RESEARCH PAPER

Beyond Structure: Conditioned Pain Modulation, Immune, Metabolic, And Genetic Drivers of Low Back Pain and Implications for Mechanism-Based Rehabilitation

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ABSTRACT
This narrative review synthesizes evidence from basic science and clinical studies to explore the molecular and genetic drivers underlying the persistence of chronic low back pain (CLBP), supporting a shift in focus beyond structural pathology.
CLBP is a multifactorial condition in which persistence of pain cannot be explained solely by structural pathology. Increasing evidence highlights the role of altered pain modulation, immune–inflammatory mechanisms, metabolic dysfunction, and genetic variability in shaping individual pain experiences.
Conditioned Pain Modulation (CPM), a key descending pain inhibitory mechanism, is often impaired in chronic pain states, contributing to heightened pain sensitivity and central sensitization. Alongside neural dysregulation, immune system activation, particularly through pro-inflammatory cytokines and antigen presentation pathways, plays a critical role in maintaining persistent inflammation and nociceptor sensitization. Mitochondrial dysfunction and impaired oxidative phosphorylation further compromise muscle function and tissue repair, exacerbating chronic pain states.
Genetic and epigenetic factors, including polymorphisms in COMT, TNF-α, TRPV1, and GCH1 genes, also influence neurotransmitter metabolism, inflammatory signalling, nociceceptor sensitivity, and pain processing pathways. These molecular variations interact with neural and immune mechanisms to modulate pain perception, stress response, and transition from acute to chronic pain. In parallel, intracellular signalling cascades involving GTP-dependent G-protein coupled receptors contribute to pain transmission, amplification, and neuroinflammation at both peripheral and central levels.
Conclusion: Recognition of these interconnected molecular mechanisms provides a robust rationale for mechanism-based rehabilitation. Physiotherapy interventions, through their influence on neural, immune, metabolic, and epigenetic pathways, offer a scientifically grounded approach to pain modulation. Integrating this epigenetic understanding into physiotherapy practice provides a foundation for personalized, mechanism-based management of chronic low back pain.
Keywords: Low Back Pain, Chronic Pain, Conditioned Pain Modulation, Epigenetics, Inflammation Mediators, Exercises.
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1. INTRODUCTION

Chronic low back pain (CLBP) is one of the most common musculoskeletal conditions and a leading cause of disability worldwide with 619 million (95% uncertainty interval 554-694) people affected globally, and with a projection of 843 million (759-933) prevalent cases by 2050[1]. When low back pain becomes chronic, persistence of pain cannot be explained merely by structural tissue damage alone. Instead, altered pain processing, immune activation, metabolic dysfunction, and genetic predisposition contribute to pain chronicity. The knowledge and understanding the underlying neurobiological, immune, and molecular mechanisms become essential before studying chronic low back pain in detail. In particular, the role of Conditioned Pain Modulation[2], immune system involvement, and genetic regulation has gained increasing importance in explaining persistent pain and treatment resistance. Many patients with LBP have self-limited episodes, but a significant proportion of subjects develop recurrent episodes or persistence of pain. The existing conservative therapies though are very effective in treating the acute or subacute

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conditions significantly reducing the symptoms, they remain less evident for chronic ones[3]. This leads to identification of cause for reduced effectiveness of conservative management in chronic conditions. Many patients present themselves with fascial, muscular or mobility issues in Musculoskeletal conditions. In subjects with low back pain the local region is affected, which will be demonstrated as muscular imbalance, reduction in fascial gliding, reduced or impaired mobility, all of which causing compensatory movement pattern. The treatment delivered by Physiotherapist focus on the structure and ideally the functions affected by pathoanatomical structure. Like, stretching focuses on length of the muscles, gliding of fascia, mobilization focuses on passive accessory movements of the joint, active and passive range of motion focuses on range of motion in degrees. Recent advances in Manual therapy focuses on microstructural correction like M2T Blade (IASTM) and MATRIX[4]. But there is scarcity of literature in the molecular mechanisms of chronic musculoskeletal pain. The molecular mechanisms involved in chronic pain is described below under the headings of conditioned pain modulation, epigenetic changes and many more.

2. CONDITIONED PAIN MODULATION AND CHRONIC LOW BACK PAIN

Conditioned Pain Modulation (CPM) refers to a phenomenon in which the experience of pain is influenced or altered by the presence of another pain stimulus. It is a mechanism of pain regulation in which one pain stimulus can either enhance or inhibit the perception of another pain. CPM is a form of descending pain control, where higher brain centers modulate the intensity of pain signals being sent to the brain[2].

