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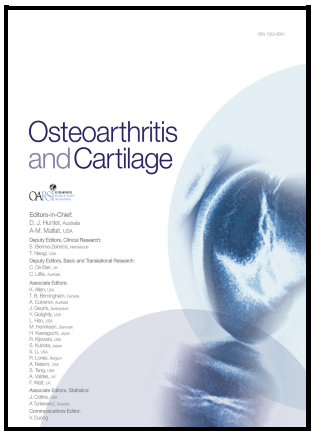

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Review article

Running head: β2-adrenoceptors kick osteoarthritis

β2-adrenoceptors kick osteoarthritis – time to rethink prevention and therapy?

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Abstract

Although, during the past decades, substantial advances emerged in identifying major local and systemic factors contributing to initiation and progression of osteoarthritis (OA), some neuroendocrine mechanisms are still not understood or even neglected when thinking about novel therapeutic options. One of which is the sympathetic nervous system that exhibits various OA-promoting effects in different tissues of the joint. Interestingly, the β2-adrenoceptor (AR) mediates the majority of these effects as demonstrated by several *in vitro*, *in vivo* as well as in clinical studies. This review article does not only summarize studies of the past two decades demonstrating that the β2-AR plays an OA-promoting role in different tissues of the joint but also aims to encourage the reader to think about next-level research to discover novel and innovative preventive and/or therapeutic strategies targeting the β2-AR in OA.

Keywords: osteoarthritis, sympathetic nervous system, β2-adrenoceptor, adrenergic therapy

Introduction

Osteoarthritis (OA), the most common chronic degenerative joint disorder, represents a substantial individual, social and economic burden worldwide, since it is the leading cause of chronic pain and disabilities [1]. Although significant advances emerged regarding identification of risk factors and therapeutics alleviating the major symptoms inflammation and pain, there is still no causal prevention or treatment for this disease [2]. We know that OA is a disease of the entire joint meaning that its pathogenesis involves not only cartilage but also all surrounding tissues [3]. Similarly, the multifactorial

nature of OA pathogenesis became clear. Besides local risk factors such as injuries, articular malalignment or joint overloading, systemic parameters like sex, age, and genetics contribute to OA development [4, 5].

Recently, increasing evidence emerged that components of the nervous system, in particular the autonomic nervous system with its two major antagonistic branches the sympathetic and parasympathetic divisions, influence different cells in joint tissues. The sympathetic nervous system (SNS) with its dominant peripheral postganglionic neurotransmitter norepinephrine (NE) , acting through different G protein-coupled adrenergic receptor (AR) subtypes, was the subject of numerous investigations in this regard [6]. In 1948, the two major α- and β-AR families were discovered by serendipity and, since then, nine AR subtypes have been identified, namely α1A, α1B, α1D, α2A, α2B, α2C, β1, β2, and β3 [7-10].

At the beginning of the 2000s, the focus of musculoskeletal research turned to the β2-AR, when researchers published that leptin-mediated inhibition of bone formation required sympathetic activity [11, 12]. Later studies identified β2-AR as the only AR subtype being responsible for the above-described effects [13, 14]. These findings were real game-changers because until this time point, β2-AR was only looked at from the cardiovascular or bronchial smooth muscle point of view [15]. Several other studies confirmed the contribution of β2-AR in regulating bone mass. For instance, the β2-AR agonists clenbuterol and salbutamol decreased bone mass in rats [16], and beta-blocker use in postmenopausal women was associated with a higher bone mineral density resulting in lower fracture risk [17]. Based on these studies, the crucial role of β2-AR in regulating bone turnover is beyond all doubt. Over the past years, it became also clear that all other healthy joint tissues do express the β2-AR [18].

In this review article, we present the current state of the art of β2-AR-mediated effects on different joint cells and tissues in cell culture and animal models with respect

to OA. We highlight the clinical relevance and discuss the potential of novel future preventive strategies and therapeutic interventions targeting the β2-AR in OA. In order to stay focused, parasympathetic contributions to OA pathogenesis or the interaction of both peripheral autonomic branches will not be addressed. However, numerous existing publications on this issue can be found in existing literature such as references [6, 18, 19].

