

REVIEW

Celecoxib: considerations regarding its potential disease-modifying properties in osteoarthritis

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Abstract

Osteoarthritis (OA) is a degenerative joint disease characterized by progressive loss of articular cartilage, subchondral bone sclerosis, osteophyte formation, and synovial inflammation, causing substantial physical disability, impaired quality of life, and significant health care utilization. Traditionally, non-steroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase (COX)-2 inhibitors, have been used to treat pain and inflammation in OA. Besides its anti-inflammatory properties, evidence is accumulating that celecoxib, one of the selective COX-2 inhibitors, has additional disease-modifying effects. Celecoxib was shown to affect all structures involved in OA pathogenesis: cartilage, bone, and synovium. As well as COX-2 inhibition, evidence indicates that celecoxib also modulates COX-2-independent signal transduction pathways. These findings raise the question of whether celecoxib, and potentially other coxibs, is more than just an anti-inflammatory and analgesic drug. Can celecoxib be considered a disease-modifying osteoarthritic drug? In this review, these direct effects of celecoxib on cartilage, bone, and synoviocytes in OA treatment are discussed.

Introduction

Osteoarthritis (OA) is the most common joint disorder in western countries, affecting over 70% of adults aged 55 to 70 years [1,2]. It is characterized by progressive loss of articular cartilage, subchondral bone sclerosis, osteophyte formation, and synovial inflammation, causing substantial physical disability, impaired quality of life, and significant health care utilization. As OA incidence increases with age, OA will become a major health issue and socio-economic problem in the coming decades [3].

Historically, OA was seen as a degenerative disease caused solely by the 'wear and tear' process of ageing cartilage. Now it is recognized as a more dynamic, complex disease involving numerous factors affecting the whole joint [4]. Various risk factors for development of OA have been identified - age, sex, and genetic and bio-mechanical factors - contributing to degeneration of articular cartilage and changes in bone and synovium.

Traditionally, non-steroidal anti-inflammatory drugs (NSAIDs) have been used to treat pain and inflammation in OA [5]. The anti-inflammatory effects of NSAIDs are mainly due to their ability to inhibit cyclooxygenase (COX), impairing production of prostaglandins, which are important mediators of the inflammatory response and pain. COX enzymes metabolize arachidonic acid, forming prostaglandin H_2 , which is subsequently metabolized by prostaglandin E synthase into prostaglandin E_2 (PGE_2) [6]. Two isoforms of the COX enzyme exist: constitutively expressed homeostatic COX-1 found in most tissues, and COX-2, which is not expressed in normal healthy tissues and cells but is induced by various pro-inflammatory, catabolic, and stress mediators, such as cytokines, growth factors, and increased loading [7]. Beneficial effects of NSAIDs are thought to be mediated by COX-2 inhibition, whereas unwanted gastrointestinal effects are caused by inhibitory effects on COX-1 [8]. This led to the development of selective COX-2 inhibitors. Celecoxib (SC-58635; 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide) was the first US Food and Drug Administration-approved selective COX-2 inhibitor and is now widely used in OA treatment [9].

Besides its anti-inflammatory properties, evidence is accumulating that celecoxib has additional disease modifying effects. Celecoxib has been shown to affect all structures involved in OA pathogenesis: cartilage, bone, and synovium [10-12]. As well as COX-2 inhibition, evidence indicates that celecoxib also modulates COX-2-independent signal transduction pathways [13]. These findings raise the question of whether celecoxib is more than just an anti-inflammatory and analgesic drug - does celecoxib also slow down OA disease progression and can it be viewed as a disease-modifying osteoarthritic

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drug? In this review, the direct effects of celecoxib on cartilage, bone, and synoviocytes in OA treatment are discussed.

It is important to note that some of the effects described may be related to the coxib class of drugs as a whole, some may be specific to celecoxib, and some may result from a general COX-inhibiting effect. This review does not intend to distinguish between these but focuses on the properties of celecoxib specifically. Only when celecoxib has been compared to other treatments have such comparisons been taken into account. Moreover, this review does not discuss the issue of side effects and clinical efficacy of celecoxib, but focuses on its potential tissue structure-modifying, mostly chondroprotective, effects.

Methods

Two electronic databases were searched for relevant publications: PubMed (1990 to March 2010) and EMBASE (1990 to March 2010). Key words used were: celecoxib/Celebrex/SC-58635, osteoarthritis/arthrosis/OA, cartilage/chondrocytes, synovium/synovial/synoviocytes, and bone. Celecoxib studies regarding its effects on cartilage, bone, and synovium were selected by screening title and abstract. Publications not written in English or not containing original data were excluded. Reviews concerning subjects like the cost-effectiveness and cardiovascular/gastrointestinal side effects of celecoxib and the use of celecoxib in cancer treatment have been published and are therefore not covered in this review.

Celecoxib: direct effects on cartilage

In OA, chondrocytes fail to maintain the equilibrium between synthesis and degradation of the extracellular matrix, resulting in progressive disruption of the structural integrity of cartilage. Initially, chondrocytes compensate for the enhanced catabolic processes by increasing synthesis of collagens and proteoglycans. However, as OA progresses, the increasing catabolic enzyme activity can no longer be counterbalanced [14]. IL-1 β and TNF- α play key roles in the destructive process by stimulating expression and release of proteases, such as collagenases and aggrecanases, including matrix metalloproteinases (MMPs) and a disintegrin and metalloproteinase with thrombospondin repeats (ADAMTS), which degrade collagen and aggrecan. These pro-inflammatory cytokines stimulate synthesis and release of nitric oxide (NO) and PGE₂ [15]. Chondrocytes from OA patients show elevated COX-2 expression, and its product PGE₂ is increased in OA cartilage [16]. The function of PGE₂ in OA is not exactly clear as it has both catabolic and anabolic effects in cartilage [17,18]. NSAIDs could potentially affect cartilage through their inhibition of PGE₂ production.

