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Role of the Sympathetic Nervous System in Mild Chronic Inflammatory Diseases: Focus on Osteoarthritis

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Keywords
Sympathetic nervous system · Neurotransmitter · Immune system · Mild chronic inflammation · Osteoarthritis

Abstract
The sympathetic nervous system (SNS) is a major regulatory mediator connecting the brain and the immune system that influences accordingly inflammatory processes within the entire body. In the periphery, the SNS exerts its effects mainly via its neurotransmitters norepinephrine (NE) and epinephrine (E), which are released by peripheral nerve endings in lymphatic organs and other tissues. Depending on their concentration, NE and E bind to specific α- and β-adrenergic receptor subtypes and can cause both pro- and anti-inflammatory cellular responses. The co-transmitter neuropeptide Y, adenosine triphosphate, or its metabolite adenosine are also mediators of the SNS. Local pro-inflammatory processes due to injury or pathogens lead to an activation of the SNS, which in turn induces several immunoregulatory mechanisms with either pro- or anti-inflammatory effects depending on neurotransmitter concentration or pathological context. In chronic inflammatory diseases, the activity of the SNS is persistently elevated and can trigger detrimental pathological processes. Recently, the sympathetic contribution to mild chronic inflammatory diseases like osteoarthritis (OA) has attracted growing interest. OA is a whole-joint disease and is characterized by mild chronic inflammation in the joint. In this narrative article, we summarize the underlying mechanisms behind the sympathetic influence on inflammation during OA pathogenesis. In addition, OA comorbidities also accompanied by mild chronic inflammation, such as hypertension, obesity, diabetes, and depression, will be reviewed. Finally, the potential of SNS-based therapeutic options for the treatment of OA will be discussed.

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Introduction

The autonomic nervous system (ANS) directs subconscious activities and regulates diverse physiological functions in the organism by its two major antagonistic branches, the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS) [1]. The SNS coordinates stressful situations, which is known as the classical "fight or flight" response. This results in an increased heartbeat, dilated pupils and bronchial tubules, decreased digestive activity, among others. Contrarily, the PNS is responsible for the "rest and digest" state. Besides the typical antagonistic action, the SNS and PNS sometimes also cause synergistic responses, and

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together, they ensure that the body reacts appropriately to different situations and adapts to acute environmental changes [2]. Under healthy conditions, the effects of the sympathetic and the parasympathetic division are well-balanced, resulting in homeostasis of physiological processes, such as heartbeat, blood pressure, respiration, digestion, or regulation of body temperature, and sexual arousal [3, 4]. Already a minimal disturbance of this fine-tuned function can result in a variety of pathological conditions [5].

Moreover, the ANS is a major integrative and regulatory mediator between the brain and the immune system. The main task of this cross-talk is to protect the body against challenges arising from the environment as well as from within the body [6]. In case of local injury or pathogen entry, the body activates local immune cells, which respond by releasing pro-inflammatory cytokines. These in turn stimulate sensitive neurons, which signal to the brain via the blood circulation and stimulate both stress axes – the hypothalamic-pituitary-adrenal (HPA) axis and the SNS [4, 7]. Activated SNS induces several immunoregulatory mechanisms that can have either pro-inflammatory or anti-inflammatory effects, or even both at the same time. The effects vary depending on different circumstances, such as local versus systemic or acute versus chronic inflammation [8]. These differential anti- or pro-inflammatory effects of SNS on different immune cell types will be described below in detail (section Sympathetic Regulation of Immune Cell Functions). The PNS monitors and regulates the inflammatory response in a reflexive manner, predominantly by blocking pro-inflammatory cytokine synthesis [9].

Chronic inflammatory diseases are the most significant cause of death worldwide [10, 11]. The number of patients suffering from such pathologies has increased dramatically over the last 3 decades, and therefore, it is indispensable to better understand the exact mechanisms of how pathophysiological factors contribute to their initiation and progression [12]. Osteoarthritis (OA) is a chronic degenerative and mild inflammatory disease that is often accompanied by numerous comorbidities [5, 13]. It manifests itself in a reduced quality of life and, accordingly, in enormous socioeconomic costs. In 2017, more than 300 million people worldwide were affected by this disease, and the burden is steadily increasing as life expectancy rises and the global population ages, placing OA at the forefront of public health challenges [14].

In this narrative review article, we summarize the existing knowledge about the influence of SNS on the immune system with special emphasis on chronic mild inflammatory diseases, especially on OA. Furthermore, as a translational perspective, we discuss potential new therapeutic strategies targeting SNS-dependent mechanisms.

The Influence of the SNS on the Immune System

Sympathetic Nerve Fibers, Neurotransmitters, and Receptors in Peripheral Tissues

Sympathetic nerve fibers express the key enzyme of catecholamine biosynthesis tyrosine hydroxylase (TH) and release sympathetic neurotransmitters via peripheral nerve endings [4, 15]. In the periphery, the SNS acts mainly through the endogenous catecholamine norepinephrine (NE) and, to a lesser extent, via epinephrine (E) [16–18]. Both neurotransmitters target specific adrenergic receptor (AR) subtypes that are expressed in most cells of the human body [19, 20]. The α1-AR subfamily comprises the subtypes α1a, α1b, and α1d; the α2-AR subfamily includes α2a, α2b, and α2c subtypes; and the β-AR subfamily contains the subtypes β1, β2, and β3 [21–24]. Different AR subtypes exhibit concentration-dependent binding affinities for sympathetic neurotransmitters. For example, NE at low physiological concentrations (10^{-8}–10^{-9} M) mainly acts via α-ARs, but at high physiological concentrations (10^{-5}–10^{-6} M), it preferentially targets β-ARs [25]. At the medium physiologic concentration (10^{-7} M), it induces both α- and β-AR signaling highly likely in an equal manner [26]. Neuropeptide Y (NPY) coexists with NE but is mainly released during high-frequency stimulation or strong reflex activation of the SNS. While NPY release is promoted by β-AR signaling, it is inhibited by the activation of α_2-adrenoceptors [27]. Adenosine triphosphate (ATP) is another excitatory neurotransmitter co-released by sympathetic nerves but also for most nerves in the peripheral and central nervous system. As ATP is very rapidly degraded after release, further characterization of ATP release in the context of sympathetic activation remains difficult [28, 29]. Depolarization of sympathetic nerve terminals simultaneously releases ATP and the ectonucleotidases CD39 and CD73, which hydrolyze ATP into nucleosides and to adenosine. In addition, many cells express these ectonucleotidases on their cell membrane [30]. Adenosine regulates several cellular processes by activate four subtypes of G protein-coupled adenosine receptors (aRs; A1, A2A, A2B, and A3) [31, 32]. In this review article, we will mainly focus on NE and discuss the major effects of adenosine, as the influences of E and the sympathetic co-transmitters NPY and ATP are still only poorly understood in the context of OA.

Sympathetic nerve fibers innervate primary and secondary lymphoid tissues and are found in close proximity to immune cells [33, 34]. Most immune cells express at least one of the nine AR subtypes, allowing a fine tuning of cellular activities in response to sympathetic activity [35, 36] (Fig. 1). Consequently, besides

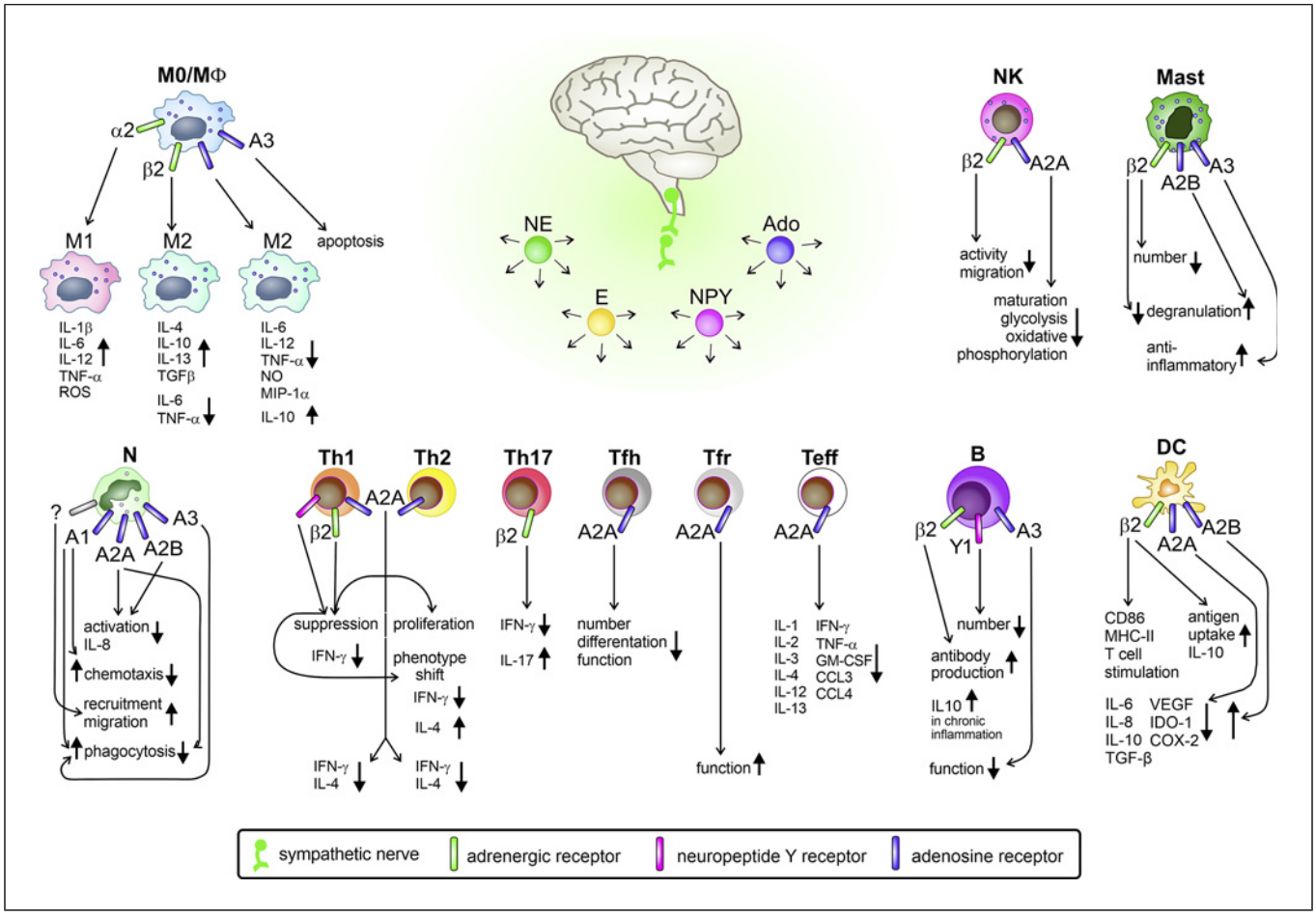

Fig. 1. SNS-mediated regulation of immune cell functions. In the periphery, the SNS exerts its effects mainly via its major neurotransmitters NE and E as well as the co-transmitters NPY and adenosine, which are released by postganglionic peripheral sympathetic nerve endings. These neurotransmitters activate different subtypes of neurotransmitter receptors on immune cells and modulate their function. Ado, adenosine; B, B cell; CCL, C-C motif chemokine ligand; DC, dendritic cell; CD, cluster of differentiation; COX, cyclooxygenase; E, epinephrine; GM-CSF, granulocyte-macrophage colony-stimulating factor; IDO, indoleamine 2,3-dioxygenase; IFN-γ, interferon γ; IL, interleukin; M, monocyte/macrophage; MHC, major histocompatibility complex; MIP-1α, macrophage inflammatory protein-1 α; N, neutrophil; NE, norepinephrine; NK, natural killer cell; NO, nitric oxide; NPY, neuropeptide Y; ROS, reactive oxygen species; T, T cell; TGFβ, transforming growth factor β; TNF-α, tumor necrosis factor α; VEGF, vascular endothelial growth factor.

local neurotransmitter concentration, the net outcome of stimulating ARs on immune cells strongly depends on the receptor repertoire. Pongratz et al. [4] speculated that the different binding affinities serve as detectors of the distance to the source of catecholamines. This might explain why some cells express both α- and β-ARs simultaneously.

Sympathetic Influences during Inflammation

Studies investigating pathologies with systemic chronic inflammation, such as RA, demonstrate the extent to which the SNS can influence immunological processes. As early as the 1930s, sympathectomy was found to reduce pain and joint swelling in RA patients [37]. The clinical cases reported by Kidd et al. [37] described RA patients whose SNS was blocked by sympathetic ganglionectomy, lumbar sympathectomy, or in a sympathectomized limb. Subsequent animal studies confirmed that the SNS has a decisive influence on RA progression, even though its effects seem to be bidirectional depending on the stage of disease. In a murine model of collagen-induced arthritis (CIA), both reduced and increased RA severities were observed after chemical sympathectomy. The outcome was found to depend on the time point of sympathectomy. It

became very clear that SNS activity has a pro-inflammatory effect in the early phase of the disease, while it acts anti-inflammatory in the late stage (reviewed by [2, 38]). The underlying control mechanisms of these and similar phenomena in various pathologies are described below. Especially, inflammatory response during RA pathogenesis was explained and used as a model to describe the effects of SNS on inflammation.

Energy supply is most important for the activation of the immune system. An activated immune system requires much more energy than in a normal, non-inflammatory state [39]. Activation of the SNS during inflammatory processes helps to provide energy-rich substrates, primarily by increasing lipolysis, glycogenolysis, muscle proteolysis, and gluconeogenesis [4]. Thus, acutely increased systemic SNS activity contributes to an adequate immune response. However, the SNS serves the immune system not only by providing energy but also regulates several other processes by directly targeting immune cells. The SNS is involved in recruitment, redistribution, and antibody production of lymphocytes [25, 40–43], antigen uptake and presentation in dendritic cells (DCs) [44], as well as T helper cell differentiation and natural killer (NK) cell activation [45]. As demonstrated by in vitro studies, SNS-induced AR signaling can modulate induction, proliferation, and effector function of distinct immune cells depending on the neurotransmitter concentration. In summary, SNS regulation can affect all phases of the immune response [46].

One major aspect of sympathetic influence on inflammation is the regulation of cytokine release: SNS activation in the brain induces the release of neurotransmitters from sympathetic nerve terminals in the periphery. Subsequently, the neurotransmitters trigger a pro- or anti-inflammatory response of immune cells depending on the distance to the nerve terminals or, with other words, depending on the neurotransmitter concentration and corresponding AR [42].

In some cases, sympathetic influence itself can undergo changes during the progression of a disease. For instance, when inflammation in RA synovium becomes chronic, sympathetic nerve fibers repulse to create an area of permitted inflammation. This denervation reduces NE concentration, promoting α-AR-mediated anti-inflammatory signaling. However, if this process persists, like in chronic inflammation, the continuous catabolism might become harmful for the organism. Pongratz and Straub concluded that this phenomenon was positively selected during evolution to treat short-term acute inflammation, but it is not appropriate to fight chronic inflammation [4]. The denervation exemplifies that chronic inflammation raises new challenges for the immune system and the whole body.

Adenosine is considered a predominantly homeostatic and protective sympathetic mediator in pathological conditions based on its anti-inflammatory properties [47, 48], although in some diseases such as cancer, disadvantageous influences may occur due to prolonged immune suppression [49, 50]. In addition, and similarly to NE action, adenosine can also exhibit opposite effects with a net pro-inflammatory outcome depending on the targeted immune cell type as well as on receptor subtype [51]. The regulatory effects of SNS neurotransmitters on specific immune cell types will be described in the following subsection.

Sympathetic Regulation of Immune Cell Functions

As described above, sympathetic activation of immune cells can have either pro- or anti-inflammatory effects, depending on the targeted receptor subtype. In macrophages, AR signaling induces polarization into an anti-inflammatory M1 or a pro-inflammatory M2 phenotype, as demonstrated in a variety of tissues and in different species [52]. As reviewed by Freire et al. [53], stimulation of β2-AR (coupled with the Gαs subunit of G protein) elevates intracellular cyclic adenosine monophosphate (cAMP) and promotes the anti-inflammatory M2 status via the PKA signaling pathway. This phenotype is characterized by expression of specific interleukins (IL) such as IL-4, IL-10, IL-13, transforming growth factor beta (TGF-β), and the inhibition of IL-6 and TNF-α [53–55]. On the other hand, activation of α2-AR (coupled with Gαi subunit of G protein) reduces cAMP levels and therefore promotes M1 properties. This includes the expression of reactive oxygen species and pro-inflammatory cytokines, such as IL-1β, IL-6, IL-12, and TNF-α [55]. It is of particular interest that the catecholamines NE and E not only have acute effects on inflammation but can also induce chronic metabolic changes. Heijden et al. [56] exposed human primary monocytes to low and high physiological levels of NE or E for 24 h. The catecholamines reduced lipopolysaccharide-induced IL-6 and TNF-α production in a dose-dependent manner, indicating an acute immunosuppressive effect. After 5 days of differentiation into macrophages, followed by re-stimulation with lipopolysaccharide on day 6, the cells exhibited increased TNF-α and IL-6 production. The initial catecholamine-stimulus induced the ability to mount an enhanced pro-inflammatory response, which was revealed after the secondary stimulation. This demonstrates that NE and E can train the innate immune

system [56]. Also, the co-transmitter NPY seems to stimulate a number of macrophage functions, including oxidative burst, adherence, chemotaxis, phagocytosis, and cytokine production. For example, NPY increased the synthesis of pro-inflammatory IL-1, IL-6, and TNF-α in human peripheral blood mononuclear cells [57]. As described above, adenosine acts predominantly anti-inflammatory via its GPCRs. This is supported by the fact that during the differentiation of monocytes to macrophages as well as in a pro-inflammatory micro-environment with elevated IL-1β and TNF-α concentrations, the expression of A1, A2A, and A3aRs increases [58–60]. The activation of adenosine receptors on macrophages results in the inhibition of TNF-α, IL-6, IL-12, nitric oxide (NO), and macrophage inflammatory protein (MIP)-1α release [61–63] as well as in the induction of anti-inflammatory IL-10 secretion. Moreover, adenosine also promotes the apoptosis of macrophages via the A3aR [64].