We identified references for this narrative review through searches of PubMed with the search terms “osteoarthritis”, “beta-adrenoceptor”, “beta adrenergic receptor”, “norepinephrine”, and “sympathetic” from inception of the database until September 2023. We also identified articles through searches of the authors’ own files. The final reference list was generated on the basis of its relevance to a descriptive account of the effects on osteoarthritis mediated by the β2-AR.

Lessons from cell cultures

Bone marrow-derived mesenchymal stromal cell-based regeneration

Due to their ability to differentiate into chondrocytes, bone marrow-derived mesenchymal stromal cells (BMSCs) have a potential as therapeutic agents for cartilage regeneration in OA [20]. The first study demonstrating a β2-AR-mediated effect on the chondrogenic potential of BMSCs and cartilage-derived chondroprogenitor cells (CPCs) was published by our group in 2014 [21]. We investigated human post-traumatic knee joint tissue and detected tyrosine hydroxylase-positive (TH+) sympathetic nerve fibers as well as TH+ joint-resident cells in the synovium, meniscus and subchondral bone marrow. These nerve fibers and TH+ cells release NE into the synovial fluid [21]. In order to answer the question, if and how NE influences the MSC-dependent regeneration of cartilage, the influence of NE on a three dimensional chondrogenic

culture was investigated. The results indicated that inhibition of sulphated glycosaminoglycan (sGAG) and type II collagen deposition in both BMSCs and CPCs derived cartilage was mediated through β2-AR [21].

Later, our team investigated the influence of NE on the proliferation capacity of BMSCs derived from knee trauma and OA patients [22]. Although proliferating stem cells do not simultaneously differentiate to chondrocytes, they can contribute to regeneration as trophic mediators [23]. This study demonstrated a clear β2-AR-dependent inhibition of BMSC proliferation through PKA and ERK1/2 -signaling pathways [22]. Surprisingly, in particular the activation of ERK1/2 was cAMP-independent, which is now recognized as a receptor signaling switch of β2-AR. Here, chronic stimulation or high NE concentrations lead after an early canonical β2-AR activation to a subsequent β2-AR phosphorylation by G protein-coupled receptor kinase 2 facilitated by PKA. This results in receptor uncoupling from the Gαs protein and allows the binding of the Gαi subunit leading to ERK1/2 activation and to opposite effects compared to cAMP. Moreover, intracellular phosphodiesterase-4 (PDE4, especially the isoform PDE4D5) binds to and recruits β-arrestin to β2-AR at the cell membrane leading to attenuated PKA-mediated β2-AR phosphorylation and switching to Gαi signaling [24-26].

In summary, not only proliferation of BMSCs being able to release cartilage-regenerative factors but also chondrogenic differentiation capacity of these cells in the joint is inhibited through β2-ARs. Accordingly, cartilage regeneration might be impaired by β2-AR activation.

Articular chondrocyte function

Besides optimizing BMSC-dependent cartilage regeneration, preserving healthy hyaline chondrocyte phenotype is one of the most important determining factors for deceleration of OA progression [27].

A study in 2016 reported that NE via the β2-AR induces the proliferation of human chondrocytes obtained from the knee joints of OA patients in both two- and three-dimensional culture [28]. While this sounds like a contradiction to above experiment with BMSCs and CPCs, increased proliferation indicates a dedifferentiation process and without an appropriate microenvironment, proliferating chondrocytes will never regain their fully-differentiated phenotype [29].

Furthermore, NE in physiologically high concentration, thus via the β2-AR, reduced the synthesis of type II collagen and the release of MMP-13 in a fibringel model. The authors also used IL-1β to mimic an OA-characteristic inflammatory microenvironment that induced IL-8 and MMP-13 secretion but also elevated sGAGs and type II collagen expression. NE reversed all effects caused by IL-1β through β2-AR activation. These results suggest that β2-AR mediates inhibitory effects on extracellular matrix deposition in both healthy and OA chondrocytes [28].

In a further study, SW1353 immortalized chondrocytic cells were stimulated using the non-selective anti-hypertensive drug carvedilol that mainly blocks β1- and β2-ARs but exhibits also a modest α1 blocking capacity [30]. Since chondrocytes do not express β1-AR and the expression of α1-AR subtypes is not detectable or very weak [28, 31], carvedilol mainly acts via the β2-AR [18, 28, 31]. Indeed, carvedilol dose-dependently reversed the inhibitory effect of IL- 1β on aggrecan and type II collagen deposition as well as IL-1β -mediated induction of MMP-1 and MMP-13 [32].