Proteoglycan turnover

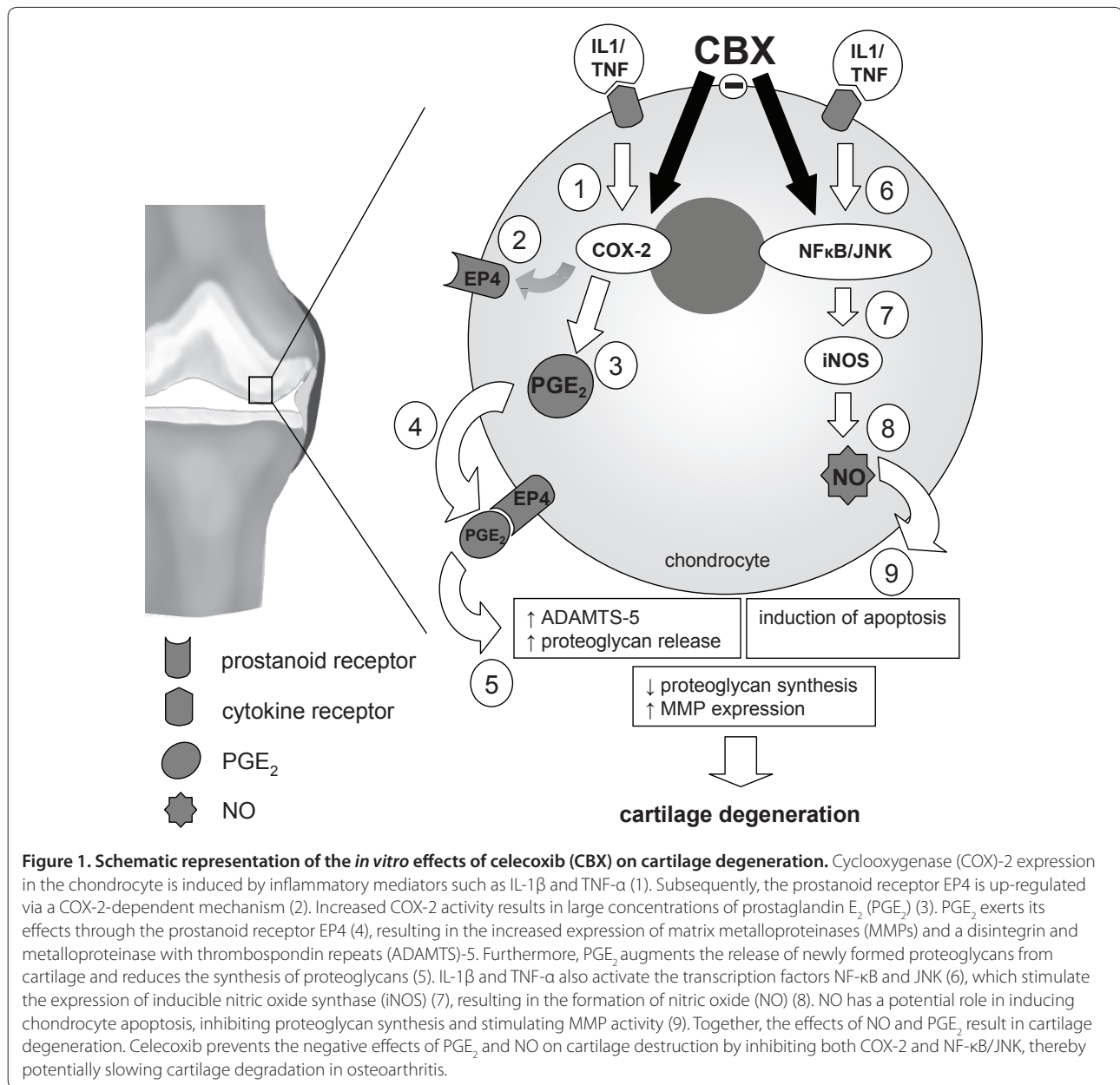
Celecoxib dose-dependently inhibits glycosaminoglycan release and stimulates proteoglycan synthesis in healthy human articular cartilage explants when exposed to peripheral blood mononuclear cells from rheumatoid arthritis patients or IL-1 β and TNF- α [19]. The fact that the decreased proteoglycan synthesis induced by IL-1 β and TNF- α is reversed by celecoxib indicates that this drug can also exert its effects directly on activated cartilage. Furthermore, in OA cartilage explants, celecoxib stimulated proteoglycan synthesis and retention of newly formed proteoglycans [20-22]. The non-selective COX inhibitors diclofenac and naproxen did not affect proteoglycan turnover in OA cartilage, and indomethacin and an experimental COX-1 selective inhibitor (SC-560) had adverse effects [20,21]. This difference in NSAID effects supports COX-2 involvement in catabolic activity regulation in cartilage, whereas COX-1 activity might have a more physiological role in chondrocytes.

No effect of celecoxib on proteoglycan turnover was observed in healthy cartilage [19,22]. This is in contrast to the protective *in vitro* effect of celecoxib on end-stage OA cartilage obtained at joint replacement surgery. For the treatment of OA in clinical practice, it would be beneficial if celecoxib could influence proteoglycan turnover in earlier stages of disease. It was shown that in both degenerated (pre-clinical) and late-stage OA cartilage, celecoxib not only stimulated proteoglycan synthesis and retention of newly formed proteoglycans, but also had favorable effects on proteoglycan content. Importantly, proteoglycan content in degenerated cartilage normalized *in vitro* during celecoxib treatment, suggesting celecoxib treatment in the early stages of OA could slow down or even reverse the destructive process [22].

