Skeletal interoception: an emerging area for musculoskeletal research

*Zhidao Xia**

Little is known about the relationship between bone and brain; however, accumulated clinical and experimental evidence suggests that there is crosstalk and a bilateral dependence between the two organs.[1] A recent review article published in *Cell Metabolism* highlights the importance of skeletal interoception and signifies a new era for musculoskeletal research.[2]

The concept of interoception was originally introduced by Sherrington in 1906 and it has been more intensively studied and refined over recent decades.[2] Interoception can be described as the sense of the internal state of the body through monitoring, communication, integration and regulation between the central nervous system (CNS) and peripheral organs.

Skeletal interoception research aims to understand how skeletal sensory nerves perceive the states of bone tissue, in which the ascending signals are sent from bone tissue via sensory nerves, dorsal root ganglia, and superficial dorsal horns of the spinal cord to the CNS, specifically the hypothalamus. After interpretation, the descending signals from the CNS regulate bone and adipose metabolism via neuroendocrinal regulation and the sympathetic nervous systems (using norepinephrine).[2]

The key skeletal interoceptive factors are prostaglandin E2 (PGE2) and its receptor, prostaglandin E receptor 4 (EP4). Under physiological conditions, PGE2 secreted by osteoblasts in bone tissue activates skeletal sensory neurons through EP4 as an ascending pathway to regulate bone formation. During osteoclastic bone resorption, osteoblasts secrete PGE2 when bone density and mechanical strength decrease. PGE2 binds to EP4 on sensory nerve fibres, and the signals are relayed to the hypothalamus through afferent nerves. Consequently, the expression of hypothalamic neuropeptide Y is downregulated to induce lipolysis of adipose tissue, and sympathetic tone is tuned down for osteoblastic bone formation.[3]

Recent anatomic, pharmacologic, and genetic studies on β-adrenergic receptor signalling in bone cells has unveiled one of the main links between the CNS and the skeleton.[4] The sympathetic nervous system regulates vessel contraction and relaxation by communicating with pericytes and smooth muscle cells through the key neurotransmitter norepinephrine. By inhibiting sympathetic activity of sinusoids in bone tissue the bone formation process is enhanced.[5] This is important for skeletal homeostasis, in which bone resorption and bone formation are coupled and balanced to maintain stable bone mass and mineral density.

It is generally believed that the causes, genetic backgrounds and pathologic processes of osteoporosis, osteoarthritis, and lower back pain are very different; however, new evidence suggests that these pathological conditions are all closely related to skeletal interoception, especially in the case of bone pain.[2, 3]

Innervation density in bone tissue decreases with age.[6] Aging-related reduction in the number of sensitive nerves in bone may contribute to bone loss and osteoporosis.[7] In comparison to normal bone, a typical porotic bone structure due to excessive osteoclastic bone resorption can also be observed in the region of the endplate in low back pain, and in subchondral bone in osteoarthritis, ankylosing spondylitis and rheumatoid arthritis.[3] Overexpression of PGE2 during inflammation and excessive bone resorption induces hypersensitivity of sensory nerves by activating EP4; meanwhile increased numbers of osteoclasts secrete Netrin-1 to induce new sensory nerve innervation into regions of bone resorption. This pathologic process is suggested to be the main mechanism that contributes to lower back pain, osteoarthritic pain, and other bone pain.[3]

As a therapeutic intervention, restoration of physiological PGE2 concentrations in skeletal tissue activates skeletal interoception to induce osteoblastic bone formation, for example, to relieve low back pain, reduce vertebral endplate porosity, and modify disease progression.[3]

Institute of Life Science, Swansea University Medical School, Swansea, UK

***Corresponding author:**
Zhidao Xia,
z.xia@swansea.ac.uk

http://doi.org/10.12336/biomatertransl.2022.04.001

How to cite this article:
Xia, Z. Skeletal interoception: an emerging area for musculoskeletal research. *Biomater Transl.* **2022**, *3*(4), 237-239.