These studies illustrate that the activation of the β2-AR results in catabolic effects on cartilage extracellular matrix and in accelerated loss of chondrocytic

phenotype due to dedifferentiation but might also inhibit production of pro-inflammatory cytokines by chondrocytes.

Synovial fibroblasts and immune cells

In order to explore AR-mediated effects on synovial inflammation, most researcher focused on the pathogenesis of rheumatoid arthritis where OA patients with low-grade secondary inflammation served as controls [33]. Although contradictory results exist regarding β2-AR-mediated TNFα or IL-1β secretion in synovial cells cultures [25, 34, 35], one study in 2000 clearly demonstrated that the release of IL-6 and IL-8 in OA synovial fibroblast culture was induced by NE in physiologically high concentrations (10^{-7}-10^{-6} M), thus through the β2-AR. In our hands, no similar effect was observed in cells obtained from rheumatoid arthritis patients [36]. This study reveals that the β2-AR might be involved in the initiation and progression of pro-inflammatory processes in OA by inducing pro-inflammatory cytokine release from synovial fibroblasts.

Besides resident fibroblasts, also infiltrating immune cells release pro-inflammatory mediators such as IL-1β, IL-6, IL-8 or TNFα. Since almost all immune cell types express β2-AR, modulation of cytokine release can take place after receptor activation. However, as described in depth in our recent review, the net β2-AR-mediated effects on immune cells vary extremely in a context-related manner, for example, depending on cell type, activation and differentiation state of the cell or duration of β2-AR activation [37]. In addition to that, the aspect of pro-inflammatory Gαs to Gαi switch might be relevant [24-26]. Therefore, no clear statement can be made about β2-AR-mediated effects on synovial inflammation or inflammation-associated OA pain (see section ‘OA pain’ below).

Animal models of OA

Temporomandibular joint OA

The first study investigating the role of β2-AR during OA pathogenesis in an animal model was published in 2015. The authors reported enhanced NE levels and β2-AR expression in the subchondral bone of rat temporomandibular joints (TMJ) after OA induction using the unilateral anterior crossbite (UAC) model. The β2-AR agonist isoproterenol aggravated subchondral bone volume loss, which is characteristic for early OA, while the β2-AR antagonist propranolol exhibited opposite effects. An osteoclastic hyperactivity mediated by increased RANKL secretion by condylar MSCs was identified as the underlying mechanism [38].

In a follow-up project, the authors generated mice lacking the β2-AR in nestin-positive MSCs and induced TMJ-OA using the UAC model. This MSC-specific deletion of β2-AR resulted in a significant attenuation of subchondral bone loss confirming the results published in 2015 [38]. In addition, the authors described diminished fibrocartilage degradation in mice lacking the β2-AR in MSCs indicated by higher cartilage thickness, increased aggrecan and type II collagen deposition, decreased MMP-3 and MMP-13 expression as well as reduced calcification of the osteochondral interface [39]. Although we know that TMJ cartilage – fibrocartilage – is quite different from hyaline cartilage, we gave the present information for completeness and because β2-AR effects are so similar as described in following subsections.

Intervertebral disc degeneration

Since also the fibrocartilaginous intervertebral disc (IVD) with its surrounding tissues has many similarities with articular joints, the role of β2-AR during IVD degeneration is of interest in this article. Interestingly, as demonstrated by our group, only the β2-AR was detectable in both healthy human and murine IVD tissues and the area of the

annulus fibrosus with β2-AR-positive cells was markedly increased in the IVD samples of SM/J mice that spontaneously develop IVD degeneration [40]. Moreover, β2-AR gene expression levels significantly correlated with the Pfirrmann grade of degeneration in human IVD samples [41].

Thus, β2-AR is upregulated by altered biomechanical conditions in the degenerating IVD and might therefore play a role in spine degeneration and the genesis of back pain.

