Novel information on the non-neuronal cholinergic system in orthopedics provides new possible treatment strategies for inflammatory and degenerative diseases

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Abstract

Anti-cholinergic agents are used in the treatment of several pathological conditions. Therapy regimens aimed at up-regulating cholinergic functions, such as treatment with acetylcholinesterase inhibitors, are also currently prescribed. It is now known that not only is there a neuronal cholinergic system but also a non-neuronal cholinergic system in various parts of the body. Therefore, interference with the effects of acetylcholine (ACH) brought about by the local production and release of ACH should also be considered. Locally produced ACh may have proliferative, angiogenic, wound-healing, and immunomodulatory functions. Interestingly, cholinergic stimulation may lead to anti-inflammatory effects. Within this review, new findings for the locomotor system of a more widespread non-neuronal cholinergic system than previously expected will be discussed in relation to possible new treatment strategies. The conditions discussed are painful and degenerative tendon disease (tendinopathy/tendinosis), rheumatoid arthritis, and osteoarthritis.

New aspects on the usefulness of interference with acetylcholine effects: basis for the present review

Medications interfering with the effects of acetylcholine (ACH) are frequently used today. Anti-cholinergic agents are widely used in the management of overactive urinary bladder and of obstructive lung disease. However, treatments leading to the upregulation of cholinergic activity are increasingly applied. New possibilities for interference with cholinergic effects are currently discussed. This is related to the existence of a widespread non-neuronal cholinergic system.

The present review summarizes hitherto known aspects of possible treatment strategies concerning interference with cholinergic effects. That includes inflammation in general, cancer, and pain conditions. However, major focus is devoted to discussions concerning conditions affecting the locomotor system and for which a non-neuronal cholinergic system has been recently shown to exist. More specifically, the conditions discussed are rheumatoid arthritis (RA) and osteoarthritis (OA), and chronically painful tendons (tendinopathy) with degenerative-like tissue changes (tendinosis). Tendinopathy is a condition in which there is chronic pain in a tender portion of the tendon. The tendons most frequently affected are the Achilles and patellar tendons. When, in addition to chronic pain, there are structural tissue changes of a degenerative-like nature, as seen by ultrasonography or magnetic resonance imaging (MRI), or by histological examination, the condition is called tendinosis. In the following text, our recent observations concerning Achilles and patellar tendinosis will be discussed. Nothing at all has been previously known concerning the existence of a non-neuronal cholinergic system in tendinosis or the synovial tissue of patients with RA or OA. The current review will, therefore, give new directions concerning the cholinergic system in these conditions.

Acetylcholine production and acetylcholine receptors

ACh was the first neurotransmitter to be identified. It is synthesized from choline and acetyl-CoA via the activity of choline acetyltransferase (ChAT).4,5 In addition to production via ChAT, ACh can be produced by carnitine acetyltransferase (CarAT). ACh is then transferred to sympathetic vesicles by vesicular acetylcholine transporter (VACHT).2 ACh is degraded by cholinesterases.1 It is converted into the inactive metabolites choline and acetate by acetylcholinesterase (AChE). It is well known that the effects of ACh are mediated via muscarinic (G-protein coupled) and nicotinic (ligand-gated ion channels) ACh receptors.3 The muscarinic ACh receptors (mAChRs) are metabotropic, and are stimulated by muscarine and ACh, whilst the nicotinic ACh receptors are ionotropic receptors stimulated by nicotine and ACh. Muscarine is an alkaloid extracted from certain mushrooms, and nicotine is an alkaloid substance found in tobacco. Five subtypes of mAChRs have been identified (M1-M5), each with different functions and properties. Certain features regarding the expression patterns of the mAChRs in regions outside the central nervous system are well known, including the fact that the M3 receptor subtype comprises more than 90% of the mAChRs in the heart. The main ACh receptor in the smooth muscle of the gastrointestinal tract is the M3 receptor. The mAChRs associated with smooth muscle cells are predominantly of the M3 and M2 subtypes. The nicotinic receptors (nAChRs) are pentameric complexes consisting of a large number of different alpha- and beta-subunits.1 The various nAChRs have

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different physiological functions. The best-characterized nAChR, which, due to its relationship to immune functions, is further discussed below, is the \( \alpha7nAChR \).

