPK activity, although the CB1 receptor is also G-protein coupled to calcium and potassium channels. Both receptors are extensively associated with pain modulation [110]. CB1 receptors are widely distributed in the CNS and peripheral sensory neurons and tissues, whereas CB2 receptors are predominantly found on immune tissues and keratinocytes with some expression in sensory and brainstem neurons [111].

Frequently, receptor systems found on peripheral sensory afferent terminals are also reflected in cells of the joint, often modulating matrix turnover. Constitutive expression of both CB1 and CB2 receptors have been isolated on chondrocytes and implicated in a potential disease-modifying role in OA [112].

Several fatty acids (e.g., anandamide, 2-arachidonylglycerol and palmitoylethanolamide) have been identified as the endogenous ligands for these receptors, while specific antagonists such as CP-945,598, SR141716A, SR-147778 for CB1 and SR144428 for CB2 have been used to characterise receptor functions. Of these compounds, CP-945,598 is in Phase III development for obesity and SR-147778 in Phase IIb for smoking cessation. The therapeutic potential of natural product-derived cannabinoids has been well known for centuries. In general, side effects such as vertigo, euphoria, dizziness and sedation, may be mediated by central CB1 receptors. This limits therapeutic application to patient populations in which the side effect/benefit profile is favourable [113]. For example, Sativex (delta[9]-tetrahydrocannabinol [THC] and cannabidiol; GW Pharmaceuticals) was approved in Canada in 2005 for neuropathic pain associated with multiple sclerosis, and by the FDA for Phase III trials in the US for cancer pain. Such a side-effect profile is unlikely to be tolerable in OA. Therefore, in order to avoid central CB1 agonism, selective CB2, peripherally restricted CB1 or dual CB1/CB2 agonists are being developed.

CB1 receptors attenuate pain by reducing peripheral nerve excitability and through inhibition of sensory transmitter release [114]. There is both a CNS and peripheral component to CB1-induced analgesia. In the CNS, brain stem structures such as the periaqueductal grey appear to be an important for stress-induced release of endocannabinoids and CB1-induced analgesia may involve activation of descending pathways that inhibit spinal excitability [115,116]. The concept of peripherally restricted CB1 agonism as an antinociceptive approach has been extensively demonstrated by local administration of selective agonists (e.g., 2-arachidonyl-2-chloroethylamide in animal models).

Diverse preclinical literature supports the role of CB2 in modulation of acute and chronic pain [117,118]. Prototypical CB2 agonists/partial agonists (e.g., HU-308, AM1241 and GW405833) exhibit efficacy in preclinical models of inflammatory and neuropathic pain, whereas JWH-133 also shows anti-inflammatory activity [119]. It is unclear how these effects are produced as few CB2 receptors are found in the CNS or on sensory neurons [120]. β-Endorphin release from non-neuronal cells or induction of CB2 expression in neurons may offer an explanation of activity. However, CB1-like side effects (sedation, catalepsy, motor impairments) have not been seen with CB2-selective compounds. A number of CB2 agonist structural series have been developed. So-called classical cannabinoids are THC analogues based on tricyclic pyran core. Opening the pyran ring produces the bicyclic derivatives (non-classical cannabinoids), for example, CP-55,940. Several companies, including Bristol-Myers Squibb, sanofi-aventis, Abbott Laboratories, AstraZeneca and Pfizer, have reported indole, benzimidazole and indazole derivatives. For a full discussion of structure–activity relationships at the CB2 receptor, readers are referred to review of Cheng and Hitchcock [121] and references contained within. Other structural series have also been reported by GlaxoSmithKline (GW-842166), Adolor (sulfonylbenzamides), Shinogi & Co. (3-carbonyl-2-pyridones and others), Ferring (alkylcarboxamidearylureas) and Solvay (imidazole-4-carboxamides). CB2 agonists are presently in Phase II clinical trial for pain, for example, PRS-211,375 (Cannabinor, Pharmos Corp.) and GW-842166 (GlaxoSmithKline). In April 2007, Pharmos Corp. reported an analgesic effect with PRS-211,375 12 mg, but no effect of 24 and 48 mg doses. The significance of this lack of dose response is being explored further, although doses were well tolerated with no serious adverse events.

Harnessing the endogenous cannabinoid system by targeting fatty acid amide hydrolysis (FAAH), the major degradation pathway for endogenous cannabinoids, is an alternative approach to CB agonism [122]. Mice lacking FAAH [123], or treatment of naive mice with inhibitors such as URB597 and OL135, significantly elevates brain anandamide and increased pain threshold in pain models [124,125]. FAAH inhibitors are beginning to enter development, for example, SSR-411298 (sanofi-aventis) is presently in Phase I development for depression and anxiety.

In summary, understanding the side effect liability in the clinic of cannabinnoid agonists will be critical to application in the OA population. Additivity of μ-opioid and cannabinoid agonism has been shown to provide pain reduction with minimal side effects in acute pain models and combinations with low-dose agonists may be the alternative route to modulate the total side-effect burden [126].