Knee joint OA

Another set of experiments was performed by us in the knee joint of mice. OA was induced by surgical destabilization of the medial meniscus [42] in chemically sympathectomized (Syx) and β2-AR-deficient mice (*Adrb2*$^{-/-}$). Syx, by applying 6OHDA, destroys about 80% of the sympathetic nerve fibers only in the periphery, thus concentrations of NE are much lower, while ARs are still expressed. In contrast, *Adrb2*$^{-/-}$ do have intact sympathetic nerve fibers but no β2-AR in the joint. Contrary to earlier *in vitro* studies, the authors did not detect any differences regarding cartilage degeneration or synovitis after OA induction in Syx and *Adrb2*$^{-/-}$ compared to controls [43, 44]. This discrepancy is likely based on the fact that cell cultures are artificial systems that can not demonstrate the full picture of pathophysiology occurring in an organism. Another reason could be that above-described animals were sacrificed after 12 weeks, and effects on cartilage might appear at later time points.

However, the calcified cartilage zone, the subchondral bone plate as well as the subchondral trabecular bone were significantly thicker in Syx mice. These changes were even stronger in *Adrb2*$^{-/-}$ animals [43, 44]. Former *in vitro* studies already demonstrated that the function of osteoblasts is suppressed and osteoclast activity is induced after the activation of β2-AR [45]. Accordingly, in Syx and *Adrb2*$^{-/-}$ mice the

opposite happened, osteoblast activity was increased and osteoclast activity reduced due low NE or β2-AR, respectively.

Moreover, in *Adrb2*$^{-/-}$ with OA an additional phenomenon emerged. These mice are not able to perform a sufficient lipolysis due to β2-AR deficiency, accordingly, they had a higher abdominal fat mass and a 30% higher body weight compared to wildtype controls. We demonstrated that the concentration of the major adipokine leptin was significantly higher in these *Adrb2*$^{-/-}$ OA mice [43, 44]. This increased leptin concentration can not lead to the classical β2-AR-dependent inhibitory effects on bone formation, which are mediated by PKA-dependent phosphorylation of activating transcription factor (ATF) leading to increased RANKL expression and subsequent osteoclast induction as well as by inhibiting osteoblast proliferation via blocking of Cyclin-D expression [46]. However, leptin is also able to mediate β2-AR-independent effects. In the arcuate nuclei of hypothalamus, leptin induces the expression of cocaine-amphetamine-regulated transcript (Cart) that inhibits RANKL-mediated osteoclast activity via an unknown mechanism [46]. This phenomenon is responsible for additional β2-AR-independent increase of osteoblast and decrease of osteoclast activities [46] and explains, why the effects in the subchondral bone are more pronounced in *Adrb2*$^{-/-}$ OA mice [43, 44].

Taken together, a number of animal studies of OA provided evidence that the β2-AR is involved in the early OA-associated subchondral bone loss by reducing osteoblast and increasing osteoclast activities. In contrast, the role of β2-AR in cartilage degradation and synovial inflammation is not yet fully understood.

OA pain

Unfortunately, no *in vivo* study investigated until now, whether and how β2-AR contributes to pain modulation in OA, although clear associations with pain severity

and β2-AR polymorphisms or beta blocker medication were observed in OA patients as described in the next chapter in detail.

In general, several studies focusing on other diseases demonstrated that β2-AR can modulate both ascending and descending pain pathways and that these effects can be opposing. Long-term and recurring activation of β2-AR on peripheral nociceptive neurons of the Aδ and C type reduces the nociceptive threshold leading to peripheral sensitization [47]. Similarly, continuous β2-AR stimulation in naive dorsal root ganglia (DRG) in a rat model of colitis induced calcitonin gene-related peptide expression, thus β2-AR activation also contributes to central sensitization by making DRG neurons hyperexcitable, which results in allodynia and/or hyperalgesia [48]. In contrast, activation of descending noradrenergic pathways, for example through norepinephrine reuptake inhibitors or β2-AR agonists, clearly led to anti-nociceptive effects. For example, systemic administration of the β2-AR agonist clenbuterol resulted in anti-allodynic effects in a rat model of persistent postsurgical hypersensitivity by reducing microglial activation and macrophage density at the site of incision [49]. In contrast, in mice subjected to partial sciatic nerve ligation, selective β2-adrenergic receptor antagonist ICI118551 reduced pain threshold by downregulating microglial p38 MAPK and astrocytic JNK [50], demonstrating again the complexity and context-dependence of β2-AR-mediated effects.

In summary, it became clear that β2-AR is principally capable of potentiating or alleviating pain. However, it is still unknown, which molecular pathways are activated in different OA stages or individual patients. Therefore, further animal as well as clinical studies addressing this aspect are needed.