The SNS does not only influence macrophages but also modulates T cell, in particular T helper (Th) cell differentiation and function. Upon activation, Th cells differentiate into different subtypes including Th1, Th2, and Th17 cells [65]. While Th1 cells secrete both pro- and anti-inflammatory cytokines, Th2 cells release anti-inflammatory cytokines, and Th17 cells mainly release the pro-inflammatory-acting IL-17 [66]. According to their cytokine secretion, these subgroups significantly influence the nature of an immune response. It is therefore particularly interesting how NE and E influence the balance of Th subtypes [65]. Sanders et al. stated that the outcome of sympathetic targeting of T cells varied in the context of activation (depending on species, agonist, T-cell subtype), even when the cells expressed β2-AR almost exclusively [53]: in Th1 cells, interferon γ (IFNγ) secretion was decreased by β-agonists (isoproterenol and fenoterol) but increased by NE treatment [67, 68]. The β2-agonist terbutaline reduced IFNγ release but elevated IL-17 levels in human purified Th17 cells [65]. Although human Th2 cells do not express ARs, they still proliferate in response to β-agonist treatment because competing Th1 cells are suppressed [35, 69, 70]. In contrast to its pro-inflammatory effect on macrophages, NPY has an inhibitory effect on T-cell activation. The co-transmitter shifts cytokine production from Th1 cells to an anti-inflammatory Th2 type, characterized by reduced IFNγ production and increased IL-4 secretion [57]. Adenosine can induce various effects also in T cells. For instance, the stimulation of A2AaR leads to the inhibition of the pro-inflammatory cytokines IL-4 and IFN-γ in both Th1 and Th2 cells [50]. In addition, adenosine via A2AaR limits the frequency and function of T follicular helper cells and induces immunosuppressive T follicular regulatory (Tfr) cells at the same time, as proven in immunized A2aRKO mice. Furthermore, the injection of an A2aR agonist after immunization suppressed T follicular helper differentiation [71]. Besides Th cells, also effector T cells are influenced by adenosine. They are even able to synthesize adenosine by themselves, contributing actively to the adnosine-dependent anti-inflammatory effects mainly mediated by the A2AaR [72].

In addition to macrophages and Th cells, B cells, NK cells, and granulocytes are also regulated by the SNS. However, these cell types are only briefly listed as there are no relevant published studies discussing their role in inflammation, specifically in OA. In general, SNS mediators are known to stimulate B-cell activation [73]. The neurotransmitter NE increased antibody production in B cells in vivo as well as in vitro [74, 75]. Fitting to this, mice lacking the NPY receptor 1 (NPY1R) had reduced peripheral B-cell concentrations [76]. In a murine model of CIA, animals treated with B cells from SNS-intact mice exhibited less severe arthritis compared to mice that were treated with B cells from sympathectomized mice. In fact, B cells from SNS-intact mice showed increased IL-10 production being responsible for the observed anti-inflammatory effect induced by NE targeting the β2-AR. However, IL-10 upregulation only occurred in B cells from immunized but not naive mice, reflecting a protective impact of the SNS in the late phase of the CIA model [77]. B-cell function is also influenced by adenosine, and similarly to effector T cells, B cells can synthesize adenosine using their extracellular enzymatic machinery and depending on their activation state [78]. While in inactivated B cells, the extracellular concentration of adenosine is higher, ATP release and subsequent adenosine synthesis decrease in activated B cells highly likely in order to avoid adenosine-dependent inhibition of B-cell function [79]. In particular, regulatory B cells are able to regulate their own function this way via A3aR [80]. The exact mechanisms have not yet been investigated in detail.

SNS activity also modulates the recruitment and migration of granulocyte neutrophils during inflammation [81]. While these processes were adversely affected in sympathectomized rats, they were supported by electrical stimulation of sympathetic nerves [81–83]. However, the receptors that are responsible for this effect have not yet been identified. Neutrophils are also able to produce adenosine by converting released ATP [84, 85]. Activation of A1aR promotes chemotaxis, whereas A2A- and A2BaRs suppress neutrophil activation [86]. Especially

targeting the A2AaR resulted in decreased IL-8 release by neutrophils [87]. Interestingly, A1-and A3aRs induce phagocytosis; however, the activation of A2AaR results in the opposite [88].

Interestingly, NK cells appear to behave in exactly the opposite way compared to B cells and granulocytes: NE and E suppress NK-cell activity and reduce their migratory capacity via β2-AR signaling [89–93]. Similarly, adenosine acted as an intrinsic negative regulator of NK-cell maturation and anti-tumor function mediated by A2aR [94]. Furthermore, another study demonstrated that these effects are rather dependent on the regulation of cellular metabolism such as inhibited oxidative phosphorylation and glycolysis than on modulation of specific inflammatory pathways [95].

Adrenergic signaling influences numerous DC functions as well such as migration, antigen uptake and presentation, and cytokine production. Majority of these effects are mediated by the β2AR, as described in the following. The treatment of mice with the β2AR agonist isoproterenol significantly reduced the severity of adjuvant-induced arthritis and decreased the expression of CD86 and MHC-II, while antigen uptake and IL-10 secretion were induced in DCs. In addition, DC-dependent stimulation of T lymphocyte proliferation and TNF-α secretion were also inhibited [96, 97]. In patients with psoriasis, the down-regulation of βAR expression and/or function in the skin lesions was observed to be responsible for a reduced responsiveness to beta-adrenergic therapeutic agents [98]. More details, which would go beyond the scope of this review with OA in focus, are comprehensively summarized in reference [99]. In mature DCs, adenosine inhibits the production of pro-inflammatory cytokines via the A2AaR, while exactly the opposite effect can be observed when the A2BaR is targeted [100]. This A2BaR-mediated pro-inflammatory effect with increased release of IL-6, IL-8, IL-10, TGF-β, vascular endothelial growth factor, indoleamine 2,3-dioxygenase (IDO-1), and cyclooxygenase 2 (COX-2) is even potentiated under hypoxic condition being characteristic for inflamed tissues [101]. Interestingly, co-localization of A2BaRs with adenosine deaminase (ADA) on DCs forms a complex with CD26 on Th1 cell surface resulting in increased TNF-α, IL-6, and IFN-γ release [102].

The effects of adrenergic neurotransmitters and adenosine on mast will be described only very briefly here. Targeting the β2-AR results in so-called mast cell stabilization characterized by decreased mast cell numbers and reduced degranulation [103], while activation of A2BaR seems to result in increased degranulation, and A3AR stimulation leads mainly to anti-inflammatory effects [104].

In general, the type and amount of produced cytokines after SNS activation change depending on the time of receptor engagement in relation to the activation and differentiation state of the cell, the molecular signaling pathway activated, the cytokine microenvironment, the cell species, and type of agonists used [42, 65]. Other factors, such as the presence of agents that modulate the adrenergic response (e.g., NE transporter mRNAs and TH), or simply age, can also influence the outcome [105, 106]. Consequently, the net effect of sympathetic neurotransmitters and their co-modulators on immune cells varies in a context-dependent manner [4, 57]. It is therefore not possible to state straightforwardly whether the SNS has a pro-inflammatory or anti-inflammatory effect, except for adenosine being predominantly anti-inflammatory. Rather, there is a complex relationship with the immune system through which there is a bi-directional influence on inflammatory processes in the organism.

Sympathetic Influence on Mild Chronic Inflammatory Diseases

As mentioned above, acute local inflammation activates the SNS, and when inflammation becomes chronic, the SNS is persistently elevated. Depending on the severity of inflammation, the resulting catabolic state can have detrimental consequences. The *International Association for the Study of Pain* defines low-grade inflammation as "the chronic production, but in a low-grade state, of inflammatory factors." Mild chronic inflammation is a hallmark of many different diseases, for example, hypertension, diabetes, depression, obesity, asthma, and Alzheimer's disease [4, 107].

Under these mild chronic inflammatory conditions, the concentrations of inflammatory factors are overall slightly higher than in healthy individuals but still remain in physiological ranges (International Association for the Study of Pain, USA [108]. This pronounced and important difference is also reflected in the cytokine levels detected for example in RA (severe chronic inflammation) and OA (mild chronic inflammation) synovial fluid, which increase with the inflammatory status of the patients [109]. Mean TNF-α, IL-6, IL-8, IL-22, and IL-33 concentrations in the synovial fluid of patients with OA were significantly lower than those of RA patients [110–112]. In the following sections, we will introduce current concepts of SNS influence on mild chronic inflammatory diseases, with special focus on OA.

Osteoarthritis

Mild Chronic Inflammation in OA

Traditionally, OA was described as a "wear and tear" disease caused primarily by degradation of articular cartilage [113]. Today, OA is considered a disease of the entire joint, affecting not only the cartilage but also synovial tissue, subchondral bone with bone marrow, menisci, tendons and ligaments, and adipose tissues, such as the infrapatellar fat pad [113, 114]. In the course of OA, these tissues increase their local production of various pro-inflammatory mediators, which induce mild chronic inflammation [115, 116]. The large majority of these pro-inflammatory triggers originate from inflammation of the synovial membrane, therefore referred to as synovitis [117].

In synovitis, innate (monocytes, macrophages) and adaptive (lymphocytic) immune cell recruitment as well as neoangiogenesis take place [116, 118]. In fact, M1 macrophages accumulate in human and murine synovial OA tissues [119]. Moreover, the M1/M2 ratio in the synovial fluid of OA patients was increased compared to controls with healthy knees [120]. The prevailing M1 type of macrophages led to production of a large number of pro-inflammatory factors including TNF-α, ILs (IL-1β, IL-6, IL-8, IL-15, IL-17, IL-21), prostaglandin E2 (PGE2), cyclooxygenase 2 (COX-2), NO and nitric oxide synthases, adipokines, damage-associated molecular patterns, and matrix metalloproteases (MMPs) (MMP1, MMP2, MMP3, MMP9, MMP13), as well as a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) (ADAMTS-4, ADAMTS-5) [121–125]. MMPs secreted by macrophages degrade cartilage and release fragments of the extracellular matrix. In turn, these fragments but also the MMPs themselves further promote synovial inflammation by activating resident macrophages ultimately creating a vicious cycle [121, 122, 126]. Despite macrophages being the main diver on inflammation among immune cells in OA, the influence of Th cells can also be relevant. In course of OA, the Th cell profile changes which is accompanied by increased IL-12, IL-23, and IL-17 levels [117, 127–130], indicating elevated Th1 and Th17 activity in OA. In fact, the elevated IL-12 release correlated with higher knee pain and function [131]. Although it is known that B cells, granulocytes, and NK cells are modulated by the SNS, it is not yet known how cell functions are altered in the context of OA.

However, above-mentioned pro-inflammatory mediators affect not only the synovium but also all surrounding tissues such as cartilage, bone, as well as ligaments and tendons. Although different OA phenotypes have been identified such as senescent, inflammatory, metabolic, endocrine, genetic, etc., inflammation emerges sooner or later in most cases [132, 133]. As inflammation plays a critical role in OA progression, the SNS has gained increasing importance in OA research over last decades [4, 134, 135].

Sympathetic Influence on Inflammation in OA

One prerequisite for sympathetic influences in OA joint tissues is the presence of effectors, namely sympathetic nerve fibers and the (co-)neurotransmitters themselves. Various in vitro and in vivo studies demonstrated the presence of these effectors in healthy, as well as OA-joint tissues. The subchondral bone marrow, the periosteum, the synovium, the IFP, the meniscus, the cartilage as well as ligaments and tendons are innervated by TH-positive sympathetic nerve fibers that release NE and its co-transmitter NPY and ATP into the synovial fluid [136–139]. Contrarily, Jenei-Lanzl et al. [136] reported that E was not detectable in the synovial fluid of trauma patients undergoing knee replacement surgery. Moreover, all above-mentioned joint tissues express distinct subtypes of ARs (reviewed in [134]).

To date, there are only few studies investigating the direct effect of the SNS on OA-related inflammation in vivo. Rösch et al. [140] reported that chemical sympathectomy in experimental OA in mice did not influence synovitis. Contrarily, high joint NE levels increased joint inflammatory parameters, such as local neutrophil infiltration and pro-inflammatory cytokine levels in zymosan-induced arthritic rats [141]. On the other hand, there are several studies investigating the influence of NE, NE-regulating enzymes, the activation and inhibition of ARs as well as the effect of NPY on inflammatory processes in cells of the synovium (Fig. 2) and cartilage (Fig. 3) in vitro. Furthermore, infiltrating immune cells as well as joint-resident cells release ATP, and in response to the elevated ATP levels, the activity of ectonucleotidases forming adenosine increases in order to control inflammation [142, 143]. The major effects of sympathetic effectors in the osteoarthritic joint are summarized in the following subsections.

Synovium

Depending on its concentration, NE regulates cytokine release in different synovial cells in OA patients. As described above, we categorized the NE concentrations used in the experiments. Depending on the physiological concentration in the human body, the following categories were defined: high (10^{-5}–10^{-6} M NE), medium (10^{-7} M NE), and low (10^{-8}–10^{-9} M NE). In synovial

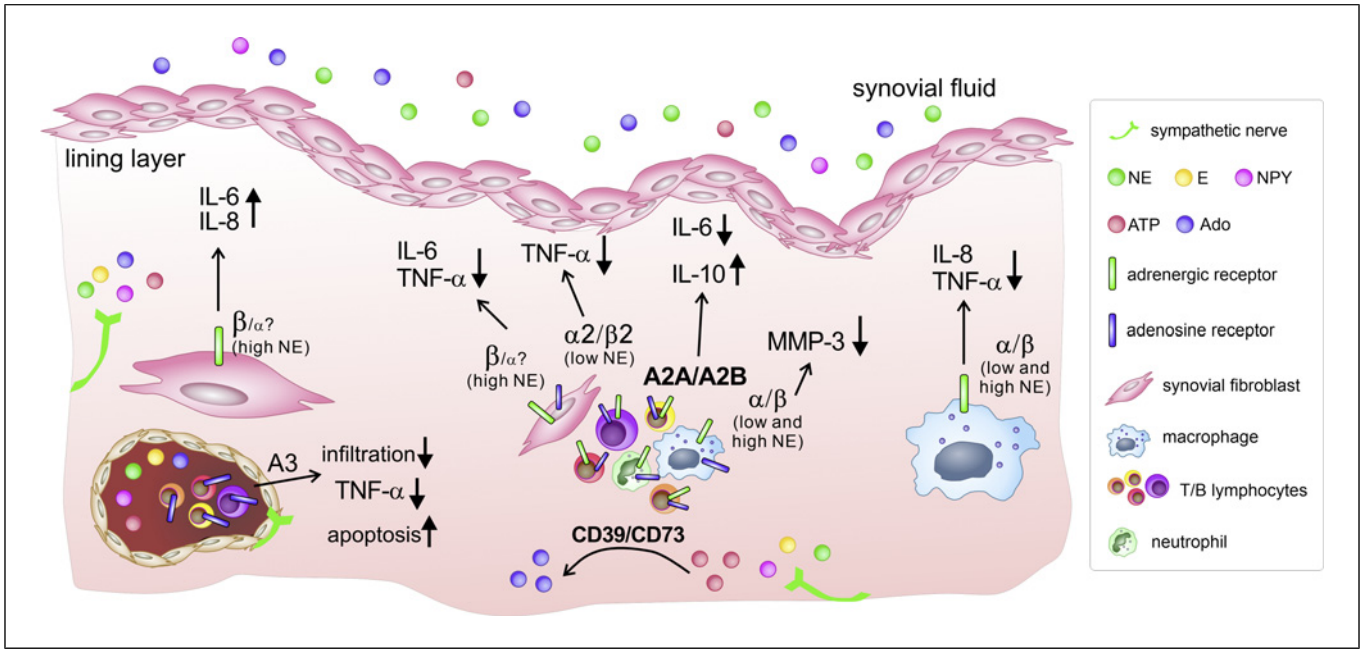

Fig. 2. Effects of sympathetic neurotransmitters on OA synovial cells. Sympathetic neurotransmitters are released by sympathetic nerve fibers and are therefore present in the synovial tissue as well as in the synovial fluid. In addition, synovial cells are able to convert ATP into adenosine. These neurotransmitters activate different receptors. Depending on cell type and targeted receptor subtype, neurotransmitter effects can be pro- or anti-inflammatory. Please see the main text for details. Ado, adenosine; ATP, adenosine triphosphate; B, B cell; CD, cluster of differentiation; E, epinephrine; IL, interleukin; MMP, matrix metalloprotease; NE, norepinephrine; NPY, neuropeptide Y; T, T cell; TNF-α, tumor necrosis factor α.

fibroblast, high to medium physiological NE concentrations increased IL-6 and IL-8 secretion and thus exerted a pro-inflammatory effect [126]. In contrast, in mixed synovial cells containing fibroblasts and immune cells, NE predominantly exerts anti-inflammatory effects [144]. Capellino et al. [145] analyzed the effect of NE in mixed synovial cells from OA patients by manipulating endogenous NE release and metabolism. Blocking of the vesicular monoamine transporter 2 (VMAT-2) led to an absence of NE storage in intracellular vesicles thus, to an elevated extracellular NE concentration and the inhibition of catechol-O-methyltransferase (COMT) prevented NE degradation. The resulting increased extracellular NE concentration inhibited TNF-α release by mixed synovial cells dose-dependently. Similarly, NE at high physiological concentrations inhibited TNF-α and IL-6 secretion in mixed synovial cells [146]. Jenei-Lanzl et al. [144] reported that a TNF-α reduction by low NE levels in mixed synovial cells was mediated by β2-and α2-AR agonists. It is also worth mentioning that synovial inflammation is accompanied by hypoxia [147]. Hypoxic conditions in mixed synovial cells of OA patients resulted in increased TH protein expression followed by increased NE synthesis. According to the above-mentioned studies, elevated NE levels further inhibited TNF-α [148]. Moreover, NE regulates not only cytokine concentrations but also the expression of MMPs. High to low physiological concentrations of NE inhibited MMP3 secretion in mixed synovial cells from OA patients and, thus, are able to counteract cartilage degeneration and further synovial cell activation [146]. High to low NE levels decreased TNF-α and IL-8 release also in synovial macrophages [149], suggesting that macrophages contribute to the anti-inflammatory response of NE in mixed synovial cells, which was not detected in synovial fibroblasts. The ambiguous effects of NE can only partly be explained by concentration-dependent binding affinities of the AR subtypes. It became clear that the effect of NE on cytokine secretion in synovial cells is cell-type dependent. Although synovial fluid levels of NPY correlate positively with the inflammatory status of OA patients, the cellular and molecular mechanisms of this correlation have not yet been investigated [137]. Interestingly, OA synovial cells start to express TH by themselves when inflammation becomes chronic in the tissue [145]. This is highly likely an attempt of the cells to control inflammation.