Skeletal interoception also plays a vital role in biomaterials research. After implantation, all materials are subject to local tissue reaction, biodegradation, angiogenesis and innervation. Some metal ions such as Mg^{2+}, Zn^{2+} and Cu^{2+} released from metal implants interact with macrophages to produce PGE2, activate sensory nerves via EP4 and consequently result in bone formation through the hypothalamus regulatory pathway.[8] However, some metal ions released from metal implants, for example, Co^{2+} and Cr^{3+}, may increase release of inflammatory factors and cause pain, pseudotumour and bone resorption.[9]

So far little is known about the role of the CNS in control of skeletal tissue regeneration in the case of the widespread implantation of biomaterials. It is very difficult to obtain such data from conventional *in vitro* experiments using cell lines or primary cells isolated from the body, because the cells are no longer regulated and controlled by the CNS. This highlights the paramount importance of the use of animal models in biomaterials research, which will be extremely difficult to replace with alternative methods.

Skeletal interoception in healthy and diseased bone condition can be summarized in **Figure 1**.

The crosstalk between brain and skeletal tissue is still poorly understood.[10] Nonetheless, such communication between two seemingly unrelated organs is in fact essential for the maintenance of our whole body homeostasis.[10] Further research is warranted to produce a deeper understanding of the underlying mechanisms, and to translate the research outcomes into clinical applications.

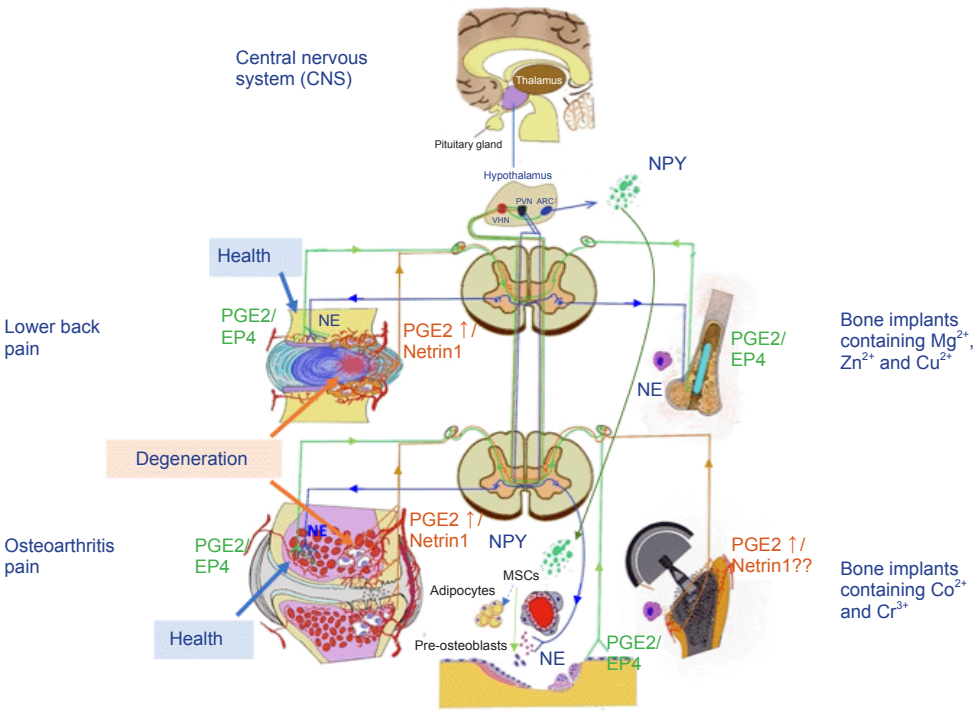

Figure 1. Skeletal interoception in healthy and diseased bone conditions. In the healthy state, when bone mass decreases, osteoblasts and bone cells release PGE2, activating EP4 on sensory nerves, and ascending signals are sent from bone tissue via sensory nerves, dorsal root ganglia, and superficial dorsal horns of the spinal cord to the CNS (green arrows), specifically in the hypothalamus. After interpretation, descending signals from the CNS regulate bone and adipose metabolism via neuroendocrinal regulation through NPY and the sympathetic nervous systems (blue arrows, NE). Bone implants containing Mg^{2+}, Zn^{2+} and Cu^{2+} activate osteogenesis also through the PGE2/EP4 pathway. Downregulation of NPY induces preosteoblasts to differentiate into osteoblasts, leading to bone formation rather than to differentiate into adipocytes to grow fat tissue. In bone degenerative conditions such as lower back pain and osteoarthritis, excessive expression of PGE2 results in angiogenesis and innervation via Netrin1 secreted by osteoclasts, and pain from hypersensitivity of sensory nerves by activating EP4 (orange arrows). CNS: central nervous system; EP4: prostaglandin E receptor 4; MSC: mesenchymal stem cell; NE: norepinephrine; NPY: neuropeptide Y; PGE2: prostaglandin E2.