There are both neuronal and non-neuronal cholinergic systems

ACh is a neurotransmitter in the central, as well as in the peripheral, nervous system. It is a major transmitter in the autonomic nervous system, the principal transmitter of the parasympathetic part of this system, and a neurotransmitter in all autonomic ganglia. On the other hand, nerve-related reactions for ChAT or CarAT have, to the best of our knowledge, not been shown in synovial tissues of joints or for tendon tissue. It is well known that ACh synthesis is not only restricted to neurons; there is also a non-neuronal cholinergic system. Accordingly, ACh is produced in surface epithelia, such as those of the airways and the intestine. Furthermore, the keratinocytes of the skin and cells in the urothelium are also ACh-producing. Additionally, cells in blood vessel walls, as well as fibroblasts in various locations, show production of ACh. An occurrence of expression of non-neuronal ACh and ACh-synthesizing activity has also previously been shown for a variety of plants and organisms including fungi, algae and bacteria. The occurrence of a non-neuronal ACh production includes the situation for certain cancer cells and for inflammatory cells. It has been shown that ACh is synthesized by cells of small lung cell carcinoma, colon cancer, and breast cancer. Furthermore, inflammatory cells have been shown to produce ACh. The effects of ACh on the functions of inflammatory cells do occur principally via effects on the \( \alpha7nAChR \). Recently we found that the tendon cells (tenocytes) in patellar and Achilles tendons showed evidence of ACh production. This was observed by analysis of ChAT and VACHT reactions at both protein and mRNA level. We have furthermore observed that mononuclear- and fibroblast-like cells of the synovium of patients with severe RA and OA show ChAT expression. We have also made original findings regarding the colon of patients with ulcerative colitis (UC). In the colon from patients with UC, cells, including inflammatory cells in the lamina propria, cells of the blood vessel walls, and cells of the epithelial layer, were identified as being capable of ACh synthesis. In the following text, the aspects of the non-cholinergic effects in the locomotor system are focused upon. In our recent studies on the synovium of joints, and tendons of man we found a marked occurrence of the \( M_2 \) type of mAChRs. Immunoreactions for the \( M_1 \) receptor were observed for the tenocytes, nerves, and blood vessel walls of Achilles and patellar tendons, and were also noted in the synovial tissue from patients with RA as well as from those with OA. An interesting aspect noted is the fact that the evidence for a non-neuronal cholinergic system in tendon and synovial tissues is particularly apparent in pathological situations. Thus, the levels of expression of enzymes catalyzing ACh production, as well as the levels of expression of mAChRs, were much more evidently seen in deranged and chronically painful tendinosis tendons than in normal tendons. A schematic drawing summarizing the non-neuronal cholinergic system of human tendinosis tendons is shown in Figure 1. Furthermore, expression of enzyme related to ACh production was marked in specimens of the synovial tissue of knee joints of RA patients exhibiting pronounced invasion of mononuclear-like cells, as well as showing the occurrence of numerous fibroblast-like cells. Such an expression was also noted for mononuclear- and fibroblast-like cells in specimens of the synovial tissue of OA patients. Concerning the synovial specimens of both RA and OA patients, these corresponded to specimens of biopsies taken during prosthesis operations.

The functions of the neuronal and non-neuronal cholinergic systems

Effects in general

The responses in the effector organs to impulses leading to release and effects of ACh from the autonomic nervous system are well described in textbooks. Typical features are a decrease in heart rate, contraction of the sphincter muscle of the iris, contraction of bronchial muscles, and increased exocrine secretion from the pancreas. These are effects of ACh released from postganglionic parasympathetic nerve fibres. In the intestine, for example, it is well known that stimulation by ACh leads to an increase in smooth muscle contraction and a stimulation of secretion. Based on results of studies on experimental animals, it has been theorized that ACh released from cholinergic nerves is involved in vasoregulation in joints. However, as described above, it has not yet been proven whether cholinergic nerves are present in the synovial tissues. There are no reports of effects of neuronally-released ACh within tendons.

