Modulation of Pain in Osteoarthritis

The Role of Nitric Oxide

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Background: Patients with osteoarthritis (OA) may experience severe pain, progressive loss of movement function, and disability. Many pain-relieving medications are not effective, and are not able to improve the existing pathology.

Objectives: This review summarizes (1) the pathology, mechanisms of pain production, and conservative management of OA with respect to pain; and (2) explains the role of nitric oxide (NO) in pain reduction and production, especially as related to OA.

Discussion: NO is produced in biologic cells by a family of enzymes referred to as the nitric oxide synthases (NOSs). The beneficial or harmful effects of different isoforms, constitutive NOS (cNOS) and inducible NOS (iNOS), respectively, suggest dual effects of NO in biologic structures. The harmful effects of NO are most often reported in the literature. We suggest that (1) NO via the beneficial cNOS pathway is decreased in joint structures exposed to chronic load-induced stresses and biochemical change-induced stresses, (2) monochromatic infrared light energy at an 890 nm wavelength, applied at the skin surface, is absorbed into blood vessels and stimulates production of NO in joints by the beneficial cNOS pathway, (3) NO from the cNOS pathway may help decrease the detrimental effects of NO induced by iNOS and produced in OA pathology, and (4) NO-based intervention may produce substantial pain relief without undesirable side effects by increasing circulation, decreasing nerve irritation, and decreasing inflammation in joints.

Key Messages: (1) The roles of NO in nociception are dual and complex. (2) NO via cNOS, produced transiently in small amounts, can bring dramatic relief to people with painful OA.

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Pain reduction is a primary goal for people with chronic pain, including patients with osteoarthritis (OA).[1] Progressive loss of movement function and disability, which are directly related to the pain associated with OA, are major reasons for lost work time, eventual exit from the workplace, permanent disability, and large medical costs.[2] Many pain-relieving medications are either not effective and/or have significant side effects.[3] Few pain-relieving medications are capable of improving the existing pathology. One exception to this generalization is the class of disease-modifying OA drugs, most of which are currently in clinical trials and have not yet been approved for use in patients.[3,4] Nitric oxide (NO)-based intervention seems at this time to produce substantial pain relief without undesirable side effects.[5,6]

Pain is the major determinant of decreased functional activity in people with OA, and movement function for people with OA is more related to the pain itself than to the disease status.[7] Not surprisingly, therefore, pain relief is the major reason why people with arthritis seek medical advice.[1] At the very least, pain reduction is sought for improvement in the quality of life or when joint replacement has to be delayed until weight is reduced or age criteria are met.

Pain-intervention methods that can improve or reverse OA pathology are actively sought in medicine, with the expectation that chronic pain will be simultaneously decreased. To this end, much research is now focused on NO, a compound with significant importance in medicine. In a cover story by *Science* in 1992, NO was noted as the "Molecule of the Year." Three scientists, Robert Furchgott, Louis Ignarro, and Ferid Murad won the Nobel Prize in Physiology or Medicine in 1998 for their pioneering studies of NO. The first clues emerged from studies showing that if the inner layers of the cells (the endothelium) of an artery or vein were absent, the smooth muscle cells of the blood-vessel wall would lose their capacity to make the vessel relax. In 1986, they discovered that a previously unrecognized substance had to be present, which regulated the tone of the smooth muscle cells of the blood-vessel walls. This unrecognized

mystery agent, an endothelium-dependent relaxing factor, was eventually identified as NO. NO has emerged as an important biologic mediator in almost all cell types and has effects on vascular tone, neurotransmission, immune function, morphogenesis, gene-expression regulation, and growth and repair of damaged tissues.[5,8]

We suggest that NO, used in a relatively new manner for pain relief, might enhance the body's own natural production of low concentrations of NO via the stimulation of constitutive NOS (cNOS) through intervention with monochromatic infrared photo energy (MIRE). Also, it might improve the OA pathology. Intervention with MIRE, for example, when applied noninvasively at the skin surface, is speculated to stimulate the body to either produce the beneficial form of NO or release it from bound sites within the cells.[9–11] Preliminary data from case studies in patients with knee OA documented by patient report that MIRE decreased pain, improved functional mobility, improved health-related quality of life, decreased the use of over-the-counter drugs, and had no reported detrimental side effects. Some patients reported improvement in sleep. One patient who was considering surgery stated that she no longer felt that surgery was needed at that time.[9,12] Even though MIRE seems to be a beneficial approach to treatment, controlled clinical studies have not occurred, and the literature is not clear on the role of NO either in improving OA pathology or in reducing pain. However, use of MIRE in OA might prove to alleviate pain, because it reduces pain in other conditions such as neuropathy.[13]

The objectives of this paper are to

I. Review the pathology, the mechanisms of pain production, and the conservative management of OA with respect to pain.
II. Explain the role of NO in pain reduction in OA.

OA PATHOLOGY AND CONSERVATIVE MANAGEMENT OF OA PAIN

OA Pathology and Causes of Pain

OA is a disease of the entire synovial joint, which consists of articular cartilage, subchondral bone, intra-articular structures, synovial fluid, synovial membrane, periarticular soft tissue of tendon, ligament, muscle, fascia, and related nerves.[14,15] All the structures in the synovial joint except the articular cartilage have pain fibers. Joints, other than synovial joints, might also have OA: in these cases, the joint structures present would be involved. OA pathology can cause pain in all of these structures, except in the articular cartilage. With disease progression, the articular cartilage becomes partially vascularized and innervated and might be associated with pain.[16]

OA is one of the most painful, functionally limiting, and disabling diseases that affects the musculoskeletal system.[1] Pathology related to mechanical overload,[17–19] and/or biochemical changes (and most likely both)[17–20] might not cause pain with initial articular cartilage degeneration. However, progressive OA usually involves increased subchondral bone density; eburnation of bone that exposes nerves, damage to the blood vessels at the tidemark between the articular cartilage and the subchondral bone, inflammation,[16] and/or irritation of periarticular soft-tissue structures and related nerves, all of which can lead to pain.[1,14–16] Of importance in this scenario is the loss of blood supply to previously well perfused structures; the result is ischemic pain[16] mediated by loss of oxygen and nutrients to nerves. A palliative role might exist for improving blood flow by increasing local NO levels.