For example, when a person experiences a painful stimulus, it might activate pathways in the brain that reduce the perception of a second painful stimulus. Alternatively, the presence of one pain stimulus could increase the intensity of another, depending on the context. CPM helps explain individual variability in pain thresholds and responses to treatment.

When low back pain becomes chronic, the effectiveness of CPM often decreases[5]. The brain's descending pain control systems become less effective, leading to impaired pain inhibition. As a result, individuals with chronic low back pain experience heightened pain sensitivity and exaggerated pain responses to normally non-painful stimuli. This reduced CPM contributes to central sensitization, where the central nervous system becomes hypersensitive to pain signals.

Central sensitization leads to increased pain sensitivity, exaggerated responses to stimuli, and difficulty in pain modulation. Chronic pain also affects emotional and cognitive aspects of pain perception, including anxiety and fear of movement, further impairing CPM and worsening pain perception. Thus, impaired CPM forms a key mechanism in the persistence and amplification of chronic low back pain.

2.1 Impaired Central Pain Modulation in Chronic Low Back Pain[5]

1. **Reduced CPM Effectiveness:** In people with chronic low back pain, the brain's descending pain control systems may become less effective at modulating pain. This means that the body may not respond as well to pain-reducing signals from other stimuli, such as a mild painful stimulus that would normally reduce pain perception in healthy individuals. As a result, the individual may experience heightened pain sensitivity.
2. **Central Sensitization:** Chronic pain, including chronic low back pain, is often associated with **central sensitization**, a condition in which the central nervous system (CNS) becomes hypersensitive to pain signals. This can lead to an exaggerated response to stimuli that would normally not be painful and can reduce the body's ability to regulate pain through mechanisms like CPM.
3. **Increased Pain Sensitivity:** With chronic low back pain, the nervous system may "learn" to be more sensitive to pain, which can lead to an increased experience of pain, even with minor stimuli. This phenomenon contributes to the difficulty of managing and treating chronic pain, as it becomes harder to modulate and manage.
4. **Altered Pain Perception:** Chronic pain can also affect the emotional and cognitive aspects of pain perception. People with chronic low back pain may develop changes in how they perceive and react to pain, such as increased anxiety or fear of movement, which can further impair CPM and exacerbate the experience of pain.

Assessment of mechanisms of pain inhibition using conditioned pain modulation (CPM) is gold standard method used in clinics in prediction of pain and analgesia. A study documented that single test-stimulus (STS) protocol with a single administration of a contact heat test-stimulus, partially overlapped in time by a remote shorter contact heat as conditioning stimulus. The authors concluded that newly developed STS-CPM paradigm was more reliable than other CPM protocols tested here, and should be further investigated for its clinical relevance. It appears that large contact size of the conditioning-stimulus and use of single rather than dual test-stimulus pain contribute to augmentation of CPM reliability. The test stimulus was applied only once and lasted 45 seconds and the conditioning stimulus was added to it for the last 25 seconds. Participants were asked to rate the pain from only the test stimulus, even though both stimuli were present. Pain ratings were again averaged over three 10-second periods with Early phase being 10–20 seconds, Middle phase being 25–35 seconds and Late phase being 35–45 seconds. Two CPM values were calculated; namely; Immediate CPM that is pain occurring during the middle phase (when both stimuli were present) compared to pain just before the conditioning stimulus started & Late CPM

that is pain occurring during the late phase compared to pain just before the conditioning stimulus started[2].

Pain does not only arise from injured tissues, but it is a brain-based experience recognized by sensory input, emotions, thoughts, memories, and context. Many brain imaging studies concluded the activation of pain matrix in brain as a response to pain signal, triggering the descending pain modulatory pathway from brainstem, playing a central role in controlling pain. The control of pain can be in two natures; either inhibiting pain or amplifying it. This pathways works efficiently in healthy individuals regulating pain appropriately. The balance between the pathways and sensation gets disturbed causing weakened inhibitory control[6].

3. IMMUNE SYSTEM AND INFLAMMATION IN CHRONIC PAIN

Before understanding chronic low back pain, it is essential to understand how the immune system contributes to persistent pain and inflammation. As chronicity increases, inflammation of soft tissues and joints also increases. The inflammatory response contributes to persistent pain and delays tissue healing.

