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Chapter 9

The Cholinergic System in Relation to Osteoarthritis

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1. Introduction

The cholinergic system is of interest for the synovial tissue of joints and for arthritic processes, including in osteoarthritis (OA). One aspect is that stimulation via the vagal nerve leads to hampering of arthritic processes. Another is that there is evidence of local acetylcholine (ACh) production within the synovial tissue of human joints, including joints in OA and rheumatoid arthritis. There is furthermore a marked presence of the nicotinic acetylcholine receptor AChRα7 (α7nAChR) in the synovial tissue. Influences on this receptor are known to have anti-inflammatory and healing effects. Overall, the concept of a "cholinergic anti-inflammatory pathway" has emerged for various parts of the body. That includes the situation in arthritis. This means that released ACh can have anti-inflammatory effects, in parallel with other favourable effects including wound-healing effects, implying that increased ACh effects might be of value in situations with arthritis. However, focus should further be made on the fact that there is not only evidence of ACh production but also ACh degradation within the synovial tissue. This is related to expressions of acetylcholinesterase (AChE). Of interest in this respect is that reductions of AChE activity via use of AChE inhibitor drugs are used in other situations (e.g. Alzheimer´s disease). The aspects concerning ACh production/degradation in the synovial tissue, the fact that vagal stimulation decreases arthritic processes and the known presence of the potent AChRα7 receptor in synovial tissue should be further considered concerning arthritis in the future. That includes the situation in OA.

2. Why focus on the cholinergic system when discussing osteoarthritis

It can seem far-fetched to consider aspects related to the cholinergic system when discussing arthritis, including osteoarthritis. It is thus namely well-known that there is no cholinergic innervation of the joints. They are on the other hand well-equipped with sensory

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and sympathetic innervations. Nevertheless, as will be discussed below, cholinergic stimulations (via the vagal nerve) have been shown to have effects for joints. It has actually also been shown that the bones of mice are functionally innervated by the vagus nerve [1]. On the whole, it is well-known that the vagus nerve plays an anti-inflammatory role in various other parts of the body [2].

Another aspect concerning joint synovial tissue and the cholinergic system has evolved. That is related to the existence of a so-called non-neuronal cholinergic system. Such a system is nowadays well-known for different parts of the body [3]. New information on this system is gradually attained. We have noticed the existence of a non-neuronal cholinergic system in the synovial tissue of the knee joint of humans [4]. We have thus observed that immunoactive cells as well as fibroblasts in the synovial tissue of patients suffering from severe arthritis [rheumatoid arthritis (RA) as well as osteoarthritis (OA)] show expressions of the acetylcholine (ACh)-synthesizing enzyme choline acetyltransferase (ChAT) at both mRNA and protein levels [4]. This observation suggests that there is a local ACh production in the synovial tissue. There is only little information on the other aspect of ACh metabolism, namely ACh degradation. This will be discussed below.

Another noteworthy aspect is the finding that there are marked expressions of the nicotinic alpha7nACh receptor (α7nAChR) in the synovial tissue of arthritic patients. These observations have been made in studies in our laboratory [5] and in studies by other researchers [6,7]. That includes patients with osteoarthritis and is related to α7nAChR expressions for the fibroblast-like and inflammatory cells within the synovial tissue as well as for the synovial lining [5,8]. This receptor is known to be involved in inflammatory and remodulation processes, most notably having anti-inflammatory effects [9,10]. The findings have lead to suggestions that increased functions of ACh via effects on the α7nAChR can be positive for the arthritic processes [8,11].

Based on the aspects described above, further considerations on the cholinergic system for arthritis are here focused on. These relate to considerations on vagal effects for joint function, possible interference of the ACh-degrading enzyme acetylcholinesterase (AChE) and the possibility that increased ACh influences on the α7nAChR might be a promising strategy.