Articular cartilage thinning and erosion decrease the capacity of the cartilage to absorb shock; therefore, the cartilage might require bone to absorb more of the shock of loading: this in turn leads to increased density of the subchondral bone[14,20] and can lead to bone marrow edema and pain.[21] Edema can also compress capillaries and deprive tissues, including nerves, of oxygen.[16] Lack of blood flow makes it impossible for healing to occur, even with oral medications, including analgesics. Surface fibrillation of articular cartilage increases with disease progression; and wear debris particles associated with surface fibrillation can create inflammation and harmful chemical changes. Surface fibrillation, if deep enough, wear debris, and the production of irritant mediators such as prostaglandins, kinins, cytokines, chemokines, ATP, serotonin, substance P, norepinephrine, and others can cause pain.[22–24]

Mechanisms of Pain Production in OA

Pain can be elicited with overload or damage to all joint structures, except the articular cartilage. Pain-producing mechanisms, both mechanical and chemical, joint structure sources of pain, and common types of pain are summarized in Table 1.

Conservative Management of OA Pain: Interventions for Pain Reduction

Pain is a protective mechanism that usually results from the stimulation of nociceptors when the stimulus exceeds the reactive threshold of the system. The purpose of pain is to increase the awareness of the potential for or the presence of damage and to provoke a response that will limit this damage.

Pain is multidimensional, dynamic, and results from complex changes in the peripheral and central nervous systems. In the case of peripheral OA, the pain originates at the site of damaged joints. Nerves might be sensitized to increased pain perception that lasts beyond the duration of the original noxious stimulus. This persistent nociceptive input leads to "neuronal plasticity," with changes in spinal cord connections. These changes contribute to the variability in pain, and the shift from acute to chronic pain. Genetic predisposition, age, and psychosocial factors might also contribute.[1,22,41] The mechanisms by which chronic pain, including OA pain, is maintained (even when the stimulus for the pain is removed) is relevant for patient management. Pain that is

TABLE 1. Mechanisms of Pain Production in OA

Mechanism of Pain Production	Source of Pain	Commonly Associated Pain/Pain Behavior
1. Trapped intravenous blood with ischemia in subchondral bone[14,15,21,25]; impaired venous drainage from bone marrow[25]; bone remodeling/repair that leads to subchondral sclerosis[15,21,25,26]	Bone, nerve	Dull, aching, deep joint pain, occurring with WB[15,22–24]* and also occurring at rest in advanced disease.[15] Not well localized[23]
	Vasculature, nerve	Throbbing, diffuse pain[23]*
2. Overload of bone and ST:		
a. In malaligned joints[14,27–32]	Bone, nerve, vasculature, synovium	Sharp or dull with WB/excessive compression > shear on bone and nerve[29,31]*
	Ligament, tendon, muscle, ligament or tendon to bone junction, joint capsule, nerve	Sharp pain when stretched with joint loading/ excessive tension on ligament/tendon to bone junction[29,31]*
b. With joint laxity[14,29,33,34]	Bone, nerve, vasculature, synovium	Sharp or dull with WB/excessive shear > compression on bone and nerve[29,33,34]*
	Ligament, tendon, muscle, ligament or tendon to bone junction, joint capsule, nerve	Sharp pain when stretched with joint loading/ excessive tension on ligament/tendon to bone junction, muscle[14]*
c. With malalignment and correlated/ compensatory postures and motions at distant joints[34]	Bone, nerve, vasculature, muscle, ligament, tendon	Sharp or dull at sites of correlated/compensatory postures or motions[34] as noted with malalignment and joint laxity*
d. With high load[14,29,35,36]	Bone, nerve, vasculature, muscle, ligament, tendon	Sharp or dull with WB/excessive compression[14,29,35]*
3. Repetitive impulsive loading[14,37]; hard/fast loading without adequate shock absorption[37]; impact forces might lead to inflammation[16]	Bone, nerve, ligament	Often no pain pre-OA or early OA; intermittent activity related sharp > dull pain; increased sharp > dull pain with activity in advanced OA[37]*
4. Microfracture from overload[14,16]	Bone, nerve	Sharp, well localized pain with WB; pain accumulates with activity[14]*
5. WB on eburnated bone[14,16]	Subchondral bone, nerve	Sharp with WB, advanced disease; pain accumulates[14,16]*
6. Periosteal outgrowth: stretch/distension of nerve in bone might be accompanied by inflammation[38] and angiogenesis[16]	Osteophytes in bone, nerve, vasculature	Sharp or dull in advanced OA; sharp or dull with periosteal distension with overgrowth at joint margins; pain with hand pressure on the osteophyte[23,38]*
7. Joint distension/stress at ligament bone insertion[38]	Joint capsule; ligament, bone	Sharp with WB or tensile stress on capsule/ ligament/bone[38]*
8. Nerve irritation: noxious mechanical stimuli (stretch, pressure, crush) in bone and in joint-related ST[1,16,22]	Nerve nociceptors[22]	Sharp, well localized pain with WB or burning pain or diffuse, dull aching pain in WB > NWB[1,16,22]*
9. Muscle fatigue with overuse[39,40]	Muscle, nerve	Dull, aching, cramping pain, localized to muscle when muscle overloaded[35,40]*
10. Muscle spasm[38]	Muscle, nerve	Dull to sharp cramping with use or rest/night pain[38]*
11. Excessive stretch of tight muscles with joint contracture[39,40]	Bone, nerve, vasculature, ligament	Sharp pain at the extremes of joint range[39,40]*
12. Excess stretch of insertion of meniscus to capsule; tear of meniscus[40]	Meniscus; nerve in peripheral 1/3 of meniscus	Sharp with stress/stretch at insertion site to capsule: inner 2/3 meniscus aneural[40]*
13. Movement across uneven joint surfaces, with crepitus (ie, osteochondromatoses, displaced torn meniscus)[40]	Joint (intra/extra) articular structures	Variable: no pain to sharp pain when the crepitus occurs[40]*
14. Inflammation		
a. In synovium, with cartilage debris, fragments, crystals; release of proinflammatory cytokines/enzymes that further destroy cartilage[16,20]	Synovium; synovial nerves	Very sharp pain at rest/with use or pain that worsens at night[38]*; synovial thickening associated with severity of pain[16]
b. Compression of synovial blood vessels, with swelling/distension within the joint capsule[16]	Synovial fluid/synovial joint space, synovial nerves	Sharp pain at rest or pain that worsens with overuse and at night[16]*
c. In bursae, with or without calcification[40]	Periarticular bursae	Sharp or dull pain with WB or at rest[38]*
d. In nerve, with peripheral and central sensitization of nerve nociceptors[22]	Nerve in synovium, bone, ligament, tendon, muscle, and vasculature	Very sharp pain at rest/with use or pain that worsens at night; upregulation or propagation of sharp pain, i.e., increased sensitivity to movement and touch; spontaneous pain without movement[22,23]*
e. Chronic synovitis and angiogenesis[16]	Synovial membrane/lining of joint, including nerves, vasculature; vasculature at osteochondral junction; vascularization in articular cartilage, osteophytes, and accompanying sensory nerves[16]	Very sharp or dull aching at rest, with use, and/or pain that worsens at night*

