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Neuropeptides and Osteoarthritis Pathology - a Portrait of their Potential Disease Impacts, and Treatable Non Pharmacologic Linkages

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Abstract

Osteoarthritis, a major cause of progressive and chronically disabling pain and inflammation among older adults, may implicate a variety of neural influences that are often overlooked. This overview inquires if recent publications on this topic from the vantage point of neuropeptides, short-chain sensory associated molecules that influence neural and chemical transmission including pain, can mediate osteoarthritis joint damage. If so, can one or more of these peptide molecules or their receptors be targeted favorably?. In this regard, peer reviewed data that extended from 1980-2025 affirm diverse neuropeptides located in nerve terminals in the CNS and periphery have a widespread ability to impact neural transmission, modulation, and signaling functions as well as joint damage and possible repair. While biological solutions remain largely ineffective, unsafe, or untested in this regard, we propose some forms of physical therapy as well as efforts to foster a state of wellbeing may be helpful, and should be carefully studied.

Keywords: Articular Cartilage, Inflammation, Neuro peptides, Osteoarthritis, Pain, Substance P, Prevention, Treatment

Introduction

Osteoarthritis, a major cause of chronic disabling pain among older adults has long been considered a biomechanically-derived non-inflammatory form of arthritis associated with aging that largely involves the progressive destruction of the articular cartilage lining of one or more freely moving joints such the knee and ankle joints [1,2]. Often receiving less attention than other more acute forms of arthritis, the disease-often considered irreversible and inevitable-is a complex one where its underlying causes remain understudied, obscure, confusing, and often in question, despite years of devoted research. Recent findings however, imply that in addition to age and the impact of mechanical disruption of one or more increasingly vulnerable joints, various nerve alterations may contribute to pain [2,3] plus the emergence of associated pathological inflammatory mechanisms that involve the synovial membrane lining the joint, along with those that can arise in other joint structures such as the bone, menisci, ligaments, tendons, and muscles [1-6]. Indeed, it appears a group of small sensory molecules or neuropeptides such as those denoted calcitonin gene-related peptide (CGRP) and substance P (SP) and present in the subchondral bone are closely linked to osteoarthritis structural bone changes as well as subsequent cartilage degradation and can act to both excite nerve transmission or decrease selected neural responses [1, 3].

The current review builds on an earlier set of studies that examined what is known about neuropeptides and that can influence behavior, and mood, as well as pain, and may be influenced by exposure to persistent or unanticipated stressful situations [7]. Moreover, if not ameliorated, their observed harmful influences on inflammatory mechanisms may have a strong bearing on the spread of osteoarthritis-induced joint pain and articular cartilage destruction [8,9] In the face of stress, there may also be a failure to excite key possible protective growth factor derivatives in the central nervous system (CNS) that might aid in repairing damaged cartilage [2, 3]. These complex interactions, while not always acknowledged, where studied, they appear highly important to continue to examine and unravel, especially if interventions to target the release of neuropeptides can favorably attenuate articular cartilage destruction mechanisms as believed [3] while serving as a target for fostering reparative interventions of nerves as well as vascular structures in this regard.

Osteoarthritis suffering can be immense and is a chronic condition that is rising rapidly in the older population in light of the lack of progress in addressing its pain and disability successfully and safely However, it appears there is increasing importance being attributed to viewing the disease as an inflammatory one wherein its pain underpinnings reflect a host of neural related pathologies where one or more neuropeptide mechanisms may be implicated.

Significance

Osteoarthritis remains the most prevalent chronic disease disabler of older adults and is one where the disease is rarely reversed. At the same time producing what seems to be 'irreversible' joint damage, and pain often of increasing numbers of joints, very few remedies for ameliorating any stage of this progressive disease prevails, despite years of research. All promising areas of research in this regard are thus of great interest to explore as well as highly desired especially by those who seek to advance successful health outcomes across the lifespan for those many aging adults at risk for osteoarthritis. To this end, the idea of examining the osteoarthritis disease cycle through a neurological lens, rather than solely through an age-associated biomechanical degenerative disease lens has been proposed for some time. In particular, one important aspect of current research that has been studied for more than 40 years [3-10] is the diverse role of neuropeptides, a class of small proteins involved in neural transmission and secretary processes [10] that may mediate joint pain and inflammation.