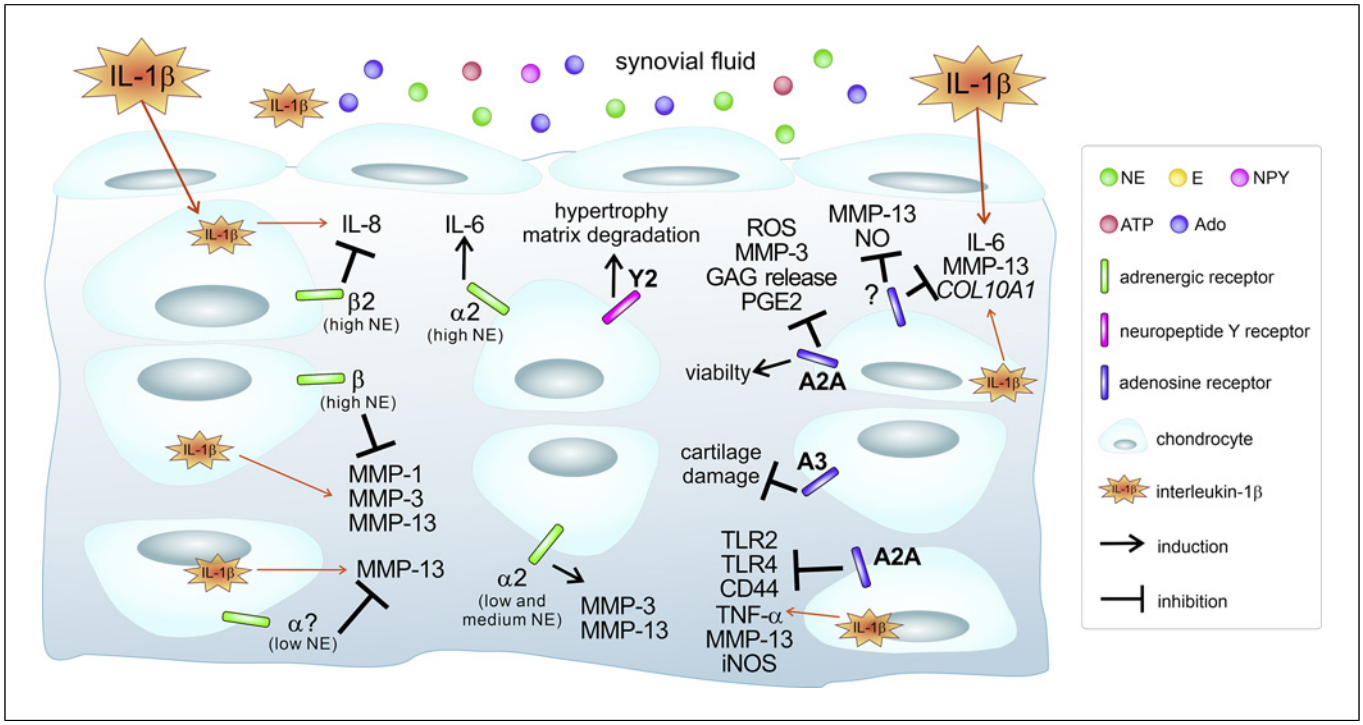

Fig. 3. Effects of sympathetic neurotransmitters on OA chondrocytes. Sympathetic neurotransmitters are only present in the synovial fluid since cartilage is avascular and aneural tissue. The effects of neurotransmitters can be pro- or anti-inflammatory and catabolic or anti-catabolic depending on the targeted receptor subtype and the presence of the pro-inflammatory cytokine IL-1β. Please see the main text for details. Ado, adenosine; CD, cluster of differentiation; *COL*, collagen encoding gene; E, epinephrine; GAG, glycosaminoglycan; IL, interleukin; iNOS, inducible nitric oxide synthase; MMP, matrix metalloprotease; NE, norepinephrine; NO, nitric oxide; NPY, neuropeptide Y; PGE, prostaglandin E; ROS, reactive oxygen species; TLR, toll-like receptor; TNF-α, tumor necrosis factor α.

However, given the complexity of neurotransmitter effects on different cell types in the synovium together with the fact that these effects can be opposite depending on the vicinity of target cells from the neurotransmitter source or receptor expression profile, this attempt seems to fail.

Synovial cells are also influenced by adenosine. A recent study demonstrated that human osteoarthritic mixed synoviocytes containing all synovial cell types such as fibroblasts and immune cells express the complete enzymatic machinery of adenosine synthesis (CD39 and CD73) in order to fight inflammation. In fact, treatment of these cells with CD73 inhibitor resulted in increased IL-6 and decreased IL-10 release, while ADA application resulted in the opposite, confirming the anti-inflammatory effects of adenosine. This study confirmed by using specific agonists that mainly the A2A- and A2BaRs mediate these effects [30]. Moreover, TNF-α and IL-8 synthesis was significantly reduced in human synovial fibroblasts after A2AaR or A3aR agonist treatment by inhibiting the p38 MAPK and NF-κB pathways [150]. Besides A2AaR, also A3aR, seems to play a role during OA pathogenesis. In a rat model of monosodium iodoacetate-induced OA, the A3aR agonist CF101 reduced the lymphocyte infiltration, decreased the release of TNF-α, and induced the apoptosis of pro-inflammatory immune cells by inhibiting NF-κB signaling [151].

Cartilage

The dose-dependence of sympathetic signaling via NE observed in the synovium has also been described in human OA chondrocytes. NE at high physiological concentrations counteracted IL-1β-induced IL-8 upregulation via β2-AR signaling. In contrast, low NE levels targeting α1-ARs exerted no anti-inflammatory effect [152]. As already described for synovial cells, NE also regulated MMP expression in OA chondrocytes. The neurotransmitter in high concentration inhibited IL-1β-induced MMP1, MMP3, and MMP13 expression in

chondrocytes of OA patients via β-AR activation [153]. Jiao et al. [154] studied chondrocytes of temporomandibular joint osteoarthritic rats, and here, NE at medium and low but not high concentrations increased MMP3 and MMP13 production by chondrocytes through the extracellular signal-regulated kinase (ERK) 1/2 and protein kinase A (PKA) pathway. The α2-AR-antagonist yohimbine counteracted this effect. Contrarily, high and low NE levels did not influence *MMP13* gene expression in human OA chondrocytes which were dedifferentiated under hypoxia for 7 days in vitro. However, a low NE concentration decreased IL-1β-induced *MMP13* expression in the same study [155]. Since NPY also promotes chondrocyte hypertrophy and cartilage matrix degradation in mice via the NPY2R, it may also be involved in MMP regulation [156]. The effects of NE on OA synovium and cartilage described above are essentially consistent with the generally accepted paradigm that NE in high concentrations targets β-ARs, inducing an anti-inflammatory effect. In contrast, at low concentrations, NE is assumed to activate α-ARs which promote pro-inflammatory effects. However, there are also studies which do not fit into this straightforward model. Ou et al. [157] treated chondrocytes derived from the osteoarthritic temporomandibular joint of mice with high physiological NE concentrations. Based on the NE level, one would expect a β-AR-mediated anti-inflammatory cell response. In this case, however, an α2-AR-induced pro-inflammatory upregulation of IL-6 occurred. Ou et al. [157] stated that the instability of NE in vitro could have resulted in a lower concentration than initially applied. Since only α2-AR but not β2-AR presence was verified via Western Blot, it could also be possible that β-AR was not expressed in these chondrocytes in vitro.

The above-described general preventive nature of adenosine seems to be true also for OA. Adenosine reduced the inflammatory processes in chondrocytes in rats with temporomandibular joint OA. In this animal model, mesenchymal stem cell-derived exosomes reduced NO and MMP13 expression in chondrocytes. This anti-inflammatory effect was induced by adenosine receptor-mediated AKT, ERK, and AMPK phosphorylation; however, the receptor subtype that mediates this effect has not been elucidated [158]. Moreover, intra-articular injection of adenosine in liposomal suspension or adenosine conjugated to nanoparticles successfully prevented the development of post-traumatic OA in rats. In the same study, chondrocytes treated with the same adenosine nanoparticles were able to reduce the IL-1β-induced *IL-6*, *MMP13*, and *COL10A1* expression [159]. Similarly, the specific A2aR agonist CGS-21680 significantly reversed the IL-1β-mediated increase in TLR-4, TLR-2 as well as CD44 expression associated with increased TNF-α, MMP13, and inducible nitric oxide synthase levels in murine articular chondrocytes [160]. Mice deficient for CD73 or A2AaR develop OA spontaneously already at 16 weeks of age [161]. Another study confirmed that A2AR deficiency results in the early development of OA due to upregulated expression of cellular senescence and aging-associated genes in articular chondrocytes [162]. In a further study, adenosine was depleted in equine cartilage explants by using ADA that led to a catabolic response indicated by concentration-dependent increase in GAG release and production of total MMP3, MMP13, PGE2, and NO. These effects were successfully reversed by the simultaneous application of the adenosine kinase inhibitor 5′-iodotubercidin (ITU) or the A2AaR agonist N(6)-[2-(3,5-dimethoxyphenyl)-ethyl]adenosine (DPMA) [163]. A2AR stimulation further enhances mitochondrial metabolism, improved the reactive oxygen species burden, proteoglycan breakdown as well as chondrocyte viability in the knee cartilage of obesity-induced OA mice [164]. Also the A2bR subtype has a potential role during OA pathogenesis since A2BR agonists inhibited MSC chondrogenesis, and thus, cartilage regeneration might be suppressed [165]. The ablation of the subtype A3aR also resulted in enhanced OA development in aged mice, while specific A3aR agonists protected the cartilage by downregulating CaMKII kinase and RUNX2 [166]. In addition, the A3aR agonist CF101 reduced cartilage damage in a rat model of monosodium iodoacetate-induced OA [151].

These examples demonstrate that the above-described paradigm of general pro- and anti-inflammatory effects of the SNS via different receptor subtypes is only a simplified model which was generated based on in vitro findings. These may provide controversial results due to divergent culture conditions such as culture duration, media and supplements, oxygen concentrations, cell sources, and species-specific differences, among others. Although it is possible to identify the net effect on a particular tissue in vivo, it is difficult to determine the extent to which the SNS contributes to this effect per cell type since other complex systemic factors (e.g., age and sex) can have additional primary or secondary effects on SNS-mediated processes. Moreover, the SNS does not only affect immune cells and chondrocytes, but there is also a feedback loop in the other direction: for example, TNF-α-induced inflammation decreased NE secretion in human differentiated sympathetic TH-positive neuron-like cells from OA patients [167]. Therefore, the relationship between the SNS and the immune system seems to be more of a complex, bidirectional interaction than a one-way street.

In summary, further research is needed to fully understand how the SNS contributes to inflammatory processes in different cells and tissues during OA progression. IL-1β induces many OA-characterizing processes in the joint and is thus the most important cytokine in OA pathophysiology [123]. Although a molecular link between IL-1β and NE is known to exist, the direct influence of NE on IL-1β in OA-related inflammation has not been elucidated yet [168]. Moreover, still no studies exist on the impact of other sympathetic neurotransmitters, such as NEs co-transmitter NPY, on the osteoarthritic joint. In addition, further tissues such as meniscus or IFP were never investigated with regard to SNS influence. Nevertheless, considering the current knowledge, SNS-mediated inflammatory events seem to play a crucial role in OA development and pathogenesis.

Other Mild Chronic Inflammatory Diseases – OA Comorbidities

As described in detail above, the permanent activity of the SNS modulates inflammatory processes in OA joints. Besides local influences, such an overactivation can have detrimental effects on other organs or even the whole body. Fitzgerald et al. [169] stated that an increased noradrenergic tone predisposes to a large number of diseases. Besides OA, further mild chronic inflammatory diseases have been described such as hypertension, diabetes, depression, obesity, asthma, or Alzheimer's disease [4, 107]. Interestingly, many of these disorders are known as OA comorbidities. A recent study performed a meta-analysis to quantify coexisting medical conditions, so-called comorbidities, of knee and hip OA patients. They identified cardiac diseases, such as hypertension, in 54% of the participants, and 24% of OA patients suffered from diabetes, while 10–14% were obese. Moreover, depression was detected in 14% of OA patients [170]. In general, 25% of OA patients exhibited three or four additional disorders, indicating the risk for multi-morbidity in OA [5]. Since above-mentioned comorbidities are also mild chronic inflammatory diseases, an OA therapy using different anti-inflammatory drugs might reduce their symptoms as well [171–175] (Fig. 4).

However, as described below in detail, therapeutics used for the different comorbidities also alleviate OA symptoms, underlining the involvement of a systemic component in the pathogenesis of OA and its comorbidities. All the above-mentioned OA comorbidities have one major characteristic in common: they all involve SNS over-activity resulting in chronic low-grade inflammation [169, 176–182]. Here, we only briefly address disease that are the major OA comorbidities and their underlying SNS-driven mechanisms. More details are provided in the cited original publications.

Hypertension

One would expect that obesity that automatically leads to the overloading of the joint is the most prevalent OA comorbidity. However, at "only" 10–14%, obesity is far behind the major comorbidity of hypertension, affecting more than 50% of OA patients [170]. This demonstrates once again that OA is not primarily a matter of wear and tear but is also driven by other factors including the immune system and obviously the SNS. The development and progression of hypertension have long been associated with SNS over-activity [183]. An increased cardiac sympathetic nerve activity was detected in borderline hypertensive patients [184]. Additionally, increased circulating NE causes extensive vasoconstriction and, subsequently, increased blood pressure. NPY serum levels are also elevated in hypertensive patients, highlighting the relationship between blood pressure and SNS mediators [185, 186]. In line with that, genetic deletion of β1-and β2-ARs reduced blood pressure in mice [187]. Moreover, normotensive individuals with a familial link to hypertension exhibited distinctly increased NE plasma concentrations [188]. This suggests that an elevated sympathetic level may be a predisposing factor not only for OA but also for the development of hypertension. The resulting chronic low-grade inflammation is a risk factor for both diseases, and it is thought to explain why people with OA have a higher risk of high blood pressure than people without OA [189]. The other way around, studies in rodents demonstrated that elevated blood pressure activates the SNS. In rats, induced hypertension raised sympathetic nerve activity and, therefore, also NE concentrations. This in turn resulted in the release of pro-inflammatory T cells in the blood and bone marrow and increased macrophage/monocyte levels in the bone marrow [190].