4.4 Prostanoids and receptors

Prostanoid COX enzyme products (PGE2, PGD2, PGF 2α, thromboxane, PGI2) are produced during inflammation. In OA synovial fluid, high concentrations of prostaglandin E2 (PGE2) are typically found (e.g., 4200 ± 300 pg/ml [127]), reflecting an active COX drive in the joint. Further along the nociceptive pathway, increased spinal cord expression of COX-1 (glia) and COX-2 (ventral horn cells) has been observed following inflammation and peripheral nerve injury [128]. Pharmacological inhibition of COX-1 and COX-2 pathways and the adverse event liabilities have been discussed previously. However, PGE2 exerts its effects via a variety of EP receptors (EP1, 2, 3, 4) present both in peripheral sensory neurons and in the spinal cord. Activation of these receptors produces a complexity of effects, ranging from calcium influx to cAMP activation or inhibition. Sensitisation of nociceptors by PGE2 is caused by the cAMP-mediated enhancement of sodium currents via ion-channel phosphorylation [129,130]. However, in the spinal cord, prostaglandin-induced hyperexcitability was enhanced by EP1 receptors, but reduced by an EP3α agonist (ONO-AE-248), suggesting further complexity in the prostanoid regulation of pain mechanisms [131]. Pfizer have entered development with an EP4 antagonist CJ-023,423, presently undergoing Phase I studies to explore gastrointestinal tolerability.

Recently, COX-3 has been identified as a splice variant of COX-1 [132]. Several NSAIDs (acetaminophen: diclofenac, phenacetin) show low efficacy and some degree of selectivity for COX-3. However, COX-3 has low enzymic capability and its distribution and low abundance in the CNS and in periphery does not make this a compelling target for analgesia.

An alternative route of PGE2 inhibition is via the blockade of PGE synthase (PGES), a major route of conversion of prostaglandin H2 to PGE2. Two isoforms of the enzyme have been identified, membrane or microsomal associated (mPGES-1) and a cytosolic enzyme (cPGES/p23), which are linked with COX-2- and COX-1-dependent PGE2 production, respectively [133,134]. Both isoforms are upregulated by inflammatory mediators. Gene deletion studies in mice indicate an important role for mPGES in acute and chronic inflammation and inflammatory pain [135]. Inhibition of mPGES is thought to be associated with lower CV risk, as PGI2 production would not be affected.

4.5 Cytokines, chemokines and their receptors

Evaluation of cytokine cascades in OA, has received considerable attention, although pharmacological intervention has been limited to use of biological approaches. Relative to RA, synovial fluid cytokines in OA are reduced, although concentrations of tumour TNF-α and IL-1β in OA and RA appear similar (**Table 1**). Cytokines induce hyperalgesia by direct and indirect actions. Thus, IL-1β activates nociceptors directly via intracellular kinase activation, but it may also cause indirect nociceptor sensitisation via the production of kinins and prostanoids [136]. TNF-α also activates sensory neurons directly via TNF-R1 and TNF-R2 receptors and initiates a cascade of inflammatory reactions through the production of IL-1, -6 and -8 [137,138], although IL-6 pathway activation may be less marked in OA than RA (**Table 1**). In the light of these observations it is not surprising that efficacy signals have been observed with anti-TNF-α or anti-IL-1β biologicals in OA, although so far there is no clear trend. For example, adalimumab (Humira; Abbott), a recombinant human IgG1 monoclonal antibody specific for human TNF, has produced a prolonged reduction of pain symptoms in OA [139], although other open-label usage in OA has failed to observe any improvements in signs and symptoms [140].

Intra-articular anakinra (Kineret; Amgen), the IL-1 receptor antagonist (IL-1Ra), has been investigated in a double-blind, safety study exploring six doses (0.05 mg up to 150 mg) in symptomatic knee OA. Efficacy was estimated as a secondary end point. A moderate, but significant, improvement in Visual Analogue Scale (VAS) pain score and WOMAC global score was observed in the third month of treatment in the 13 patients who received IL-1Ra 150 mg [141]. However, a follow-up double-blind, placebo-controlled, multicentre trial of a single intra-articular injection of anakinra in 170 patients with OA of the knee failed to demonstrate significant improvement in the WOMAC index at week 4 (primary end point) after 50 or 150 mg doses [142].

Potentially, the short half-life of anakinra could underpin the lack of efficacy, although trials with longer half-life anti-IL-1 approaches (e.g., AMG-108 [Amgen]) have yielded similar results. AMG-108 is also an anti-IL-1R1 human monoclonal antibody and was studied in 146 patients with OA. AMG-108 also failed to meet primary end point of significant pain reduction in a Phase II study in OA [143].