Indeed, as touted for some time as a highly worthy topic for examination [2, 4, 7, 11-14], this neural oriented line of inquiry remains one that could open the doors to a better understanding of osteoarthritis cartilage metabolism and biology, plus the pathology of progressive osteoarthritis. In addition to possible intervention implications, as far back as 2008, it was argued that in the context of the resolution of inflammation and induction of immune tolerance essential to stabilize immune homeostasis alone one may be able to understand the urgent need for efforts to avert or limit the occurrence of inflammation, for example, after an injury or in the face of repeated trauma as is found in osteoarthritis [15].

Exploring this topic is of great relevance as research is showing osteoarthritis is a complex and increasingly prevalent condition, and one affecting an estimated 600 million people worldwide and significantly, as well as disabling them and markedly reducing their quality of life. In particular, as opposed to earlier concepts of the disease, it appears increasingly that understanding osteoarthritis as both an inflammatory and neurological disease while presenting challenges for diagnosis, offers the possibility of being able to mitigate its especially degrading neuroactive effects and possible neuropathic pain. This process, in turn appears to have a possible additionally adverse impact on diverse neuropeptide systems and neural transmission within the spinal cord, as well as the autobomic nervous system and joint free nerve endings and somatosensory actions.

Methods

To achieve the overall aims of the present review, and to ascertain whether neuropeptides are indeed clinically relevant in the context of osteoarthritis development and progression we examined pertinent articles listed on PUBMED, PubMed Central, and Google Scholar that appeared to inform about neuropeptides and osteoarthritis and/or articular cartilage pathology.

Since [7,12,13] have provided salient reviews on this topic, only articles published in the last few years were sought specifically. This research material was not restricted to any particular animal model or explants and both preclinical, as well as clinical data were considered relevant as the literature is not voluminous considering there are over 600 possible peptides derived from 29 prohormone precursors that may be implicated, in particular those being substance P and peptides derived from proenkephalin, calcitonin gene-related peptide, and somatostatin. These neuropeptides in turn are challenging to study in isolation but are of high interest because they may serve as targets for new therapeutic interventions in neurological pain control efforts, as well as articular cartilage destruction and repair.

As a result, only a narrative overview of recent peer reviewed English language full length publications is provided herein, and articles not referring to neuropeptides and/or osteoarthritis in some way, as well as incomplete reports, were excluded.

Results

Search results between January 1, 1970-November 20, 2025 show the following numbers of potential publications in response to a topic search on PUBMED (Table 1).

Table 1

Key Search Terms	PUBMED [Nov 24/25]
Neuropeptides	387, 404
Osteoarthritis	133, 767
^Neuropeptides + osteoarthritis	564
Neuropeptides + articular cartilage	237

Note: ^These data do not accurately reflect the topic information sought, and include articles on anterior cruciate ligament injury, osteoarthritis model validation, stem cells, obesity, diabetes, sleep, cancer, and rheumatoid arthritis.

General Observations

Of the many valid studies, there are clearly many that currently confirm that neuropeptide signaling molecules [10] located in unmyelinated free nerve endings in joints, plus the subchondral bone and synovia of freely moving joints, as well as in the central nervous system [5,13,14] are inflammatory mediators as well as neurotransmitters. While their actions may help to offset cartilage senescence and harmful oxidative intra cellular stresses [14,15] others such as substance P, calcitonin gene-related peptide, vasoactive intestinal peptide and neuropeptide Y are generally deemed the major neuropeptides involved in the generation of joint pain, rather than serving a protective role. Others may serve a protective neuropeptife role and show an affinity to being able to revive degrading chondrocyte aging manifestations [14]. On the other hand, neuropeptides can also serve as vasodilators [15] that reportedly potentiate a variety of chemotactic agents that can promote joint tissue inflammation.