In general, adenosine is known to exert blood pressure-decreasing effects [191]. Hereby, active vasodilation is caused by the A2aRs [192–194], while the negative chronotropic, inotropic, and dromotropic influences in the heart are mediated by the A1aRs [192, 193]. A3R also contributes to the regulation of blood pressure by decreasing the steady-state level of cAMP in smooth muscle cells [195]. However, the effects mediated by the adrenergic systems seem to be dominant; otherwise, the co-released adenosine would be able to counteract adrenergic effects. According to the above-mentioned studies, increased SNS activity and hypertension create a classical

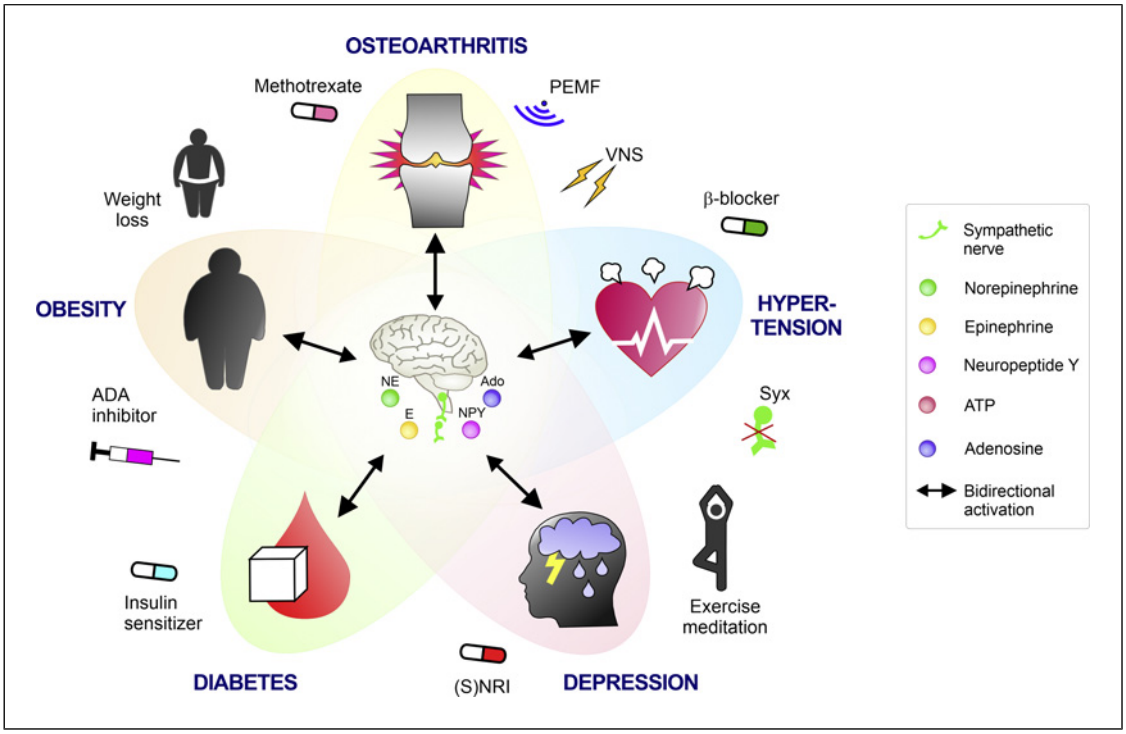

Fig. 4. Interaction of OA with its major comorbidities and potential therapeutic options. OA and its major comorbidities, hypertension, diabetes, obesity, and depression, are mild chronic inflammatory diseases and influence or even boost each other. Since not only OA but also all comorbidities are triggered by adrenergic SNS activity in particular, treatment strategies targeting the adrenergic system such as β-blocker treatment or (S)NRIs might also be potential therapeutic interventions to counteract mild chronic inflammation in OA. Also weight loss and diabetes management using insulin sensitizers would dampen the SNS-disease cycle. In addition, inducing the adenosinergic SNS effects by inhibiting ADA or using PEMF or even the activation of PNS by VNS might result in successful inhibition of mild chronic inflammation and improvement of the symptoms associated with OA and its comorbidities. ADA, adenosine deaminase; Ado, adenosine; E, epinephrine; NE, norepinephrine; NPY, neuropeptide Y; PEMF, pulsed electromagnetic field; (S)NRI, serotonin or/and norepinephrine reuptake inhibitor; Syx, sympathectomy; VNS, vagus nerve stimulation.

vicious circle situation resulting in mild chronic inflammation and probably also in accelerated OA progression.

Diabetes

Type 2 diabetes mellitus and OA are prevalent conditions that often coexist [196]. In OA, SNS activation and related mild chronic inflammation induce macrophage polarization and shift the balance to a more inflammatory M1 phenotype. The infiltration of M1 macrophages into adipose and cardiac tissues is associated with systemic and cardiac insulin resistance, resulting in diabetes [197]. During the past decades, the role of the SNS in insulin resistance has been proven in several studies [198]. Increased plasma NE concentrations in young adulthood predisposed for the development of insulin resistance [199, 200]. This effect was confirmed in an animal study demonstrating that sympathectomy by denervation of epididymal fat pads improved insulin sensitivity in rats with a high-fat diet (HFD) [201]. In addition, NPY serum levels are higher in patients with diabetes compared with those without this disease [186]. Interestingly, the sympathetic co-transmitter adenosine, in particular by binding to the A2aR, has beneficial effects on β-cells, similar to the effects opposing to adrenergic influence on hypertension. The activation of A2aR in β-cells leads to increased survival, proliferation, and accordingly to increased regeneration [202]. But again, disadvantageous adrenergic effects seem to be dominant.

These findings demonstrate that the elevated SNS activity and the resulting inflammation in OA are risk factors for diabetes. On the other hand, chronic hyperglycemia and insulin resistance promote low-grade inflammation

and aggravate OA pathology. As OA and diabetes negatively affect each other, it is not surprising that both conditions are predicted to increase in prevalence (reviewed by [196]). Increased sympathetic activity and low-grade chronic inflammation are obviously the causal link between the two diseases.

Obesity

It has long been assumed that the disease-accelerating impact of obesity on OA occurs due to elevated mechanical loading [203, 204]. However, since obesity also increases the risk of OA in non-weight-bearing joints such as the hands [205], metabolic factors must also have an influence [206]. Obesity is characterized by excessive accumulation of adipose tissue that releases adipokines (leptin, adiponectin) and pro-inflammatory cytokines, resulting in elevated TNF-α, IL-1β, and IL-6 serum levels [207]. Increased levels of the same cytokines were also found in the synovial fluid, synovial membrane, subchondral bone, and cartilage of OA patients, demonstrating the relationship between obesity and OA [208]. Moreover, these cytokines are known to increase sympathetic activity. In rodents fed HFD, SNS activity increased simultaneously with rising leptin concentrations, demonstrating that leptin acts as a major driver of increased sympathetic outflow in obesity [209, 210]. In young non-obese men, even a modest weight gain of 5 kg was associated with increased muscle sympathetic nerve activity [211], and in rabbits fed a HFD, increased activation of the SNS in the kidneys occurred already 1 week after the start of feeding [209]. Moreover, obesity induces NPY production in macrophages from adipose tissues [212]. These results indicate that sympathetic activation occurs as a consequence of obesity. Moreover, the fact that elevated plasma NE concentrations in young adulthood predisposed for future weight gain suggests that, in turn, increased SNS activity may cause obesity [199, 200]. There are only few studies describing a potential influence of adenosine on obesity. Hereby, the A2aR subtype seems to play the major role, which is abundantly expressed in adipose tissue [213]. The activation of this receptor protected mice from HFD-induced obesity by inducing the so-called "browning" of the white adipose tissue [214]. In addition, A2aR exhibited protective effects in obesity-associated inflammation of the adipose tissue in mice fed with HFD by suppressing the pro-inflammatory activation of macrophages, as indicated by decreased *IL-1*, *IL-6*, and *TNF* mRNA expression [215]. Thus, as already described for hypertension and diabetes, the pathologic processes occurring in obesity and during OA manifestation are obviously also linked to the SNS.

Depression

As stated by Slavich and Irwin, socially threatening situations activate distinct brain regions, which process experiences of negative affect and rejection-related distress. The connection to some of these brain regions further induces systemic inflammation by modulating the SNS and its mediators, such as NPY [216, 217]. The key mediators of this response are pro-inflammatory cytokines, which interfere with many pathophysiological domains that are distinct in depression, including neurotransmitter metabolism, neuroendocrine function, synaptic plasticity, and behavior. In fact, patients with depression exhibited statistically higher TNF-α and IL-6 blood levels than those without depression [218]. This SNS-mediated increased pro-inflammatory tone may be capable to promote inflammation-induced cartilage catabolism in OA. On the other hand, the chronic low-grade inflammatory status in OA has been shown to alter behavior [219]. Depression and obesity are common comorbidities in patients with knee OA. All three pathologies, depression, obesity, and OA, are associated with increased pro-inflammatory cytokine release. This leads to sedentary behavior and reduced physical activity, which in turn exacerbates pain, inactivity, and cartilage degradation. These conditions are mutually reinforcing, reflecting a complex mind-body interaction (reviewed by [220]). The net effects of adenosine on depressive-like behaviors seem to be anti-depressive and anxiolyti; however, different receptor subtypes mediate opposing effects, as demonstrated in numerous studies using selective agonists in mice or even subtype-specific knockout models. While targeting the subtypes A1-and A3aR results in anti-depressive effects, the activation of A2aR leads to pro-depressant-like effects, as reviewed in [221]. However, inflammatory processes in depression including also glial activation result in the disruption of adenosine homeostasis; thus, the above-described beneficial effects might be suppressed.

The studies listed above reveal that the SNS influences not only OA itself but also its comorbidities. As these diseases in turn affect the SNS, a vicious circle is generated, resulting in the worsening of mild chronic inflammation in OA, hypertension, obesity, diabetes, and depression. As low-grade inflammation is the common risk factor for these diseases, prescribing and monitoring SNS-based anti-inflammatory interventions may represent a new avenue for OA therapy.

SNS as Therapeutic Target in Mild Chronic Inflammation

As described before, the SNS plays a crucial role in the control of the immune system and accordingly contributes to the pathogenesis of mild chronic inflammatory diseases such as OA and associated comorbidities. This leads to the assumption that downregulation of the SNS may be beneficial to counteract inflammatory reactions in OA. Particularly in the stages of OA, when inflammation is more pronounced, these anti-inflammatory effects may have therapeutic value [121]. This hypothesis is supported by the fact that upregulation of parasympathetic tone via vagal electrical stimulation is successfully used in RA therapy to induce local and systemic anti-inflammatory effects [222]. Currently, there is no curative treatment for OA, and therefore, there is an urgent need for novel causal therapy options.

SNS-modulating drugs are commonly used to treat hypertension, diabetes, obesity, and depression. Studies demonstrating that some of these treatments might also counteract OA will be described in the following. We are also evaluating other therapy options that modulate the ANS to reduce inflammation, which may be helpful in OA.

Sympathectomy and AR Blockade

There are several ANS-based techniques available, which may help to restore the balance between pro- and anti-inflammatory factors in OA or shift it in favor of the anti-inflammatory side. For this, either the activity of the SNS can be reduced or the activity of the PNS can be increased. As early as 1889, surgical sympathectomy was used to interrupt the SNS signaling pathway in patients with diseases such as epilepsy, exophthalmic goiter, idiocy, and glaucoma [223]. Although sympathectomy is no longer used to treat these specific diseases, it is sometimes performed in patients with other conditions, such as hyperhidrosis [224]. To achieve this, the bilateral thoracic sympathetic ganglia are destructed by endoscopic resection, ablation, or clipping [223]. The first case in OA was described in 1966, where sympathectomy was performed on a patient with vasospastic syndrome in the fingers. As only the left hand was affected, sympathectomy was performed on the left hand. Within the following 24 years, the patient developed severe polyarthritis of all the fingers of the right hand and all the toes. In contrast, the sympathectomized left hand remained non-arthritic indicating an OA protective effect of sympathectomy in OA patients [225]. As surgical destruction of nerves is also a drastic technique, chemical sympathectomy may be a milder alternative to reduce SNS-related inflammation in OA. However, in murine studies using 12-week-old male mice, peripheral chemical sympathectomy by 6-hydroxy-dopamine did not influence the severity of cartilage degeneration and synovial inflammation in experimental OA; only subchondral bone sclerosis was accelerated [226]. Highly likely, a longer experimental period or using older mice of both sexes would be more appropriate to see SNS-mediated effects in murine OA models. Immunotoxins also provide an efficient method to generate highly specific neuronal lesions [227]. The combination of the ribosome-inactivating protein saporin coupled to an antibody targeting the sympathetic neurotransmitter synthesizing enzyme dopamine β-hydroxylase (DBH) enables selective destruction of sympathetic nerves. In rats, systemic injection of this immunotoxin yielded in the selective lesion of peripheral noradrenergic sympathetic neurons [227]. However, no studies using this technique have been tested with respect to OA until now. The substrate guanethidine does not destroy sympathetic nerves but instead depletes NE and inhibits catecholamine release after sympathetic nerve stimulation [228]. It is currently used to treat hypertension, and it also decreases pain in patients with resistant shoulder pain or RA [229, 230]. However, several clinical studies have reported the development of guanethidine tolerance in humans which may have implications for its use in the possible treatment of OA [231].

Selectively blocking ARs is another option used to inhibit signaling via the SNS. Indeed, the α2A-AR antagonist BRL-44408 maleate reduced macrophage infiltration and inflammatory response in rats with acute respiratory distress syndrome [232]. Moreover, inhibiting β-AR-mediated signaling might be beneficial, not only with respect to OA but also for its comorbidities. This option will be discussed in more detail below.

Anti-Hypertensive Drugs – β-Blockers

Pharmacological blockade of the SNS by β-AR antagonists, or β-AR blockers (β-blockers), is commonly used to treat hypertension [184]. Recently, first evidence emerged that β-blockers are linked to a lower risk of OA in humans. Nakafero et al. [233] studied the association between β-blocker prescription and first primary-care consultation for knee and hip OA. They reported that the β1-AR antagonist atenolol and the nonselective β-AR antagonist propranolol were associated with a lower incidence of knee OA. Interestingly, the effect disappeared after the end of β-blocker intake. Moreover, β-blocker medication was also associated with less OA pain [233]. In line with these

results in OA patients, Nackley-Neely et al. [234] described an analgesic effect of β-blockers in rats. Here, the intraperitoneal injection of a COMT-inhibitor leading to elevated NE concentrations resulted in increased mechanical and thermal pain sensitivity, and the administration of the unselective blocker propranolol significantly counteracted this effect. In order to identify the β-AR subtype that mediated this analgesic effect, COMT-treated rats were treated with subtype-specific antagonists, demonstrating that administration of β2-AR or β3-AR antagonists (ICI118,551 or SR59230A) partially blocked hyperalgesia while β1-AR blocking via betaxolol did not [234].

However, with regard to multi-morbidity in OA patients, also the possible adverse effects of β-AR antagonists have to be taken into account. In general, the intake of β-blockers such as atenolol (β1-AR antagonist) and metoprolol (β1-AR and, with lower affinity, also a β2-AR antagonists) can worsen glucose intolerance and increases the risk for new-onset type 2 diabetes mellitus in patients with hypertension [235–239]. Moreover, β2-AR blocking has been associated with higher rates of cardiovascular events in patients with diabetes and heart disease [240]. Obese patients seem to be especially sensitive to the adverse metabolic effects and are also affected by further weight gain caused by β-blocking drugs [241]. Potential mechanisms for the weight gain are reduced total energy expenditure and the inhibition of β-AR-agonis-induced lipolysis, which is particularly detrimental in leptin-resistant obese patients [242]. However, newer β-blockers, such as carvedilol (nonselective β- and α1-AR antagonist), appear to have solved these issues because they lower insulin resistance and improve lipid profiles without increasing weight gain [241, 243]. These findings confirm again that OA and its comorbidities are strongly associated.

Diabetes Medication – Insulin Sensitizers

The SNS is able to reduce insulin secretion and, therefore, directly increase blood glucose levels [244, 245]. Metformin is an antidiabetic drug that decreases glucose blood concentration in diabetic patients [246]. Experiments in obese rats demonstrated that metformin treatment increased the electrical activity of sympathetic branch nerves of the superior cervical ganglia by 20% [247]. Some authors state that metformin also lowers blood pressure in hypertension [248, 249], but due to contradictory observations, these results are currently considered controversial [250, 251]. In addition, a very recent study demonstrated that metformin medication was associated with a reduced risk of total knee replacement as well as reduced pain [252].

In contrast to metformin, pioglitazone decreased muscle SNS activity in patients with type 2 diabetes [253–255]. However, the intake of pioglitazone in individuals who were insulin resistant and obese resulted in limited sympathetic inhibition and did not influence whole body NE spillover [256]. According to that, the plasma glucose-reducing drug empagliflozin did not modulate muscle sympathetic nerve activity in patients with type 2 diabetes [257]. However, metformin and pioglitazone are often used as a combination therapy of insulin-sensitizing agents, thus the net effect might be beneficial due to slight SNS inhibition [253]. Interestingly, also pioglitazone treatment was OA-preventive in studies using rabbit, canine, or guinea pig OA models [258–260]. In conclusion, the impact of the SNS on the effect mechanism of antidiabetic drugs needs further investigation.

Obesity Management – Weight Loss

Since weight loss improves leptin and insulin resistance by reducing SNS activity, it is not only an intervention for patients with concomitant obesity, but also beneficial for patients with hypertension and diabetes [261]. Different studies investigated the effect of weight gain on human muscle sympathetic nerve activity, which was assessed via microneurography at a peroneal nerve. Experimental weight gain caused lean subjects' sympathetic nerve activity to increase by about 20% [211]. Accordingly, diet-induced weight loss resulted in about 15% decreased SNS activity and 43% less NE spillover [262]. Moreover, Masuo et al. [263] reported that caloric restriction resulted in a reduction in plasma NE levels. Costa et al. [264] evaluated the modulation of the ANS through diet and exercise-based weight changes by measuring heart rate variability. Weight loss increased parasympathetic activity and simultaneously decreased the SNS. In line with that, weight gain upregulated the PNS and reduced SNS activity.

In OA patients, weight loss delays the progression of joint structural damage and provides clinically significant improvements in pain [265]. The above-described SNS-modulating effects raise the hypothesis that the SNS contributes to these benefits.

Antidepressants – Serotonin and NE Reuptake Inhibitors

Serotonin-NE reuptake inhibitors (SNRIs) and selective NE reuptake inhibitors (NRIs) increase the concentration of NE in the brain and are commonly used to treat depression and neuropathic or chronic pain

[266, 267]. Burnham et al. [268] described that NE binds to spinal α2-ARs on C-fiber terminals to reduce excitatory transmitter release. Subsequently, postsynaptic hyperexcitability is decreased, resulting in pain reduction. Due to their analgesic effect, some of these drugs, e.g., duloxetine (SNRI) or tapentadol (NRI), were also effective to treat chronic OA pain in late stages, which was a result of the dysfunction of central pain pathways called central sensitization [269–271]. In line with that, intraperitoneally or subcutaneously injected milnacipran (SNRI) reduced allodynia (pain hypersensitivity) in a model of OA pain in rats. In naive animals and in the early inflammatory phase of the model, the α2-antagonist atipamezole reversed the inhibitory effects of milnacipran. However, this inhibition was not detected at a later time point, suggesting a decreased NE release in the dorsal horn or reduced α2-AR density as the condition becomes chronic [268].