Chemokines are peripheral and central regulators of chronic inflammation. Receptors have been detected throughout the CNS in microglial cells, astrocytes, oligodendrocytes and in isolectin B4 and substance-P-positive primary afferent neurons [144,145]. Chemokines can contribute directly to hyperalgesia through G-protein-coupled sensitisation of ligand-gated channels (e.g., TRPV1), heterologous desensitisation of opioid receptors and through sensitisation of sensory neurons [145,146]. For example, CC chemokine ligand 2 (CCL2) and CCL3 (MIP-1a) sensitise TRPV1 to capsaicin via removal of an intracellular phospholipid inhibitor [145]. Furthermore, CCL2, CCL3, CCL5 and CXC chemokine ligand 8 (CXCL8) also desensitise μ-opioid receptors. Therefore, the phasic synovitis that accompanies OA may serve as a priming

event for subsequent hyperalgesia mediated in part by chemokine- and cytokine-induced priming of sensory afferents or desensitisation of endogenous opiate systems.

4.6 Adrenergic receptors

The joint capsule, synovium and bone are richly innervated by sympathetic post-ganglionic neurons. A dynamic interplay exists between sympathetic innervation and the control of vascular tone, bone turnover, inflammatory status and sensory innervation in the joint. In RA, sympathetic innervation is reduced, probably by increased release of sympathetic nerve repellents such as semaphorins. At present, there is no data to support sympathetic denervation in OA [147], although waxing/waning of sympathetic innervation in the joint offers an attractive hypothesis for OA inflammatory flare.

Induced expression of α-1 and α-2 adrenergic receptors on sensory neurons or on post-ganglionic sympathetic terminals has been reported [148,149]. Under these conditions sensory neurons can be directly activated by the endogenous release of sympathetic transmitters. Although clonidine and other α-2 agonists such as dexmedetomidine have been used as systemic analgesics, working via the spinal cord by block of pre- and post-synaptic excitability, sedation and hypotension are target-related systemic side effects of these compounds. Direct intra-articular administration, for example, following joint replacement, may offer therapeutic advantage.

4.7 Glutamate regulation and glutamate receptors

In OA, synovial fluid levels of glutamate are significantly elevated above controls [150]. Glutamate acts through receptor-coupled ligand-gated ion channels (AMPA/kainate receptors: ionotropic glutamate receptors [iGluRs]) and GPCR-coupled receptors (metabotropic glutamate receptors [mGluRs]). Injections of glutamate or metabolically stable receptor selective agonists such as NMDA, AMPA and kainate, cause a reduction in thermal and mechanical thresholds for pain, while application of iGluR and mGluR antagonists attenuate pain in acute models [151,152]. Glutamate may also have a disease-modifying role, with receptors found on non-neuronal cells (i.e., osteoblasts, osteoclasts, and chondrocytes mediating bone remodeling and cartilage mechanotransduction, respectively) [153,154].

NMDA antagonists show robust attenuation of pain behaviours, but provoke a number of side effects (sedation, confusion, motor deficits) and thus have insufficient therapeutic window. There has been a refocus on more specific NMDA-receptor subtype blockers (NR1 and NR2) directed towards the strychnine-insensitive $glycine_B$ modulatory site to avoid side effects. This site modulates the NMDA channel only during the sustained stimulation of the receptor, which is considered to occur during chronic pain. Selective NR1-Gly antagonists have been claimed to reduce pain with reduced side effects [155,156]. However, clinical experience has not confirmed this. GV-196771 did not show efficacy against clinical pain, possible due to inadequate penetration into the CNS [157].

Alternative initiatives have targeted other NMDA-receptor subtypes such as the NR2B receptor, which has a specific distribution in sensory pathways. Blockade of this receptor has also been claimed to produce antinociception (ifenprodil, traxoprodil [CP-101,606]) with reduced side effects [158]. Evotec Neurosciences (EVT-101, EVT-103) is investigating NR2B subtype-selective antagonists, under licence from Hoffmann-La Roche, for the treatment of neurological conditions. EVT-101 has successfully completed Phase I clinical trials and was well tolerated with no significant adverse events and a pharmacokinetic profile consistent with once- or twice-daily oral dosing. Several other companies including Merck (MK-0657) and Gedeon Richter (RGH-896) have compounds in early Phase I trials for Parkinson's disease, depression and neuropathic pain [159,160].

Metabotropic glutamate receptors, particularly mGluRs 1 and 5, have been reported to play a key role in sustaining heightened central excitability in chronic pain with minimal involvement in acute nociception. Thus, spinal administration of selective agonists such as dihydroxy phenyl glycine produced allodynia, whereas mGluR5 was shown to be significantly overexpressed in some, but not all, chronic pain models [161]. Peripheral mGluR5 receptors have also been claimed to modulate pain. Thus, local administrations of mGluR5 antagonists (MPEP, SIB-1757) have been effective in reducing pain behaviour, suggesting a potential for these agents in pain therapy [162,163].

Metabotropic group II receptors (mGluR 2 and 3) also modulate pain transmission. mGluR 2 is located in sensory neurons and presynaptic nerve terminals, whereas mGluR 3 is found all over the brain. mGluR3 can be selectively increased in the spinal dorsal horn neurons after peripheral ultraviolet (UV) injury [164]. mGluR 2/3 receptor activation appears necessary to reduce nerve terminal excitability and to modulate pain transmission, as treatment with the agonist L-acetyl carnitine reduced inflammatory hyperalgesia and mechanical allodynia, and increased expression of mGlur2/3. The effect of L-acetyl carnitine was attenuated by LY-379268, an mGlu2/3 antagonist [165].