OA patient studies

β2-AR polymorphisms

In 2010, a clinical association study was published reporting that two single nucleotide polymorphisms (SNPs) of the *ADRB2* gene were associated with more pain in different pathologies [51]. This study was not OA-specific but provided a first indication that β2-AR polymorphisms might also influence OA-related chronic pain. In 2018, others investigated whether the genetic variability of β2-AR influences the functionality of peripheral blood lymphocytes in OA patients carrying different *ADRB2* allelic variants. Isolated lymphocytes were stimulated with the specific β2-AR agonist isoproterenol. Although no differences in lymphocyte function were detected, the response of β2-AR to isoproterenol was 50% reduced in all OA patients compared to healthy persons as indicated by reduced intracellular cAMP levels [52]. β2-AR downregulation or desensitization caused by genetic variability could be responsible for this disturbed β2-AR function. One further reason for such unexpected responses could be the shortly described β-arrestin-dependent Gαs to Gαi switch and subsequent reduced cAMP-dependent PKA phosphorylation. As demonstrated in our own study and described above, a pro-inflammatory Gαs-to-Gαi switch does in fact occur in mixed synovial cells obtained from OA patients[25].

Taken together, genetic variability of β2-AR and β-arrestin-dependent modifications of the G protein-related intracellular signaling can lead to OA-promoting pro-inflammatory cellular responses in the synovial tissue (see also ref [26]).

Subchondral bone remodeling

As described above, animal OA models provided evidences that sympathetic activity regulates bone remodeling via the β2-AR in the early stage of the disease [38, 39, 44]. A further interesting phenomenon in humans was observed in 2022. This study analyzed

the subchondral bone of OA patients with varus-deformed knee joints exhibiting significantly higher medial loading, higher Osteoarthritis Research Society International (OARSI) score and subchondral bone thickening. Compared to the less loaded lateral side, gene and protein expression of the β2-AR was significantly increased in osteoclasts of the medial subchondral bone [53]. These results indicate that in contrast to early OA, β2-AR induces subchondral bone thickening in the late OA phase. This is also in line with above-described findings in the IVD [40]. However, increased receptor expression on the medial side could also be a consequence of bone thickening.

Thus, it becomes increasingly clear that β2-AR in the subchondral bone has a disease-promoting bone-thickening role in the late stage of osteoarthritic disease.

Beta-blocker effects

One promising approach to uncover the role of β2-AR in OA is the comparative analysis of OA-specific symptoms in beta-blocker users versus non-users. Older non-selective beta-blockers bind to both β1- and β2-ARs and most modern beta-blockers are selective β1-AR antagonists [54]. Moreover, most joint-resident cells do not express the β1-AR, except infiltrating immune cells. In contrast, the β2-AR is present in all joint tissues. Thus, most beta-blocker effects in the joint would target the β2-AR [18].

The first study in this regard described that the increase of medial tibiofemoral joint space width or Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) knee pain score were reduced in patients with a β1-AR-selective beta-blocker medication (after a 36-month follow-up [55]. An independent study confirmed these findings one year later demonstrating that both non-selective and selective beta-blocker medication was associated with a lower prevalence of OA-related joint pain.

Finally, a recent study showed in over 111.000 beta-blocker users with OA compared to the same number of non-OA individuals that the incidence of OA decreased after 2.75-11.29 years. The authors reported that both non-selective and selective beta-blocker prescription was also associated with reduced knee and hip pain although the greatest effect size was observed for the non-selective beta-blocker propranolol [56].

In summary, beta-blocker medication seems to reduce the risk of osteoarthritic joint degeneration and associated pain reconfirming the contribution of β2-AR to OA pathogenesis.

Targeting β2-AR for OA prevention and treatment – Pros and Cons

The fact that β2-AR activation results in OA-promoting effects in all cell types of the joint causes us to presume that blocking this receptor alone or in combination with conservative interventions might represent a potential preventive or therapeutic option for OA. Systemic administration of beta-blockers could be an effective option to prevent or alleviate the OA-driving influences mediated by β2-AR (Fig.2). As described above, systemic beta-blocker medication not only reduced the risk of degenerative or pro-inflammatory changes in the joint but also reduced pain genesis [55-57]. This means that one possibility would be a preventive administration of non-selective or β2-AR-selective beta-blockers especially in individuals with increased susceptibility such as post-menopausal women [58] or persons after joint trauma [59]. Taking some major OA-associated comorbidities such as hypertension, heart failure or coronary artery disease [60] into consideration, systemic low dose beta-blocker treatment of OA patients could result in additional beneficial influences However, caution is advised here because beta-blockers can also have adverse effects. The most relevant general side effects are lightheadedness, slight incoordination, nausea and vomiting [61]. Furthermore, some clinical studies reported that beta blocker medication may increase the risk of further

