Neuroscience 573 (2025) 518–520

Contents lists available at ScienceDirect

Neuroscience

journal homepage: www.elsevier.com/locate/nsc

Review

Disentangling the Gordian Knot of parasympathetic innervations in arthritic joint

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ARTICLE INFO

Keywords:
Synovial joints
Cholinergic profiles
Parasympathetic system
Neural remodelling
Arthritis

ABSTRACT

Healthy synovial joints receive innervations exclusively from sensory and sympathetic axons. In arthritis, however, they acquire cholinergic innervations with parasympathetic effects. The origin of cholinergic fibres in inflamed joints remains elusive. Based on clinical and preclinical evidence, we propose two models explaining their rise: (1) through sprouting and invasion of cholinergic sympathetic or parasympathetic axons from the periosteum of juxta-articular bones and (2) via phenotypic switch of intrinsic sympathetic (norepinephrinergic) fibres of synovial joints to cholinergic. The widely acknowledged anti-inflammatory and immunosuppressants effects of parasympathetic drive suggests a protective role of the newly aquired cholinergic innervations in arthritic joints.

Introduction

Anatomically, the nerve supply of healthy synovial joints involves sensory and autonomic fibres. Sensory innervations, of which >80 % are nociceptive, include thin myelinated A-δ and unmyelinated C fibres of the synovium, articular capsule, ligaments and subchondral bone with periosteum (Schaible and Grubb, 1993). The remaining sensory axons represent thick proprioceptive A-β fibres with Ruffini, Golgi and Pacini terminals (Halata et al., 1985; Juneja et al., 2018). The autonomic innervation of healthy synovial joints appears to be supplied entirely by tyrosine-hydroxylase (TH) positive fibres, releasing norepinephrine with sympathetic effects (Stangl et al., 2015). Unlike distributed sensory innervations, most sympathetic profiles in synovial joints line up along feeding blood vessels (Halata et al., 1985). Histochemical examination of healthy synovial joints for specific markers failed to detect cholinergic fibres or nerve terminals (Fig. 1**a, c**), consistent with the absence of parasympathetic effects therein (Stangl et al., 2015; Courties et al., 2017).

Remarkably, cholinergic fibres prevail in the neural landscape of inflamed synovial joints (Fig. 1**b, d**) (Stangl et al., 2015). Preclinical and clinical studies show that the density of cholinergic fibres in arthritic joints can correlate with the severity of inflammation, with their level rising in moderately affected tissue, while in severely inflamed areas, they undergo degeneration. Given the anti-inflammatory and immunosuppressive effects of parasympathetic drive (Koopman et al., 2017; Marsal et al., 2021), the rise of cholinergic innervations in arthritic joints might have an ameliorative influence, possibly via activation of nicotinic receptors of local macrophages, fibroblast-like synoviocytes and other local cells (Koopman et al., 2017; Lauwers et al., 2021). Immunohistochemical evidence from animal and human studies suggests two different models of the rise of cholinergic innervations in the inflamed synovial joint: (1) through sprouting and invasion of parasympathetic and cholinergic sympathetic axons of the periosteum into the inflamed joint (Fig. 1**a, b**) and (2) via phenotypic switch of intrinsic TH-positive sympathetic axons into cholinergic (Fig. 1**c, d**). In the context of current discussion, it is worth mentioning the well-established examples of anatomically sympathetic innervations of sweat glands and periosteum, which are immunoreactive to cholinergic markers and release acetylcholine (Gadomski et al., 2022; Hu et al., 2018).

Immunohistochemical studies demonstrate that in rat and mouse

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https://doi.org/10.1016/j.neuroscience.2025.03.061
Received 22 February 2025; Accepted 25 March 2025
Available online 1 April 2025

lower limbs, cholinergic axons of the periosteum originate from the central parasympathetic nucleus of the lower spinal cord (Bajayo et al., 2012; Eimar et al., 2013). By applying retrograde tracing techniques, it was shown that VAChT-positive fibres in the distal femoral metaphysis of the trabecular bone have their preganglionic neurons in the sacral parasympathetic centre (Bajayo et al., 2012). Interestingly, in developing rats, VIP-immunoreactive cholinergic fibres are observed first on the fourth postnatal day, starting at the diaphyseal periosteum, followed by expansion to metaphyseal and sub-junctional epiphyseal areas on the eighth day (Sisask et al., 1996). These observations support the notion that periosteal cholinergic innervations might provide a source for new cholinergic fibres of arthritic joint with parasympathetic effects, with released by the inflamed tissue neurotrophins and growth factors stimulating elongation and invasion of periosteal axonal sprouts into the affected joint area (Fig. 1**b**).