4.8 Ion channels

4.8.1 Transient receptor potential channels

Although the mammalian transient receptor potential (TRP) channel represents a large receptor family, subdivided into six subfamilies: TRPA, TRPC, TRPM, TRPP, TRPV, and mucolipin, pharmaceutical interest has primarily focused on TRPV1. TRPV1 is a non-selective cation channel, gated by capsaicin, noxious heat (> 45°C), acidic pH (< 5.3), and regulated by a variety of inflammatory agents including protons, bradykinin, ATP, PGE2, 12-lipoxygenase products, protease-activated receptor-2, anandamide, CCL3 and nerve growth factor (NGF). Sensitisation of

TRPV1 involves a variety of pathways that regulate receptor phosphorylation [166].

Pharmacological approaches to TRPV1 have encompassed low-dose agonists that desensitise the channel, high-dose agonists that cause frank dysfunction of sensory afferents with a long-lasting, but reversible, dying back of sensory fibres, and receptor antagonists. TRPV1-based analgesia strategies in OA have primarily focused on agonists. For example, in 12 subjects with knee OA randomised to intra-articular injection of placebo or capsaicin 1 mg (ALGRX-4975 [Adlea; Anesiva]), prior to knee replacement. ALGRX-4975 was found to decrease VAS scores without effecting proprioreception or joint histopathology [167].

Antagonist approaches can be broadly classed into those that block the effects of capsaicin-, acid- and heat-mediated channel activation (e.g., the pyrrodinyl urea SB-705498), or those that demonstrate a selectivity to capsaicin (e.g., capsazepine). The most advanced compounds so far have entered the clinic (i.e., SB-705498 [GlaxoSmithKline], NGD-8243/MK-2295 [Neurogen/Merck]) and have consistently shown attenuation of experimentally induced hyperalgesia caused by capscacin injection or a UV burn injury.

Pharmacological intervention in other TRP channels is at an early stage. For example, TRPA1 (ANKTM1) is co-localised with TRPV1, is activated by capsaicin and mustard oil, but can also be sensitised by inflammatory mediators including bradykinin, known to be significantly elevated in osteoarthritic synovial fluid and is known to produce cold-induced burning pain [168]. Furthermore, selective compounds for this channel have been reported to be antinociceptive (e.g., HC-030031 [Hydra]) [169].

4.8.2 *Purinergic receptors regulated channels*

A variety of purinergic (P2X) receptors have been implicated in chronic inflammatory pain. These are activated by ATP released by inflammation and tissue injury. Probably the most validated purinergic receptors in chronic pain are P2X3, P2X4 and P2X7.

During inflammatory pain P2X3-mediated sensory nerve excitability is enhanced, whereas antisense reduction of P2X3 receptors reduces inflammatory hyperalgesia as well as that evoked by the stable ATP ligand α-,β-Me-ATP [170]. Antagonists including 2′,3′-*O*-(2,4,6-trinitrophenyl)-ATP (TNP-ATP), pyridoxal-phosphate-6-azophenyl-2′,4′-disulfonic acid, and suramin, reduce pain behaviour. More selective, and drug-like, antagonists such as A-3174919 reduced pain in a number of acute and chronic pain models, supporting the possibility for future analgesia therapy [171].

P2X4 and P2X7, have also been suggested to modulate pain through altered central excitability and the release of neuroglial-cell products. Astrocytes, microglial and satellite cells release a variety of inflammatory mediators including IL1-β, TNF-α, prostanoids and nitric oxide following ATP-induced stimulation. Furthermore, increased expression of P2X4 has been shown to occur in spinal microglial after peripheral nerve lesions and this was related to painful mechanical allodynia. This behaviour was blocked by spinal administrations of the selective P2X4 antagonist TNP-ATP [172].

Increased P2X7 expression has been found in peripheral macrophages following inflammation, but this receptor is also expression in spinal neurons and microglia following peripheral nerve injury [173]. In keeping with an important role in chronic pain, both microglia and P2X7 receptors are upregulated in human chronic pain patients, whereas deletion of the P2X7 receptor gene produced a complete absence of mechanical and thermal pain in mice [174].

It is worth noting that other nucleotide-gated ion channels have also been shown to be important for regulating peripheral excitability. Thus, the Na/K repolarising 'pacemaker current', Ih, which is activated during membrane hyperpolarisation, is important for generation of rhythmic and spontaneous action potentials in sensory neurons. Ih currents are controlled by cyclic nucleotides (cAMP and cGMP) via a family of hyperpolarisation-activated, cyclic nucleotide-gated (HCN1 – 4) channels constitutively expressed in sensory nerves and differentially distributed after inflammatory nerve injuries [175,176].