3. The vagus nerve in relation to arthritis

It has since several years been considered that effects via the vagal nerve can be of functional importance for the synovial tissue, not least in situations with arthritis. Thus, stimulatory effects on the vagal nerve have been show to be hampering for experimentally-induced arthritic processes [6] and paw inflammation [12]. There is on the other hand an exacerbation of the experimental arthritis after vagotomy [6,13]. The findings concerning the vagus nerve and vagotomy are unexpected as there is no vagal, nor other cholinergic, innervation in synovial tissue. One possibility that is discussed is that the effects are indirect, namely via vagal effects on other sites such as the region of the spleen [14] (see also [6]). It is well known that

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there are communications between the vagal nerve and the splenic nerve via the celiac and superior mesenteric ganglia (for a review, see [15,16]).

It is known that signaling via the vagus nerve that is leading to anti-inflammatory effects is initiated in the brainstem nuclei of the vagus nerve, secondarily leading to effects on the peripheral ganglia referred to above. This is part of the so-called inflammatory reflex whereby peripheral afferent nerves are primarily sensed, secondarily leading to efferent effects [17], in this case via the efferent part of the vagus nerve. It is well-known that the vagus nerve is a main component in the neuro-endocrine homeostasis via effects through its afferent and efferent neurons (for a review, see [2]).

From a functional point of view, it is of interest to note that ACh released from cholinergic nerves like the vagus nerve has immunomodulatory effects. These effects are considered to be anti-inflammatory [9,12]. The concept of a "cholinergic anti-inflammatory pathway" has hereby emerged [10,18], including for the synovial tissue [11]. In accordance with this, it is shown that electrical stimulation of the vagus nerve leads to an attenuation in macrophage activation [19].

It has been shown that subdiaphragmatic vagotomy in mice leads to reduced bone mass, bearing in mind that the mouse skeleton normally has a vagal innervation [1]. In a recent sudy it was shown that the severity of collagen-induced arthritis was reduced by electrical vagus nerve stimulation using a cuff electrode [20]. The cuff electrode that was used is analogous to the one used in treatment of drug-resistent epilepsy [21]. It was suggested that electrical neurostimulation via use of implanted vagus nerve stimulation cuff electrodes can be useful in treatment tests for various immune-mediated inflammatory disorders in man [20].

4. The α7nAChR in relation to arthritis

The α7nAChR is considered to be much involved in the obtaining of anti-inflammatory effects of ACh in various situations [3,22]. It is namely shown that this receptor contributes to anti-inflammatory effects of ACh in several models [12,23]. α7nAChR agonists are shown to suppress the production of various cytokines such as TNF alpha [12,22].

Based on what is described above, it is of great interest to note that the α7nAChR is present in the synovial tissue. That has been shown for the synovial tissue of patients with OA [5,8], RA [7,11] and psoriatic arthritis [7]. The findings concerning the α7nAChR have led to suggestions that interference with this receptor in clinical situations with arthritis might be useful [24,25]. α7nAChR agonists are not least suggested to be candidates as treatments for RA [26]. In accordance with such a proposal are the findings that synovial fibroblasts respond in vitro to cholinergic stimulation, via the α7nAChR, leading to a potent inhibition of proinflammatory cytokines [27]. Studies on the healing of skin wounds do also suggest that the α7nAChR is involved in the repair processes that occur for these wounds [28]. It is also shown that the α7nAChR is involved in the repair of wounds of respiratory epithelium [29].

5. AChE in relation to arthritis

The main ACh-degrading enzyme is acetylcholinesterase (AChE). The bulk of AChE of the neurons is in the axons and AChE is known to be associated with the membrane of this [30]. AChE is shown to be functional in embryonic muscle before it is accumulated at the sites of nerve-muscle contact [31]. AChE activity is also shown for a large number of non-neuronal cell types. That includes T-cells [32], fibroblasts of various locations [33], cells in lung tissue [34], cells of human gingival and esophageal epithelia [35] and embryonic stem cells [36]. AChE is also typically confined to the membranes of red blood cells [37]. Other components of the cholinergic system are also present in these cell types.