In this regard, the interplay between these aforementioned neuropeptides and others and especially their influence on destructive enzymes or cytokines appears to underpin the mechanisms whereby mechanical or structural stimuli and others are evoked, transmitted and modulated and finally perceived as joint damage manifestations. That is, emerging evidence indicates that there is a close interaction between the different neuropeptides located in various joint structures such as the CNS and spinal cord, subchondral bone, synovium and articular cartilage and menisci that may influence the process of load adaptation found in the context of joint injury, and inflammation, as well as osteoarthritis associated joint pain [1,5,16].

Research also shows many cells localized to the articular cartilage tissue itself express receptors for a variety of neuropeptide molecules,

such as substance P, thus implying the chondrocyte itself can contribute to osteoarthritis chronic pain production [17]. Moreover, the release of neuropeptides from chondrocytes may impair cartilage metabolism of high import in the context of attenuating inflammatory sources of osteoarthritis derangement and the restoration of optimal cartilage metabolism. Alternately, left unchecked much damage as depicted below in Figure 1 can be predicted in this regard.

Evidence supporting the interactions depicted in Figure 1 stem from several key publications. These collectively reveal that unlike early relatively universal beliefs about osteoarthritis as a non inflammatory arthritic disease, a more informed view is that it does indeed involve disputed inflammatory cells such as T cells and macrophages. Additionally, even if this feature is not a constant one it may be valid. This disease that causes so much suffering must at the very least be considered to encompass a low grade inflammatory process wherein the increased release of inflammatory mediators including various forms of interleukins, and an array of neuropeptide products may prevail. The disease process appears to specifically induce enzymes that can mediate cartilage breakdown to be activated directly as well as indirectly by a variety of neuropeptide stimuli [1,18-25] that can impact bones and related tissues, such as articular cartilage, and induce noxious pain sensitization manifestations. By contrast, to mitigate this cycle of destruction, blocking the inflammatory signaling processes as well as efforts to protect vulnerable joints from injury may limit the onset of highly disabling neuropathic pain.

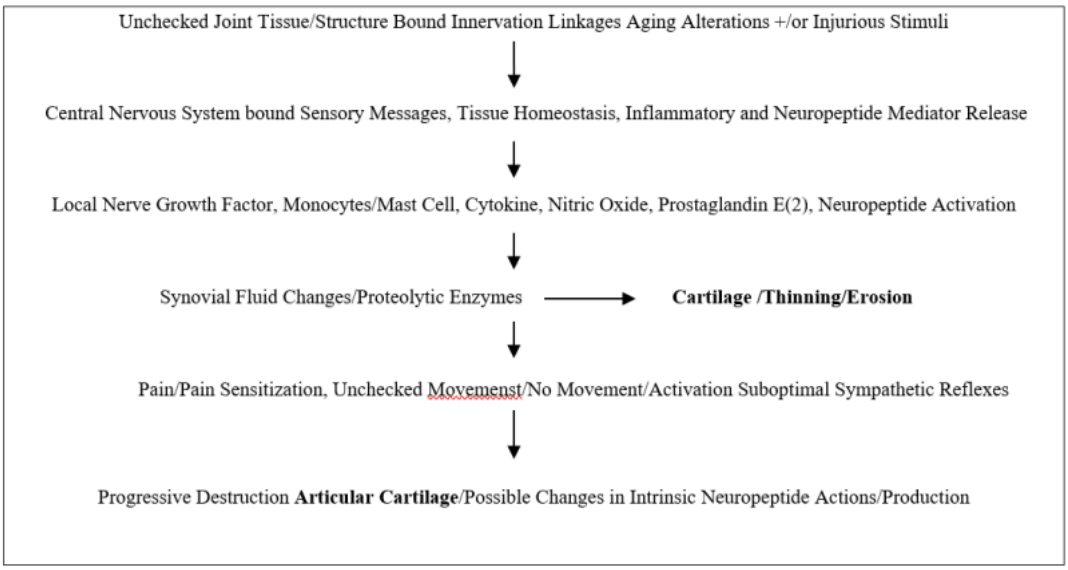

Figure 1: Hypothesized interactive mechanisms of multiple neuropeptide actions and articular cartilage pathology [Adapted from: 5,7,19-24].