Vagus Nerve Stimulation

The vagus nerve is the main nerve of the PNS and exhibits analgesic and anti-inflammatory functions. The anti-inflammatory effect is mediated by the release of acetylcholine, which binds to the α7 nicotinic acetylcholine receptor. This receptor is also expressed on macrophages and, when activated, inhibits pro-inflammatory cytokine production [272].

Traditionally, vagus nerve stimulation (VNS) has been performed using an implanted electrical electrode which is connected to a subcutaneously implanted generator. Alternatively, the vagus nerve can also be stimulated percutaneously, providing a non-invasive technique [273]. Electrical stimulation of the vagus nerve is already approved as an anti-inflammatory therapy for refractory epilepsy and depression and is also being investigated for the treatment of musculoskeletal diseases, such as RA [9, 274]. VNS decreased pro-inflammatory TNF-α levels in patients with epilepsy and also in RA patients [274]. Recently, a proof-of-concept pilot trial reported symptomatic efficacy of VNS in hand OA patients [275]. Compared to the highly inflammatory form of RA, OA is characterized by low-grade inflammation. However, hand OA is a special case as inflammatory debris accumulates in the hand due to the proximity of many affected joints. To date, there has been no study to assess whether VNS is effective in reducing OA-related inflammation in other sites, such as the knee and hip. A preclinical study has shown that the absence of the α7 nicotinic acetylcholine receptor is associated with more severe lesions in OA, demonstrating the influence of the vagal nerve in disease pathology [276]. Therefore, it would be worthwhile to test whether VNS would be helpful for anti-inflammatory therapy in OA patients with affected joints other than the hand.

Adenosine-Related Therapy Options

Since adenosine predominantly exhibits anti-inflammatory effects, it may also be a suitable target for suppressing SNS-driven pro-inflammatory processes [30]. Especially because OA patients possess elevated ADA levels in the synovium, indicating an increased conversion of adenosine to its metabolite inosine [277]. In order to increase endogenous adenosine levels in OA patients, one could inhibit ADA activity and simultaneously stimulate adenosine synthesis by activating its synthesizing enzymes CD39/CD73 in the synovial tissue [30]. Moreover, methotrexate, a traditional disease-modifying antirheumatic drug, is used to increase adenosine levels in RA patients. The effect of methotrexate is mainly based on the blocking of the enzyme 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase (ATIC), leading to AICAR accumulation, which then blocks ADA [278]. This results in the inhibition of neutrophils, lymphocytes, macrophages, DCs, and monocytes with reduced net TNF-α and IL-6 levels [279]. In fact, methotrexate is also effective in OA since it can reduce OA pain [280, 281]. Alternatively, adenosine receptor expression and/or function could be modulated. For example, pulsed electromagnetic field results in the upregulation of A2AAR and A3AR in bovine chondrocytes and synoviocytes [282]. Furthermore, pulsed electromagnetic field was able to potentiate the aR-mediated decrease of PGE2, IL-6, and IL-8 in human chondrocytic and osteoblastic cell lines [283].

As described above, increasing adenosine levels or even better targeting specific receptors in order to achieve the best effects would also be beneficial for all major comorbidities [191, 202, 221, 284]. This section above described just a few of potential techniques for modulating the ANS for therapeutic purposes. According to the literature, some of these approaches may have the potential to improve OA-related inflammation. However, it is important to note that the interaction between the SNS and the PNS is necessary for a healthy immune response. Therefore, to stop inflammation in OA, SNS activity cannot simply be reduced systemically. As described above, the SNS also has anti-inflammatory effects depending on the location, timing, and environment of stimulation. Thus,

when treating OA patients, basal SNS and PNS activity should ideally be determined and adjusted individually, taking into account the possible resistance and sensitization of the patient [285].

Taken together, many interventions for OA comorbidities and other inflammatory diseases include ANS-modulating drug; however, the full potential of these treatment options has not yet been elucidated in OA therapy. Considering potential side effects, some of these treatment options may also counteract OA symptoms. Nevertheless, confirmatory randomized controlled trials are needed before clinical practice in OA therapy will change.

Conclusion

The SNS influences important immunological processes, including the regulation of cytokine release by immune cells in acute and chronic inflammation. Acute inflammation leads to an increase in the activity of the SNS, which in turn releases its neurotransmitter NE and co-transmitters in lymphatic organs and sites with local inflammation. Thereupon, immune cells process these signals in a context-dependent manner. Thereby, their response can be both pro- or anti-inflammatory depending on the cell (sub)type, its state of activation and differentiation, the target receptor, the cytokine environment as well as the stage of disease.

When inflammation becomes chronic, the constant activation of the SNS can result in detrimental effects. In turn, continuous pro-inflammatory and concomitant degenerative processes induce the SNS again, and a vicious cycle might emerge. On the other hand, certain sympathetic agents, such as adenosine, induce anti-inflammatory mechanisms at the same time. However, under pathological catabolic conditions, these effects appear to be weak or disturbed, for example, due to metabolizing enzymes such as ADA. This is not only true in severe but also in mild chronic inflammatory diseases. This bidirectional influence of the SNS also occurs in the course of OA: Adrenergic stimulation induces both anti- and pro-inflammatory as well as anabolic and catabolic mechanisms via AR signaling, mainly via α2-and β2-AR. The nature of the net effect depends on the neurotransmitter concentration and the presence or severity of inflammation. However, recent clinical studies investigating joint destruction and pain intensity in OA patients clearly demonstrated that the β2-AR plays a crucial disease-promoting role during OA progression [233, 286]. In contrast, the SNS also exerts predominantly anti-inflammatory and anti-catabolic effects via adenosine receptors (mainly by targeting A2A and A2B); thus, adenosine is protective with regard to OA pathogenesis. However, these beneficial effects found in vitro and in vivo seem to be suppressed or simply not the same in OA patients, for example, due to disturbed CD39/CD73 function or higher ADA activity.

Interestingly, many other mild chronic inflammatory disorders such as hypertension, obesity, diabetes, and depression are associated with OA. While SNS activation induces extensive vasoconstriction in hypertensive patients, it promotes insulin resistance in diabetic patients, and thus, inflammatory processes in different organs or regions of the body might further potentiate the SNS-inducing effect.

Although inflammation is the major common denominator in all above-mentioned OA comorbidities, medications used to treat them often rely on modulating ANS-dependent processes. Therefore, besides inhibiting mild chronic inflammation by anti-inflammatory drugs, the appropriate systemic downregulation of the SNS activity might be a potential therapeutic intervention also in OA. Rebalancing of sympathetic and parasympathetic activities could be mediated by surgical or chemical sympathectomy, the blocking of β2-AR, or, alternatively, the increase of adenosine signaling or vagus nerve stimulation. However, to be able to develop such causal ANS-based therapeutic approaches for OA treatment, we need to improve our knowledge about the underlying mechanisms fine-tuning the immune system.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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References

1 Waxenbaum JA, Reddy V, Varacallo M. Anatomy, autonomic nervous system. StatPearls. Treasure island (FL): StatPearls PublishingCopyright © 2023 StatPearls Publishing LLC.; 2023.
2 Koopman FA, Stoof SP, Straub RH, Van Maanen MA, Vervoordeldonk MJ, Tak PP. Restoring the balance of the autonomic nervous system as an innovative approach to the treatment of rheumatoid arthritis. Mol Med. 2011;17(9–10):937–48.
3 Scott-Solomon E, Boehm E, Kuruvilla R. The sympathetic nervous system in development and disease. Nat Rev Neurosci. 2021;22(11):685–702.
4 Pongratz G, Straub RH. The sympathetic nervous response in inflammation. Arthritis Res Ther. 2014;16(6):504.
5 Morris JL, Letson HL, Gillman R, Hazratwala K, Wilkinson M, McEwen P, et al. The CNS theory of osteoarthritis: opportunities beyond the joint. Semin Arthritis Rheum. 2019;49(3):331–6.
6 Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES. The sympathetic nerve: an integrative interface between two supersystems: the brain and the immune system. Pharmacol Rev. 2000;52(4):595–638.
7 Czura CJ, Friedman SG, Tracey KJ. Neural inhibition of inflammation: the cholinergic anti-inflammatory pathway. J Endotoxin Res. 2003;9(6):409–13.
8 Schaible HG, Straub RH. Function of the sympathetic supply in acute and chronic experimental joint inflammation. Auton Neurosci. 2014;182:55–64.
9 Courties A, Berenbaum F, Sellam J. Vagus nerve stimulation in musculoskeletal diseases. Jt Bone Spine. 2021;88(3):105149.
10 Cotran R, Kumar V, Collins T. Robbins pathologic basis of disease. 6th ed. Philadelphia, Pa: Saunders; 1999. p. 1019–20.
11 GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1736–88.
12 McCain J. The disease burden of the most common autoimmune diseases. Manag Care. 2016;25(7):28–32.
13 Roos EM, Arden NK. Strategies for the prevention of knee osteoarthritis. Nat Rev Rheumatol. 2016;12(2):92–101.
14 Safiri S, Kolahi AA, Smith E, Hill C, Bettampadi D, Mansournia MA, et al. Global, regional and national burden of osteoarthritis 1990-2017: a systematic analysis of the Global Burden of Disease Study 2017. Ann Rheum Dis. 2020;79(6):819–28.
15 Eisenhofer G, Kopin IJ, Goldstein DS. Catecholamine metabolism: a contemporary view with implications for physiology and medicine. Pharmacol Rev. 2004;56(3):331–49.
16 Straub RH. Lehrbuch der klinischen Pathophysiologie komplexer chronischer Erkrankungen. Band 2: spezielle Pathophysiologie. Vandenhoeck & Ruprecht; 2006.
17 Courties A, Sellam J, Berenbaum F. Role of the autonomic nervous system in osteoarthritis. Best Pract Res Clin Rheumatol. 2017;31(5):661–75.
18 Buxton IL, Brunton LL. Alpha-adrenergic receptors on rat ventricular myocytes: characteristics and linkage to cAMP metabolism. Am J Physiol. 1986;251(2 Pt 2):H307–13.
19 Ahles A, Engelhardt S. Polymorphic variants of adrenoceptors: pharmacology, physiology, and role in disease. Pharmacol Rev. 2014;66(3):598–637.
20 Wu Y, Zeng L, Zhao S. Ligands of adrenergic receptors: a structural point of view. Biomolecules. 2021;11(7):936.
21 Bylund DB, Eikenberg DC, Hieble JP, Langer SZ, Lefkowitz RJ, Minneman KP, et al. International union of pharmacology nomenclature of adrenoceptors. Pharmacol Rev. 1994;46(2):121–36.
22 Dixon RA, Kobilka BK, Strader DJ, Benovic JL, Dohlman HG, Frielle T, et al. Cloning of the gene and cDNA for mammalian beta-adrenergic receptor and homology with rhodopsin. Nature. 1986;321(6065):75–9.
23 Hein L. Adrenoceptors and signal transduction in neurons. Cell Tissue Res. 2006;326(2):541–51.
24 Kobilka BK, Matsui H, Kobilka TS, Yang-Feng TL, Francke U, Caron MG, et al. Cloning, sequencing, and expression of the gene coding for the human platelet alpha 2-adrenergic receptor. Science. 1987;238(4827):650–6.
25 Straub RH, Pongratz G, Weidler C, Linde HJ, Kirschning CJ, Glück T, et al. Ablation of the sympathetic nervous system decreases gram-negative and increases gram-positive bacterial dissemination: key roles for tumor necrosis factor/phagocytes and interleukin-4/lymphocytes. J Infect Dis. 2005;192(4):560–72.
26 Grässel SG. The role of peripheral nerve fibers and their neurotransmitters in cartilage and bone physiology and pathophysiology. Arthritis Res Ther. 2014;16(6):485.
27 Lundberg JM, Franco-Cereceda A, Hemsén A, Lacroix JS, Pernow J. Pharmacology of noradrenaline and neuropeptide tyrosine (NPY)-mediated sympathetic cotransmission. Fundam Clin Pharmacol. 1990;4(4):373–91.
28 Burnstock G. Introduction to purinergic signaling. Methods Mol Biol. 2020;2041:1–15.
29 Pablo Huidobro-Toro J, Verónica Donoso M. Sympathetic co-transmission: the coordinated action of ATP and noradrenaline and their modulation by neuropeptide Y in human vascular neuroeffector junctions. Eur J Pharmacol. 2004;500(1–3):27–35.
30 Sohn R, Junker M, Meurer A, Zaucke F, Straub RH, Jenei-Lanzl Z. Anti-inflammatory effects of endogenously released adenosine in synovial cells of osteoarthritis and rheumatoid arthritis patients. Int J Mol Sci. 2021;22(16):8956.
31 Fredholm BB, IJzerman AP, Jacobson KA, Linden J, Müller CE. International union of basic and clinical pharmacology. LXXXI. Nomenclature and classification of adenosine receptors--an update. Pharmacol Rev. 2011;63(1):1–34.
32 Fredholm BB. Adenosine, an endogenous distress signal, modulates tissue damage and repair. Cell Death Differ. 2007;14(7):1315–23.
33 Felten DL, Felten SY, Bellinger DL, Carlson SL, Ackerman KD, Madden KS, et al. Noradrenergic sympathetic neural interactions with the immune system: structure and function. Immunol Rev. 1987;100:225–60.
34 Bellinger DL, Nance DM, Lorton D. Innervation of the immune system. Wiley Blackwell Handbook Psychoneuroimmunol. 2013:24–72.
35 Bellinger DL, Lorton D. Autonomic regulation of cellular immune function. Auton Neurosci. 2014;182:15–41.
36 Carr DJ, Blalock JE. Neuropeptide hormones and receptors common to the immune and neuroendocrine systems: bidirectional pathway of intersystem communication. Psychoneuroimmunology. 1991:573–88.
37 Kidd BL, Cruwys S, Mapp PI, Blake DR. Role of the sympathetic nervous system in chronic joint pain and inflammation. Ann Rheum Dis. 1992;51(11):1188–91.
38 Härle P, Möbius D, Carr DJ, Schölmerich J, Straub RH. An opposing time-dependent immune-modulating effect of the sympathetic nervous system conferred by altering the cytokine profile in the local lymph nodes and spleen of mice with type II collagen-induced arthritis. Arthritis Rheum. 2005;52(4):1305–13.
39 Straub RH, Cutolo M, Buttgereit F, Pongratz G. Energy regulation and neuroendocrine-immune control in chronic inflammatory diseases. J Intern Med. 2010;267(6):543–60.
40 Hori T, Katafuchi T, Take S, Shimizu N, Niijima A. The autonomic nervous system as a communication channel between the brain and the immune system. Neuroimmunomodulation. 1995;2(4):203–15.
41 Powell ND, Sloan EK, Bailey MT, Arevalo JM, Miller GE, Chen E, et al. Social stress up-regulates inflammatory gene expression in the leukocyte transcriptome via β-adrenergic induction of myelopoiesis. Proc Natl Acad Sci U S A. 2013;110(41):16574–9.
42 Sanders VM. The beta2-adrenergic receptor on T and B lymphocytes: do we understand it yet? Brain Behav Immun. 2012;26(2):195–200.