4.8.3 *Voltage-gated sodium channels*

The clinical utility of non-selective voltage-gated sodium (Na_v) channel blockade in OA pain patients has been well established with the use of local anaesthetics, such as intra-articular levobupivacaine, the active enantiomer of bupivacaine. Other evidence from commonly used therapies in OA pain also implicate a role for Na_v in OA pain. Several tricyclic antidepressants block Na_v at clinically relevant concentrations and in a rank order that correlates with analgesic efficacy.

Mammalian Na_v are characterised by an α subunit and one or more β subunits. In general, the α subunit has been considered to form the route of sodium permeation into the cell, whereas the β subunit modulates channel kinetics and gating. In dorsal root ganglia, Na_v channels can be pharmacological distinguished by sensitivity to tetrodotoxin (TTX). A variety of TTX-sensitive (Na_v 1.3, Na_v 1.7) and TTX-insensitive (Na_v 1.8, Na_v 1.9) channels are involved in regulating sensory neural excitability [177,178]. Broadly, Na_v 1.7, 1.8 and 1.9 are mainly expressed in the peripheral nervous system, Na_v 1.1 and 1.6 in the peripheral and central nervous system and Na_v 1.2 in the CNS. Changes in the expression, trafficking and redistribution of Na_vs, following inflammation (e.g., human tooth pulp or nerve injury) are considered to account for the ectopic generation of afferent nerve firing [179,180].

Systemically used non-selective Na channel blockers are poorly tolerated. Although intravenous administration has been reported to produce long-lasting pain relief both in animal models [181] and in intractable neuropathic pain [182],

a narrow therapeutic window exists. This is due to cardiotoxicity and CNS sedation/confusion produced by Na_v 1.5 and 1.2 channel block, respectively. Based on expression data, selectivity for Na_v 1.7, 1.8 or 1.9 might be expected to avoid CNS side effects and muscle side effects of Na_v 1.5 (cardiac muscle) and Na_v 1.4 (skeletal muscle) inhibition. Few subtype-specific inhibitors have been reported so far, although Abbott/Icagen have reported a sodium channel blocker (A-803467) that is highly selective for Na_v 1.8 channels, and demonstrates efficacy in mechanistic models of neuropathic and inflammatory pain models [183].

4.8.4 *Calcium channels*

Na_v channels are subdivided into two major categories: low-voltage-activated calcium channels (T-type channels) and high voltage-activated. High-voltage-activated channels are further subdivided, based on pharmacology and biophysical characteristics into L-, N-, R-, P- and Q-types. Several have been shown to be prominently involved in pain regulation [180]. The N-type calcium channel is an important regulator of nerve terminal excitability and neurotransmitter release. N-type channels can be regulated particularly through GPCR signalling by analgesic drugs such as opioids, with a resultant modulation of sensory transmitter release (e.g., substance P, CGRP, glutamate) at both spinal and at peripheral sensory nerve terminals. Ion-channel trafficking may also be affected, for example, activation of the opioid receptor-like receptor by nociceptin causes channel internalisation and downregulation of calcium entry [184].

Deletion of the N-type channel gene reduces inflammatory and neuropathic pain [185,186]. Moreover selective blockers such as ziconotide (SNX-111; Prialt), a synthetic form of Ω-conotoxin, and verapamil have been used to characterise channel activity. In addition, ziconitide has been used experimentally and clinically by spinal intrathecal administration for pain relief [187,188]. Building on this concept, small-molecule channel blockers, are now reported to be undergoing clinical evaluation (e.g., MK-6721 [NMED-160], although development of this particular compound has been halted due to reports of not having required pharmaceutical properties) [188].

Low-voltage-activated T channels also appear important for pain transmission and as targets for pain therapy. Thus, they are expressed in superficial laminae of the spinal cord and in dorsal root ganglion neurons [180]. T-channels play a prominent role in regulating spinal excitability and spinal sensitisation following repetitive C-fibre stimulation [189]. Moreover, nerve injury-induced hyper-responsiveness was blocked by the T-channel blocker ethosuximide [190], which also attenuated mechanical allodynia in animal models of vincristine and paclitaxel-induced neuropathic pain [191].

Finally, high-voltage-activated channels are comprised of four subunits: an $\alpha 1$ subunit, and auxiliary subunits, $\alpha 2\delta$, β, and γ. There are four human $\alpha 2\delta$ genes described, $\alpha 2\delta 1 - 4$, which associate into different subsets of channels and have different tissue distributions. Pregabalin and gabapentin are inhibitors of $\alpha 2\delta 1$ and $\alpha 2\delta 2$. These drugs are thought to act as presynaptic inhibitors of the release of excitatory neurotransmitters in hyperactive neurons. It is not surprising therefore, that they are effective in states of enhanced neuronal activation during inflammation and nerve lesioning (spinal cord injury, diabetic neuropathy neuropathic cancer pain, HIV-associated neuropathy) [192,193]. Pregabalin has been assessed in hip (81% of patients) and knee OA (19% of patients) in a 12-week, double-blind, placebo-controlled, multi-centre study in 296 patients at 300 and 600 mg/day. The primary efficacy end point was weekly mean pain score derived from daily pain diaries. Secondary end points included WOMAC, patient and clinician global assessment and mean quality of sleep. No response was observed in all patients versus primary end point. At the highest dose of 600 mg/day at some intermediate time points, in patients with hip OA, significant improvements were observed in WOMAC pain and functional subscales as well as patient and clinician global assessment. Sleep quality was also significantly improved at weeks 1 – 8 and at study completion [194].