It is of relevance to notice that interference with AChE activity can be performed and that treatments for which this is done are used clinically. That includes the situations in myastenia gravis and Alzheimer´s disease. In the case of myastenia gravis, where there is an occurrence of few receptors, the treatment is of value in order to extend the effects of ACh [38]. The AChE inhibitor drugs donepezil, galantamine and rivastigmine are being tried for patients with Alzheimer´s disease [39]. In this case, where there is a reduced concentration of ACh, the point with the AChE inhibitors is to increase the concentration of the transmitter. A cholinergic deficiency is a feature that can be important for the development of the cognitive decline that occurs in Alzheimer´s disease. There are also other fields of usage of AChE inhibitors; they are e.g. used in insecticides and nerve gases.

There is very little information on the patterns of AChE activity for synovial tissue. Nevertheless, AChE activity, in parallel with other components of cholinergic function, has been clearly detected in the knee joint synovial tissue of patients with RA and OA in a study using RT-PCR methods [40]. In our laboratory, existence of AChE activity in human knee joint synovial tissue has also been observed histochemically (unpublished observations).

The most well known function of AChE is to terminate neurotransmission at the cholinergic synapses via splitting of ACh. ACh is hereby hydrolyzed into choline and acetate. The degradation is rapid. However, AChE is also known to exhibit several non-classical roles, features that are of importance when considering both the neuronal and non-neuronal cholinergic systems [41]. That includes effects on cell differentiation and synaptogenesis along the nervous system, hydrolysis of neuropeptides, and effects in heart morphogenesis (for a review, see [42]). One cell type for which AChE is highly expressed is re-epithelialising epidermal keratinocytes during in vivo healing of mouse skin [43].

The exact functions of AChE in relation to the regulations of the non-neuronal cholinergic system at its various locations in the body are somewhat unclear [3]. It may be that the magnitude of ACh degrading activity is low in tissues like airway epithelium [44,45], and in cells of the placenta [33]. How the situation is for synovial tissue remains to be defined. Nevertheless, as there indeed is an occurrence of AChE in the synovial tissue it is likely that the function of the ACh that is produced in synovial tissue is limited to the precise area where it is produced. It may well be so that up- and down-regulations of production and release of ACh in the synovial tissue are parallelled by up- and down-regulations of AChE activity. In

line with such a proposal is the finding that the immunological stimulation that leads to T-cell activation and upregulation of ACh synthesis and ACh receptor expression also leads to a marked ACh degradation [46].

Further studies on the importance and function of AChE for synovial tissue are needed in order to reveal the possible usefulness of interference with the effects of the enzyme in arthritis.

6. Concluding remarks

This review shows three aspects of the cholinergic system in relation to arthritis. It is obvious that stimulation of the vagal nerve has effects, that there is a non-neuronal cholinergic system in the synovial tissue and that there in parallel with expressions favouring ACh production also are expressions favouring ACh degradation in the synovial tissue. Although a lot of the information is related to the situation in RA, the various features of the cholinergic system are also related to the situation in OA. All these features concerning the cholinergic system highlight the relevance of further studies on the functional importance of this system for joint function, including the situation in OA.

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References

[1] Bajayo A, Bar A, Denes A, Bachar M, Kram V, Attar-Namdar M, Zallone A, Kovacs KJ, Yirmiya R, Bab I. (2012). Skeletal parasympatheitic innervation communicates central IL-1 signals regulating bone mass accrural. Proc Natl Acad Sci USA. Vol 109, pp15455-15460

[2] Bonaz B, Pico C, Sinniger V, Mayol JF, Clarencon D. (2013). Vagus nerve stimulation: from epilepsy to the cholinergic anti-inflammatory pathway. Neurogastroenterology and Motility. Vol 25, pp. 208-221