In this regard we agree with [26] who confirm a protective approach is very important to address by those who seek to limit osteoarthritis disability as there are many pain pathways that could otherwise be activated and account for the observed spread of the disease to involve other joints, sclerosis of the subchondral bone, patellar dislocation at the knee joint, osteophyte formation, synovial proliferation and severe cartilage abrasion [27].

Grässel et al. [7,12,16] confirm the plausibility and possible clinical utility of the above findings that shows a variety of cell types that can synthesize and secrete specific types of neuropeptides such as substance P and that appear to be involved in the pathology of inflammation and the progression of osteoarthritis. Hence even though some neuropeptide neurotransmitters are critical for the maintenance of joint tissue and bone homeostasis and may have a positive impact on articular cartilage structural and metabolic processes [28-30], their abnormal presence may evoke much joint damage, as well as changes in the individual's mechanical responses to impact, mobility, and pain [29].

In theory, attaining or maintaining an optimal neuropeptide presence and one that does not evoke subnormal damaging responses may minimize articular cartilage damage [31,32] and prove highly beneficial even if not remediable [21-23,33,34]. This approach directed to importance of efforts to avert day to day micro injuries, may help reduce destructive neuropeptide activation processes that tend to perpetuate inflammatory pain and lower life quality [21].

Overview of Possible Non Pharmacologic Osteoarthritis Management Potential

The idea that osteoarthritis is not only age related, but has a strong neural underpinning, and that alone or in combination neuropeptides in this neural network could modulate osteoarthritis pain and inflammation appears to warrant efforts to avert their unwanted activation [2]. By contrast, as outlined in Figure 1, an unbalanced or noxious array of neuropeptide generated reactions has the potential to induce chronic joint effusion, plus the release of various tissue degrading inflammatory molecules and enzymes [22] that mediate progressive joint damage and a possible loss of their protective effects [21-23].

In this regard, efforts to reduce pain accompanying osteoarthritis using analgesic medication and/or non-steroidal anti-inflammatory drugs, frequently prove ineffective, however, and can have adverse effects on articular cartilage metabolism, or a variety of systemic toxic side-effects, possibly because this approach does not take into account the enormously diverse and complex neural correlates mediated by neuropeptides and other signalling sources. Further, since no drug appears to currently reverse or delay the progression of osteoarthritis, their long-term efficacy has been challenged.

However, several current authors propose that a greater appreciation of the very complex and intricate neural networks implicated in osteoarthritis may be helpful in heightening osteoarthritis repair processes or averting downgrading mechanisms, as may a broad array of adjunctive methods other than medications, or surgery, with virtually no side effects.

Here below we propose clinicians consider how osteoarthritis might be managed effectively so as to provide possible more harmoniously environment for neural mediators and moderators though an insightful selection of a combination of physical therapeutic approaches. Only general points are noted here and those selected are based on

evidence of a possible benefit that should be applicable to most joint sites commonly affected by osteoarthritis.

We assume here that while not offering a cure, or following the ideas of precision medicine an integrated set of physical approaches can possibly prevent abnormal cell-matrix interactions within osteoarthritic cartilage, and is thus able to help preserve its compressive stiffness and elasticity to a higher degree than not. In particular, because mechanical stimuli are essential for the growth and maintenance of cartilage and aberrant mechanical loading can lead to cartilage damage, careful mechanical manipulation of the cell micro-environment may foster tissue reconstitution and reduce matrix damage attributable to degradative enzymes by damaged cartilage cells.