Whereas the *in vitro* effects of celecoxib on OA cartilage are beneficial, results obtained with isolated chondrocytes are not consistent. In a mechanically stretched monolayer of chondrocytes, celecoxib had a positive effect on aggrecan expression and reduced the release of chondroitin sulfate [23]. In contrast, celecoxib had no positive effect on proteoglycan turnover of osteoarthritic chondrocytes cultured in alginate beads [24], of a monolayer of chondrocytes [25], nor in an *in vitro* model of post-traumatic OA [26]. This variation in the effects of celecoxib could potentially be due to differences in chondrocyte culture models, whereas cartilage explants probably better reflect the *in vivo* situation.

Prostaglandin E₂-induced catabolism

A possible way in which celecoxib exerts its effect on proteoglycan turnover is inhibition of PGE₂ production. PGE₂ is highly expressed in OA cartilage and studies indicate a pivotal role for PGE₂ in OA cartilage metabolism [27]. Expression of PGE₂ and COX-2 in OA



cartilage is strongly inhibited by celecoxib [10,21,22, 28,29]. PGE₂ enhances IL-1 β -/TNF- α -induced proteoglycan release, resulting in decreased proteoglycan content in cartilage explants [28]. The effect of PGE₂ on the synthesis of proteoglycans remains controversial; in OA cartilage, proteoglycan synthesis is inhibited by PGE₂ [17], whereas PGE₂ does not affect proteoglycan synthesis rate in healthy cartilage [28]. This discrepancy could be due to differences in expression levels of individual members of the EP receptor family (EP1 to EP4) through which PGE₂ exerts its effects. EP4 has been implicated in mediating catabolic effects because it is highly expressed in OA cartilage [17]. IL-1-induced expression of EP4 in

cultured OA chondrocytes is decreased by celecoxib [29], but not consistently [17]. The overall negative effect of PGE₂ on proteoglycan turnover in cartilage might be mediated through the EP4 receptor (Figure 1).

PGE₂ inhibits collagen synthesis and stimulates expression of MMP and ADAMTS-5, proteolytic enzymes involved in the degradation of collagens and proteoglycans [17,30,31]. Theoretically, celecoxib could also prevent cartilage destruction by inhibiting induction of MMP expression in OA cartilage. Both inhibitory and stimulatory effects of celecoxib on IL-1-induced expression of MMP-13 in OA chondrocytes have been reported [10,17]. Also, there is no agreement on the effect of

celecoxib on MMP-1 expression in cartilage [10,25,32]. Celecoxib reverses IL-1 β -induced ADAMTS-5 expression in OA cartilage explants [17]. As such, it could prevent enhanced proteoglycan turnover in OA by affecting both MMP and ADAMTS-5 expression. But our understanding of the influence of celecoxib on PGE₂-induced cartilage catabolism is clearly far from complete and it would be worthwhile to explore this role in more detail.

Nitric oxide, NF- κ B, and chondrocyte apoptosis

NO plays an important role in cartilage destruction in OA - for example, by inhibiting matrix synthesis, activating MMPs, and inducing chondrocyte apoptosis [33-35]. Because NO is an attractive target in OA treatment, several studies have addressed the question of whether celecoxib influences NO production, although little agreement has been reached. Several studies found inhibitory effects of celecoxib on NO production in chondrocytes [25,32,36], whereas others did not [28,37]. These contradictory effects are potentially due to differences in culture models, treatment duration, and celecoxib concentration used.

In articular chondrocytes, NO production is regulated by NF- κ B, JunNH₂-terminal kinase (JNK) and p38 [32,38]. Celecoxib was shown to suppress NO production by inactivating JNK and NF- κ B [32]. An inhibitory effect of celecoxib on NF- κ B signaling in OA chondrocytes was reported previously [10]. NF- κ B has an essential role in OA pathogenesis, being involved in cytokine stimulation, MMP and ADAMTS expression, and diminished secretion of extracellular matrix proteins by chondrocytes. Inhibition of NF- κ B could potentially be beneficial in OA treatment. Interestingly, it was reported that celecoxib reduces expression of IL-1 [37] and IL-6 [24], both inflammatory cytokines involved in OA pathogenesis [39]. It is currently unknown how celecoxib mediates its effects on cytokine expression and NF- κ B activity.

Celecoxib induced apoptosis in a dose-dependent manner in chondrocytes derived from cartilage from patients with OA [25], although reduced apoptosis via COX inhibition by celecoxib has also been reported [26].

In general, celecoxib has favorable effects on cartilage destruction *in vitro*, thereby theoretically slowing down disease progress *in vivo* (Figure 1).