OA comorbidities such as diabetes mellitus or obesity [62]. In addition, this medication would not be feasible for example in case of individuals with asthma or chronic obstructive pulmonary disease (COPD) because these persons need local β2-agonist treatment to achieve bronchodilatation [63]. The use of biased β2-AR antagonists that selectively regulate only one part of the signaling pathways might be a more feasible option, in this case without inhibiting cAMP-mediated bronchodilatation [64]. Alternatively, photoswitchable β2-agonists or antagonists with spatiotemporal control of adrenergic signaling might represent a solution of such a dilemma [65]. Particularly in terms of pain, a β2-AR-blocker that is not able to cross the blood-brain barrier (like sotalol or atenolol but only β2-specific), would inhibit the ascending potentiation of pain. These examples make clear that a thorough risk assessment as well as strict and frequent control examinations would be necessary when taking beta-blocker medication into consideration for OA prevention or therapy. We agree that β2-AR-blocker therapy has some challenges but it is always necessary to define the target – the β2-AR. After our pathophysiological understanding of the target, we might invent ways to overcome obstacles and side effects.

The most goal-oriented strategy would be a targeted long-term blocking or desensitizing of β2-ARs locally in the joint or even tissue-specifically (Fig.2). Such an approach might block catabolic effects in cartilage, pro-inflammatory effects in the synovium, or nociceptor sensitization. For local β2-AR inhibition, intraarticular injection of β2-AR antagonists encapsulated in PEG-microspheres [66] or of engineered exosomes carrying β2-AR blockers might represent effective future strategies [67]. However, also these treatment options are associated with adverse effects since a local intraarticular treatment is an invasive intervention accompanied by the risk of complications such as infections [68].

Taken together, we have to recognize that our knowledge about β2-adrenergic treatment options with regard to OA is more than limited. Future studies should explore the undoubtly existing potential of β2-AR-blocking drugs in more detail in order to develop novel treatment strategies that target OA locally in the joints to avoid systemic side effects. This will enable us to shift away from a symptomatic therapy presently applied to a personalized prevention and causal treatment of OA.

Conclusions

During the past two decades, significant advances were made contributing to our understanding of β2-AR-mediated effects on OA pathogenesis (Fig.1). We have learned that all tissues in articular joints express this receptor [18], although for a long time β2-AR were thought to be mainly expressed in smooth muscles, lung, cerebellum, liver, pancreas, salivary gland or fat tissue [69-72]. The first evidence of a possible contribution of β2-AR to OA initiation or progression was the observation that β2-AR meditated signaling disturbed the regenerative chondrogenic capacity of joint-resident MSCs [21, 22]. Following studies in chondrocyte cultures revealed the loss of chondrogenic phenotype indicated by induction of proliferation as well as inhibition of sGAG and type II collagen synthesis [28]. Interestingly, no similar effects were seen in animal models, most likely due to the short observation period of few weeks. However, β2-AR was responsible for OA-characteristic subchondral bone changes in rat and murine OA models by inducing osteoclast but inhibiting osteoblast functions [38, 39, 43, 44]. It became clear that altered biomechanical conditions in joint tissues is associated with upregulated β2-AR expression [40, 53], which perpetuates the OA-promoting effects of this receptor.

Certain β2-AR polymorphisms lead to an additional pro-inflammatory response in synovial cells potentiating disease progression [25, 51, 52]. And last but not least, clinical studies investigating OA patients, thus with the highest relevance, revealed that beta-blocker reduced both radiographic signs of cartilage degeneration and OA-associated pain intensity [55-57]. We start to realize that the β2-AR definitely contributes to the initiation and progression of OA in different joint tissues in various ways.

We need to take advantage of the above-described information and design experiments investigating the potential of drugs blocking β2-AR-mediated OA-promoting effects locally or even systemically considering the OA-associated comorbidities. This will allow us the development of novel preventive or therapeutic options and thus pave the way for future individualized OA management.