[3] Kawashima K, Fujii T. (2008).Basic and clinical aspects of non-neuronal acetylcholine: Overview of non-neuronal cholinergic systems and their biological significance. Journal of Pharmacological Sciences. Vol 106, pp. 167-173

[4] Grimsholm O, Rantapää-Dahlqvist S, Dalén T, Forsgren S. (2008). Unexpected findings of a marked non-neuronal cholinergic system in human knee joint synovial tissue. Neuroscience Letters. Vol. 442, pp. 128-133

[5] Forsgren S. The cholinergic system can be of unexpected importance in osteoarthritis. (2011). In: Rotschild BM, editor. Osteoarthritis, In Tech – Open Access Publisher

[6] van Maanen, MA, Lebre MC, van der Poll T, LaRosa GJ, Elbaum D, Vervoordeldonk MJ, Tak PP. (2009). Stimulation of nicotinic acetylcholine receptors attenuates collagen-induced arthritis in mice. Arthritis and Rheumatism, Vol.60, pp. 114-122

[7] Westman, M.; Engström, M.; Catrina, AI., Lampa, J. (2009). Cell specific synovial expression of nicotinic alpha 7 acetylcholine receptor in rheumatoid arthritis and psoriatic arthritis. Scandinavian Journal of Immunology, Vol.70, pp. 136-140

[8] Waldburger, JM.; Boyle, DL.; Pavlov, VA.; Tracey, KJ., Firestein, GS. (2008). Acetylcholine regulation of synoviocyte expression by the alpha7 nicotinic receptor. Arthritis and Rheumatism, Vol.58, pp. 3439-3449

[9] de Jonge WJ, Ulloa L. (2007). The α7 nicotinic acetylcholine receptor as a pharmalogical target for inflammation. British Journal of Pharmacology. Vol. 151, pp. 915-929

[10] Tracey, KJ. (2007). Physiology and immunology of the cholinergic antiinflammatory pathway. Journal of Clinical Investigation Vol.117, pp. 289-296

[11] Van Maanen MA, Stoof S, LaRosa G, Vervoordeldonk M, Tak PP. (2010). Role of the cholinergic system in rheumatoid arthritis: aggravation of arthritis in nicotinic acetylcholine receptor α7 subunit gene knockout mice. Annals of Rheumatic Disease. Vol. 69, pp. 1717-1723

[12] Borovikova LV, Ivanova S, Zhang M, Yang H, Botchina GI, Watkins LR, Wang H, Abumrad N, Eaton JW, Tracey KJ. (2000). Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Vol. 405, pp. 458-462

[13] Li T, Zuo X, Wang Y, Zhuang H, Zhang L, Zhang H, Xiao X. (2010). The vagus nerve and nicotinic receptors involve inhibition of HMGB1 release and early pro-inflammatory cytokines function in collagen-induced arthritis. Journal of Clinical Immunology. Vol. 30, pp. 213-220

[14] Huston JM, Ochani M, Rosas-Ballina M, Liao H, Ochani K, Pavlov VA, Gallawitsch-Puerta, Ashok M, Czura CJ, Foxwell B, Tracey KJ, Ulloa L. (2006). Splenectomy inac-

tivates the cholinergic antiinflammatory pathway during lethal endotoxemia and polymicrobial sepsis. Journal of Experimental Medicine. Vol. 203, pp. 1623-1628

[15] Koopman FA, Stoof SP, Straub RH, van Maanen MA, Vervoordeldonk MJ, Tak PP. (2011). Restoring the balance of the autonomic nervous system as an innovative approach to the treatment of rheumatoid arthritis. Molecular Medicine. Vol. 17, pp. 937-948

[16] Rosas-Ballina M, Olofsson PS, Ochani M, Valdes-Ferrer SI, Levine YA, Reardon C, Tusche MW, Pavlov VA, Andersson U, Chavan S, Mak TW, Tracey KJ. (2011). Acetylcholine-synthesizing T cells relay neural signals in a vagus nerve circuit. Science. Vol 334, pp. 98-101