Celecoxib: effects on synoviocytes

Inhibition of signal transduction and pro-inflammatory mediators

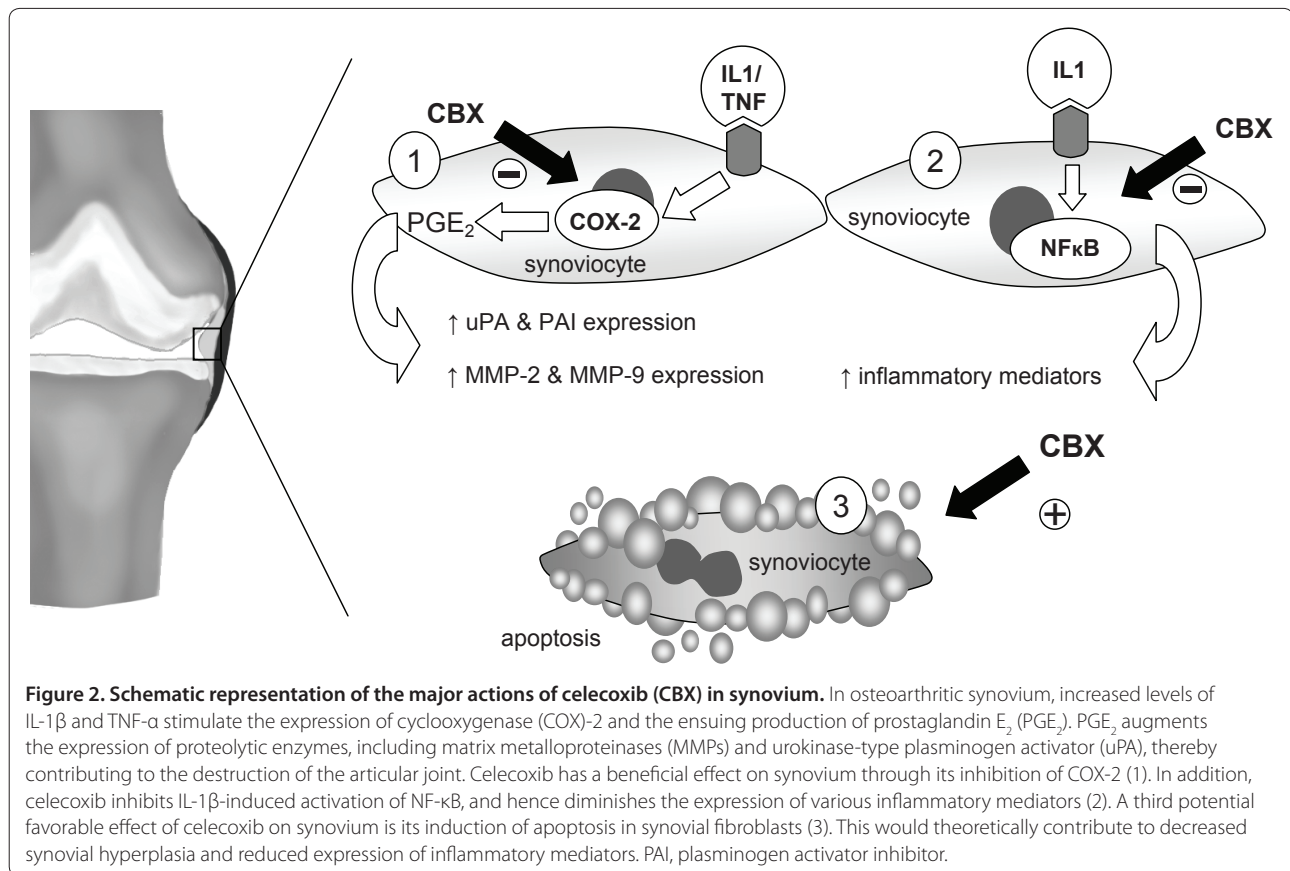
Although originally viewed as a non-inflammatory arthropathy, a pivotal role of synovial inflammation in OA progression is now recognized. Imaging studies have shown synovium changes in early and late OA [40]. Histologically, synovium from OA patients shows hyperplasia, increased lining layer thickness, blood vessel

formation and mononuclear cell infiltration, mainly consisting of macrophage like cells. IL-1 β and TNF- α levels are increased in OA synoviocytes, potentially contributing to disease progression by activating chondrocytes and synovial fibroblasts [41,42]. Enhanced PGE₂ and COX-2 expression in synovial fluid and synovial membrane have been observed [43,44]. Several effects of celecoxib on synovium, with a focus on fibroblasts, have been described. Celecoxib reversed IL-1 β -induced PGE₂ and COX-2 protein expression in synovial fibroblasts. Furthermore, celecoxib inhibited IL-1 β -induced activation of NF- κ B in synovial fibroblasts from OA patients [10]. NF- κ B induces expression of large numbers of inflammatory mediators and plays a major role in the initiation and maintenance of synovitis, synovial hyperplasia, and inhibition of synovial apoptosis in rheumatoid arthritis. Although less is known concerning the function of NF- κ B in osteoarthritic synovium, it is clear that celecoxib could reduce expression of various inflammatory mediators by down-regulation of NF- κ B [45].

Proteolysis

Among the downstream factors of NF- κ B are MMPs, which play a crucial role in cartilage degradation in OA. Both MMP-1 and MMP-13 levels are enhanced in OA; MMP-1 is predominantly released by synovial cells, and MMP-13 is highly expressed by chondrocytes [46]. MMP-2 and MMP-9 are also elevated in the osteoarthritic joint. MMP-2 expression is regulated by COX-2. Several NSAIDs, including celecoxib, inhibit MMP-2 secretion in OA synovial fibroblast cultures [47]. Furthermore, celecoxib can decrease the expression of MMP-9 and urokinase-type plasminogen activator (u-PA) and its inhibitor PAI [47]. Alterations in u-PA and PAI expression have been found in osteoarthritic tissue and contribute to a disturbed proteolytic balance [48].