Hypothetical Advantageous Therapeutic Strategies

Given the multiplicity of determinants that may underlie the development of osteoarthritic joint disease, and the considerable potential for cartilage repair that may exist, non-pharmacological and non-operative interventions that carefully consider the role of neuropeptide mechanisms and their stabilization may possibly be quite impactful. For example noxious impacts emanating from destructive neuropeptide processes may be ameliorated by carefully:

1. Eliminating the most detrimental forces falling on the joint surface
2. Improving the ability of the surrounding joint tissues to absorb, distribute and respond to harmful mechanical loading forces more physiologically.
3. Eencouraging movements that facilitate joint nutrition, but avoid excess stretching.
4. Having patients assume responsibility for their joint protection strategies and adherence to their treatment plan
5. Focusing on therapies that the individual can and should be able to implement independently on a regular basis including:

- Joint Rest/Whole Body Rest
- Assistive Deviceson , Braces, Splints and Orthoses
- Electrical Muscle Stimulation
- Ergonomic and Environmental Adaptations
- Non Fatiguing or Non Stressful Joint Use
- Weight Control
- Non impactful Strengthening/Endurance Exercise
- Optimising Nutrition

To be optimally effective, it appears such strategies should be implemented at the earliest possible point in time and be continued throughout the life course of the older adult, as required. A team approach with the individual playing an active role in their own self-care is highly recommended, as is a multi-component therapeutic program. Precautions to avoid unrealistic treatment goals that can lead to frustration, depression, misunderstanding, and inappropriate withdrawal from activities and family and consideration of the patient's social, emotional and psychological needs, are also essential for the achievement of optimal outcomes. Also, because excessive loading of a pain-free but affected osteoarthritic joint can potentially cause further joint damage if the protective pain reflex is inhibited, or if a sensory deficit prevails, it may be necessary to caution patients not to increase their activities of daily living unduly over any treatment period. Clients may also need to avoid carrying out rapid impact loading activities, movement that overstretch the joint[s]. Both the physical and the psychological status of the patient should be assessed periodically to determine dosage and a menu of recommendations, and emphasis should be placed on improving self-management skills, perceptions and beliefs about control, and importance of adherence to programmatic recommendations.

Other Thoughts

Since many early osteoarthritis cases may not experience pain, efforts to screen for changes in neuropeptide levels and peptidase enzymes that can degrade cartilage are indicated [35,36].

Factors other than isolated attempts to deactivate one or more neuropeptide products may also warrant consideration, for example, and instructions not to limit physical activities entirely as this could create more rather than less joint vulnerability. At the same time, efforts to eliminate or reduce cognitions that mitigate against positive progress, persistent joint effusion, tendinitis or bursitis around an affected osteoarthritis, along with harmful bone derived vascular factors are strongly indicated.

Discussion

This current overview that focused on whether neuropeptides are remediable mediators of articular cartilage damage, the hallmark of osteoarthritis has shown that there is possibly a series of pathways that can be stimulated or debased that implicate neuropeptide networks anabolic as well as catabolic. Although constituting a noticeable minor percentage of all studies that have researched osteoarthritis, available research on neuropeptides in general shows they are influential in multiple cellular signaling realms but may fail to be protective in many cases, for example in unexplained osteoarthritis [7,11,37].

Based on what is known, it is apparent one or more interventions to counter degrading neuropeptide actions and foster anabolic protective influences can likely relieve pain, reduce inflammation, maintain joint structures or repair them, such as bone and cartilage homeostasis, and inhibit osteoarthritis progression [1,7,21,34,38, 39].

In a cause-effect transactional model of osteoarthritis underpinnings, the data presented here are however confusing because neuropeptides have dual potentials and mixed modes of action. In addition, osteoarthritis is no longer considered an age generated disease alone, but clearly implicates multiple joint tissues progressively, and with wide variations. Moreover, until recently, factors such as neuropeptides have not been well described in the osteoarthritis literature on disease solutions despite the possible importance of the nervous system as an entity for maintaining tissue homeostasis [7,12,40,41].