The function of non-neuronal ACh is in

Figure 1. Schematic drawing of human tendon tissue showing the occurrence of a non-neuronal cholinergic system in tendinosis. Violet dots represent acetylcholine (ACh) that is locally produced in tenocytes of pathological appearance (unfilled arrow). Normal looking tenocytes (filled arrow) do not produce ACh. ACh can influence 1) nerves, 2) cells of blood vessel walls, and 3) the tenocytes themselves. These structures have been shown to be supplied with muscarinic ACh receptors of subtype \( M_2 \) (M:\( R \)). Image by Gustav Andersson.
principle related to autocrine/paracrine actions.44-48 Thus, the cells types producing ACh are also equipped with receptors for this substance. That includes, for example, the situation for the non-neuronal cholinergic system of the granulose cells in the human ovary.33 More precisely, the functions of the non-neuronal cholinergic system are mainly related to effects on differentiation and growth, secretion, barrier functions, and immunomodulation (for reviews, see Kawashima and Fujii44 and Wessler and Kirkpatrick45). Important ACh effects are those on angiogenesis,13,35 proliferation rates,13,36 and wound healing.13,36

It is frequently emphasized that the ACh that is produced by the inflammatory cells has effects on those cells, suggesting that ACh modulates the activity of inflammatory cells via autocrine and paracrine loops.41 The influences of ACh on the inflammatory cells may be related to the time scale with acute stimulation leading to proinflammatory effects whilst chronic stimulation, on the other hand, has anti-inflammatory effects.4 The overwhelming majority of studies on ACh effects in relation to inflammation do, nevertheless, support the view that ACh has anti-inflammatory effects (see further below).

The cholinergic anti-inflammatory pathway

Based on findings by several groups, the existence of a so-called ‘cholinergic anti-inflammatory pathway’ has been proposed.44,45 This implies that ACh, released in response to activation of nerve fibres like those of the vagal nerve, has effects on local inflammation.46 Electrical stimulation of the vagus nerve leads to inhibition in the synthesis of TNFα, and attenuates the release of different pro-inflammatory cytokines.47,48 The vagal anti-inflammatory effects are known to be mediated by the Jak2/STAT3 signaling on macrophages49 or via inhibition of the transcription factor NF-kappα.50 It should be remembered that there are variations between different organs concerning the occurrence of anti-inflammatory effects via stimulation of the vagus nerve. Such a stimulation has a marked anti-inflammatory effect within the gastrointestinal tract,42 but a limited anti-inflammatory effect in the lungs.42

The spleen has been shown to be important in mediating the anti-inflammatory effects that occur in response to electrical stimulation of the vagus nerve.41 The cholinergic anti-inflammatory pathway is shown to regulate the production of TNFα by macrophages via effects on preganglionic neurons related to the vagus nerve and via effects on postganglionic neurons originating in the celiac-superior mesenteric plexus and projecting within the splenic nerve.49 The findings that muscarinic receptor antagonists mediate anti-inflammatory actions favor the suggestion that there is a cholinergic anti-inflammatory pathway.46 Nevertheless, it is the 7nAChR that is the ACh receptor, that is the essential receptor for the inhibition of cytokine synthesis via the cholinergic anti-inflammatory pathway.49,51 One structure that may be a target for anti-inflammatory cholinergic mediators is the endothelium, as the endothelium is a key regulator of leukocyte trafficking during inflammation.52

The occurrence of anti-inflammatory effects of the parasympathetic nervous system has been shown in different ways. The anti-inflammatory effects that cholecystokinin is known to have are thus mediated by the vagus nerve and activation of the vagus nerve prevents manipulation-induced inflammation of the smooth muscle layers.53 Interestingly, it is suggested that anti-inflammatory effects not only occur via the neuronal but also the non-neuronal cholinergic system,49 and furthermore, that the release of non-neuronal ACh from local cells, such as inflammatory cells, is triggered by neurally-released ACh.20

Changes in magnitude of the non-neuronal cholinergic system: occurrence of up- and downregulations

The new information obtained in our laboratory shows that there is a more clearly marked non-neuronal cholinergic system in tendinosis tendons than in normal tendons.27,28 Furthermore, there is an extensive expression of M3 receptors in tendinosis tendons, but clearly less so in normal tendons. It is also a fact that the non-neuronal cholinergic system is represented to a large extent in the synovial tissue in RA if the tissue is heavily infiltrated with inflammatory cells and fibroblasts.29 Many of these cells show expression for the ACh-synthesizing enzyme ChAT. Upregulation of the cholinergic system also occurs in other situations, for example such an upregulation has been reported for cancer cells.27 It has also been shown that the cholinergic system is up-regulated in the superficial skin in atopic dermatitis.30 However, the situation is apparently different in certain acute situations. Thus, there is a decrease in non-neuronal ACh synthesis in an acute model of allergic airway inflammation.32 Whether upregulation of ACh production in non-neuronal cells is of positive or negative character for the tissue is only partly known. Obtaining a reduction in pulmonary ACh content in experimental studies of lung injury was considered to be of positive character, protecting the lung tissue.32 Further aspects on this question are discussed below.