The immune system initiates and maintains inflammation through immune cells such as macrophages, dendritic cells, and T cells. Major Histocompatibility Complex (MHC) class I and II molecules present antigens to T cells, activating immune responses that sustain inflammation.

Two types of antigen presentation pathways are involved:

1. **Upregulation** indicates increased antigen presentation to T cells, meaning immune cells become more active in presenting injury signals. This leads to chronic inflammation and pain sensitization.
2. **Downregulation** refers to decreased immune cell activation, resulting in reduced inflammation and pain.

Persistent immune activation enhances nociceptor sensitization, contributing to chronic pain states and impaired pain modulation.

Some authors argue that Pain is created and controlled by the brain and not only occurs due to injury. Sensory signals are not solely but in combination with thoughts, emotions, attention, expectations, and past experiences are responsible for pain. As described above, pain involves a network of brain areas (pain matrix) that handle both physical and emotional-cognitive aspect of pain. In chronic pain, the brainstem system related to pain signalling becomes disturbed causing either reduced/amplified pain sensation. As a result, pain can persist even without ongoing tissue damage. The role of neuroimmune interactions, particularly the activation of microglia and macrophages in the spinal cord and brain release the pro-inflammatory mediators. These mediators enhance nociceptive signalling and contribute to central sensitization. Persistent activation of glial cells maintains the chronic pain state by shifting the balance toward pain facilitation within the central nervous system. Thus, chronic pain not only involves neural dysfunction but also immune-driven modulation of pain pathways[7].

Chronic low back pain (CLBP) is closely related to persistent immune and inflammatory processes, unlike as traditionally thought of being purely mechanical or structural in origin. It is associated with ongoing activation of immune cells such as T cells, macrophages, and other glial cells which release pro-inflammatory mediators. Pro-inflammatory mediators like interleukin-1β, interleukin-6, tumour necrosis factor-α, and IL-17 signal increases the excitability of neurons within the spinal cord and brain, promoting central sensitisation. Once the central sensitization occurs, the pain is amplified and sustained even in the absence of ongoing tissue damage. Genes such as S100A8 and S100A12, act as damage-associated molecular patterns (DAMPs), and are responsible for further amplification of inflammation by activating immune receptors and sustaining nociceptive signalling. Overall, the CLBP involves neuro-immune dysregulation, helping explain pain chronicity, heightened pain sensitivity, and poor response to treatments that focus only on peripheral structures[8].

4. OXIDATIVE PHOSPHORYLATION AND MITOCHONDRIAL DYSFUNCTION

Oxidative phosphorylation is the process by which cells generate energy using oxygen within the mitochondria. It is the process involving series of enzyme complexes and electron transport chain whose main goal is to produce ATP. In the context of low back pain, oxidative phosphorylation plays a major role in muscle function and inflammatory response which affects the tissue repair. Muscles require energy to function properly, if muscles are the sole cause of low back pain, and are inflamed then the function is impaired as the oxidative phosphorylation which fuels the contraction. Thus, contraction becomes altered because of altered metabolic activity or insufficient ATP production. Also, mitochondrial dysfunction commonly seen in chronic low back pain leads to reduced oxidative phosphorylation less efficient ATP production. Mitochondrial dysfunction is also termed as downregulating of Mitochondrial genes which causes reduced oxidative phosphorylation thus hampering ATP production leading to muscular contractile dysfunction.

Intervertebral disc degeneration (IDD) is one of the foremost causes of chronic low back pain, accounting for about 40% of cases. A key factor responsible for disc degeneration is oxidative stress. The oxidative stress occurs when harmful molecules called reactive oxygen species (ROS) increase out of the limit within the body's antioxidant defence. Excess ROS damage the discal cells, accelerate cell ageing and death, increase inflammation, and break down the disc's extracellular matrix. These all signs lead to decreased height of the disc, disc herniation, and pain. Oxidative stress also disrupts important cellular signalling pathways and creates a vicious cycle of inflammation and degeneration. Existing treatment

strategies mainly focus on relieving symptoms but do not stop degeneration[9].