4.9 Neurotrophins and their receptors

NGF appears to be important in OA aetiology as synovial fluid concentrations are elevated in several arthritidies [195]. NGF has emerged as a key regulator of sensory neuron excitability and as an important mediator of injury-induced nociceptive and neuropathic pain [196-198]. NGF acts via TrkA and p75 to activate a number of kinase pathways (e.g., p38 kinase), leading to altered gene transcription and the increased synthesis of sensory neuropeptides (substance P, CGRP), ion channels (TRPV1, NaV1.8, ASIC3) [199-201], membrane receptors such as bradykinin and P2X3 and structural molecules including neurofilament, and channel anchoring proteins such as the annexin light chain p11 [202].

In OA, NGF has been detectable in synovial fluid, although not universally so. Thus, NGF was detected in 4 out of 27 OA patients [123], whereas autoantibody titres to NGF were observed in the sera and synovial fluid of patients that are capable of endogenously neutralising NGF function [195]. Therefore, it may be that NGF is a key neurotrophin in a subset of OA patients, in which free concentrations exceed that which is endogenously neutralised. Proof of concept for a pivotal role of NGF in OA pain has been achieved with RN624, a humanised anti-NGF mAb, that has been reported to be efficacious in reducing pain and improving mobility in OA [203]. Other biologicals targeting NGF are in early stage of development (e.g., Amgen [AMG-403] in Phase I). Few small-molecule NGF antagonists are available, but ALE-0540, which inhibits the binding of NGF to Trk A and p75, and PD90780, which inhibits NGF binding to p75, have been proposed to have efficacy in chronic pain models [204,205].