(*continued*)

TABLE 1. (*continued*)

Mechanism of Pain Production	Source of Pain	Commonly Associated Pain/Pain Behavior
f. Neurogenic inflammation in nerve, with the activation of sensory fibers from injured structures that result not only in transmission to the central nervous system, but also in reverse transmission to activate local arterioles, causing vasodilation/muscle contraction[22,23]	Sensory nerves	Sharp pain with use. Very sharp pain at rest or pain that worsens at night; (mediated by biologically active chemicals: substance P, calcitonin gene-related peptide, somatostatin, and others)[22,23]*

*Pain behavior on the basis of the clinical opinion of authors.
ST indicates joint-related soft tissue = joint capsule, vasculature, synovium, ligament, muscle, tendon; WB, weight bearing.

not addressed in a timely manner could be prolonged unnecessarily and compromise the health-related quality of life of the person with OA.

Pain is closely linked with physical activity, defined as exercise and daily functional movement, in people with OA. The links include the lack of pain warning that can occur with initial articular cartilage degeneration; pain with joint overuse, which can eventually lead to physical inactivity; pain with minimal physical activity for people who are sedentary; and pain with advanced OA pathology, first with activity and later even with rest.[42–44]

Wisely guided physical activity that improves the signs and symptoms of OA and avoids damaging mechanical loading is critical for people with OA.[31] Unfortunately, pain and the fear of injury cause people with OA to resist physical activity.[43] People with OA have often been instructed to avoid exercise; often, they are not instructed in how to exercise and move properly and safely. No single physical activity is universally recommended for people with OA, because people differ in risk factors such as weight, skeletal alignment, and movement-performance problems. Knee-joint skeletal malalignment and joint laxity are 2 situations for which physical-activity recommendations are modified from the standard physical therapy (PT) management for knee OA.[31–34]

"Nonpharmacologic treatments currently considered to have sufficient levels of scientific evidence are education, exercise, appliances, and weight reduction."[36,45] Because physical inactivity is the leading cause of overall morbidity and mortality for all people with and without pathology, it is important to promote and maintain pain-free and nondamaging physical activity in people with OA.[42,43] It is of interest that physical activity causes an increased production of NO during the flow of blood through the muscle beds. This process, known as "shear stress," occurs during the more rapid movement of blood along the surface of endothelial cells.[5,8]

Current PT standard care, including physical activity and other interventions for pain reduction, is included in Table 2. Every effort has been made to include currently available levels of evidence, including literature documentation and/or expert opinion.

The interventions leading to pain reduction, listed in Table 2, can occur by decreasing stress on overloaded structures, encouraging more normal tissue remodeling accompanying skeletal realignment therapies, improving muscle balance, decreasing the shock of high-impact loading on joints, decreasing nerve irritation, decreasing inflammation, improving appropriate flexibility and strength in joint structures, and by using other modalities. "International guidelines advocate nonpharmacologic treatments as first-line management for people with OA."[45]

Pharmacologic interventions used to manage OA pain have variable success and can produce considerable side effects. The variable success of these medications might be due to their inability to control the multiple pain-generating factors in the numerous structures, inability to halt the pathology, and to effect disease-accompanying alterations in the blood flow. Medications/drugs used in treatment have been reviewed in several references.[3,4,94] Because most pharmacologic interventions have side effects, people with OA often prefer nonpharmacologic interventions or, at least, as few pharmacologic interventions as possible.