43 Seeley EJ, Barry SS, Narala S, Matthay MA, Wolters PJ. Noradrenergic neurons regulate monocyte trafficking and mortality during gram-negative peritonitis in mice. J Immunol. 2013;190(9):4717–24.
44 Yanagawa Y, Matsumoto M, Togashi H. Enhanced dendritic cell antigen uptake via alpha2 adrenoceptor-mediated PI3K activation following brief exposure to noradrenaline. J Immunol. 2010;185(10):5762–8.
45 Groneberg DA, Folkerts G, Peiser C, Chung KF, Fischer A. Neuropeptide Y (NPY). Pulm Pharmacol Ther. 2004;17(4):173–80.
46 Winklewski PJ, Radkowski M, Demkow U. Relevance of immune-sympathetic nervous system interplay for the development of hypertension. Adv Exp Med Biol. 2016;884:37–43.
47 Borea PA, Gessi S, Merighi S, Vincenzi F, Varani K. Pathological overproduction: the bad side of adenosine. Br J Pharmacol. 2017;174(13):1945–60.
48 Borea PA, Gessi S, Merighi S, Varani K. Adenosine as a multi-signalling guardian angel in human diseases: when, where and how does it exert its protective effects? Trends Pharmacol Sci. 2016;37(6):419–34.
49 Antonioli L, Csóka B, Fornai M, Colucci R, Kókai E, Blandizzi C, et al. Adenosine and inflammation: what's new on the horizon? Drug Discov Today. 2014;19(8):1051–68.
50 Antonioli L, Fornai M, Blandizzi C, Pacher P, Haskó G. Adenosine signaling and the immune system: when a lot could be too much. Immunol Lett. 2019;205:9–15.
51 Pasquini S, Contri C, Borea PA, Vincenzi F, Varani K. Adenosine and inflammation: here, there and everywhere. Int J Mol Sci. 2021;22(14):7685.
52 Bellinger DL, Millar BA, Perez S, Carter J, Wood C, ThyagaRajan S, et al. Sympathetic modulation of immunity: relevance to disease. Cell Immunol. 2008;252(1–2):27–56.
53 Freire BM, de Melo FM, Basso AS. Adrenergic signaling regulation of macrophage function: do we understand it yet? Immunother Adv. 2022;2(1):ltac010.
54 Grailer JJ, Haggadone MD, Sarma JV, Zetoune FS, Ward PA. Induction of M2 regulatory macrophages through the β2-adrenergic receptor with protection during endotoxemia and acute lung injury. J Innate Immun. 2014;6(5):607–18.
55 Tavares LP, Negreiros-Lima GL, Lima KM, E Silva PMR, Pinho V, Teixeira MM, et al. Blame the signaling: role of cAMP for the resolution of inflammation. Pharmacol Res. 2020;159:105030.
56 van der Heijden C, Groh L, Keating ST, Kaffa C, Noz MP, Kersten S, et al. Catecholamines induce trained immunity in monocytes in vitro and in vivo. Circ Res. 2020;127(2):269–83.
57 Wheway J, Herzog H, Mackay F. NPY and receptors in immune and inflammatory diseases. Curr Top Med Chem. 2007;7(17):1743–52.
58 Thiele A, Kronstein R, Wetzel A, Gerth A, Nieber K, Hauschildt S. Regulation of adenosine receptor subtypes during cultivation of human monocytes: role of receptors in preventing lipopolysaccharide-triggered respiratory burst. Infect Immun. 2004;72(3):1349–57.
59 Khoa ND, Postow M, Danielsson J, Cronstein BN. Tumor necrosis factor-alpha prevents desensitization of Galphas-coupled receptors by regulating GRK2 association with the plasma membrane. Mol Pharmacol. 2006;69(4):1311–9.
60 Khoa ND, Montesinos MC, Reiss AB, Delano D, Awadallah N, Cronstein BN. Inflammatory cytokines regulate function and expression of adenosine A(2A) receptors in human monocytic THP-1 cells. J Immunol. 2001;167(7):4026–32.
61 Haskó G, Pacher P, Deitch EA, Vizi ES. Shaping of monocyte and macrophage function by adenosine receptors. Pharmacol Ther. 2007;113(2):264–75.
62 Lee HS, Chung HJ, Lee HW, Jeong LS, Lee SK. Suppression of inflammation response by a novel A adenosine receptor agonist thio-Cl-IB-MECA through inhibition of Akt and NF-κB signaling. Immunobiology. 2011;216(9):997–1003.
63 Ohta A, Sitkovsky M. Role of G-protein-coupled adenosine receptors in downregulation of inflammation and protection from tissue damage. Nature. 2001;414(6866):916–20.
64 Joós G, Jákim J, Kiss B, Szamosi R, Papp T, Felszeghy S, et al. Involvement of adenosine A3 receptors in the chemotactic navigation of macrophages towards apoptotic cells. Immunol Lett. 2017;183:62–72.
65 Carvajal Gonczi CM, Tabatabaei Shafiei M, East A, Martire E, Maurice-Ventouris MHI, Darlington PJ. Reciprocal modulation of helper Th1 and Th17 cells by the β2-adrenergic receptor agonist drug terbutaline. FEBS J. 2017;284(18):3018–28.
66 Miossec P, Kolls JK. Targeting IL-17 and TH17 cells in chronic inflammation. Nat Rev Drug Discov. 2012;11(10):763–76.
67 Torres KC, Antonelli LR, Souza AL, Teixeira MM, Dutra WO, Gollob KJ. Norepinephrine, dopamine and dexamethasone modulate discrete leukocyte subpopulations and cytokine profiles from human PBMC. J Neuroimmunol. 2005;166(1–2):144–57.
68 Borger P, Hoekstra Y, Esselink MT, Postma DS, Zaagsma J, Vellenga E, et al. Beta-adrenoceptor-mediated inhibition of IFN-gamma, IL-3, and GM-CSF mRNA accumulation in activated human T lymphocytes is solely mediated by the beta2-adrenoceptor subtype. Am J Respir Cell Mol Biol. 1998;19(3):400–7.
69 Sanders VM, Baker RA, Ramer-Quinn DS, Kasprowicz DJ, Fuchs BA, Street NE. Differential expression of the beta2-adrenergic receptor by Th1 and Th2 clones: implications for cytokine production and B cell help. J Immunol. 1997;158(9):4200–10.
70 Lubahn CL, Lorton D, Schaller JA, Sweeney SJ, Bellinger DL. Targeting α- and β-adrenergic receptors differentially shifts Th1, Th2, and inflammatory cytokine profiles in immune organs to attenuate adjuvant arthritis. Front Immunol. 2014;5:346.
71 Abbott RK, Silva M, Labuda J, Thayer M, Cain DW, Philbrook P, et al. The GS protein-coupled A2a adenosine receptor controls T cell help in the germinal center. J Biol Chem. 2017;292(4):1211–7.
72 Romio M, Reinbeck B, Bongardt S, Hüls S, Burghoff S, Schrader J. Extracellular purine metabolism and signaling of CD73-derived adenosine in murine Treg and Teff cells. Am J Physiol Cell Physiol. 2011;301(2):C530–9.
73 Kin NW, Sanders VM. It takes nerve to tell T and B cells what to do. J Leukoc Biol. 2006;79(6):1093–104.
74 Kasprowicz DJ, Kohm AP, Berton MT, Chruscinski AJ, Sharpe A, Sanders VM. Stimulation of the B cell receptor, CD86 (B7-2), and the beta 2-adrenergic receptor intrinsically modulates the level of IgG1 and IgE produced per B cell. J Immunol. 2000;165(2):680–90.
75 Kohm AP, Mozaffarian A, Sanders VM. B cell receptor- and beta 2-adrenergic receptor-induced regulation of B7-2 (CD86) expression in B cells. J Immunol. 2002;168(12):6314–22.
76 Wheway J, Mackay CR, Newton RA, Sainsbury A, Boey D, Herzog H, et al. A fundamental bimodal role for neuropeptide Y1 receptor in the immune system. J Exp Med. 2005;202(11):1527–38.
77 Pongratz G, Melzer M, Straub RH. The sympathetic nervous system stimulates anti-inflammatory B cells in collagen-type II-induced arthritis. Ann Rheum Dis. 2012;71(3):432–9.
78 Sakowicz-Burkiewicz M, Kocbuch K, Grden M, Maciejewska I, Szutowicz A, Pawelczyk T. Impact of adenosine receptors on immunoglobulin production by human peripheral blood B lymphocytes. J Physiol Pharmacol. 2012;63(6):661–8.
79 Przybyła T, Sakowicz-Burkiewicz M, Pawełczyk T. Purinergic signaling in B cells. Acta Biochim Pol. 2018;65(1):1–7.
80 Saze Z, Schuler PJ, Hong CS, Cheng D, Jackson EK, Whiteside TL. Adenosine production by human B cells and B cell-mediated suppression of activated T cells. Blood. 2013;122(1):9–18.
81 Haug SR, Heyeraas KJ. Modulation of dental inflammation by the sympathetic nervous system. J Dent Res. 2006;85(6):488–95.
82 Csillag M, Berggreen E, Fristad I, Haug SR, Bletsa A, Heyeraas KJ. Effect of electrical tooth stimulation on blood flow and immunocompetent cells in rat dental pulp after sympathectomy. Acta Odontol Scand. 2004;62(6):305–12.

83 Abo T, Kawamura T. Immunomodulation by the autonomic nervous system: therapeutic approach for cancer, collagen diseases, and inflammatory bowel diseases. Ther Apher. 2002;6(5):348–57.
84 Barletta KE, Ley K, Mehrad B. Regulation of neutrophil function by adenosine. Arterioscler Thromb Vasc Biol. 2012;32(4):856–64.
85 Wang X, Chen D. Purinergic regulation of neutrophil function. Front Immunol. 2018;9:399.
86 Riff R, Naamani O, Mazar J, Haviv YS, Chaimovitz C, Douvdevani A. A(1) and A(2A) adenosine receptors play a protective role to reduce prevalence of autoimmunity following tissue damage. Clin Exp Immunol. 2021;205(3):278–87.
87 Frasson AP, Menezes CB, Goelzer GK, Gnoatto SCB, Garcia SC, Tasca T. Adenosine reduces reactive oxygen species and interleukin-8 production by Trichomonas vaginalis-stimulated neutrophils. Purinergic Signal. 2017;13(4):569–77.
88 Corriden R, Self T, Akong-Moore K, Nizet V, Kellam B, Briddon SJ, et al. Adenosine-A3 receptors in neutrophil microdomains promote the formation of bacteria-tethering cytonemes. EMBO Rep. 2013;14(8):726–32.
89 Theorell J, Gustavsson AL, Tesi B, Sigmundsson K, Ljunggren HG, Lundbäck T, et al. Immunomodulatory activity of commonly used drugs on Fc-receptor-mediated human natural killer cell activation. Cancer Immunol Immunother. 2014;63(6):627–41.
90 Rosenne E, Sorski L, Shaashua L, Neeman E, Matzner P, Levi B, et al. In vivo suppression of NK cell cytotoxicity by stress and surgery: glucocorticoids have a minor role compared to catecholamines and prostaglandins. Brain Behav Immun. 2014;37:207–19.
91 Benschop RJ, Nijkamp FP, Ballieux RE, Heijnen CJ. The effects of beta-adrenoceptor stimulation on adhesion of human natural killer cells to cultured endothelium. Br J Pharmacol. 1994;113(4):1311–6.
92 Schedlowski M, Hosch W, Oberbeck R, Benschop RJ, Jacobs R, Raab HR, et al. Catecholamines modulate human NK cell circulation and function via spleen-independent beta 2-adrenergic mechanisms. J Immunol. 1996;156(1):93–9.
93 Benschop RJ, Schedlowski M, Wienecke H, Jacobs R, Schmidt RE. Adrenergic control of natural killer cell circulation and adhesion. Brain Behav Immun. 1997;11(4):321–32.
94 Young A, Ngiow SF, Gao Y, Patch AM, Barkauskas DS, Messaoudene M, et al. A2AR adenosine signaling suppresses natural killer cell maturation in the tumor microenvironment. Cancer Res. 2018;78(4):1003–16.
95 Chambers AM, Wang J, Lupo KB, Yu H, Atallah Lanman NM, Matosevic S. Adenosinergic signaling alters natural killer cell functional responses. Front Immunol. 2018;9:2533.
96 Malfait AM, Malik AS, Marinova-Mutafchieva L, Butler DM, Maini RN, Feldmann M. The β2-adrenergic agonist salbutamol is a potent suppressor of established collagen-induced arthritis: mechanisms of action. J Immunol. 1999;162(10):6278–83.
97 Wu H, Chen J, Song S, Yuan P, Liu L, Zhang Y, et al. β2-adrenoceptor signaling reduction in dendritic cells is involved in the inflammatory response in adjuvant-induced arthritic rats. Sci Rep. 2016;6:24548.
98 Steinkraus V, Steinfath M, Stöve L, Körner C, Abeck D, Mensing H. Beta-adrenergic receptors in psoriasis: evidence for down-regulation in lesional skin. Arch Dermatol Res. 1993;285(5):300–4.
99 Takenaka MC, Guereschi MG, Basso AS. Neuroimmune interactions: dendritic cell modulation by the sympathetic nervous system. Semin Immunopathol. 2017;39(2):165–76.
100 Schnurr M, Toy T, Shin A, Hartmann G, Rothenfusser S, Soellner J, et al. Role of adenosine receptors in regulating chemotaxis and cytokine production of plasmacytoid dendritic cells. Blood. 2004;103(4):1391–7.
101 Novitskiy SV, Ryzhov S, Zaynagetdinov R, Goldstein AE, Huang Y, Tikhomirov OY, et al. Adenosine receptors in regulation of dendritic cell differentiation and function. Blood. 2008;112(5):1822–31.
102 Pacheco R, Martinez-Navio JM, Lejeune M, Climent N, Oliva H, Gatell JM, et al. CD26, adenosine deaminase, and adenosine receptors mediate costimulatory signals in the immunological synapse. Proc Natl Acad Sci U S A. 2005;102(27):9583–8.
103 Peachell P. Regulation of mast cells by beta-agonists. Clin Rev Allergy Immunol. 2006;31(2–3):131–42.
104 Rudich N, Ravid K, Sagi-Eisenberg R. Mast cell adenosine receptors function: a focus on the a3 adenosine receptor and inflammation. Front Immunol. 2012;3:134.
105 Li W, Knowlton D, Woodward WR, Habecker BA. Regulation of noradrenergic function by inflammatory cytokines and depolarization. J Neurochem. 2003;86(3):774–83.
106 Donoso V, Gomez CR, Orriantia MA, Pérez V, Torres C, Coddou C, et al. The release of sympathetic neurotransmitters is impaired in aged rats after an inflammatory stimulus: a possible link between cytokine production and sympathetic transmission. Mech Ageing Dev. 2008;129(12):728–34.
107 Berk M, Williams LJ, Jacka FN, O'Neil A, Pasco JA, Moylan S, et al. So depression is an inflammatory disease, but where does the inflammation come from? BMC Med. 2013;11:200.
108 Lasselin J. Low-grade inflammation and the brain (Internet). USA: International Association for the Study of Pain. (Available from: https://www.iasp-pain.org/publications/relief-news/article/low-grade-inflammation-brain/).
109 Fraser A, Fearon U, Billinghurst RC, Ionescu M, Reece R, Barwick T, et al. Turnover of type II collagen and aggrecan in cartilage matrix at the onset of inflammatory arthritis in humans: relationship to mediators of systemic and local inflammation. Arthritis Rheum. 2003;48(11):3085–95.
110 Talabot-Ayer D, McKee T, Gindre P, Bas S, Baeten DL, Gabay C, et al. Distinct serum and synovial fluid interleukin (IL)-33 levels in rheumatoid arthritis, psoriatic arthritis and osteoarthritis. Jt Bone Spine. 2012;79(1):32–7.
111 Mitra A, Raychaudhuri SK, Raychaudhuri SP. Functional role of IL-22 in psoriatic arthritis. Arthritis Res Ther. 2012;14(2):R65.
112 Valcamonica E, Chighizola CB, Comi D, De Lucia O, Pisoni L, Murgo A, et al. Levels of chemerin and interleukin 8 in the synovial fluid of patients with inflammatory arthritides and osteoarthritis. Clin Exp Rheumatol. 2014;32(2):243–50.
113 Berenbaum F, Walker C. Osteoarthritis and inflammation: a serious disease with overlapping phenotypic patterns. Postgrad Med. 2020;132(4):377–84.
114 Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: a disease of the joint as an organ. Arthritis Rheum. 2012;64(6):1697–707.
115 Griffin TM, Scanzello CR. Innate inflammation and synovial macrophages in osteoarthritis pathophysiology. Clin Exp Rheumatol. 2019;37(5):57–63.
116 Sellam J, Berenbaum F. The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis. Nat Rev Rheumatol. 2010;6(11):625–35.
117 Haubruck P, Colbath AC, Liu Y, Stoner S, Shu C, Little CB. Flow cytometry analysis of immune cell subsets within the murine spleen, bone marrow, lymph nodes and synovial tissue in an osteoarthritis model. J Vis Exp. 2020(158).
118 Raghu H, Lepus CM, Wang Q, Wong HH, Lingampalli N, Oliviero F, et al. CCL2/CCR2, but not CCL5/CCR5, mediates monocyte recruitment, inflammation and cartilage destruction in osteoarthritis. Ann Rheum Dis. 2017;76(5):914–22.
119 Zhang H, Lin C, Zeng C, Wang Z, Wang H, Lu J, et al. Synovial macrophage M1 polarisation exacerbates experimental osteoarthritis partially through R-spondin-2. Ann Rheum Dis. 2018;77(10):1524–34.
120 Liu B, Zhang M, Zhao J, Zheng M, Yang H. Imbalance of M1/M2 macrophages is linked to severity level of knee osteoarthritis. Exp Ther Med. 2018;16(6):5009–14.
121 Benito MJ, Veale DJ, FitzGerald O, van den Berg WB, Bresnihan B. Synovial tissue inflammation in early and late osteoarthritis. Ann Rheum Dis. 2005;64(9):1263–7.
122 Smith MD, Triantafillou S, Parker A, Youssef PP, Coleman M. Synovial membrane inflammation and cytokine production in patients with early osteoarthritis. J Rheumatol. 1997;24(2):365–71.