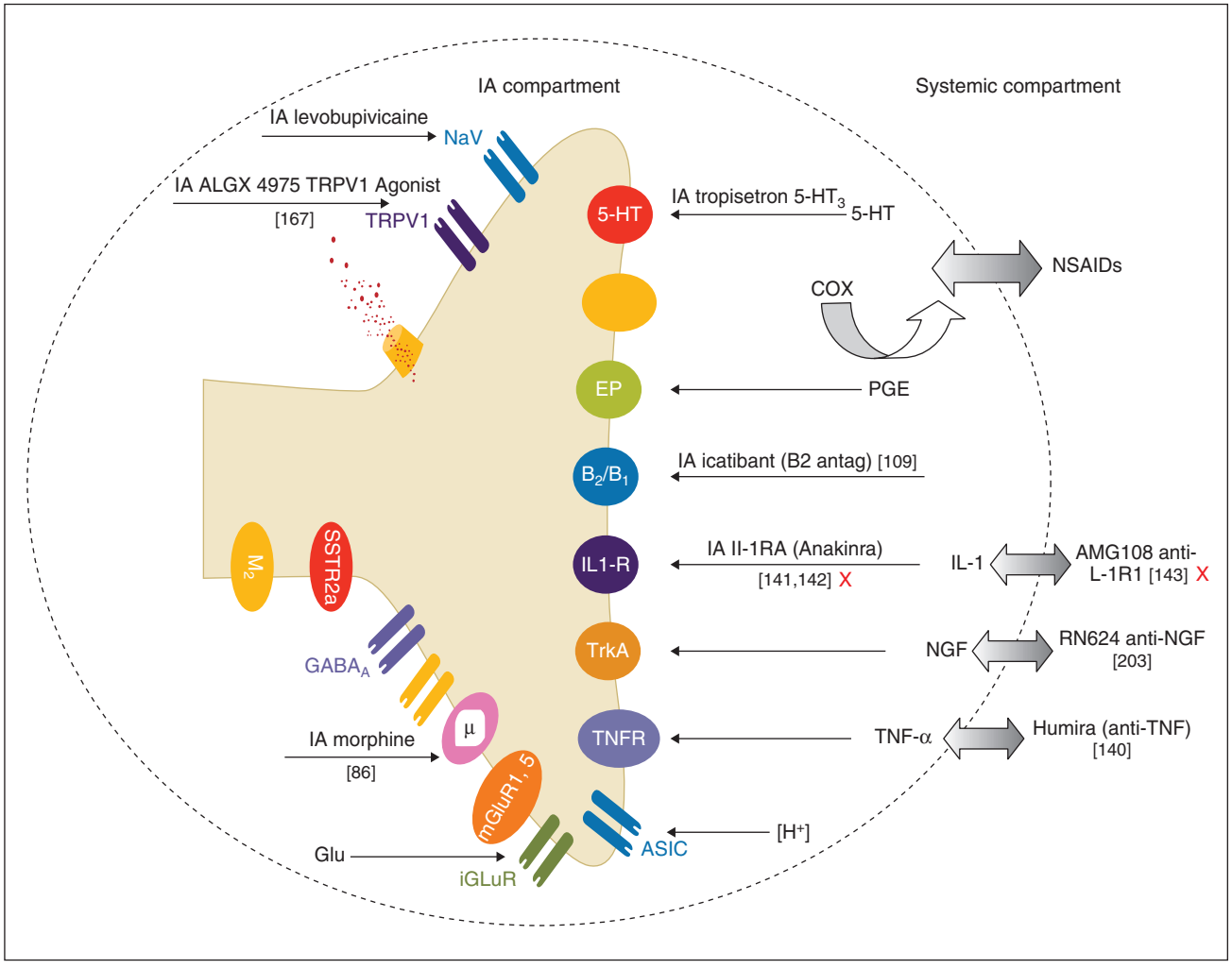

Figure 2. Mediators of peripheral sensitisation in clinical knee OA and key interventions. Mediators have been extensively profiled in knee synovial fluid assays from OA patients (see **Table 1** for more detail). Some of these mediators are highlighted along with any therapeutic interventions that have been tested in man. These pathways have been explored with varying degrees of clinical success, in which clinical failure was identified (**X**) and the supportive key references are annotated [ ].

ASIC: Acid-sensingion channels; B1/B2: Bradykinin receptor 1/2; $GABA_A$: $GABA_A$ receptor; Glu: Glutamate; IA: Intra-articular; IL-1R: IL-1 receptor; m/iGluR: Metabotropic/ionotropic glutamate receptor; NaV: Voltage-gated sodium channel; NGF: Nerve growth factor; PGE: Prostaglandin E; TNFR: TNF receptor; TRPV1: Transient receptor potential vanilloid 1; Trk A: Tyrosine kinase A.

5. CNS

So far this article has focused on peripheral sensory input although clearly modulation through cognitive, genetic, (**Figure 2**), affective and environmental influences forms the net pain experience (**Figure 1**). In OA pain, local anaesthetic studies and quantitative sensory testing instruments indicate that enhanced pain sensitivity is maintained by a peripheral afferent barrage, and that this normalises after treatment in the majority of patients [29-31]. Thus, Kosek and Ordeberg [31] have elegantly demonstrated that during painful hip OA, patients are unable to effectively activate diffuse noxious inhibitory controls (DNIC) that normalise following surgical intervention (hip replacement or osteotomy) [31]. Whether an inability to effectively activate DNIC is symptomatic of a more generalised dysfunction in descending pain modulatory systems is unclear at present. Lesions of the periaqueductal grey, known to participate in central μ-opiate-based analgesia, do not seem to effect DNIC, although neurons of the medullary subnucleus reticularis dorsalis are thought to be critical for DNIC [206]. However, these neurons receive a broad range of inputs from the cortex (somatosensory, motor, insula) the rostral ventral medulla, hypothalamus, amygdala and reticular formation, therefore, loss of DNIC could be a net dysfunction in any of these regions [206]. The use of antidepressant analgesics in OA is still being explored in clinical development as a potential opportunity to modulate monoaminergic transmission and thus normalise disinhibition.