Author contributions

ZJL and RHS: Conceptualization, writing - original draft, writing – review and editing, final draft. ZJL: figure design.

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Competing interests

ZJL and RHS declare no competing interests.

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Figure legends

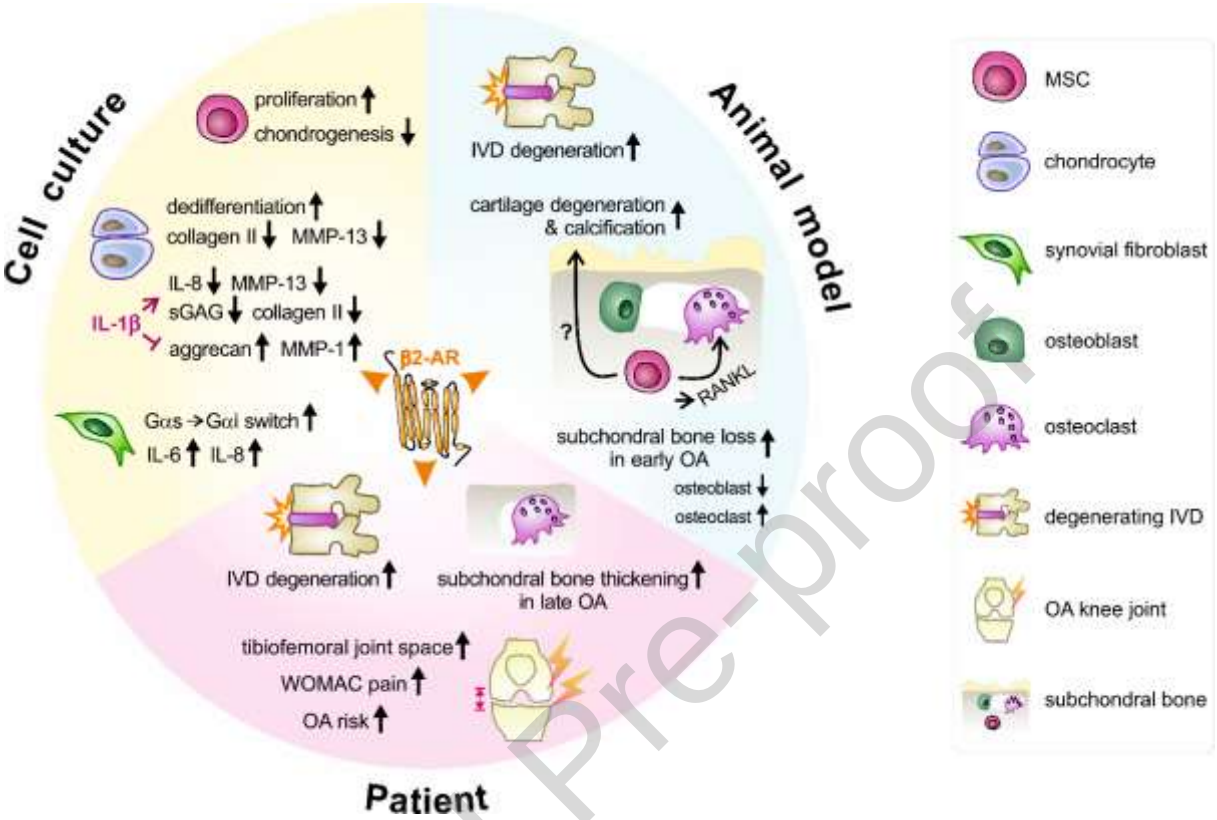

Fig.1. Involvement of β2-AR in OA initiation and progression. Activation of β2-AR in joint tissues by its classical natural ligand norepinephrine or by the adipokine leptin influences numerous processes during joint degeneration as demonstrated by cell culture research, experimental animal models as well as clinical studies in patients suffering from OA or disc degeneration. Upward arrows represent induction/increase, while downward arrows mean inhibition/decrease. Please see the main text for details. Abbreviations: G αs – stimulatory α subunit of the G protein, G αi – inhibitory α subunit of the G protein, IL-interleukin, IVD – intervertebral disc, MMP – matrix metalloprotease, OA – osteoarthritis, RANKL - Receptor Activator of NF-κB Ligand, sGAG – sulphated glycosaminoglycans, WOMAC - Western Ontario and McMaster Universities Osteoarthritis Index