It was shown that celecoxib, but no other selective COX-2 inhibitors, enhances MMP-1 and MMP-13 protein expression in IL-1 β -stimulated synoviocytes [10,49]. This observation does not corroborate the inhibitory effect of celecoxib on MMP-1 expression in rheumatoid arthritis synoviocytes [50]. This discrepancy could be due to different concentrations used, celecoxib being stimulatory at low concentrations (0.5 to 1 μ M) and inhibitory at higher concentrations (5 to 10 μ M). Evidently, a stimulatory effect of celecoxib on synovial MMP-1 and MMP-13 expression could be detrimental in OA treatment [10]. In conclusion, celecoxib influences the balance of proteolytic enzymes in OA synovium, and although this appears to be generally beneficial (reducing expression of MMP-2, MMP-9, and uPA), adverse effects have been reported as well (increasing expression of MMP-1 and MMP-13).



Apoptosis

Recently, it was shown that celecoxib dose-dependently inhibits proliferation and induces apoptosis in synovial fibroblasts obtained from OA patients [51,52]. This is in agreement with findings in rheumatoid arthritis [53-55]. Remarkably, various other COX-2 selective inhibitors, including nimesulide and rofecoxib, did not induce apoptosis of synovial fibroblasts, indicating that celecoxib stimulates apoptosis in a COX-2-independent manner [51]. In cancer cells celecoxib has been shown to modulate apoptosis pathways by inhibiting anti-apoptotic proteins, elevating Ca²⁺ concentration and altering NF- κ B signaling (reviewed in [56]). Although the exact pro-apoptotic mechanism of celecoxib in synovial tissue remains to be established, it is evident that anti-proliferative and pro-apoptotic effects of celecoxib on synovium are beneficial in reducing synovial hyperplasia and potentially slow down synovitis-mediated OA disease progress.

Taken together, celecoxib modulates several pathogenic mechanisms of synovial cells that are not always affected by other NSAIDs, suggesting that celecoxib may have additional, COX-2-independent value in the treatment of OA (Figure 2).

Celecoxib: effects on subchondral bone

Subchondral bone in osteoarthritis

Subchondral bone sclerosis and osteophyte formation are radiographic hallmarks of end-stage OA. Several studies suggest that bone remodeling in OA is biphasic: an early decrease in trabecular bone formation, followed by an increase in subchondral bone density and stiffness [57,58]. The initial thinning of the subchondral plate coincides with changes in articular cartilage, suggesting a pivotal role for the cartilage and subchondral bone interaction in OA progression. In established OA, the increased subchondral bone stiffness probably contributes to further cartilage degeneration [59].

Osteoclastogenesis

Osteoclasts play a pivotal role in the destruction of subchondral bone [4,14,59]. Osteoclastogenesis and activation of mature osteoclasts are critically regulated by the receptor activator of NF- κ B ligand (RANKL). RANKL mediates its function by binding to its cell-surface receptor RANK on osteoclast precursor cells and osteoclasts, thus stimulating differentiation and activation of osteoclasts. It is mainly expressed by osteoblasts and stromal cells, where expression of RANKL is

COX-2-dependent [60]. During inflammation RANKL is also produced by T lymphocytes and fibroblast-like synoviocytes. Osteoprotegerin (OPG), a soluble decoy receptor for RANKL, can prevent the biological effects of RANKL, and the ratio between OPG and RANKL determines whether the balance is in favor of bone resorption or bone formation [61,62]. Interestingly, two osteoblast subpopulations were identified in OA, one with a low OPG/RANKL ratio that favors bone resorption, and one with a high OPG/RANKL ratio that promotes bone formation [61,63]. Inhibition of COX-2 by NSAIDs diminishes RANKL production by osteoblasts, and since RANKL is an important inducer of osteoclastogenesis, celecoxib inhibited osteoclast differentiation in co-cultures of osteoblasts and bone marrow-derived cells [12,64]. Besides affecting osteoclastogenesis indirectly through its effect on osteoblasts, celecoxib also directly influenced osteoclast precursor cells by inhibiting COX-2 expression. Adding celecoxib to bone marrow-derived monocyte/macrophage cells, in the absence of stromal cells, suppresses RANKL-induced osteoclast differentiation [65,66]. This celecoxib effect was reversed by PGE₂, indicating that RANKL-induced COX-2 and PGE₂ expression in osteoclast precursors is critically involved in osteoclastogenesis [65] (Figure 3).

Osteoclast activity

Besides inhibiting osteoclast differentiation, celecoxib is able to almost completely inhibit the activity of human osteoclasts [66]. Slightly lesser effects were observed with indomethacin, and no effects were seen with a selective COX-1 inhibitor, suggesting a COX-2-dependent pathway is involved [66]. However, other mechanisms might be involved in inhibiting osteoclast activity as well. Celecoxib, as well as other sulfonamide-type COX-2 inhibitors, contain an aryl sulfonamide moiety that inhibits carbonic anhydrase II [67]. Abundantly expressed on the inner surface of osteoclasts, carbonic anhydrase II catalyzes conversion of CO₂ and H₂O into bicarbonate and H⁺. Acidification in the resorption pit is required for dissolution of the inorganic matrix of bone [68]. Treatment with celecoxib reduced carbonic anhydrase activity and thereby inhibited osteoclast activity, an effect not observed for COX-inhibitors without this sulfonamide moiety [12].