MIRE, a nonpharmacologic treatment, has been cleared by the Food and Drug Administration for use in pain relief, produces no known side effects, and might be a good option to reduce pain for people with OA.[9–11] In addition, Michlovitz and Nolan[11] provided a literature review and stated that MIRE promotes vascular perfusion, enhances tissue oxygenation, nutrient delivery, removal of the waste products of metabolism, and increases ATP in human lymphocyte cells.

From these statements and on the basis of clinical experience, the authors interpreted this to mean that MIRE can slow down or prevent the deterioration of joint structures, possibly by decreasing acute and chronic inflammation, increasing blood flow, and promoting the healing of joint structures. We emphasize that MIRE is adjunctive to a comprehensive physical therapy/occupational therapy approach to pain in people with OA.

NO PATHWAYS IN OA

NO Function in the Body and With OA Pathology

NO is produced in all human cells by a family of enzymes called nitric oxide synthases (NOS).[5,95–97] Synthases are enzymes that remain structurally the same while inducing chemical change and, in this instance, they synthesize NO from the amino acid, L-arginine.[8,96]

TABLE 2. Physical Therapy Interventions for Pain Reduction in OA

Intervention	Amount of Pain Relief	Level of Evidence/Expert Opinion
1. Heat[46]	1. Temporary[46]; level of pain relief not reported	1. *Welch et al[47]: few trials in OA, but in RA heat found effective, well-liked, safe; recommended use for pain; †Mazzuca et al[48]: heat-retention knee sleeve might reduce pain *Brosseau et al[49]: poor evidence: no significant pain relief ‡Hurley and Walsh[46]: poor evidence; however, frequently used for pain
2. Cold[46]	2. Temporary[46]; level of pain relief not reported	2. *Welch et al[47]: few trials in OA; however, in RA cold found effective, well liked, safe; recommended use for pain *Brosseau et al[49]: poor evidence: no significant pain relief ‡Hurley and Walsh[46]: poor evidence; however, frequently used for pain
3. Ultrasound (US)[50]	3. Temporary[50]: level of pain relief not reported	3. *Robinson et al[50]: US demonstrates no benefit in hip and knee OA over placebo/short-wave diathermy; poor evidence regarding use to decrease pain *van der Windt et al[51] and §Gam et al[52]: poor evidence for pain relief
4. Low-level laser therapy (LLLT): infrared light, 684-904 nm[53]	4. Temporary[53]: level of pain relief not reported	4. *Brosseau et al[53]: LLLT effectiveness for pain relief not conclusive §Beckerman et al[54]; RCTs: Stelian et al[10]; deBie and Verhagen[55]
5. Transcutaneous electrical nerve stimulation (TENS); acupuncturelike TENS (AL-TENS)[56]	5. Significant: TENS: In one RCT, 256-min pain relief with 40-min duration of treatment[57]	5. *Osiri et al[56]: TENS and AL-TENS effective in pain control over placebo RCTs: Cheing et al[57]
6. Pulsed electrical stimulation (PES): electromagnetic field therapy[58]	6. Significant pain relief[58]: small-to-moderate treatment effect in the knee	6. *Hulme et al[58]: PES effective in decreasing knee pain; RCTs: Trock et al[59] Trock et al[60] Zizic et al[61]: variable treatment frequency, duration, dosage
7. Manual therapy (MT): restoration of soft tissue and articular flexibility[62]	7. Significant pain relief: MT + supervised exercise, moderate-to-large combined-treatment effect	7. RCT: Deyle et al[62]: MT + supervised exercise effective vs. no treatment to decrease pain Other RCTs: Hoeksma et al[63,64]; few studies in OA ‡Fitzgerald and Oatis[65]
8. Massage[46]	8. Temporary[46]; level of pain relief not reported	8. §Philadelphia Panel Clinical Practice Guidelines, 2001[66]: no evidence that massage decreases pain ‡Hurley and Walsh[46]: no trials in OA; massage used for subjective benefits
9. Aquatics (Balneotherapy)	9. Temporary; level of pain relief not reported	9. *Verhagen et al[67]: no evidence of efficacy/effectiveness to reduce pain; no SRs for OA; few RCTs: Foley et al[68]; Patrick et al[69]; Guillemin et al[70]; Green et al[71]; Nguyen et al[72]
10. Therapeutic exercise; physical activity (land-based strengthening, aerobic, and combination programs)	10. Significant pain relief established: small-to-moderate treatment effects	10. *Fransen et al[73]; *van Barr et al,[74,75]; RCT: Minor and Sanford[76]; ‡Hurley[77]; Strengthening exercise effective in decreasing knee pain *Brosseau et al[78]; *Westby[79]: aerobic exercise effective in decreasing knee pain RCTs: Sharma et al[31–33]: pain reduced if exercise is appropriate for subgroups of patients with joint laxity and malalignment
11. Patient education: disease process/self-management, not movement performance	11. Significant pain relief: small, but significant pain-treatment effect	11. *Warsi et al[80]; *Riemsma et al[81]; §Superio-Cabuslay et al[82] Numerous RCTs: education (self-management, home/class-based exercise, cognitive behavioral/coping, telephone, spouse) effective in decreasing pain
12. Management of skeletal malalignment and joint protection in weight bearing	12. Significant pain relief established: small-to-large individual treatment effects	12. RCT: Sharma et al[31]: varus/valgus knee alignment increase risk for medial/lateral knee OA progression; severity of pain is

(*continued*)

TABLE 2. (*continued*)