For many conditions it seems as if an increased ACh effect would be welcome. Cancer is a major exception (see further below).

Treatments leading to interference with cholinergic effects

General aspects

Anti-cholinergics are useful in certain clinical situations. However, treatments leading to cholinergic upregulation may also have a positive outcome. Thus, as will be further discussed below, treatment with AChE inhibitors, leading to increased ACh levels, has been found to be a treatment of choice in Alzheimer’s disease. Furthermore, the concept of the cholinergic anti-inflammatory pathway implies that inducing increased ACh effects may be favorable for inflammatory situations. There are also other reports suggesting that increased ACh effects may be helpful clinically. The results of recent studies on cystic fibrosis suggest that treatment with muscarinic receptor agonists may be beneficial.27 Furthermore, in a recent experimental study on acute allergic airway inflammation, the occurrence of a downregulations of non-neuronal ACh synthesis and release machinery was furthermore suggested to contribute to epithelial shedding and ciliated dysfunction.25

Treatment with AChE inhibitors

Over recent decades, a number of therapies aimed at up-regulating cholinergic function have been tested as treatment for Alzheimer’s disease, with AChE inhibitors being the group of substances that are best developed (for a review, see Shah et al57). Thus, compounds frequently used nowadays for the treatment of mild forms of this disease are blockers of AChE activity. The basis for this is the well-known fact that there is a loss of cholinergic function in Alzheimer’s disease and that AChE is the enzyme that degrades ACh. AChE inhibitors are also used in myasthenia gravis.30 Cholinergic agonism, via administration of an AChE inhibitor, has also been tested for multiple sclerosis (MS) patients, and this agonism was hereby shown to alter cognitive processing and to enhance brain functional connectivity.58 In studies on experimental autoimmune encephalomyelitis, which is a model for the pathology of MS, it was found that treatment with an AChE inhibitor suppressed neuroinflammation and showed immunomodulatory activity.59 A scheme of the anti-inflammatory outcome that is achieved using AChE inhibitors during experimental neuroinflammation has recently been depict-
ed by Brenner and collaborators. These authors found that the AChE inhibitors induced cholinergic upregulation and effects on the neuroinflammation via α7nAChR expressing cells.

It has been shown that treatment of mice with AChE inhibitors attenuates the production of interleukin-1β in both the hippocampus and blood, showing that cholinergic enhancement produces both central and peripheral anti-inflammatory effects. The results of studies on endotoxemia also suggest that centrally acting cholinergic enhancers may have anti-inflammatory properties. Inhibition of brain AChE via treatment with AChE inhibitors has recently been shown to suppress systemic inflammation, suggesting that the brain’s cholinergic muscular networks communicate with the anti-inflammatory pathway thereby suppressing peripheral inflammation.

Obtaining of cholinergic anti-inflammatory effects via the nicotinic pathway

Nicotine is more active than ACh in inhibiting the production of pro-inflammatory mediators by macrophages. The anti-inflammatory effects of nicotine on these cells can be counteracted by selective α7-antagonists. Influences on the nAChRs via nicotine have been tested in clinical situations, especially in UC. The therapeutic benefit is, however, limited, and troublesome side-effects of nicotine occur.

The effects of ACh stimulation on the α7nAChR may, due to the known relationship between this receptor and inflammation, be of importance in inflammatory conditions. Accordingly, it is suggested that α7nAChRs play a critical role in the protection against the development of neurodegenerative diseases. The use of selective α7nAChR agonists has, furthermore, been shown to be of value in order to diminish cytokine production by macrophages and inflammation in several animal models of inflammation (for a review, see de Jonge and Ulloa).

Possible usefulness of interference with cholinergic effects in certain conditions

Cancer

It is well-known that ACh receptors, including both mAChRs and nAChRs, are functionally present on certain cancer cells (for reviews, see Paleari et al. 2008 and Song and Spindel 2008). This includes the cancer cells in small cell lung carcinoma (SCLC), in which the cells have been shown to synthesize and secrete ACh, and to be equipped with mAChRs and nAChRs. The M3 mAChR is over-expressed in tumor cells of colon cancer. In recent studies it was shown that cells of the human colon cancer cell line HT-29 express the α7nAChR subtype.