The second potential mechanism of the rise of cholinergic innervations in inflamed joints appears to involve reprogramming of inherent TH-positive sympathetic fibres (Fig. 1**c, d**). In vitro and developmental studies show that such phenotypic switch could be triggered by ciliary neurotrophic factor (CNTF), interleukins and progesterone (Stangl et al., 2015; Gadomski et al., 2022; Slonimsky et al., 2003). The possibility of the switch of catecholaminergic sympathetic into cholinergic profiles has also been supported by data from studies demonstrating the prevalence of anatomically sympathetic cholinergic axons in bones during early development, with their sharp drop by birth, followed by complete loss, which correlates with proportionate enhancement of TH-positive sympathetic profiles over the same developmental period (Gadomski et al., 2022). In the bone of mice, such a phenotypic switch can be triggered by the rise in interleukins caused by inflammation and exercise, which appears to stimulate bone formation and tissue regeneration (Gadomski et al., 2022). Mechanistic studies showed that the cocktail of cytokines and immune factors released in the inflamed joint could trigger a switch of TH-positive catecholaminergic fibres into cholinergic (Stangl et al., 2015; Guo et al., 2018). This process involves alterations in epigenetic mechanisms affecting the activity of multiple genes and regulatory proteins (Basu and Tiwari, 2021; Ciceri et al., 2024). Interestingly, partial reprogramming of sympathetic neurons has also been reported, leading to the rise of dual-function