Intervention	Amount of Pain Relief	Level of Evidence/Expert Opinion
		associated with severity of varus/valgus alignment; ‡Riegger-Krugh et al[34]: skeletal malalignment can alter joint load distribution, produce correlated and compensatory motions and postures at adjacent/distant joints, and create pain
a. Weight reduction (WR)	Small-to-large effect	a. RCTs: Messier et al[83]: WR decreases pain; but few RCTs; Felson et al[35,84]: weight loss reduces risk of OA/might prevent pain in the future; ‡Felson[29]
b. Footwear, orthotics	Small effect	b. *Brouwer et al[85]: orthotics decrease knee pain; few RCTs: Toda et al[86]: lateral wedge insole with elastic strapping of the subtalar joint for genu varus decreases pain
c. Bracing	Small effect	c. *Brouwer et al[85]: valgus brace decreases knee pain RCT: Matsuno et al[87]: generation II valgus "unloader" brace decreases varus and pain
d. Walking/work home devices	Effect not measured	d. RCTs: Krebs et al[88]: Contralateral cane use reduces peak acetabular contact pressure, which might impact pain in the future; Tackson et al[89]: Walking, stationary bike generate lower in-vivo hip-pressure measurements than isometric hip/standing exercise; data challenges traditional protocols: clinician choice of exercise might affect pain
e. Household modifications	Effect not measured	e. No RCTs regarding pain; historical evidence effective for pain relief in clinical practice[90]
13. Movement reeducation: to improve movement performance and prevent abnormal strategies; decrease impact loading in gait	13. Significant pain relief established: size of treatment effect not described	13. RCT: Voloshin et al[91]: Muscle fatigue leads to decreased ability to absorb dynamic load, joint injury; Voloshin et al[92]: increased walking speed increases dynamic loading/ might induce pain; ‡Radin et al[37]: Repetitive impulsive loading increases joint loading; decreasing rate of loading might help decrease pain; ‖McGibbon et al[93]: repetitive stress from excessive muscle contraction can cause acetabular cartilage degeneration, which might lead to joint pain

*Systematic review (SR), Cochrane Database of Systematic Reviews (CDSR).
§Meta-analysis.
†Pilot Study.
‖Case Study.
‡Expert opinion.
RCT indicates randomized controlled clinical trial.

Isoforms are specific forms of the enzyme.[95–97] There are 2 major isoforms of NOS: inducible NOS (iNOS), induced in cells by trauma, injury, or infection, and constitutive NOS (cNOS), continuously produced by, and active in, cells. Only one form of iNOS exists. 2 forms of cNOS are found in many cell types: eNOS (endothelial NOS) and bNOS or nNOS (brain or neuronal NOS, respectively).[95,96] A third form, OA-NOS, recently identified in OA joints, will not be discussed further, as its clinical significance has not been determined.[98]

We recommend the iNOS, cNOS, bNOS, and nNOS as the most descriptive and easy-to-use terminology. NO will be differentiated either as NO via cNOS or as NO via iNOS, representing its production via the constitutive or induced isoforms, respectively. NOS numerical terminology is used extensively in the literature,[95,99] numbered by order of discovery and developed on the basis of chemical structure and other chemical characteristics. However, the simple term NOS provides no clue to the origin of NO and no information as to whether it was induced or generated from a constitutive isoform; hence, unfortunately, it is often used inappropriately.

NO serves as a fast-acting chemical messenger between and within cells. NO can be either beneficial or harmful. The beneficial or harmful role in tissues and organ systems is determined by the isoform,[5,20,95,96] the amount (concentration) produced,[5,95,96] the stimulus required for activation,[5,95,96] the characteristic chemical

behavior,[5,95] and the chemical environment in which NO is generated.[5,6,100] Contributions to the dual role of NO will be discussed in this section. Dual effects create confusion and confirm the complexity of the NOSs and NO in the body.

Controversy exists regarding the role of NO in OA.[5,6,95,100–104] The destructive effects of NO are often reported in the literature[5,20,22,96,102] versus the protective effects,[6,101,103] and the isoform being discussed is not always specified.[20,104]

The cNOS isoform is generally considered to be the beneficial healing form of NOS. This isoform is dependent on calcium as a stimulus for activation.[5,95,96] NO via cNOS is thus regulated and produced in small quantities or low concentrations; it serves as a fast-acting chemical messenger for cell-to-cell communication in physiologic processes essential to healthy organisms, and promotes homeostasis.[5,95,96,103] The cNOS synthase forms might promote pain reduction in OA, as described in the section NO and Pain Reduction in OA.

The iNOS isoform is usually considered to be the damaging form in which NO accumulates. The iNOS form, already bound to calcium (Ca^{++}), is independent of Ca^{++} for activation. It produces NO in large quantities or in high concentrations, which might be harmful or even toxic, especially to OA cartilage and chondrocytes.[5,20,95,96] Expression of iNOS in OA joints is induced by the exposure of the cells to proinflammatory cytokines, including interleukin-1β (IL-1β), tumor necrosing factor-α, leukemia inhibitory factor, IL-17, and IL 6.[20,94,105,106] Therefore, both iNOS and these cytokines are produced in response to tissue injury or mechanical trauma. Excessive production of NO via iNOS can lead to the reaction of NO with reactive oxygen species, resulting in oxidative injury and then destruction of cells.[5,95] Reactive oxygen species include compounds such as superoxides, which form reactive oxygen intermediaries such as peroxynitrite ($ONOO^-$) or peroxynitrous acid (ONOOH).

Also, NO dual roles are determined by characteristic chemical behavior, and are highly dependent on the variable physiologic and pathophysiologic chemical microenvironment in which NO is generated.[5,6,95,100] NO is a molecule with potent, diverse actions in cartilage,[6,101,104,107] bone,[95,108–111] synovium,[16,105] vasculature,[8,102,103,105,108,112] and nerve.[1,22,41,96,105] NO is small, hydrophobic, highly diffusible, and has a short half-life (4 to 6 seconds) within the local cell microenvironment. NO, a reactive nitrogen species, might interact, with a strong affinity to oxygen or transition metals such as iron and sulfur, to produce beneficial or harmful effects. Beneficial reactions with NO include interactions with iron, containing substrates such as guanylate cyclase, in smooth muscle to cause vasodilation and the restoration of blood flow; and with sulfur to form nitrosothiols, such as hemoglobin, which either release NO for vasodilation or store NO for future beneficial use.[5,95,96] An example of destructive reactions with oxygen has already been described.