Author contributions
The author reviewed the publications and prepared this viewpoint.
Financial support
None.
Acknowledgement
None.
Conflicts of interest statement
None.
Editor note: Zhidao Xia is an Editorial Board member of *Biomaterials Translational*. He was blinded from reviewing or making decisions on the manuscript. The article was subject to the journal's standard procedures, with peer review handled independently of this Editorial Board member and his research group.

1. Otto, E.; Knapstein, P. R.; Jahn, D.; Appelt, J.; Frosch, K. H.; Tsitsilonis, S.; Keller, J. Crosstalk of brain and bone-clinical observations and their molecular bases. *Int J Mol Sci.* **2020**, *21*, 4946.
2. Lv, X.; Gao, F.; Cao, X. Skeletal interoception in bone homeostasis and pain. *Cell Metab.* **2022**. doi: 10.1016/j.cmet.2022.09.025.
3. Zhen, G.; Fu, Y.; Zhang, C.; Ford, N. C.; Wu, X.; Wu, Q.; Yan, D.; Chen, X.; Cao, X.; Guan, Y. Mechanisms of bone pain: Progress in research from bench to bedside. *Bone Res.* **2022**, *10*, 44.
4. Elefteriou, F.; Campbell, P.; Ma, Y. Control of bone remodeling by the peripheral sympathetic nervous system. *Calcif Tissue Int.* **2014**, *94*, 140-151.
5. Hu, B.; Lv, X.; Chen, H.; Xue, P.; Gao, B.; Wang, X.; Zhen, G.; Crane, J. L.; Pan, D.; Liu, S.; Ni, S.; Wu, P.; Su, W.; Liu, X.; Ling, Z.; Yang, M.; Deng, R.; Li, Y.; Wang, L.; Zhang, Y.; Wan, M.; Shao, Z.; Chen, H.; Yuan, W.; Cao, X. Sensory nerves regulate mesenchymal stromal cell lineage commitment by tuning sympathetic tones. *J Clin Invest.* **2020**, *130*, 3483-3498.
6. Steverink, J. G.; Oostinga, D.; van Tol, F. R.; van Rijen, M. H. P.; Mackaaij, C.; Verlinde-Schellekens, S.; Oosterman, B. J.; Van Wijck, A. J. M.; Roeling, T. A. P.; Verlaan, J. J. Sensory innervation of human bone: an immunohistochemical study to further understand bone pain. *J Pain.* **2021**, *22*, 1385-1395.
7. Burt-Pichat, B.; Lafage-Proust, M. H.; Duboeuf, F.; Laroche, N.; Itzstein, C.; Vico, L.; Delmas, P. D.; Chenu, C. Dramatic decrease of innervation density in bone after ovariectomy. *Endocrinology.* **2005**, *146*, 503-510.
8. Qiao, W.; Pan, D.; Zheng, Y.; Wu, S.; Liu, X.; Chen, Z.; Wan, M.; Feng, S.; Cheung, K. M. C.; Yeung, K. W. K.; Cao, X. Divalent metal cations stimulate skeleton interoception for new bone formation in mouse injury models. *Nat Commun.* **2022**, *13*, 535.
9. De Haan, R.; Pattyn, C.; Gill, H. S.; Murray, D. W.; Campbell, P. A.; De Smet, K. Correlation between inclination of the acetabular component and metal ion levels in metal-on-metal hip resurfacing replacement. *J Bone Joint Surg Br.* **2008**, *90*, 1291-1297.
10. Rousseaud, A.; Moriceau, S.; Ramos-Brossier, M.; Oury, F. Bone-brain crosstalk and potential associated diseases. *Horm Mol Biol Clin Investig.* **2016**, *28*, 69-83.

Received: November 2, 2022
Revised: November 3, 2022
Accepted: November 18, 2022
Available online: December 28, 2022