However, as clearly suggested by the literature, neurogenic modulators such as neuropeptides can influence nerve afferent responses [3] that may underpin the primary pathogenic events seen in osteoarthritis, as well as negating an active role for protective forms of neuropeptide in the central nervous system [37]. Whether this leads to progressive damage of joint tissues [unless very careful measures are taken to prevent this], neuropeptide alterations are likely to be implicated in both primary/autoimmune or secondary/degenerative processes and thereby those that lead to unrelenting peripheral experiences and suffering and activation of the neuro-endocrine axis as well as non-neurogenic inflammatory mediators [24]. Sellam and Birnbaum [42] support this idea by referring to the fact that osteoarthritis catabolic and proinflammatory mediators such as cytokines, nitric oxide, prostaglandin E(2) and neuropeptides are produced by the inflamed synovium and that this situation can alter the balance of cartilage matrix degradation and repair, leading to excess production of those proteolytic enzymes responsible for cartilage breakdown. Other data show cartilage alterations can generate or amplify synovial inflammation, creating a vicious destructive and painful circle of degradation as

was depicted in Figure 1 [35,36,43,44].

In this regard, it appears neuropeptides, serving as cellular messengers can potentially modulate or mediate the actions in these theorized cascades and appear more destructive than not in this regard or less effective, especially if their chondrocyte PAC-1 cell receptors are damaged, degraded, blocked, or reduced in number [43]. Although, a contrary view of a possible favorable impact of neuropeptides on joint health in experimental treatments has been reported, this finding needs to be examined further in the realm of chronic osteoarthritis as it occurs in the older adult as preclinical findings may not replicate those occurring in the actual osteoarthritic disease process at all closely. Moreover, while theoretic solutions may prove unsafe or impractical if applied as a biological remedy to counter pain [3] a strong role for pro nociceptive neuropeptides cannot be ruled out. It can be concluded though that even if effective in relieving pain, the failure to appreciate the immensely vital interactive role of the nervous and vascular systems in osteoarthritis damage and repair processes as one affecting the entire joint [35] could potentially lead to a hastening, rather than any slowing of the disease progression, or a failure to advance healing when it is actually possible.

However, the idea that treatment/control of disease activity and pain in osteoarthritis can be achieved successfully in the long-term by blocking the cascade of neuropeptides leading to initiation and/or amplification of inflammatory process combined with effects on central nociceptive and neuroendocrine responses is a well articulated one currently. It lacks empirical support however, and, while promising, blocking a possible inflammatory cascade in the context of a mouse model seemed hard to validate or generalize to the bedside, especially if it does not account for age associated proprioceptive changes, nor address inherent trophic mechanisms that might prevail, and the fact only one neuropeptide is examined, and not others. As well, the present findings may clearly not capture the entire picture of neuropeptide based pain origins in osteoarthritis since most studies do not focus on the central nervous system and most are completed on previously healthy animals in a short time frame in various models of the disease that often seems arbitrary [45]. In addition, many laboratory studies and their predominant focus on rat joints may fail to clearly emulate the multiple osteoarthritis human disease processes and/or the mediating role of human behaviors, and other pain determinants on disease risk, progression, and outcomes. In addition, relatively neglected is the contribution of osteoarthritis pain in the molecular pathways that have the potential to mediate nerve and vascular tissue disease abnormalities and signals received from surrounding tissue structures [3,46].

In short, while we did not currently conduct any meta-analysis in this report, and articles selected may not include every related research report, it is evident very carefully construed more targeted research is essential in this realm in efforts to unravel the mechano-neural underpinnings of osteoarthritis pathology and the role of neuropeptides in this regard [8]. In our view, this line of research may be more helpful than focusing on developing anti-inflammatory therapies alone, including those directed towards retarding degrading neuropeptide molecules [45]. Indeed, it appears the role of synovial and articular cartilage neuropeptides, and their link to cytokine production holds significant promise for revealing the complex nature of the interacting and destructive cartilage pathways observed in preclinical and clinical contexts.