It is known that the level of cholinergic signaling is up-regulated in squamous cell carcinoma, and that stimulation of cells of mammary adenocarcinoma cell lines with carbachol increases their proliferation via M3 mAChR-mediated pathways. It is suggested that mAChR antagonists may be useful adjuncts for SCLC treatment, and that blocking cholinergic signaling can limit the growth of squamous lung carcinoma. In accordance with the latter suggestion, α7nAChR antagonists are anticipated to be a useful adjunct to the treatment of such lung cancer. The potential implications of mAChRs in tumor progression and the possible use of muscarinic ligands in cancer therapy have been recently reviewed. The fact that cholinergic signaling is increased in certain cancers may reinforce the usefulness of ACh blockade in these situations. It should be stressed that stimulation of ACh leads to an increase in cell proliferation and to angiogenesis. The fact that ACh stimulation leads to these features indeed favors the proposal that blocking the effects of ACh may be beneficial in cancers showing an up-regulation of cholinergic features. The fact that ACh inhibits long-term hypoxia-induced apoptosis in mouse stem cells, and that nicotine increases cell growth of a human colon cancer cell line, the effect being depressed by an antagonist to the α7nAChR, also supports such a suggestion.

Pain conditions

Interference with cholinergic effects may have some relevance in relation to pain. ACh has been shown to induce pain when applied to human skin. However, cholinergic effects have mainly been found to be of an analgesic nature. Administration of muscarinic agonists with effects on the central nervous system can thus induce pronounced analgesic effects. Inflammatory joint pain can be partly modulated via muscarinic cholinergic receptors as shown in animal model studies, e.g., analgesia induced by an AChE inhibitor has been shown in a rat model. The possible usefulness of targeting the mAChRs in antinociception has been recently discussed.

Chronic pain is the major symptomatic feature of tendinosis, and the pain mechanisms for this disease are still largely unknown and frequently discussed. The aspects of tendon pain in relation to the non-neuronal cholinergic system in tendon tissue are discussed below.

Tendinosis

In tendinosis, a non-inflammatory degenerative-like condition in which an increase in tissue cells (tenocytes) and a hypervascularity/neovascularization are typical phenomena, it is likely that the proliferation of tenocytes and the angiogenesis are related to an initial tissue healing process in response to mechanically induced micro-trauma. The tenocytes are the cells that produce not only the collagen but also various signal substances that are likely to have important roles in the turnover of the extracellular matrix. However, the blood vessel changes may in the long run be a drawback. Thus, hypervascularity and neovascularization have been correlated with the chronic pain experienced in tendinosis, and new treatment methods focusing on destroying the region with hypervascularity/neovascularization by injection of the sclerosing substance polidocanol have not only led to pain relief but also in the long-term perspective also to tendon remodeling.

Given the information that tenocytes of tendinosis tendons produce ACh, and that there are mAChRs on the tenocytes and on the cells of the blood vessel walls, it is possible that the non-neuronal ACh might have effects on cell proliferation, collagen production, and blood vessel regulation in tendinosis. It is already known that ACh can increase the proliferation of myofibroblastic cells, and that stimulation of ACh receptors on certain fibroblasts may augment collagen accumulation. Also, as previously discussed, agonists of ACh receptors are known to promote angiogenesis. It might be that treatments that lead to increased cholinergic effects on the tenocytes and the blood vessels might be attractive in early stages of tendinosis. At these stages, an increased tenocyte population and an increased vascularity are likely to be of value for the tendon. On the other hand, less cholinergic influences on the blood vessels may be desirable in chronic stages. It may also be that an excess of tenocytes is a drawback for tendon function in the long run. The functional importance of the ACh production in the tenocytes, and the marked existence of mAChRs on these cells, as well as on blood vessel walls in tendinosis tendons, should be further explored.

One should bear in mind that signal substances other than ACh, e.g., catecholamines and glutamate, are produced by tenocytes in tendinosis tendons and that the tenocytes are equipped with receptors for various signal substances. Furthermore, there is a production of neurotrophins in the tenocytes and the existence of the p75 neurotrophin receptor in these cells. This means that interactions between a number of substances that are delivered locally have to be considered. Some of the substances produced, such as glutamate, are
likely to be toxic rather than related to wound healing. It may be that interference with cholinergic effects should be combined with interference with the effects of other type(s) of signal substances.