Osteoprotegerin/RANKL in chondrocytes

Recently, it was found that human chondrocytes express OPG, RANKL and RANK [61,69]. Interestingly, the OPG/RANKL ratio is significantly lower in OA chondrocytes compared to healthy chondrocytes [70]. This shift in OPG/RANKL ratio is mediated by PGE₂ [69,71], and inhibition of PGE₂ production by celecoxib resulted in a

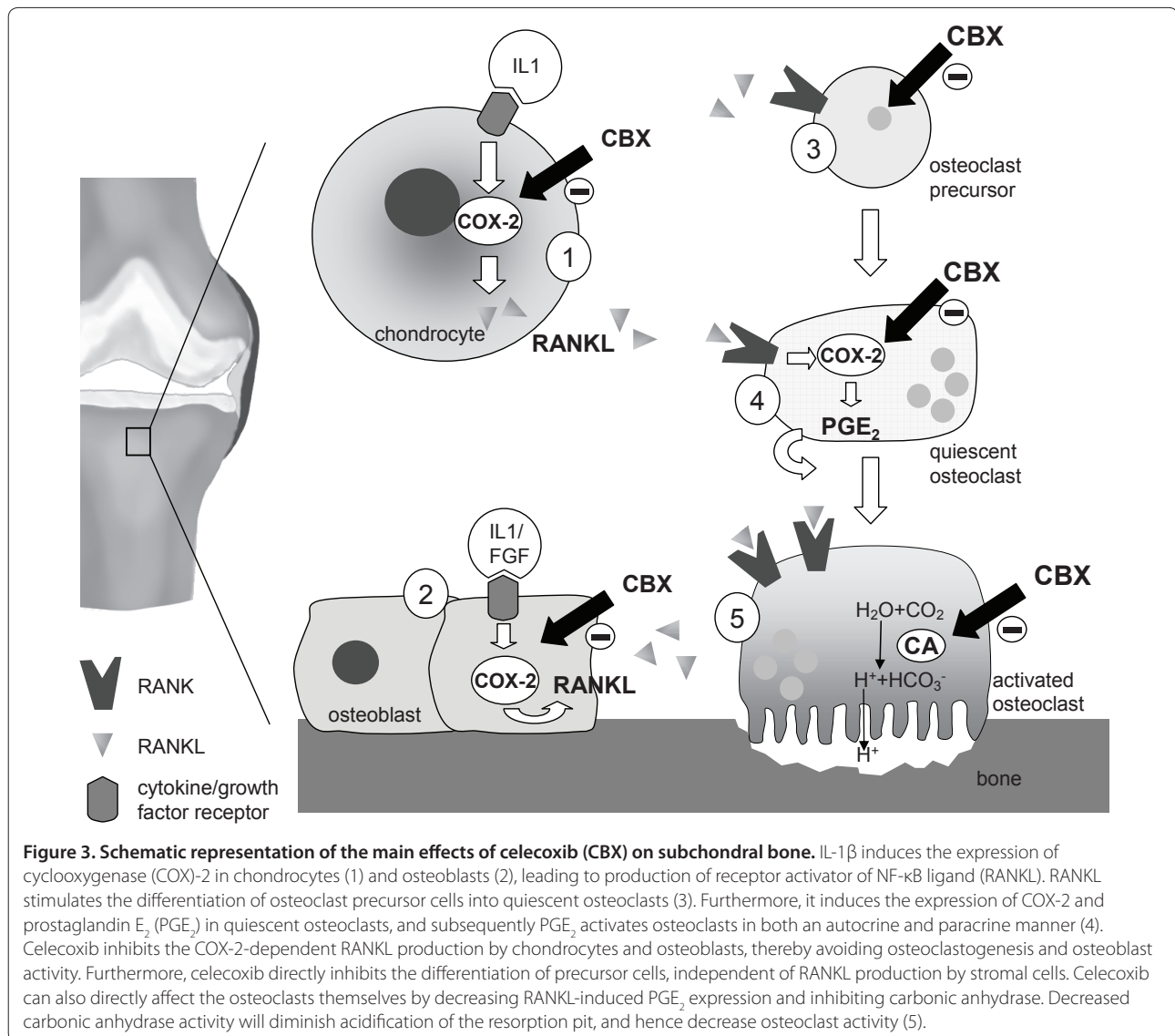
higher OPG/RANKL ratio [71,72]. It was shown that RANKL produced by chondrocytes can stimulate osteoclastogenesis [73,74] and, furthermore, as a chemo-attractant for peripheral blood monocytes, it could attract osteoclast precursor cells to the joint [75]. Inhibition of chondrocyte RANKL expression by celecoxib might thus prevent subchondral bone loss (Figure 3).

Celecoxib: effects *in vivo*

Cartilage

In vitro experiments have shown a cartilage-sparing effect of celecoxib in OA cartilage; however, *in vivo* data, from either human or animals, are scarce. Contrary to its positive effects on cartilage degeneration *in vitro*, no chondroprotective effect of celecoxib in the canine groove model of OA was observed [76]. Although PGE₂ levels in the joint were inhibited, celecoxib did not improve cartilage histopathology or proteoglycan turnover. This lack of chondroprotective effect might have been due to increased loading of the joint in the celecoxib-treated group compared to the placebo-treated group, where no analgesics were given [76]. Conversely, celecoxib was shown to reduce cartilage damage in collagen-induced osteoarthritis in rabbits; histopathological evaluation showed less cartilage erosion, reduced cartilage fibrillation and decreased loss of chondrocytes. Proteoglycan content, determined by Safranin-O staining intensity, was higher than in the placebo-treated group [77]. Next to the direct effects of celecoxib, the anti-inflammatory effects of celecoxib may have caused this chondroprotective effect as the model depends on inflammation and the number of inflammatory cells and the PGE₂ concentration in synovial fluid was significantly reduced by celecoxib.