Multiple conflicting NO effects in synovial membrane, cartilage, bone, nerve, and joint structures have been identified. It is not surprising that either an increase or a decrease in pain in OA has been linked to NO, probably because of an underappreciation of the isoform(s) involved.[6,96,101,105,109,110] NO is only one of a multitude of mediators that can affect pain in OA. NO via iNOS, which is produced with inflammation, might participate in or induce cell injury: this could be the primary cause of chronic pain.[5,20,95,105] Additionally, NO might play a role[41,105,107–112] in 3 other highly interrelated stimulators of structural damage and pain production in OA: inflammation; edema, vascular reactivity, and destruction; and nerve irritation and damage (Table 3).

NO and Pain Reduction in OA

NO via cNOS, produced transiently in small amounts, might bring relief to people with painful OA. Four pathways for pain reduction related to NO are proposed[5,95–97,119–121]: the blood-flow pathway, which can normalize/restore the blood flow, thus reducing ischemic pain; the nerve-transmission pathway, which can restore nerve-membrane potential and conductance; the opioid-receptor pathway, which might stimulate the body's normal pain-reduction pathways and open the ion channels at receptor sites to decrease nerve excitability; and the anti-inflammation pathway, which might reduce inflammation and, secondarily, promote improved oxygenation at the sites of pain. Reduction of inflammation and improvement in oxygenation affects not only the vascular system, but also the nerves themselves.

Pain Reduction/NO and the Blood-flow Pathway

In response to the shear stress of the pulsative blood flow, a constant supply of NO via cNOS is generated by endothelial cells.[8] The inner wall of the blood vessel, the endothelium, with its adjacent smooth muscle layer (tunica media), and its outer layer of epithelium (tunica adventicia) are illustrated in Figure 1.

With OA pathology, MIRE, which might induce local elevations in the physiologic amounts of NO via cNOS or by displacement of NO from hemoglobin, might be able to improve blood flow in the synovium and in the overly dense subchondral bone directly. MIRE might accomplish this by causing vasodilation, and restoring O_2, growth factors, and nutrients; secondary to the return of aerobic metabolism, MIRE might reduce acidosis in cells.[5]

Michlovitz and Nolan[11] believe that photo energy releases NO from red blood cells. Authors of this review believe that the photons of MIRE might alter the red blood cells passing near the light-emitting diodes, thus releasing NO from hemoglobin. Alternatively, MIRE photons might stimulate the production of NO by opening the endothelial cell calcium channels. When calcium is present, it binds to eNOS. L-arginine, in the presence of calcium-activated eNOS, produces NO. NO rapidly diffuses into the adjacent smooth muscle cells, where it binds to soluble guanylate cyclase (sGC).

TABLE 3. Stimulators of Pain Production in OA

1. Inflammation
   - Acute inflammation: sudden onset[16,22,106]
     - Mechanical, chemical, or thermal stimuli at high threshold levels[20]; pain by activation of myelinated[22] or sensitization of unmyelinated nerve in joint structures[16]
       - Physical trauma[16]
       - Acute synovitis[16]
   - Chronic inflammation[16,22,106,113]
     - Excessive mechanical, chemical, or thermal stimuli at high threshold levels; pain from prolonged activation of myelinated[22] or sensitization of unmyelinated nerve in joint structures[16]
       - Excessive/repetitive overload[106] in bone/joint soft tissues
       - Chronic synovitis with chronic edema, hypoxia, acidosis, poor perfusion of joints[16,105]
       - Chronic irritation with activation of nociceptors via overstimulation of the immune system by[16,20]
         - Proalgesic mediators produced by invading immune cells[16]
         - Mediators from resident cells, ie, cytokines, chemokines, nerve-growth factor, prostaglandins, ATP, others[16,20,22]
         - Mediators from damaged cartilage, bone, and synovium, ie, hydrogen ions and kinins (bradykinin)[16,20,22,114]
2. Edema, vascular reactivity, and cellular destruction/damage
   - Mechanical, chemical, or thermal stimuli at high threshold levels[20]; pain by activation/sensitization[1,22] of nerve in joint structures[16] or peripheral nerve injury/growth[114]
     - Acute synovitis[16,94]
     - Chronic synovitis[16,114]
     - Angiogenesis/new nerve innervation stimulated by inflammation,[16] hypoxia,[115] swelling[16,102,105,106,115,116]
       - Vascularized/innervated articular cartilage; pain with innervation of cartilage via nerve from subchondral bone[16]
       - Osteophyte formation via ossification/innervation of joint cartilage; pain via these new nerves stimulated by overload, hypoxia, and acidosis within cartilage[16]
     - Normal loading with swollen joints; pain due to ischemia, reperfusion with joint-structure damage[16,106]
     - Cumulative low-level mechanical loading/injury[16,117]
     - Decreased cell energy sources (O_2, glucose, ATP) in smooth muscle cells of blood vessel walls; pain via altered nerve-membrane potential[102,105,106,116]
     - Advancing age in cartilage/joint structures[117,118]; pain possible with increased susceptibility of cells to destructive mediators
3. Nerve irritation and damage
   - Mechanical, chemical, or thermal stimuli at high threshold levels[20]; pain by sensitization and activation of primary sensory afferent nerves[22]; pain by sensitization of receptors to mechanical/other stimuli, direct receptor activation,[22] or peripheral nerve injury/growth[114]
     - Pain sensation transmitted by nociceptors
     - Sharp, sudden, well localized pain transmitted from primary sensory afferent A delta fibers[16,22,23]
     - Diffuse, dull, aching, or burning pain from unmyelinated C fibers[16,22,23]
     - Increase in permeability of nociceptors at pain threshold and movement of ions across nerve membrane
     - Increase in nerve-membrane potential from stimuli at noxious levels to produce pain messages
     - Transmission of pain messages to higher central nervous system centers, where perceived as pain[20]