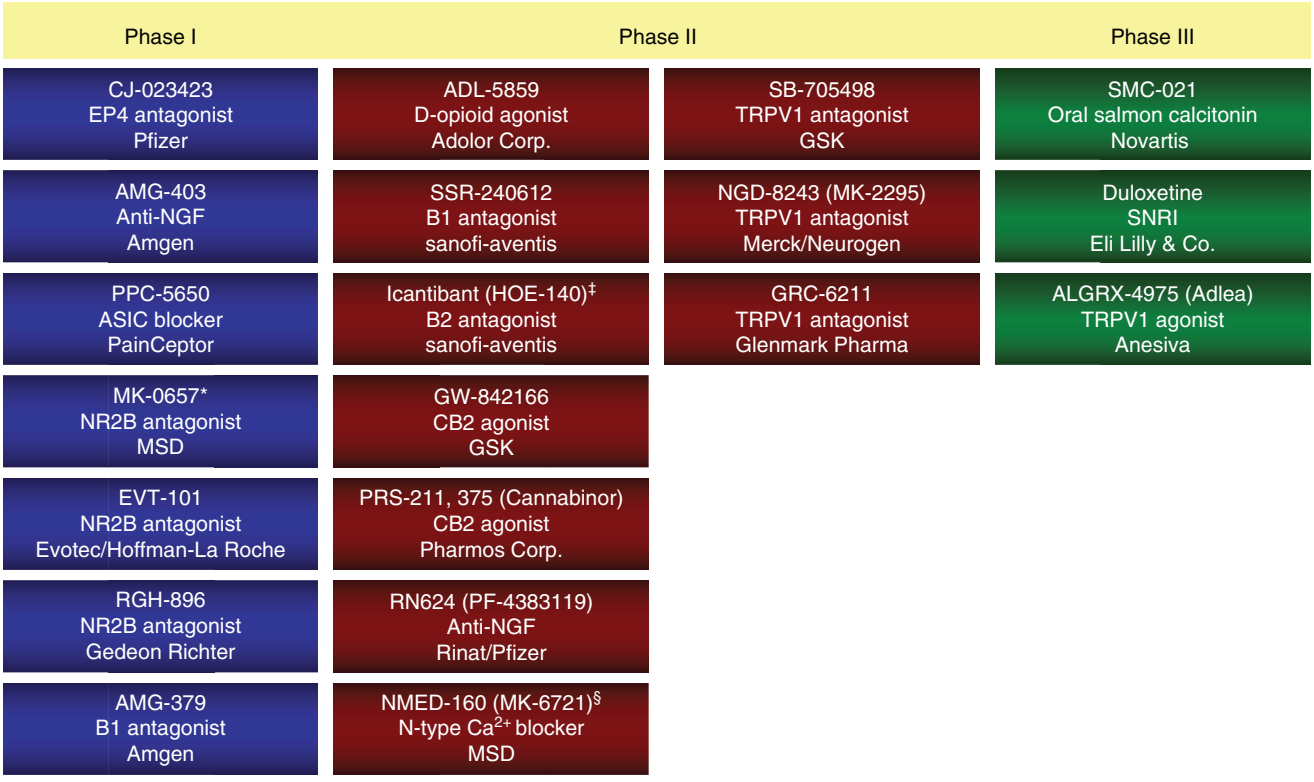

Figure 3. Development progress of compounds exemplified in text.

*In development for Parkinson's disease.

‡No longer listed in pipeline update for OA.

§Removed from development due to poor pharmaceutical characteristics.

Eli Lilly are presently exploring duloxetine in several pain indications including OA [207].

6. Summary

Many emerging therapies are presently in development for treatment of OA (**Figure 3**), offering the opportunity to diversify treatment choice for the patient. However, patient groups, regulatory authorities and payers have underscored the need for differentiated therapies. In particular, improvements in efficacy and side-effect burden. Many of the approaches may carry an adverse event liability. Whether these are tolerable in the OA setting, will emerge as compounds move into larger patient populations than presently being explored in Phase II.

Disease understanding has grown exponentially in the last 20 years. We are beginning to understand the heterogeneity of the patient population and public-private ventures such as 'The Osteoarthritis Initiative', [208], a multi-centre, longitudinal, prospective study of knee OA, will aid biomarker evaluation and perhaps, eventually, individualised therapy. Disease biology and mechanistic understanding of pain pathways can now be explored for the novel mechanisms of the foreseeable future.

7. Expert opinion

Over the last 25 years therapeutic intervention and new drug registration for the management of OA pain has been dominated by reformulation or derivatives of NSAIDs, opiates or intra-articular steroids. As a result, there is marginal differentiation within these drug classes and therapeutic options have changed little in over half a century. Several authors, including the FDA, have speculated on the factors driving an apparent lack of diversity in analgesic drug development, citing issues such as: animal models validated with old, prototypic drugs; proof-of-concept studies in clinical models that do not extrapolate to chronic pain syndromes and trial design (e.g., development of individual responder methodology) [209]. At present, there is a reasonable diversity of mechanisms in early development for OA pain; indeed, this is probably an underestimate (**Figure 3**). Our growing knowledge of disease and pain biology is generating novel opportunities and may also help align these with key patient segments likely to respond to specific therapies. Although these approaches are being pursued, the concern is that many of the current mechanisms in development may not prove tolerable in an OA population. Many patients have concomitant conditions (high blood

pressure, stomach problems/ulcers, osteoporosis, heart disease) and patients often self medicate in addition to prescription medicines. The reality may be that variability in tolerability in broader Phase III populations and even post-launch may continue to be an issue for current approaches and hard to predict. With regard to this issue, the worldwide withdrawal of Vioxx® (rofecoxib) due to increased cardiovascular risk has, to some extent, driven a closer examination of risk/benefit from payors and regulatory authorities. Drugs in development are increasingly submitting larger safety databases and also being explored in comparison to 'gold-standards', both of which are time consuming and expensive.

Accurate, definition of patients and subgroups may be key to providing an assessment of likely risk/benefit in a cost-effective manner. Investment in early discovery to accurately understanding disease setting for the target and the patients who exhibit this pathophysiology, individualised medicine (biomarkers, translational medicine initiatives) and/or modified trial design (e.g., patient enrichment, individualized responder methodologies) are all responses to this particular challenge.

The mechanism-driven hypothesis of pain and analgesia is a driver of new drug development. However, it is the incorporation of all OA disease factors and broader holistic thinking of the collective issues in optimising efficacy (benefit) and improving safety (risk liability) as early in development as possible that will provide great drugs.

Declaration of interest

S Read is an employee and shareholder of AstraZeneca. A Dray is employed and supported full time by AstraZeneca

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