To further understand the pain mechanisms in tendinosis, the newly developed treatments for this condition should be considered. The sclerosing injection treatment, mentioned above, targets the regions of tendinosis Achilles and patellar tendons showing pathologically high blood flow. These regions conform to outer parts of the tendons (the paratendinous connective tissue). Our findings of an abundance of mAChRs in blood vessel walls in tendinosis tendons show that these vessels are under marked cholinergic influence. Nevertheless, it is probable that the pain-relief is not primarily related to effects on the vasculature but to effects on the nerves located close to the blood vessels. Consequently, it is interesting to note that we have also found mAChRs on nerve fascicles in the tendinosis tendons.

To what extent the ACh effects, and those of other nerve signal substances such as substance P in the sensory innervation, are related to the pain symptoms in tendinosis must, however, await further studies.

Rheumatoid arthritis

It is evident that the infiltrating inflammatory cells, as well as the proliferating fibroblast-like cells, in the synovium become part of a non-neuronal cholinergic system in advanced RA, as verified by the expression of enzyme related to ACh production (ChAT). Such cells in synovial specimens of OA patients also show this feature. In both conditions, the existence of ChAT production was noted in specimens obtained after prosthesis operations. It may be that the existence of ACh production in these cells is related to trophic/modulatory and anti-inflammatory, rather than damaging, effects in the chronic stages of RA and OA. This could be seen as an attempt to balance the production of pro-inflammatory substances.

A favorable outcome in arthritis via cholinergic agonism has recently been shown experimentally in mice. Based on evaluating the effect of adding nicotine to the drinking water of mice with collagen-induced arthritis (CIA), the effects of vagotomy and the effects of treatment with an α7nAChR agonist, the authors concluded that there exists a cholinergic anti-inflammatory pathway in the murine CIA model of RA. An existence of α7nAChRs on the fibroblast-like synovocytes in human synovium has also been shown and ACh was found to inhibit cytokine expression through a post-transcriptional mechanism in these cells. It was suggested in the study by Waldburger and collaborators, it was suggested that the α7nAChR is a potential therapeutic target for RA. In studies on a rat model of knee joint inflammation published as early as 1998, it was shown that a centrally administered AChE inhibitor, neostigmine, led to enhanced levels of endogenous ACh, which in turn functioned as an analgesia-modulating compound at both central and peripheral sites of inflammatory pain.

It can be speculated that treatments that contribute to additional ACh effects could be useful in order to prevent the establishment of a marked derangement and damage of synovial tissues in advanced stages of RA and OA. Such interference would, thus, possibly lead to anti-inflammatory features. In accordance with such a suggestion are the recent findings by Goldstein and collaborators. In their studies it was shown that the occurrence of a diminished cholinergic anti-inflammatory pathway activity is associated with increased levels of high mobility group box-1, a cytokine that is implicated in the pathogenesis of arthritis, in patients with RA.

Conclusions

In summary, the basis for the present review is the fact that new indications for interference with cholinergic effects should be considered. The reason is that there exists a widespread local production of ACh in various tissues; a non-neuronal cholinergic system. ACh receptors are present in parallel. The effects of non-neuronal ACh are related to autocrine/paracrine effects and effects on angiogenesis, cell proliferation, wound-healing, and inflammation. Our recent observations on the situation in tendinosis, RA, and OA show that there is an unexpected presence of a non-neuronal cholinergic system in these conditions. This means that new ideas for interference with cholinergic effects are indeed welcome for these situations.

What should be the focus for further studies evaluating the usefulness of interfering with cholinergic effects in various parts of the body? One field that should be further examined is the development of selective nicotinic agonists for men. The fact that selective α7nAChR agonists have been found to have positive effects in a dextran sulphate-induced colitis model for mice supports a suggestion that such agonists may be useful in inflammatory disorders. The idea that the α7nAChR is a target of importance in RA is discussed in the present review.

Another field that should be further concentrated on is research on the possible usefulness of AChE inhibitors in peripheral inflammatory disorders. Questions related to selectivity and specificity are, however, also warranted in this case.

In conclusion, knowledge of the occurrence of a marked local signal substance production within a diseased tissue, and the occurrence of receptors for the substances within the tissue, is on the whole of great importance for establishing new possible treatment strategies. It is obvious that it is not necessary that cholinergic nerves are present in order to make ACh available for the tissue; the substances can be locally produced. This means that not only should the neuronal but also the non-neuronal cholinergic system be taken into consideration when considering new treatments interfering with cholinergic effects. This includes disorders related to orthopedics, namely tendinosis, RA and OA.

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