As per Figure 1, this disease process if unabated, could in turn, selectively activate a group of receptors termed NK1 that are located on the cartilage cell membrane, potentially accelerating cartilage degeneration, joint pain, inflammation, subnormal proprioception, and possible risk of further injury if synovial peptogenic nerves are activated as a result [47,48]. On the other hand, since these conditions may overlap, simply applying substance P receptor antagonists or others in an effort to help reduce arthritis pain and swelling may increase rather than decrease the rate of any ongoing adverse changes in osteoarthritis cartilage. At the same time, other studies suggest that substance P can also exhibit anti-inflammatory and regenerative properties through the recruitment of mesenchymal stem cells that might be useful to explore. However, it is clear that to initiate a variety of efficacious signal transduction pathways and synaptic connections that can optimally regulate pathophysiological processes in bone and cartilage tissue, more study of diverse neuropeptides is indicated [17,43]. In addition, findings in rats under controlled conditions may not replicate the human physiological condition or related inflammatory state and histopathological complexity of the osteoarthritic joint and involvement of small neuromolcules at all comparably [49-50].

Moreover, the role of genetics and possible variable types of pain models that underpin osteoarthritis also warrant study [40]. Whether a well-conceived exercise approach that fosters improvements in joint shock absorption and proprioception, alongside an anti-inflammatory eating plan, and mindfulness meditation or enforced mini rest periods has effects comparable to standard practices as well as new drug developments is strongly indicated as well. Other possible physical approaches include the use of topical capsaicin, acupuncture, infrared light applications, weight control, and avoidance of harmful analgesics. Specific attention to reducing joint swelling is strongly indicated as well [45,51].

In the interim it can be assumed a host of neuropeptides can generate severe unrelenting pain, as well as osteoarticular damage, but there may arguably be a chance for targeting these pain factors selectively or indirectly proactively or in real time without any reliance on drugs, for example, through careful applications of laser acupuncture, laser and shock wave therapy that have been shown to influence CGRP expression levels. As well, topical administration of carnosine, efforts to foster bone health, as well as a modest or low intensity strengthening program may yield considerable pain benefits [50,52,53-56]. Close attention to how poor proprioception can impact neuropeptide presence [57] and bone damage interactively [49] in addition to averting negative cross-talk between nerves and the vascular system may also reduce a tendency towards neuropeptide catabolic factor release [13,22,58]. Indeed, it appears, carefully construed interventions may not only modulate bone regeneration, and bone remodeling, but may favorably impact on articular cartilage homeostasis, exercise outcomes, inflammation, immune processes, and the stimulation of classic neurological actions that protect joints [12,59-63]. Also promising is a role for carnosine, a naturally occurring dipeptide (b-alanine and l-histidine) that has emerged as a potential geroprotector with antioxidative, anti-inflammatory, and anti-glycating properties and benefits that extend to muscle function, exercise performance, and cognitive health [55,64-70].

Conclusion

Based on what we know about small neuropeptide molecules, we believe that carefully considered related research will help to solidify how best to mitigate a fair degree of suffering in most older adults at risk for or suffering from chronic disabling osteoarthritis pain as follows:

Key Points

To be useful clinically, much more translational research employing advanced biomechanical and biochemical assays is needed to examine and temporally unravel the very complex molecular and cellular interactions that exist between the immune and nervous system that may be involved in the development of osteoarthritis as well as subsequent attempts to regain joint homeostasis.

Until then, or even thereafter, in light of the possible co-existing catabolic and anabolic neuropeptide properties that may be harnessed or unfold at different times and differentially under different environ-

mental, pain, loading mechanisms, and genetic conditions and phenotypic key osteoarthritis dispositions, establioshing how to moderate or avert these imbalances will remain imperative in our view.

To foster wellbeing among vulnerable older adults, it seems likely a holistic personalized physical campaign targeted to protect the body from impacts that stress the nervous and vascular as well as skeletal systems along with fortifying muscle protection, cognitive, and bone health appears the most viable route to consider in the interim all things considered.

At a minimum, it appears a failure to appreciate the inflammatory influences of the many neuropeptides that impact neural behavior at the molecular, cellular, tissue, muscle, peripheral and cortical nerve pathways and levels, will likely foster the sequences portrayed in Figure 1, plus immense excess societal suffering and incremental costs.

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