123 Jenei-Lanzl Z, Meurer A, Zaucke F. Interleukin-1β signaling in osteoarthritis - chondrocytes in focus. Cell Signal. 2019;53:212–23.
124 Martel-Pelletier J, Pelletier JP. Is osteoarthritis a disease involving only cartilage or other articular tissues? Jt Dis Relat Surg. 2010;21(1):2–14.
125 Murray PJ, Allen JE, Biswas SK, Fisher EA, Gilroy DW, Goerdt S, et al. Macrophage activation and polarization: nomenclature and experimental guidelines. Immunity. 2014;41(1):14–20.
126 Raap T, Jüsten HP, Miller LE, Cutolo M, Schölmerich J, Straub RH. Neurotransmitter modulation of interleukin 6 (IL-6) and IL-8 secretion of synovial fibroblasts in patients with rheumatoid arthritis compared to osteoarthritis. J Rheumatol. 2000;27(11):2558–65.
127 Na HS, Park JS, Cho KH, Kwon JY, Choi J, Jhun J, et al. Interleukin-1-Interleukin-17 signaling Axis induces cartilage destruction and promotes experimental osteoarthritis. Front Immunol. 2020;11:730.
128 Askari A, Naghizadeh MM, Homayounfar R, Shahi A, Afsarian MH, Paknahad A, et al. Increased serum levels of IL-17a and IL-23 are associated with decreased vitamin D3 and increased pain in osteoarthritis. PLoS One. 2016;11(11):e0164757.
129 Deligne C, Casulli S, Pigenet A, Bougault C, Campillo-Gimenez L, Nourissat G, et al. Differential expression of interleukin-17 and interleukin-22 in inflamed and non-inflamed synovium from osteoarthritis patients. Osteoarthritis Cartilage. 2015;23(11):1843–52.
130 Sakkas LI, Johanson NA, Scanzello CR, Platsoucas CD. Interleukin-12 is expressed by infiltrating macrophages and synovial lining cells in rheumatoid arthritis and osteoarthritis. Cell Immunol. 1998;188(2):105–10.
131 Nees TA, Rosshirt N, Zhang JA, Reiner T, Sorbi R, Tripel E, et al. Synovial cytokines significantly correlate with osteoarthritis-related knee pain and disability: inflammatory mediators of potential clinical relevance. J Clin Med. 2019;8(9):1343.
132 Mobasheri A, Batt M. An update on the pathophysiology of osteoarthritis. Ann Phys Rehabil Med. 2016;59(5–6):333–9.
133 Van Spil WE, Kubassova O, Boesen M, Bay-Jensen AC, Mobasheri A. Osteoarthritis phenotypes and novel therapeutic targets. Biochem Pharmacol. 2019;165:41–8.
134 Sohn R, Rösch G, Junker M, Meurer A, Zaucke F, Jenei-Lanzl Z. Adrenergic signalling in osteoarthritis. Cell Signal. 2021;82:109948.
135 Carlesso LC, Sturgeon JA, Zautra AJ. Exploring the relationship between disease-related pain and cortisol levels in women with osteoarthritis. Osteoarthritis Cartilage. 2016;24(12):2048–54.
136 Jenei-Lanzl Z, Grässel S, Pongratz G, Kees F, Miosge N, Angele P, et al. Norepinephrine inhibition of mesenchymal stem cell and chondrogenic progenitor cell chondrogenesis and acceleration of chondrogenic hypertrophy. Arthritis Rheumatol. 2014;66(9):2472–81.
137 Grässel S, Muschter D. Do neuroendocrine peptides and their receptors qualify as novel therapeutic targets in osteoarthritis? Int J Mol Sci. 2018;19(2):367.
138 Ryan LM, Rachow JW, McCarty DJ. Synovial fluid ATP: a potential substrate for the production of inorganic pyrophosphate. J Rheumatol. 1991;18(5):716–20.
139 Wang L, Zhang L, Pan H, Peng S, Lv M, Lu WW. Levels of neuropeptide Y in synovial fluid relate to pain in patients with knee osteoarthritis. BMC Musculoskelet Disord. 2014;15:319.
140 Rösch G, Muschter D, Taheri S, El Bagdadi K, Dorn C, Meurer A, et al. β2-Adrenoceptor deficiency results in increased calcified cartilage thickness and subchondral bone remodeling in murine experimental osteoarthritis. Front Immunol. 2021;12:801505.
141 Bassi GS, Ulloa L, Santos VR, Del Vecchio F, Delfino-Pereira P, Rodrigues GJ, et al. Cortical stimulation in conscious rats controls joint inflammation. Prog Neuro-Psychopharmacol Biol Psychiatry. 2018;84(Pt A):201–13.
142 Sattar N, McCarey DW, Capell H, McInnes IB. Explaining how "high-grade" systemic inflammation accelerates vascular risk in rheumatoid arthritis. Circulation. 2003;108(24):2957–63.
143 Varani K, Padovan M, Govoni M, Vincenzi F, Trotta F, Borea PA. The role of adenosine receptors in rheumatoid arthritis. Autoimmun Rev. 2010;10(2):61–4.
144 Jenei-Lanzl Z, Zwingenberg J, Lowin T, Anders S, Straub RH. Proinflammatory receptor switch from Gαs to Gαi signaling by β-arrestin-mediated PDE4 recruitment in mixed RA synovial cells. Brain Behav Immun. 2015;50:266–74.
145 Capellino S, Cosentino M, Wolff C, Schmidt M, Grifka J, Straub RH. Catecholamine-producing cells in the synovial tissue during arthritis: modulation of sympathetic neurotransmitters as new therapeutic target. Ann Rheum Dis. 2010;69(10):1853–60.
146 Miller LE, Grifka J, Schölmerich J, Straub RH. Norepinephrine from synovial tyrosine hydroxylase positive cells is a strong indicator of synovial inflammation in rheumatoid arthritis. J Rheumatol. 2002;29(3):427–35.
147 Muz B, Khan MN, Kiriakidis S, Paleolog EM. Hypoxia. The role of hypoxia and HIF-dependent signalling events in rheumatoid arthritis. Arthritis Res Ther. 2009;11(1):201.
148 Jenei-Lanzl Z, Capellino S, Kees F, Fleck M, Lowin T, Straub RH. Anti-inflammatory effects of cell-based therapy with tyrosine hydroxylase-positive catecholaminergic cells in experimental arthritis. Ann Rheum Dis. 2015;74(2):444–51.
149 Straub RH, Günzler C, Miller LE, Cutolo M, Schölmerich J, Schill S. Anti-inflammatory cooperativity of corticosteroids and norepinephrine in rheumatoid arthritis synovial tissue in vivo and in vitro. FASEB J. 2002;16(9):993–1000.
150 Varani K, Vincenzi F, Tosi A, Targa M, Masieri FF, Ongaro A, et al. Expression and functional role of adenosine receptors in regulating inflammatory responses in human synoviocytes. Br J Pharmacol. 2010;160(1):101–15.
151 Bar-Yehuda S, Rath-Wolfson L, Del Valle L, Ochaion A, Cohen S, Patoka R, et al. Induction of an antiinflammatory effect and prevention of cartilage damage in rat knee osteoarthritis by CF101 treatment. Arthritis Rheum. 2009;60(10):3061–71.
152 Lorenz J, Schäfer N, Bauer R, Jenei-Lanzl Z, Springorum RH, Grässel S. Norepinephrine modulates osteoarthritic chondrocyte metabolism and inflammatory responses. Osteoarthritis Cartilage. 2016;24(2):325–34.
153 Hwang HS, Lee MH, Go DJ, Kim HA. Norepinephrine modulates IL-1β-induced catabolic response of human chondrocytes. BMC Musculoskelet Disord. 2021;22(1):724.
154 Jiao K, Zeng G, Niu LN, Yang HX, Ren GT, Xu XY, et al. Activation of α2A-adrenergic signal transduction in chondrocytes promotes degenerative remodelling of temporomandibular joint. Sci Rep. 2016;6:30085.
155 Speichert S, Molotkov N, El Bagdadi K, Meurer A, Zaucke F, Jenei-Lanzl Z. Role of norepinephrine in IL-1β-induced chondrocyte dedifferentiation under physioxia. Int J Mol Sci. 2019;20(5):1212.
156 Kang X, Qian Z, Liu J, Feng D, Li H, Zhang Z, et al. Neuropeptide Y acts directly on cartilage homeostasis and exacerbates progression of osteoarthritis through NPY2R. J Bone Miner Res. 2020;35(7):1375–84.
157 Ou F, Huang Y, Sun J, Su K, He Y, Zeng R, et al. Yohimbine ameliorates temporomandibular joint chondrocyte inflammation with suppression of NF-κB pathway. Inflammation. 2021;44(1):80–90.
158 Zhang S, Teo KYW, Chuah SJ, Lai RC, Lim SK, Toh WS. MSC exosomes alleviate temporomandibular joint osteoarthritis by attenuating inflammation and restoring matrix homeostasis. Biomaterials. 2019;200:35–47.
159 Liu X, Corciulo C, Arabagian S, Ulman A, Cronstein BN. Adenosine-functionalized biodegradable PLA-b-PEG nanoparticles ameliorate osteoarthritis in rats. Sci Rep. 2019;9(1):7430.
160 Campo GM, Avenoso A, D'Ascola A, Scuruchi M, Prestipino V, Nastasi G, et al. Adenosine A2A receptor activation and hyaluronan fragment inhibition reduce inflammation in mouse articular chondrocytes stimulated with interleukin-1β. FASEB J. 2012;279(12):2120–33.
161 Corciulo C, Lendhey M, Wilder T, Schoen H, Cornelissen AS, Chang G, et al. Endogenous adenosine maintains cartilage homeostasis and exogenous adenosine inhibits osteoarthritis progression. Nat Commun. 2017;8:15019.
162 Friedman B, Larranaga-Vera A, Castro CM, Corciulo C, Rabbani P, Cronstein BN. Adenosine A2A receptor activation reduces chondrocyte senescence. FASEB J. 2023;37(4):e22838.

163 Tesch AM, MacDonald MH, Kollias-Baker C, Benton HP. Endogenously produced adenosine regulates articular cartilage matrix homeostasis: enzymatic depletion of adenosine stimulates matrix degradation. Osteoarthritis Cartilage. 2004;12(5):349–59.
164 Castro CM, Corciulo C, Solesio ME, Liang F, Pavlov EV, Cronstein BN. Adenosine A2A receptor (A2AR) stimulation enhances mitochondrial metabolism and mitigates reactive oxygen species-mediated mitochondrial injury. FASEB J. 2020;34(4):5027–45.
165 Tan L, Zhao B, Ge FT, Sun DH, Yu T. Shockwaves inhibit chondrogenic differentiation of human mesenchymal stem cells in association with adenosine and A2B receptors. Sci Rep. 2017;7(1):14377.
166 Shkhyan R, Lee S, Gullo F, Li L, Peleli M, Carlstrom M, et al. Genetic ablation of adenosine receptor A3 results in articular cartilage degeneration. J Mol Med. 2018;96(10):1049–60.
167 Herrmann M, Anders S, Straub RH, Jenei-Lanzl Z. TNF inhibits catecholamine production from induced sympathetic neuron-like cells in rheumatoid arthritis and osteoarthritis in vitro. Sci Rep. 2018;8(1):9645.
168 Zefferino R, Di Gioia S, Conese M. Molecular links between endocrine, nervous and immune system during chronic stress. Brain Behav. 2021;11(2):e01960.
169 Fitzgerald PJ. Is elevated noradrenaline an aetiological factor in a number of diseases? Auton Autacoid Pharmacol. 2009;29(4):143–56.
170 Calders P, Van Ginckel A. Presence of comorbidities and prognosis of clinical symptoms in knee and/or hip osteoarthritis: a systematic review and meta-analysis. Semin Arthritis Rheum. 2018;47(6):805–13.
171 Cohen SB, Proudman S, Kivitz AJ, Burch FX, Donohue JP, Burstein D, et al. A randomized, double-blind study of AMG 108 (a fully human monoclonal antibody to IL-1R1) in patients with osteoarthritis of the knee. Arthritis Res Ther. 2011;13(4):R125.
172 Grosso G, Laudisio D, Frias-Toral E, Barrea L, Muscogiuri G, Savastano S, et al. Anti-inflammatory nutrients and obesity-associated metabolic-inflammation: state of the art and future direction. Nutrients. 2022;14(6):1137.
173 da Cruz Nascimento SS, Carvalho de Queiroz JL, Fernandes de Medeiros A, de França Nunes AC, Piuvezam G, Lima Maciel BL, et al. Anti-inflammatory agents as modulators of the inflammation in adipose tissue: a systematic review. PLoS One. 2022;17(9):e0273942.
174 Pollack RM, Donath MY, LeRoith D, Leibowitz G. Anti-inflammatory agents in the treatment of diabetes and its vascular complications. Diabetes Care. 2016;39(Suppl 2):S244–52.
175 Kohler O, Krogh J, Mors O, Benros ME. Inflammation in depression and the potential for anti-inflammatory treatment. Curr Neuropharmacol. 2016;14(7):732–42.
176 Al-Sharea A, Lee MKS, Whillas A, Michell DL, Shihata WA, Nicholls AJ, et al. Chronic sympathetic driven hypertension promotes atherosclerosis by enhancing hematopoiesis. Haematologica. 2019;104(3):456–67.
177 De Miguel C, Rudemiller NP, Abais JM, Mattson DL. Inflammation and hypertension: new understandings and potential therapeutic targets. Curr Hypertens Rep. 2015;17(1):507.
178 DeLalio LJ, Sved AF, Stocker SD. Sympathetic nervous system contributions to hypertension: updates and therapeutic relevance. Can J Cardiol. 2020;36(5):712–20.
179 Hinterdobler J, Schott S, Jin H, Meesmann A, Steinsiek AL, Zimmermann AS, et al. Acute mental stress drives vascular inflammation and promotes plaque destabilization in mouse atherosclerosis. Eur Heart J. 2021;42(39):4077–88.
180 Lontchi-Yimagou E, Sobngwi E, Matsha TE, Kengne AP. Diabetes mellitus and inflammation. Curr Diab Rep. 2013;13(3):435–44.
181 Scanzello CR. Role of low-grade inflammation in osteoarthritis. Curr Opin Rheumatol. 2017;29(1):79–85.
182 Thorp AA, Schlaich MP. Relevance of sympathetic nervous system activation in obesity and metabolic syndrome. J Diabetes Res. 2015;2015:341583.
183 Mancia G, Parati G. The role of blood pressure variability in end-organ damage. J Hypertens Suppl. 2003;21(6):S17–23.
184 Ahmari N, Hayward LF, Zubcevic J. The importance of bone marrow and the immune system in driving increases in blood pressure and sympathetic nerve activity in hypertension. Exp Physiol. 2020;105(11):1815–26.
185 Li B, Ma S, Guo S, Li N, Liu D, Wang H, et al. Altered features of neurotransmitters: NPY, α-MSH, and AgRP in type 2 diabetic patients with hypertension. J Int Med Res. 2020;48(5):300060520919580.
186 Hirsch D, Zukowska Z. NPY and stress 30 years later: the peripheral view. Cell Mol Neurobiol. 2012;32(5):645–59.
187 Ahmari N, Schmidt JT, Krane GA, Malphurs W, Cunningham BE, Owen JL, et al. Loss of bone marrow adrenergic beta 1 and 2 receptors modifies transcriptional networks, reduces circulating inflammatory factors, and regulates blood pressure. Physiol Genomics. 2016;48(7):526–36.
188 Bianchetti MG, Weidmann P, Beretta-Piccoli C, Rupp U, Boehringer K, Link L, et al. Disturbed noradrenergic blood pressure control in normotensive members of hypertensive families. Br Heart J. 1984;51(3):306–11.
189 Veronese N, Stubbs B, Solmi M, Smith TO, Noale M, Schofield P, et al. Knee osteoarthritis and risk of hypertension: a longitudinal cohort study. Rejuvenation Res. 2018;21(1):15–21.
190 Ahmari N, Santisteban MM, Miller DR, Geis NM, Larkin R, Redler T, et al. Elevated bone marrow sympathetic drive precedes systemic inflammation in angiotensin II hypertension. Am J Physiol Heart Circ Physiol. 2019;317(2):H279–89.
191 Shen FM, Su DF. The effect of adenosine on blood pressure variability in sinoaortic denervated rats is mediated by adenosine A2a-Receptor. J Cardiovasc Pharmacol. 2000;36(5):681–6.
192 Shryock JC, Belardinelli L. Adenosine and adenosine receptors in the cardiovascular system: biochemistry, physiology, and pharmacology. Am J Cardiol. 1997;79(12a):2–10.
193 Mubagwa K, Mullane K, Flameng W. Role of adenosine in the heart and circulation. Cardiovasc Res. 1996;32(5):797–813.
194 Ledent C, Vaugeois JM, Schiffmann SN, Pedrazzini T, El Yacoubi M, Vanderhaeghen JJ, et al. Aggressiveness, hypoalgesia and high blood pressure in mice lacking the adenosine A2a receptor. Nature. 1997;388(6643):674–8.
195 Zhao Z, Francis CE, Ravid K. An A3-subtype adenosine receptor is highly expressed in rat vascular smooth muscle cells: its role in attenuating adenosine-induced increase in cAMP. Microvasc Res. 1997;54(3):243–52.
196 Veronese N, Cooper C, Reginster JY, Hochberg M, Branco J, Bruyère O, et al. Type 2 diabetes mellitus and osteoarthritis. Semin Arthritis Rheum. 2019;49(1):9–19.
197 Kalupahana NS, Moustaid-Moussa N, Claycombe KJ. Immunity as a link between obesity and insulin resistance. Mol Aspects Med. 2012;33(1):26–34.
198 Sowers JR. Diabetes mellitus and vascular disease. Hypertension. 2013;61(5):943–7.
199 Julius S, Jamerson K. Sympathetics, insulin resistance and coronary risk in hypertension: the "chicken-and-egg" question. J Hypertens. 1994;12(5):495–502.
200 Masuo K, Kawaguchi H, Mikami H, Ogihara T, Tuck ML. Serum uric acid and plasma norepinephrine concentrations predict subsequent weight gain and blood pressure elevation. Hypertension. 2003;42(4):474–80.
201 Cao W, Shi M, Wu L, Li J, Yang Z, Liu Y, et al. Adipocytes initiate an adipose-cerebral-peripheral sympathetic reflex to induce insulin resistance during high-fat feeding. Clin Sci. 2019;133(17):1883–99.
202 Csóka B, Törő G, Vindeirinho J, Varga ZV, Koscsó B, Németh ZH, et al. A(2A) adenosine receptors control pancreatic dysfunction in high-fat-diet-induced obesity. FASEB J. 2017;31(11):4985–97.
203 Runhaar J, Koes BW, Clockaerts S, Bierma-Zeinstra SM. A systematic review on changed biomechanics of lower extremities in obese individuals: a possible role in development of osteoarthritis. Obes Rev. 2011;12(12):1071–82.

