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EDITORIAL

Benefit of sunlight and melatonin on back pain and inflammation

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Chronic back pain is a common reoccurring issue affecting over 570 million people globally.[1] It represents the second leading cause of disability worldwide, constituting a major welfare and economic problem.[2] Traditionally, the notion that the aetiology of chronic back pain is unknown in the majority of cases has been erroneously perpetuated. More emphasis has been put on identifying the precise pain generator in chronic back pain, with common causes including: radicular pain, facet joint pain, sacroiliac pain, pain related to lumbar stenosis, and discogenic pain.[2] Among them, intervertebral disc degeneration is one of the most common identifiable causes of chronic back pain, and previous studies show a clear link between radiological as well as microscopic intervertebral disc (IVD) degeneration and chronic back pain.[3] In a healthy adult IVD, homeostasis between extracellular matrix synthesis and degradation is controlled by growth factors and cytokines. An imbalance in the homeostasis trending towards catabolic reactions and inflammatory changes leads to structural degeneration of the IVD, likely contributing to the development of chronic back pain.[3,4] In order to overcome the burden of chronic back pain, research efforts have been focused on investigating the molecular aspects of the IVD degeneration pathophysiology along with novel therapeutic approaches, such as Suramin (a medication normally used to treat African sleeping sickness and river blindness).[5]

In this month's edition of *Bone & Joint Research,* two studies present the role of inflammation on human IVD cells. Ruiz-Fernández et al[6] demonstrated that monomeric CRP (mCRP) increases nitric oxide synthase 2 (NOS2), cyclooxygenase-2 (COX2), matrix metalloproteinase 13 (MMP13), vascular cell adhesion protein 1 (VCAM1), interleukin 6 (IL-6), interleukin 8 (IL-8), and lipocalin 2 (LCN2) expression in annulus fibrosus (AF) cells and in the human nucleus pulposus (NP) immortalized cell lines, revealing for the first time functional activity of mCRP in healthy and degenerative human AF and NP disc cells. The authors highlight that mCRP induces sustained multigenic inflammatory responses in healthy tissues without previous exposure to a pro-inflammatory micro-environment. The study by Ruiz-Fernández et al[6] shows that the effect of mCRP in healthy and degenerative AF cells is mediated by phosphoinositide 3-kinase (PI3K), extracellular signal-regulated kinase 1/2 (ERK 1/2), and Nuclear Factor-kappaB (NF-κβ) p65 signalling pathways. Another important aspect of this research is that mCRP has multiple cell targets and that the above mCRP mediators are activated in a similar manner both in healthy and degenerative AF disc cells, confirming that mCRP action does not depend on a previous inflammatory state. Overall, mCRP induces the expression of multiple pro-inflammatory and catabolic factors in human IVD cells. This finding suggests that even in healthy tissues, systemic inflammation can have a molecular influence on IVD tissues and, over the span of a lifetime, it is likely to have a degenerative effect. On the other hand, local mechanical loading from inappropriate posture or body habitus can also contribute to pro-inflammatory processes impacting IVD degeneration.[7]

In a review by Molinos et al,[8] several techniques aimed at decreasing IVD inflammation have been discussed including injectable molecules, such as interleukin 1 (IL-1) inhibitors or tumour necrosis factor alpha (TNF-α) blockers.[8,9] Gene therapy based on transforming growth factor beta 1 (TGF-β1) transfection of rabbit IVD cells shows potential to enhance proteoglycan synthesis and, therefore, reverse degenerative processes.[10]

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Nevertheless, both techniques are expensive, and their application in the wider general public to decrease IVD degeneration is unrealistic and still poses many risks associated with side effects of the therapy. In this line of research, the anti-inflammatory and protective properties of melatonin on nucleus pulposus cells (NPCs) were described by Ruiz-Fernández et al[6] in this month's edition of *Bone & Joint Research*.

Melatonin is secreted principally by the pineal gland at night under normal environmental conditions, controlling the sleep-wake cycle.[11] The role of melatonin on human health has been a topic of recent research interest, with studies highlighting that sunlight and melatonin increase health and lifespan.[12,13] The study by Bai et al[14] is the first to highlight that NPCs derived from patient intervertebral discs express melatonin receptors and their activation decreases cellular pyroptosis, the inflammatory cell death process, induced by reactive oxygen species. Pretreatment with 50 nM of melatonin for 24 hours before treatment of hydrogen peroxide significantly upregulated the expression of nuclear factor-erythroid 2-related factor 2 (Nrf2) transcription factor and downregulated the pyroptosis-related protein NLRP3, cleaved casp-1, and cleaved IL-1β. Furthermore, the expression of Nrf2 was altered when the melatonin receptor was activated or inhibited, revealing that Nrf2 was downstream of the melatonin receptor. In this line of research, the study by Bai et al[14] demonstrated that the protective effect of melatonin on pyroptosis depends on the Nrf2 upregulation. Importantly, by showing for the first time the presence of melatonin receptors MT-1A-R in human NPCs, Bai et al[14] clarified that melatonin functions via the melatonin receptor. Overall, by elucidating melatonin's significant role in cellular response to inflammation, which contributes to tissue destabilization and back pain, there is a hope to streamline larger future efforts investigating population sunlight-based interventions. The therapeutic and beneficial effect of sunlight and melatonin is widely documented in the literature, such as reducing the risk of dementia as well as reducing postoperative pain and increasing recovery.[15,16] Melatonin has even been reported to affect the degree of osseointegration of titanium implants.[17] Danilov and Kurganova[18] also discuss the involvement of melatonin efficacy in relation to pain syndromes. In a similar vein, other studies have shown that bright light therapy, even in low doses, improves perceived pain intensity in patients who suffer from chronic back pain.[19]

In conclusion, chronic back pain is a major global problem and inflammation of IVD seems to be at the centre of it, however the pathophysiology of disc degeneration, the epigenetics, and therapeutic approaches remain unclear. Nevertheless, the papers in this month's edition of *Bone & Joint Research* show a link between the susceptibility to inflammatory changes, IVD degeneration, and the anti-inflammatory role of melatonin in IVD. Increasing exposure to freely accessible sunlight can potentially be a consistent, cost-effective, and clinically acceptable method in preventing chronic back pain and in increasing quality of life in the ageing population.

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