[17] Andersson U, Tracey KJ. (2012). Reflex principles of immunological homeostasis. Annual Reviews of Immunology. Vol 30, pp. 313-335

[18] Pavlov, VA., Tracey, KJ. (2005). The cholinergic anti-inflammatory pathway. Brain Behaviour Immunology, Vol.19, pp. 493-499

[19] de Jonge, W, van der Zanden E, The FO, Bijlsma MF, van Westerloo DJ, Bennink RJ, Barthoud HR, Uematsau S, Akira S, van den Wijngaard RM, Boeckxstaens GE. (2005). Stimulation of the vagus nerve attenuates macrophage activation by activating the Jak2-STAT3 signaling pathway. Nature Immunology, Vol.6, pp. 844-851

[20] Levine Y, Koopman F, Faltys M, Caravaca A, Bendele A, Zitnik R, Vervoordeldonk M, Tak PP. (2014). Neurostimulation of the cholinergic anti-inflammatory pathway ameliorates disease in rat collagen-induced arthritis. Plos ONE 9(8): e104530. doi: 10.1371

[21] Beekwilder JP, Beems T. (2010). Overview of the clinical applications of vagus nerve stimulation. Journal of Clinical Neurophysiology. Vol 27, pp. 130-138

[22] Wang H, Yu M, Ochani M, Amella CA, Tanovic M, Susarla S, Li JH, Wang H, Yang H, Ulloa L, Al-Abed Y, Czura CJ, Tracey KJ. (2003). Nicotinic acetylcholine receptor alpha7 subunit is an essential regulator of inflammation. Nature. Vol. 42, pp. 384-388

[23] Ulloa, L. (2005). The vagus nerve and the nicotinic anti-inflammatory pathway. Nature Review of Drug Discovery, Vol.4, pp. 673-784

[24] Pan, XH.; Zhang, J.; Yu, X.; Qin, L.; Kang, L., Zhang, P. (2010). New therapeutic approaches for the treatment of rheumatoid arthritis may rise from the cholinergic anti-inflammatory pathway and antinociceptive pathway. ScientificWorldJournal, Vol.10, pp. 2248-2253

[25] Zhang, P.; Qin, L., Zhang, G. (2010). The potential application of nicotinic acetylcholine receptor agonists for the treatment of rheumatoid arthritis. Inflammation Research, publ online 2010, 59(6):415-7, DOI 10.1007/s00011-010-0160-1

[26] Bruchfeld A, Goldstein RS, Chavan S, Patel NB, Rosas-Ballina M, Kohn N, Qureshi AR, Tracey KJ. (2010). Whole blood cytokine attenuation by cholinergic agionists ex

vivo and relationship to vagus nerve activity in rheumatoid arthritis. Journal of Internal Medicine. Vol. 268, pp. 94-101

[27] Das UN. (2011). Can vagus nerve stimulation halt or ameliorate rheumatoid arthritis and lupus? Lipids Health Disease. Vol 10: 19

[28] Fan YY, Yu TS, Wang T, Liu WW, Zhao R, Zhang ST, Ma WX, Zheng JL, Guan DW. (2011). Nicotinic acetylcholine receptor alpha7 subunit is time-dependently expressed in distinct cell types during skin wound healing in mice. Histochemistry and Cell Biology, publ online, 135(4): 375-87 DOI: 10.1007/s00418-001-0798-y

[29] Tournier JM, Maoche K, Coraux C, Zahm JM, Cloez-Tayarani I, Nawrocki-Raby B, Bonnomet A, Burlet H, Lebargy F, Polette M, Birembaut P. (2006). Alpha3alpha5beta2-nicotinic acetylcholine receptor contributes to the wound repair of the respiratory epithelium by modulating intracellular calcium in migrating cells. American Journal of Pathology, Vol.168, pp. 55-68.