204 King LK, Birmingham TB, Kean CO, Jones IC, Bryant DM, Giffin JR. Resistance training for medial compartment knee osteoarthritis and malalignment. Med Sci Sports Exerc. 2008;40(8):1376–84.
205 Oliveria SA, Felson DT, Cirillo PA, Reed JI, Walker AM. Body weight, body mass index, and incident symptomatic osteoarthritis of the hand, hip, and knee. Epidemiology. 1999;10(2):161–6.
206 Anandacoomarasamy A, Fransen M, March L. Obesity and the musculoskeletal system. Curr Opin Rheumatol. 2009;21(1):71–7.
207 Head GA, Lim K, Barzel B, Burke SL, Davern PJ. Central nervous system dysfunction in obesity-induced hypertension. Curr Hypertens Rep. 2014;16(9):466.
208 Wang T, He C. Pro-inflammatory cytokines: the link between obesity and osteoarthritis. Cytokine Growth Factor Rev. 2018;44:38–50.
209 Armitage JA, Burke SL, Prior LJ, Barzel B, Eikelis N, Lim K, et al. Rapid onset of renal sympathetic nerve activation in rabbits fed a high-fat diet. Hypertension. 2012;60(1):163–71.
210 Muntzel MS, Al-Naimi OA, Barclay A, Ajasin D. Cafeteria diet increases fat mass and chronically elevates lumbar sympathetic nerve activity in rats. Hypertension. 2012;60(6):1498–502.
211 Gentile CL, Orr JS, Davy BM, Davy KP. Modest weight gain is associated with sympathetic neural activation in nonobese humans. Am J Physiol Regul Integr Comp Physiol. 2007;292(5):R1834–8.
212 Singer K, Morris DL, Oatmen KE, Wang T, DelProposto J, Mergian T, et al. Neuropeptide Y is produced by adipose tissue macrophages and regulates obesity-induced inflammation. PLoS One. 2013;8(3):e57929.
213 Cai Y, Chen X, Yi B, Li J, Wen Z. Pathophysiology roles for adenosine 2A receptor in obesity and related diseases. Obes Rev. 2022;23(10):e13490.
214 Gnad T, Scheibler S, von Kügelgen I, Scheele C, Kilić A, Glöde A, et al. Adenosine activates brown adipose tissue and recruits beige adipocytes via A2A receptors. Nature. 2014;516(7531):395–9.
215 Pei Y, Li H, Cai Y, Zhou J, Luo X, Ma L, et al. Regulation of adipose tissue inflammation by adenosine 2A receptor in obese mice. J Endocrinol. 2018;239(3):365–76.
216 Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. Psychol Bull. 2014;140(3):774–815.
217 Redrobe JP, Dumont Y, Quirion R. Neuropeptide Y (NPY) and depression: from animal studies to the human condition. Life Sci. 2002;71(25):2921–37.
218 Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol. 2006;27(1):24–31.
219 Naumovs V, Groma V, Mednieks J. From low-grade inflammation in osteoarthritis to neuropsychiatric sequelae: a narrative review. Int J Mol Sci. 2022;23(24):16031.
220 Jacobs CA, Mace RA, Greenberg J, Popok PJ, Reichman M, Lattermann C, et al. Development of a mind body program for obese knee osteoarthritis patients with comorbid depression. Contemp Clin Trials Commun. 2021;21:100720.
221 Gomes JI, Farinha-Ferreira M, Rei N, Gonçalves-Ribeiro J, Ribeiro JA, Sebastião AM, et al. Of adenosine and the blues: the adenosinergic system in the pathophysiology and treatment of major depressive disorder. Pharmacol Res. 2021;163:105363.
222 Cruz CJ, Dewberry LS, Otto KJ, Allen KD. Neuromodulation as a potential disease-modifying therapy for osteoarthritis. Curr Rheumatol Rep. 2023;25(1):1–11.
223 Moraites E, Vaughn OA, Hill S. Endoscopic thoracic sympathectomy. Dermatol Clin. 2014;32(4):541–8.
224 Hashmonai M. The history of sympathetic surgery. Thorac Surg Clin. 2016;26(4):383–8.
225 Lilly GD. Effect of sympathectomy on development of chronic osteoarthritis: case report. Ann Surg. 1966;163(6):856–8.
226 Rösch G, El Bagdadi K, Muschter D, Taheri S, Dorn C, Meurer A, et al. Sympathectomy aggravates subchondral bone changes during osteoarthritis progression in mice without affecting cartilage degeneration or synovial inflammation. Osteoarthritis Cartilage. 2022;30(3):461–74.
227 Wrenn CC, Picklo MJ, Lappi DA, Robertson D, Wiley RG. Central noradrenergic lesioning using anti-DBH-saporin: anatomical findings. Brain Res. 1996;740(1–2):175–84.
228 Woosley RL, Nies AS. Guanethidine. N Engl J Med. 1976;295(19):1053–7.
229 Gado K, Emery P. Intra-articular guanethidine injection for resistant shoulder pain: a preliminary double blind study of a novel approach. Ann Rheum Dis. 1996;55(3):199–201.
230 Levine JD, Fye K, Heller P, Basbaum AI, Whiting-O'Keefe Q. Clinical response to regional intravenous guanethidine in patients with rheumatoid arthritis. J Rheumatol. 1986;13(6):1040–3.
231 Rankin GO, Haas GJ Jr. Effects of captopril on the development of tolerance to guanethidine. Fed Proc. 1984;43(5):1342–5.
232 Cong Z, Li D, Tao Y, Lv X, Zhu X. α(2A) -AR antagonism by BRL-44408 maleate attenuates acute lung injury in rats with downregulation of ERK1/2, p38MAPK, and p65 pathway. J Cell Physiol. 2020;235(10):6905–14.
233 Nakafero G, Grainge MJ, Valdes AM, Townsend N, D Mallen C, Zhang W, et al. β-blocker prescription is associated with lower cumulative risk of knee osteoarthritis and knee pain consultations in primary care: a propensity score-matched cohort study. Rheumatology. 2021;60(12):5686–96.
234 Nackley AG, Tan KS, Fecho K, Flood P, Diatchenko L, Maixner W. Catechol-O-methyltransferase inhibition increases pain sensitivity through activation of both beta2- and beta3-adrenergic receptors. Pain. 2007;128(3):199–208.
235 Müller G, Lübow C, Weindl G. Lysosomotropic beta blockers induce oxidative stress and IL23A production in Langerhans cells. Autophagy. 2020;16(8):1380–95.
236 O'Brien M, Koo J. The mechanism of lithium and beta-blocking agents in inducing and exacerbating psoriasis. J Drugs Dermatol. 2006;5(5):426–32.
237 Bangalore S, Parkar S, Grossman E, Messerli FH. A meta-analysis of 94,492 patients with hypertension treated with beta blockers to determine the risk of new-onset diabetes mellitus. Am J Cardiol. 2007;100(8):1254–62.
238 Padwal R, Mamdani M, Alter DA, Hux JE, Rothwell DM, Tu K, et al. Antihypertensive therapy and incidence of type 2 diabetes in an elderly cohort. Diabetes Care. 2004;27(10):2458–63.
239 Wang L, Li Y, Ning N, Wang J, Yan Z, Zhang S, et al. Decreased autophagy induced by β(1)-adrenoceptor autoantibodies contributes to cardiomyocyte apoptosis. Cell Death Dis. 2018;9(3):406.
240 Tsujimoto T, Sugiyama T, Shapiro MF, Noda M, Kajio H. Risk of cardiovascular events in patients with diabetes mellitus on β-blockers. Hypertension. 2017;70(1):103–10.
241 Lambert EA, Straznicky NE, Dixon JB, Lambert GW. Should the sympathetic nervous system be a target to improve cardiometabolic risk in obesity? Am J Physiol Heart Circ Physiol. 2015;309(2):H244–58.
242 Pischon T, Sharma AM. Use of beta-blockers in obesity hypertension: potential role of weight gain. Obes Rev. 2001;2(4):275–80.
243 Bell DS, Bakris GL, McGill JB. Comparison of carvedilol and metoprolol on serum lipid concentration in diabetic hypertensive patients. Diabetes Obes Metab. 2009;11(3):234–8.
244 Iliyana Atanasova PK, Atanasova I, Kirilov G. Metformin reduces cardiometabolic risk factors in people at high risk for development of type 2 diabetes and cardiovascular disease. J Diabetes Metab. 2014;5(12).
245 Hanson MA, Gluckman PD. Early developmental conditioning of later health and disease: physiology or pathophysiology? Physiol Rev. 2014;94(4):1027–76.
246 He L. Metformin and systemic metabolism. Trends Pharmacol Sci. 2020;41(11):868–81.
247 Franco C, Previate C, Trombini AB, Miranda RA, Barella LF, Saavedra LPJ, et al. Metformin improves autonomic nervous system imbalance and metabolic dysfunction in monosodium L-glutamate-treated rats. Front Endocrinol. 2021;12:660793.
248 Landin-Wilhelmsen K. Metformin and blood pressure. J Clin Pharm Ther. 1992;17(2):75–9.

249 Zhou L, Liu H, Wen X, Peng Y, Tian Y, Zhao L. Effects of metformin on blood pressure in nondiabetic patients: a meta-analysis of randomized controlled trials. J Hypertens. 2017;35(1):18–26.
250 Wulffelé MG, Kooy A, de Zeeuw D, Stehouwer CD, Gansevoort RT. The effect of metformin on blood pressure, plasma cholesterol and triglycerides in type 2 diabetes mellitus: a systematic review. J Intern Med. 2004;256(1):1–14.
251 Schäfers RF. Do effects on blood pressure contribute to improved clinical outcomes with metformin? Diabetes Metab. 2003;29(4 Pt 2):6s62–70.
252 Chen S, Ruan G, Zeng M, Chen T, Cao P, Zhang Y, et al. Association between metformin use and risk of total knee arthroplasty and degree of knee pain in knee osteoarthritis patients with diabetes and/or obesity: a retrospective study. J Clin Med. 2022;11(16):4796.
253 Staels B. Metformin and pioglitazone: effectively treating insulin resistance. Curr Med Res Opin. 2006;22(Suppl 2):S27–37.
254 Kobayashi D, Takamura M, Murai H, Usui S, Ikeda T, Inomata J, et al. Effect of pioglitazone on muscle sympathetic nerve activity in type 2 diabetes mellitus with α-glucosidase inhibitor. Auton Neurosci. 2010;158(1–2):86–91.
255 Krespi PG, Makris TK, Hatzizacharias AN, Triposkiadis P, Tsoukala C, Kyriaki D, et al. Moxonidine effect on microalbuminuria, thrombomodulin, and plasminogen activator inhibitor-1 levels in patients with essential hypertension. Cardiovasc Drugs Ther. 1998;12(5):463–7.
256 Straznicky NE, Grima MT, Sari CI, Eikelis N, Lambert GW, Nestel PJ, et al. A randomized controlled trial of the effects of pioglitazone treatment on sympathetic nervous system activity and cardiovascular function in obese subjects with metabolic syndrome. J Clin Endocrinol Metab. 2014;99(9):E1701–7.
257 Jordan J, Tank J, Heusser K, Heise T, Wanner C, Heer M, et al. The effect of empagliflozin on muscle sympathetic nerve activity in patients with type II diabetes mellitus. J Am Soc Hypertens. 2017;11(9):604–12.
258 Li Y, Zhang Y, Chen C, Zhang H, Ma C, Xia Y. Establishment of a rabbit model to study the influence of advanced glycation end products accumulation on osteoarthritis and the protective effect of pioglitazone. Osteoarthritis Cartilage. 2016;24(2):307–14.
259 Boileau C, Martel-Pelletier J, Fahmi H, Mineau F, Boily M, Pelletier JP. The peroxisome proliferator-activated receptor gamma agonist pioglitazone reduces the development of cartilage lesions in an experimental dog model of osteoarthritis: in vivo protective effects mediated through the inhibition of key signaling and catabolic pathways. Arthritis Rheum. 2007;56(7):2288–98.
260 Kobayashi T, Notoya K, Naito T, Unno S, Nakamura A, Martel-Pelletier J, et al. Pioglitazone, a peroxisome proliferator-activated receptor gamma agonist, reduces the progression of experimental osteoarthritis in Guinea pigs. Arthritis Rheum. 2005;52(2):479–87.
261 Kalil GZ, Haynes WG. Sympathetic nervous system in obesity-related hypertension: mechanisms and clinical implications. Hypertens Res. 2012;35(1):4–16.
262 Straznicky NE, Lambert EA, Lambert GW, Masuo K, Esler MD, Nestel PJ. Effects of dietary weight loss on sympathetic activity and cardiac risk factors associated with the metabolic syndrome. J Clin Endocrinol Metab. 2005;90(11):5998–6005.
263 Masuo K, Rakugi H, Ogihara T, Lambert GW. Different mechanisms in weight loss-induced blood pressure reduction between a calorie-restricted diet and exercise. Hypertens Res. 2012;35(1):41–7.
264 Costa J, Moreira A, Moreira P, Delgado L, Silva D. Effects of weight changes in the autonomic nervous system: a systematic review and meta-analysis. Clin Nutr. 2019;38(1):110–26.
265 King LK, March L, Anandacoomarasamy A. Obesity & osteoarthritis. Indian J Med Res. 2013;138(2):185–93.
266 IsHak WW, Wen RY, Naghdechi L, Vanle B, Dang J, Knosp M, et al. Pain and depression: a systematic review. Harv Rev Psychiatry. 2018;26(6):352–63.
267 Whiteside GT, Dwyer JM, Harrison JE, Beyer CE, Cummons T, Manzino L, et al. WAY-318068: a novel, potent and selective noradrenaline re-uptake inhibitor with activity in rodent models of pain and depression. Br J Pharmacol. 2010;160(5):1105–18.
268 Burnham LJ, Dickenson AH. The antinociceptive effect of milnacipran in the monosodium iodoacetate model of osteoarthritis pain and its relation to changes in descending inhibition. J Pharmacol Exp Ther. 2013;344(3):696–707.
269 Zhang W, Robertson WB, Zhao J, Chen W, Xu J. Emerging trend in the pharmacotherapy of osteoarthritis. Front Endocrinol. 2019;10:431.
270 Kern KU, Sohns M, Heckes B, Elling C. Tapentadol prolonged release for severe chronic osteoarthritis pain in the elderly: improvements in daily functioning and quality of life. Pain Manag. 2020;10(2):85–95.
271 Schwittay A, Sohns M, Heckes B, Elling C. Tapentadol prolonged release for severe chronic osteoarthritis pain in the elderly-A subgroup analysis of routine clinical practice data. Pain Res Manag. 2020;2020:5759265.
272 Rosas-Ballina M, Tracey KJ. Cholinergic control of inflammation. J Intern Med. 2009;265(6):663–79.
273 Courties A, Deprouw C, Rousseau A, Berard L, Touati A, Kalsch J, et al. Transcutaneous vagus nerve stimulation in erosive hand osteoarthritis: protocol for the randomised, double-blind, sham-controlled ESTIVAL trial. BMJ Open. 2022;12(3):e056169.
274 Koopman FA, Chavan SS, Miljko S, Grazio S, Sokolovic S, Schuurman PR, et al. Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in rheumatoid arthritis. Proc Natl Acad Sci U S A. 2016;113(29):8284–9.
275 Courties A, Deprouw C, Maheu E, Gibert E, Gottenberg JE, Champey J, et al. Effect of transcutaneous vagus nerve stimulation in erosive hand osteoarthritis: results from a pilot trial. J Clin Med. 2022;11(4):1087.
276 Courties A, Do A, Leite S, Legris M, Sudre L, Pigenet A, et al. The role of the non-neuronal cholinergic system in inflammation and degradation processes in osteoarthritis. Arthritis Rheumatol. 2020;72(12):2072–82.
277 Nakamachi Y, Koshiba M, Nakazawa T, Hatachi S, Saura R, Kurosaka M, et al. Specific increase in enzymatic activity of adenosine deaminase 1 in rheumatoid synovial fibroblasts. Arthritis Rheum. 2003;48(3):668–74.
278 Friedman B, Cronstein B. Methotrexate mechanism in treatment of rheumatoid arthritis. Jt Bone Spine. 2019;86(3):301–7.
279 Bedoui Y, Guillot X, Sélambarom J, Guiraud P, Giry C, Jaffar-Bandjee MC, et al. Methotrexate an old drug with new tricks. Int J Mol Sci. 2019;20(20):5023.
280 Conaghan PG, Cook AD, Hamilton JA, Tak PP. Therapeutic options for targeting inflammatory osteoarthritis pain. Nat Rev Rheumatol. 2019;15(6):355–63.
281 Mehrpoor G, Soltani H, Owlia MB. Methotrexate; a trustworthy answer to an inflammatory response in osteoarthritis. J Res Med Sci. 2022;27:66.
282 Varani K, Vincenzi F, Ravani A, Pasquini S, Merighi S, Gessi S, et al. Adenosine receptors as a biological pathway for the anti-inflammatory and beneficial effects of low frequency low energy pulsed electromagnetic fields. Mediators Inflamm. 2017;2017:2740963.
283 Vincenzi F, Targa M, Corciulo C, Gessi S, Merighi S, Setti S, et al. Pulsed electromagnetic fields increased the anti-inflammatory effect of A-A and A adenosine receptors in human T/C-28a2 chondrocytes and hFOB 1.19 osteoblasts. PLoS One. 2013;8(5):e65561.
284 Lahesmaa M, Oikonen V, Helin S, Luoto P, U Din M, Pfeifer A, et al. Regulation of human brown adipose tissue by adenosine and A(2A) receptors - studies with ((15)O)H(2)O and ((11)C)TMSX PET/CT. Eur J Nucl Med Mol Imaging. 2019;46(3):743–50.
285 Sternberg Z. Sympathetic nervous system dysfunction in multiple sclerosis, linking neurodegeneration to a reduced response to therapy. Curr Pharm Des. 2012;18(12):1635–44.
286 Li M, Zeng Y, Nie Y, Wu Y, Liu Y, Wu L, et al. The effects of different antihypertensive drugs on pain and joint space width of knee osteoarthritis: a comparative study with data from Osteoarthritis Initiative. J Clin Hypertens. 2021;23(11):2009–15.