Few studies have described the *in vivo* effects of celecoxib on cartilage destruction in OA patients [37, 44,78-80]. However, these studies generally have limitations with respect to their small size and short duration. A way to study drug effects is to treat patients with severe knee OA waiting for joint replacement surgery and analyze the cartilage *ex vivo*. In this manner, a beneficial effect of celecoxib on cartilage degradation after 4 weeks of treatment was observed [78]. Although no differences in the histopathological Mankin score were observed, proteoglycan synthesis rate and retention of newly formed proteoglycans was significantly increased in celecoxib-treated OA patients compared to indomethacin-treated or untreated patients. The expression of key players in the destructive process, NO and PGE₂, was inhibited by both celecoxib and indomethacin [78]. Hence, differences in cartilage proteoglycan turnover between celecoxib- and indomethacin-treated patients could result from specific effects of indomethacin-induced COX-1 inhibition on cartilage [20,21], or from



COX-2-independent actions of celecoxib [13]. Using a similar approach, long-term (3 months) effects of celecoxib and aceclofenac were studied in OA patients [37]. It was demonstrated that expression of COX-2, microsomal prostaglandin E synthase-1 (mPGES-1) and inducible NO synthase, an enzyme involved in NO generation, was strongly reduced in both celecoxib- and aceclofenac-treated patients. Only celecoxib was shown to inhibit expression of the PGE₂ receptors EP2 and EP4, as well as TNF- α and IL-1 β , in articular cartilage. A positive correlation exists between TNF- α /IL-1 β levels and cartilage damage [81], suggesting a chondroprotective effect of celecoxib *in vivo*.

The effects of celecoxib treatment on disease progression are more ambiguous [79,80,82]. In an observational study, conventional NSAID use was associated with

enhanced cartilage destruction compared to selective COX-2 inhibitors. Furthermore, the COX-2 inhibitors rofecoxib and celecoxib showed beneficial effects on tibial cartilage defects in knee OA compared to no medication [82]. Recently, the effect of celecoxib treatment (200 mg daily, 12 months) on cartilage volume loss was studied compared to a historical cohort of patients receiving standard care [79]. Using quantitative magnetic resonance imaging, no protective celecoxib effect on knee cartilage was found. Only one randomized controlled trial has addressed the effects of celecoxib on cartilage degeneration [80]. Patients who met radiographic criteria grade 2 and 3 (Kellgren and Lawrence) were blinded and given celecoxib, chondroitin sulfate, glucosamine or placebo. Unexpectedly, no differences in joint space narrowing (measured radiographically) or

disease progression between celecoxib- and placebo-treated groups were observed after 2 years follow-up [80]. Less than anticipated loss of joint space width in the placebo-treated group hampered the study and prevented a strong conclusion. Moreover, the results found in these studies were obtained in an un-controlled trial set-up and, as such, could be affected by the selection of patients. Also, the numbers of patients used in most studies is rather limited.

Figure 4 summarizes the suggested *in vivo* effects of celecoxib. The beneficial *in vitro* effects and the somewhat controversial *in vivo* effects on cartilage, mostly based upon weak evidence, clearly indicate the requirement for properly designed randomized controlled trials on the potential disease-modifying osteoarthritic drug effects of celecoxib.

Synovium

Celecoxib has been shown to reduce synovitis, leukocyte infiltration and synovial hyperplasia in different arthritis animal models [83-85]. In the synovium of severe knee OA patients, inhibitory effects of celecoxib on IL-1 β and TNF- α expression have been demonstrated [44,78]. Furthermore, celecoxib reduced IL-6 concentrations in the synovial fluid of patients with moderately severe OA after 2 weeks of treatment [86]. Interestingly, aceclofenac and indomethacin had no or only moderate effects on cytokine expression in these studies [44,78].

Reduction of pro-inflammatory cytokines in synovial fluid by celecoxib could be the result of decreased production by chondrocytes, as has been shown *in vitro* [24]. However, synovial macrophages are also an important source of pro-inflammatory cytokines [42]. *Ex vivo* analysis of OA synovium after *in vivo* celecoxib treatment showed a significant reduction in synovial macrophage numbers, which was not observed for aceclofenac [44]. This macrophage depletion might be due to enhanced apoptosis in response to celecoxib, which has a pro-apoptotic effect on synoviocytes and macrophages [51, 53,55]. Decreasing macrophage numbers would result in lower pro-inflammatory mediator levels in synovial fluid. Only one study has addressed the influence of celecoxib on MMP activity in synovial tissue; despite controversial results on MMP activity in synoviocytes *in vitro*, no celecoxib effect on MMP activity was demonstrated *in vivo* [78].

In conclusion, under certain conditions pro-inflammatory cytokines play a crucial role in OA pathogenesis by inhibiting proteoglycan synthesis, inducing chondrocyte apoptosis and activating other cells. Preventing enhanced production of these inflammatory mediators by celecoxib will likely slow disease processes. Several lines of evidence indicate that synovial changes can be among the first to occur in OA (reviewed in [87]),