Guanylate cyclase (sGC) is an enzyme that catalyzes the transformation of guanosine triphosphate to cyclic guanosine monophosphate (cGMP).[8] Phosphorylation or the addition of a phosphate group to smooth muscle proteins via cGMP causes vascular relaxation; thereafter, it might cause a decrease in the pain due to the swelling

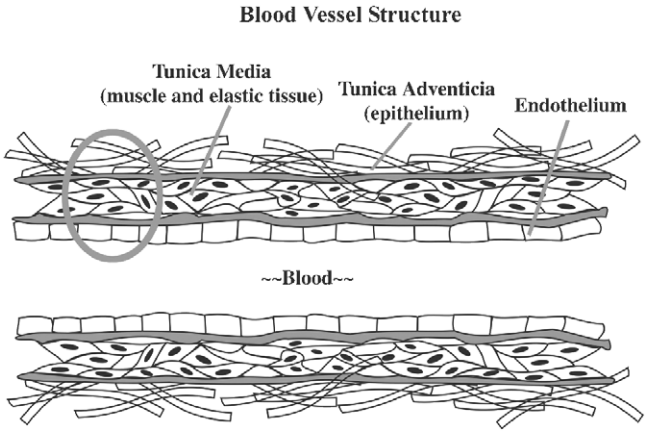

FIGURE 1. Blood-vessel structure.

that had caused local hypoxia or ischemia. Duarte and colleagues have also shown that NO via cGMP, causes phosphorylation of the ATP-dependent potassium channel; they have proposed that this is one of the ways in which peripheral and central analgesia occurs when morphine is used to suppress pain.[119–121] This is discussed below in Pain Reduction/NO and the Opioid Receptor Pathway. Additionally this vasodilation mechanism might improve nutrition via the synovial fluid, flush out the trapped blood in the subchondral bone, and promote the healing of soft-tissue injury or bone damage[5,8,11,95] (Fig. 2).

Pain Reduction/NO and the Nerve Transmission Pathway

Pain reduction also can be produced via a nerve-related mechanism in blood vessels, decreasing the irritation of the nerves in the synovium, bone, and soft tissues. Anytime there is loss of vascularity in the nerves themselves, pain is caused by abnormal nerve-impulse conduction or abnormal nerve-membrane potential. MIRE applied at the skin surface might act via the NO-cGMP pathway previously described (Fig. 2), to

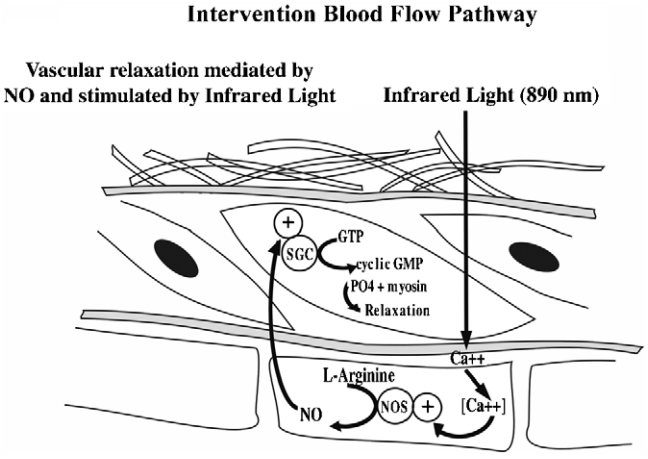

FIGURE 2. Blood-flow pathway-vascular relaxation mediated by NO.

decrease pain. NO produced by cNOS in nerve vasculature indirectly restores normal nerve-membrane potential and impulse generation by restoring blood flow, O_2, and nutrients to nerve cells. Clearly, vasodilation restores blood flow and results in pain reduction.[11,102,105,116]

Pain Reduction/NO and the Opioid Receptor Pathway

Opioids decrease pain by decreasing nerve excitability either before or after afferent terminals are reached, and slow down or stop nerve transmission of pain information.[119–125] Opioid receptors in cells in joints are activated during inflammation[22,123,124,126,127] and bind with peptides such as endorphins, enkephalins, and dynorphins, which decrease both inflammation and pain.[122] Intra-articular injection of morphine immediately before knee arthroscopy successfully reduces the need for postoperative analgesia.[128]

The opioid-receptor pathway of pain reduction is proposed via a lock-and-key (opioid peptide-receptor) interaction on the nerve-cell membrane,[124] which stimulates NO production, regulates permeability of nerve membranes to calcium and potassium, and controls nerve-signal transmission to reduce pain[119–125,129] (Fig. 3). MIRE, applied at the skin surface, is proposed by these authors to stimulate the calcium channels to open initially. Increased calcium binds to nNOS, and the activated nNOS + L-arginine produces NO. NO via the cGMP pathway acts on the nerve-cell membrane to open potassium channels and reduce calcium influx from calcium channels. It, thus, hyperpolarizes the membrane and stops pain transmission. Therefore, NO can act as a surrogate for opioids, bypassing the need for the drug to bind to the appropriate receptor. Tapping into the body's natural opioid mechanisms via the use of MIRE might eliminate the side effects of opioid drugs: it seems to relieve pain in OA.