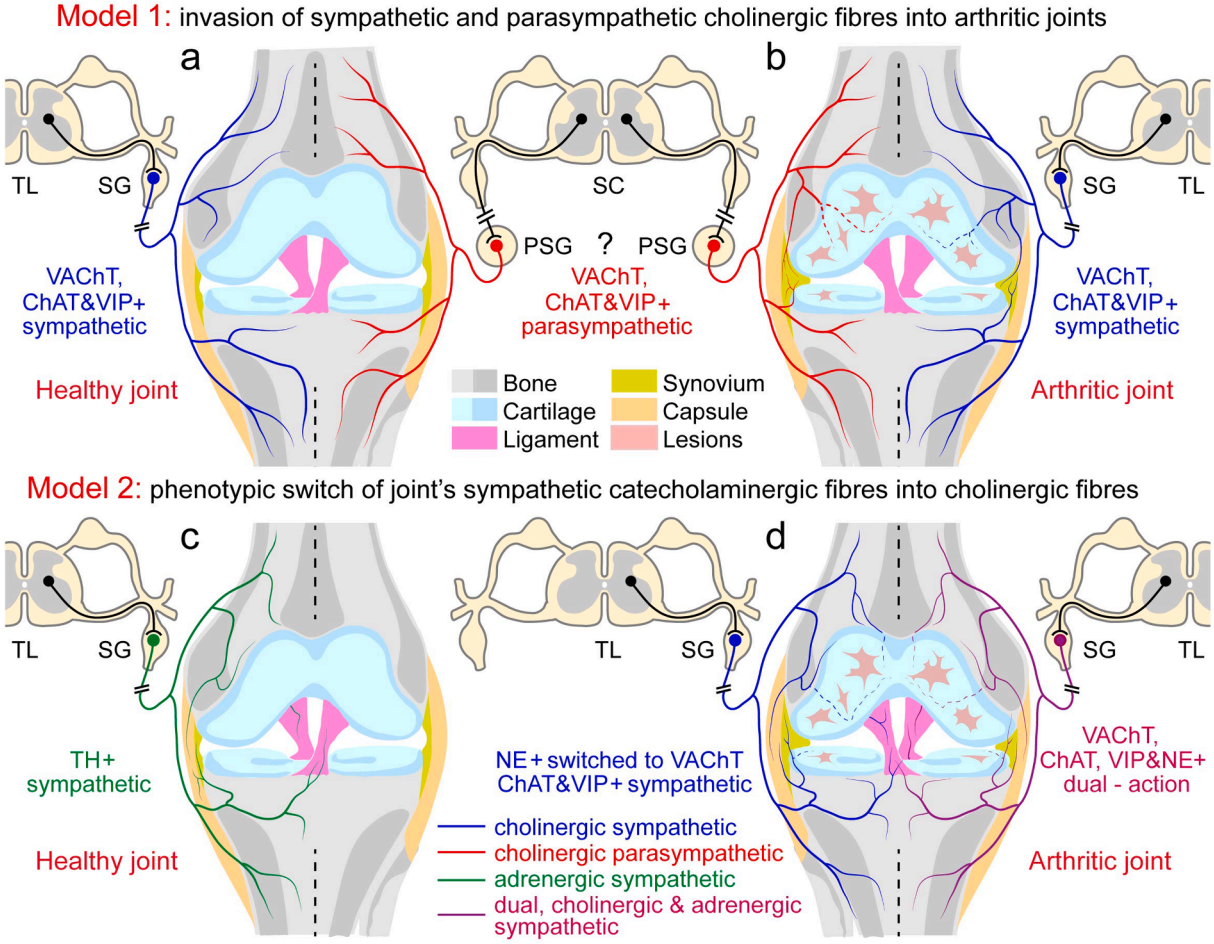

Fig. 1. Two suggested models of the rise of cholinergic innervations in arthritic joints. For illustration purpose, only autonomic innervations are schematised. Model 1: **(a, b)** A healthy synovial joint is devoid of choline acetyltransferase (ChAT) -, vesicular acetylcholine transporter (VAChT) - and vasoactive intestinal peptide (VIP) - reactive cholinergic fibres of sympathetic and parasympathetic systems, which are present in the periosteum of articulate bones **(red and blue, a)**. In inflamed joints, cholinergic fibres of the periosteum of articulate bones undergo sprouting and growth with collaterals invading the synovial tissue and possibly cartilage and other structures of the arthritic joint **(red and blue, b)**. Model 2: **(c, d)** A healthy joint is supplied by TH-positive adrenergic (norepinephrinergic, NE sympathetic) fibres **(c)**. In inflamed joints, change of the microenvironment induces reprogramming of sympathetic neurons, transforming TH-positive profiles into VAChT, ChAT and VIP immunoreactive cholinergic fibres, or into dual TH- and cholinergic marker positive innervations **(d)**. Although cholinergic innervations are reported predominantly in inflamed synovium, reprograming sympathetic fibres can lead to their sprouting and growth into various compartments of joints (dashed lines indicate new collaterals invading into the synovial joint). TL-Thoracolumbar segment of the spinal cord; SC-Sacral segment of the spinal cord; SG-Sympathetic Ganglion; PSG-Parasympathetic Ganglion; NE-Norepinephrine. Question mark (?) at PSG indicates that the anatomical location of the parasympathetic ganglion supplying cholinergic innervations to the lower limb - knee joints remains unknown. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

catecholaminergic and cholinergic fibers immunoreactive to TH and cholinergic markers (Wolinsky and Patterson, 1983). It is worth stressing that in inflamed synovial joints, the acquisition of cholinergic phenotype is not limited to neurons, as evident from the increase of cholinergic markers in fibroblast-like synoviocytes and local macrophages (Lauwers et al., 2021; Schubert et al., 2012).

To conclude, unlike healthy synovial joints devoid of parasympathetic cholinergic innervations, inflamed synovial joints show distinct cholinergic profiles with likely parasympathetic effects. The origin of cholinergic innervations in inflamed joints remains controversial, with the remodelling mechanisms warranting in-depth research and consideration of multiple regulatory factors and signalling mechanisms. In the broader context of neuroinflammation and neural remodelling, discussed herein processes might be at play also in other chronically inflamed organs and tissues, including in cancer and in the brain affected by neurodegenerative and psychiatric diseases. The telltale inflamed joints, thus, in addition to exposing previously unrecognised neuroplastic changes, may assist in disentangling the Gordian Knot of neuroinflammation in the broader context to set a new course for research and therapy.

Author contributions

Conception and design: SM, SB, SVO; Drafting, revising and critical comments: DN, SB, SVO; Illustrations SM, SVO; Review and approval of the final version: SM, SB, SVO.

CRediT authorship contribution statement

Sharon Mathew: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Stergios Boussios:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing. **Saak V. Ovsepian:** Conceptualization, Funding acquisition, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The project was supported by the University of Greenwich, Innovation Award 2024 and the Research Excellence Framework Program.

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