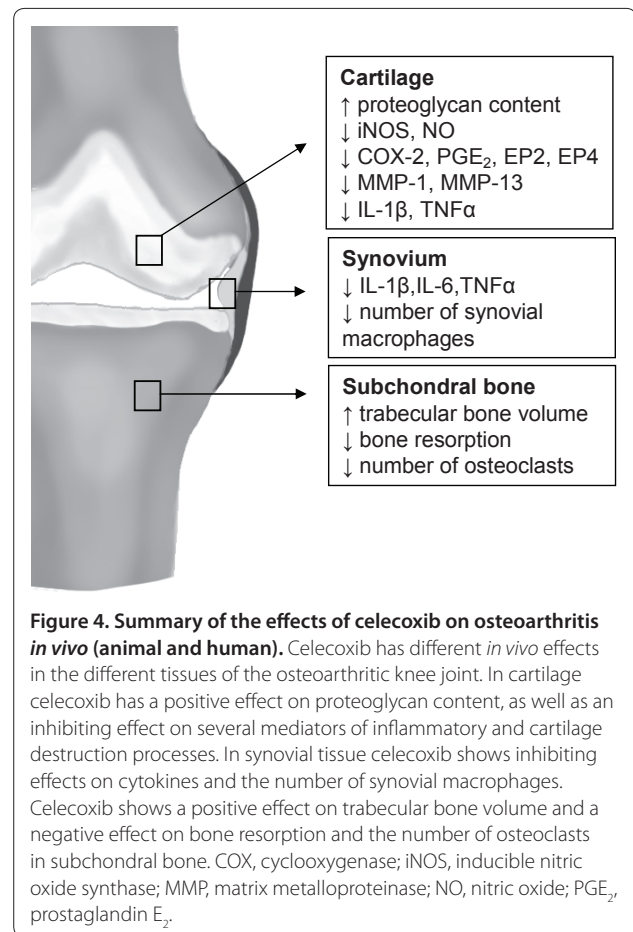


Figure 4. Summary of the effects of celecoxib on osteoarthritis *in vivo* (animal and human). Celecoxib has different *in vivo* effects in the different tissues of the osteoarthritic knee joint. In cartilage celecoxib has a positive effect on proteoglycan content, as well as an inhibiting effect on several mediators of inflammatory and cartilage destruction processes. In synovial tissue celecoxib shows inhibiting effects on cytokines and the number of synovial macrophages. Celecoxib shows a positive effect on trabecular bone volume and a negative effect on bone resorption and the number of osteoclasts in subchondral bone. COX, cyclooxygenase; iNOS, inducible nitric oxide synthase; MMP, matrix metalloproteinase; NO, nitric oxide; PGE₂, prostaglandin E₂.

suggesting early treatment could slow or maybe prevent joint damage. As little research has focused on the effects of celecoxib on synovial tissue, further research should elucidate the effects of celecoxib in disease progression.

Bone

Various studies have shown a beneficial effect of celecoxib on bone *in vivo* [12,88-90]. Celecoxib, but not other NSAIDs, reduced bone mineral density loss [12,88,90] and enhanced trabecular bone volume in adjuvant- and collagen-induced arthritis in rats [88-90]. The increased trabecular bone volume correlated with reduced serum type I collagen C-telopeptide, a bone resorption marker representing osteoclast activity [12,88], and other bone resorption parameters [89]. Whereas celecoxib did not affect bone formation, it suppressed osteoclast numbers in tibia of arthritic animals [89,90]. These celecoxib effects were partly mediated by RANKL, as celecoxib decreased expression of RANKL in synovial tissue, bone marrow cells and cartilage *in vivo* [71,89]. As shown *in vitro*, celecoxib inhibited both osteoclastogenesis and osteoclast activation, thereby directly diminishing bone destruction.

Despite celecoxib being used for treatment of OA for many years, no effects of it on serum markers of bone resorption and formation or on structural changes in bone have been reported. As celecoxib has beneficial effects on bone resorption *in vitro* and *in vivo* in animal models, it would be interesting to explore these effects on bone metabolism in OA patients in more detail.

Conclusion

Despite celecoxib being approved for OA treatment for over a decade, few studies have addressed the disease-modifying properties of this selective COX-2 inhibitor, specifically *in vivo*. This review does not address the clinical risk and side effects related to the clinical benefits of celecoxib but focuses on the disease-modifying properties of this compound. However, the increased risk of myocardial infarction and worsening of high blood pressure can not be ignored when prescribing celecoxib. These issues have been extensively described in other reviews and are still under discussion at present. Also, it is not the intention of this review to compare in a systematic way the disease-modifying effects of celecoxib with other coxibs and conventional NSAIDs. As such, all effects described might be partly class-specific and partly celecoxib-specific. Nonetheless, celecoxib's chondroprotective effects - prevention of synovial hyperplasia, and inhibition of bone destruction *in vitro* and *in vivo* specifically in animal models - suggest that it and maybe other coxibs could potentially slow OA disease progression in humans. At present, however, good quality randomized controlled trials examining the disease-modifying effects of celecoxib are lacking. Future studies should elucidate the actual role of celecoxib and other selective coxibs as disease-modifying osteoarthritic drugs.

Abbreviations

ADAMTS, a disintegrin and metalloproteinase with thrombospondin repeats; COX, cyclooxygenase; IL, interleukin; JNK, JunNH₂-terminal kinase; MMP, matrix metalloproteinase; NF, nuclear factor; NO, nitric oxide; NSAID, non-steroidal anti-inflammatory drug; OA, osteoarthritis; OPG, osteoprotegerin; PAI, plasminogen activator inhibitor; PGE₂, prostaglandin E₂; RANK(L), receptor activator of NF-κB (ligand); TNF, tumor necrosis factor; u-PA, urokinase-type plasminogen activator.

Competing interests

MZ, JAGR, FPJGL and SM declare that they have no competing interests. The work of TNB is supported by an unrestricted grant from Pfizer. JWJB received a consultancy fee from Pfizer (<US\$10,000).

Authors' contributions

All authors contributed to the design, drafting and revision of the manuscript, and all authors approved the final submission.

Published: 21 September 2011

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doi:10.1186/ar3437

Cite this article as: Zweers MC, et al.: Celecoxib: considerations regarding its potential disease-modifying properties in osteoarthritis. *Arthritis Research & Therapy* 2011, **13**:239.