Other pain-reduction mechanisms via NO and nerve-transmission pathways are controversial. NO, via nNOS and iNOS, has been reported to be both antinociceptive and pronociceptive via the NO-cGMP pathway in the nerve.[22,96] As noted above, this might be related to a misunderstanding of the concentrations of NO produced by iNOS or nNOS.

Pain Reduction/NO and the Inflammation Pathway

Inflammation in OA is accompanied by increased production of NO via iNOS in the synovium, bone, nerve, and cartilage,[105] which contributes to microvascular, nerve, and chondrocyte injury, and either initial or eventual pain.[16] Increasingly, inflammation, hypoxia, acidosis, edema, angiogenesis, and new nerve growth have been described during OA,[16,113,114] and each can be accompanied by pain. MIRE is proposed by these authors to promote homeostasis or oxidant/antioxidant balance in cells by stimulating the production of NO via cNOS. NO via cNOS is proposed to relieve pain by restoring the blood flow,[11] which had been compromised by the swelling and compression of capillaries. Decreasing the swelling, increasing the oxygen and nutrients to structures, and decreasing the waste products[11] and cytokine accumulation can collectively aid in restoring the normal nerve-membrane potential.[16,100,102]

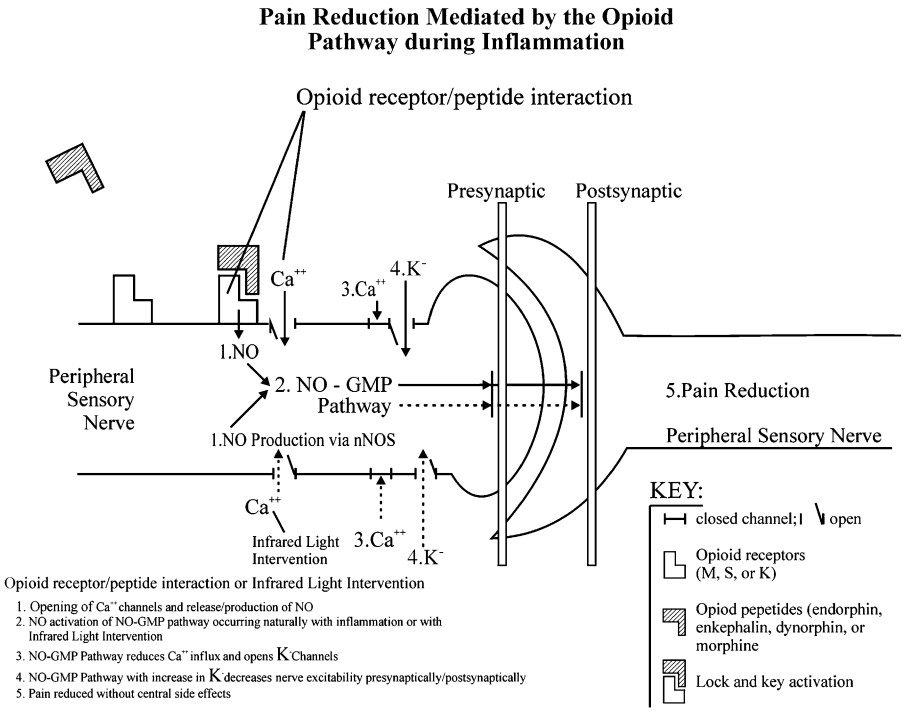

FIGURE 3. Opioid-receptor pathway.

MIRE at 890 nm

MIRE, at a wavelength of 890 nm (1 nm = 10^{-9} m or one billionth of a meter) was chosen by the authors from numerous commercial MIRE units, because of its greater success clinically in pain reduction in these patients with knee OA. MIRE at 890 nm, absorbed by many cell types, can stimulate the production of NO via cNOS to reduce pain. MIRE at 890 nm is delivered to the joint using flexible 4 1/4″ × 2 1/4″-treatment pads, each containing 60 near-infrared diodes. The uniform average power and total energy density from the diode array of each pad are reported to be 9.0 mW/cm^2 and 43.2 J/cm^2, respectively, per recommended 30-minute session.[11] Eight treatment pads are available in the clinical model, and 2 to 4 in the home unit. The unit chosen delivers a short-acting thermal effect; however, the near-infrared light (MIRE) at 890 nm creates the NO-related treatment effect. Short-term elevations in NO increase cGMP, and the phosphorylation effects that follow sustain the blood flow for as long as 3 hours.[129,130]

SUMMARY

The roles of NO in nociception are dual and far more complex than originally thought.[96] The beneficial effects of NO can be described as antinociceptive, whereas the harmful effects are considered to be pronociceptive.[96] NO via the cNOS pathway is decreased in joint structures exposed to chronic load-induced and biochemical change-induced stresses. NO-based intervention through cNOS is proposed to decrease pain and possibly improve OA pathology without detrimental side effects, by changing the cell microenvironments of the vascular and nerve pathways in joint structures. High concentrations of NO produced by iNOS are associated with injury, such as in OA; pain might be due to the side effects of these very high concentrations of NO. NO with MIRE at the 890-nm intervention can help decrease the detrimental effects of NO induced by iNOS and produced with pathology. The dual roles of NO have resulted in much confusion about the NO mechanism in pain production and reduction.

Future plans include studying comparative pain relief with MIRE at 890 nm and other modalities versus controls in people with OA, because positive clinical outcome measures have been demonstrated in preliminary studies. Our hope is that physicians and others will want to join this clinical and academic pursuit, to discover whether MIRE at 890 nm can provide a nonpharmacologic intervention that prevents pain; leads to better outcomes, including positive changes in health-related quality of life; and, perhaps, improves OA pathology, when combined with conventional, established PT interventions.

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