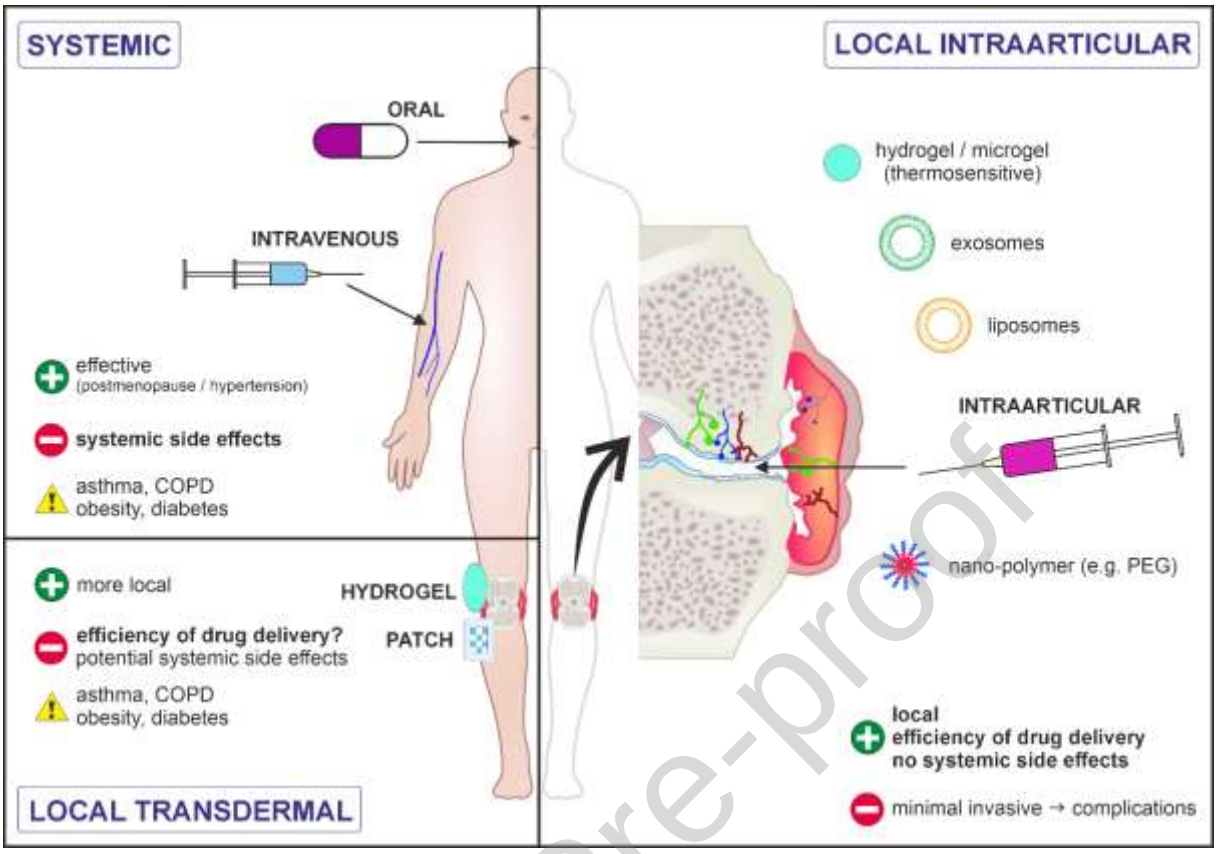

Fig.2. Potential β2-AR-dependent therapeutic options for OA. In order to block β2-AR-mediated catabolic and/or pro-inflammatory processes in the joint, non-specific beta blockers or specific β2-AR anatgonists (biased, photoswitchable, BBB non-penetrating, long-term desensitizing) may be applied systematically or locally respectively. Systemic therapy can include oral intake or intravenous injection, while local treatment can take place by application of hydrogels or patches as well as intraarticular injection of β2-AR blocker in form of hydrogels, exosomes, liposomes or nanoparticles. Advantages (green plus icon), disadvantages (red minus icon) and caveats in certain patient groups (yellow triangle with exclamation mark) for each application method is presented. Please see the main text for details.

Abbreviations: BBB – blood-brain-barrier, COPD - chronic obstructive pulmonary disease, PEG - polyethylene glycol