[30] Papp M, Bozsik G. (1966). Comparison of the cholinesterase activity in the reticular formation of the lower brain stem of cat & rabbit. Journal of Neurochemistry. Vol. 12, pp. 697-703

[31] Ziskind-Conhaim L, Inestrosa N, Hall Z. (1984). Acetylcholinesterase is functional in embryonic rat muscle before its accumulation at the sites of nerve-muscle contact. Developmental Biology. Vol. 103, pp. 369-377

[32] Szelenyi J, Baratha E, Hollan S. (1982). Acetylcholinesterase activity of lymphocytes: an enzyme characteristic of T-cells. British Journal of Haematology. Vol. 150, pp. 241-245

[33] Sastry BV, Sadavongvivad C. (1979). Cholinergic systems in non-nervous tissues. Pharmacological Review. Vol. 30, pp. 65-132

[34] Adler M, Reutter SA, Moore DH, Filbert MG. (1991). Regulation of acetylcholine hydrolysis in canine tracheal smooth muscle. European Journal of Pharmacology. Vol. 205, pp. 73-79

[35] Nguyen VT, Hall LL, Gallacher G, Ndoye A, Jolkovsky DL, Webber RJ, Buchli R, Grando SA. (2000). Choline acetyltransferase, acetylcholinesterase, and nicotinic acetylcholine receptors of human gingival and esophageal epithelia. Journal of Dental Research. Vol. 79, pp. 939-949

[36] Paraoanu LE, Steinert G, Koehler A, Wessler I, Layer PG. (2007). Expression and possible functions of the cholinergic system in a murine embryonic stem cell line. Life Sciences. Vol. 80, pp. 2375-2379

[37] Bartels CF, Zelinski T, Lockridge O. (1993). Mutation at codon 322 in the human acetylcholinesterase (ACHE) gene accounts for YT blood group polymorphism. American Journal of Human Genetics. Vol. 52, pp. 928-936

[38] Taylor P. (1996). Anticholinesterase agents. In "The Pharmalogical Basis of Therapeutics". Eds; Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG. New York, McGraw-Hill, pp. 161-176

[39] Pohanka. (2011). Alzheimers disease and related neurodegenerative disorders: implication and counteracting of melatonin. Journal of Applied Biomedicine. Vol. 9, pp. 185-196

[40] Schubert J, Beckmann J, Hartmann S, Morhenn H-G, Szalay G, Heiss C, Schnettler R, Lips KS. (2012). Expression of the non-neuronal cholinergic system in human knee synovial tissue from patients with rheumatoid arthritis and osteoarthritis. Life Sciences. Vol. 91, pp. 1048-1052

[41] Silman I, Sussman JL. (2005). Acetylcholinesterase: classical and non-classical functions and pharmacology. Current Opinion in Pharmacology. Vol. 5, pp. 293-302

[42] Tripathi A, Srivastava UC. (2008). Acetylcholinesterase: A versatile enzyme of nervous system. Annals of Neuroscience. Vol. 15, no 4

[43] Anderson A, Ushakov D, Ferenczi M, Mori R, Martin P, Saffell J. (2008). Morphoregulation by acetylcholinesterase in fibroblasts and astrocytes. Journal of Cellular Physiology. Vol. 215, pp. 82-100

[44] Degano B, Prevost MC, Berger P, Molimard M, Pontier S, Rami J, Escamilla R. (2001). Estradiol increases the acetylcholine-elicited airway reactivity in ovariectomized rats through an increase in epithelial acetylcholinesterase activity. American Journal of Respiration and Critical Care Medicine. Vol. 16, pp. 1849-1854

[45] Kummer W, Lips KS, Pfeil U. (2008). The epithelial cholinergic system of airways. Histochemistry and Cell Biology. Vol. 130, pp. 219-234

[46] Kawashima K, Fujii T, Moriwaki Y, Misawa H. (2012). Critical roles of acetylcholine and the muscarinic and nicotinic acetylcholine receptors in the regulation of immune function. Life Sciences. Vol. 91, pp. 1027-1032

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