5. GENETIC AND EPIGENETIC MODULATORS OF PAIN SENSITIVITY

5.1 COMT Gene and Pain Perception

This is the gene commonly found in human body, which is responsible for breaking down the dopamine and epinephrine enzymes. Normally they function to reduce the function of these enzymes by breaking them down. The functions of dopamine and epinephrine is to reduce the pain and stress of human being commonly present in chronic condition. It is studied and well documented that, any musculoskeletal injury or painful condition even including stress tend to increase the activity of COMT, which makes the person believe that he is either depressed or in chronic musculoskeletal pain. Thus, relationship between COMT activity and perception of pain and stress is highly correlated. Several studies have documented that, this upregulation of COMT activity during chronic musculoskeletal pain like Fibromyalgia, Chronic back pain is the major responsible factor for severe perception of pain and stress[10]. The val158met variation can influence how well this enzyme works. The val158met SNP (which means a single change in the DNA at position 158) affects the activity of the COMT enzyme. People with the val version of this gene tend to have higher COMT activity, meaning they break down dopamine faster. This results in lower dopamine levels in areas of the brain that influence pain perception and stress. Higher COMT activity (val/val) means quicker breakdown of dopamine and potentially a lower threshold for pain or a reduced ability to cope with pain[11]. People with the met version of this gene have lower COMT activity, meaning they maintain higher dopamine levels and may have better emotional regulation, stress coping, and pain tolerance. Lower COMT activity (met/met) may provide better pain tolerance and a better ability to handle pain because of higher dopamine levels.

The Val158Met polymorphism affects COMT enzyme activity[10-11].

- **Val/Val genotype** is associated with high COMT activity and increased pain sensitivity.
- **Met/Met genotype** is associated with low COMT activity and better pain tolerance.

Several studies have documented increased COMT activity in chronic musculoskeletal pain conditions such as fibromyalgia and chronic low back pain, contributing to increased pain perception and stress.

Lara S F Carneiro studied the Impact of physical exercise on catechol-O-methyltransferase activity in depressive patients. Catechol-O-methyltransferase (COMT) is a catabolic enzyme involved in the degradation of bioactive molecules including the neurotransmitters epinephrine, norepinephrine, and dopamine. "Higher COMT activity" refers to a greater rate of dopamine breakdown by the COMT enzyme, typically associated with the Val allele, resulting in lower dopamine levels in the brain, while "lower COMT activity" means a slower breakdown of dopamine, usually linked to the Met allele, leading to higher dopamine levels; essentially, individuals with higher COMT activity have less dopamine available compared to those with lower COMT activity. The authors concluded that Chronic exercise therapy combined with pharmacotherapy leads to significant decrease in S-COMT activity. Our results provide evidence that exercise interferes with S-COMT activity, a molecular mechanism involved in depression. The relationship between the COMT gene and pain is rooted in how COMT affects dopamine regulation. Dopamine is key in how we experience pain. High dopamine activity is associated with better pain tolerance and coping, while lower dopamine levels might make pain feel more intense or harder to manage[12].

Patrick H Finan studied that *COMT* Moderates the Relation of Daily Maladaptive Coping and Pain in Fibromyalgia. He conducted a study on 45 women with Fibromyalgia recording their daily ratings of pain and two forms of maladaptive coping: pain catastrophizing and pain attention. Participants were tested for a specific genetic variation in the COMT gene. This variation is called val158met and it's a single nucleotide polymorphism (SNP), which means a tiny change in a single base of DNA (in this case, at position 158 of the gene). COMT stands for catechol-O-methyltransferase, which is an enzyme involved in breaking down certain neurotransmitters (like dopamine, which plays a role in mood, pain, and stress responses). The val158met variation can influence how well this enzyme works. This means the genetic variation (COMT genotype) influenced the relationship between two factors: how people cope with stress (maladaptive coping processes) and their pain levels. Specifically, the COMT genotype might affect how someone copes with stress, which in turn could affect how they experience pain on a daily basis. The val158met SNP (which means a single change in the DNA at position 158) affects the activity of the COMT enzyme. People with the val version of this gene tend to have higher COMT activity, meaning they break down dopamine faster. This results in lower dopamine levels in areas of the brain that influence pain perception and stress. Higher COMT activity (val/val) means quicker breakdown of dopamine and potentially a lower threshold for pain or a reduced ability to cope with pain. People with the met version of this gene have lower COMT activity, meaning they maintain higher dopamine levels and may have better emotional regulation, stress coping, and pain tolerance. Lower COMT activity (met/met) may provide better pain tolerance and a better ability to handle pain because of higher dopamine levels[13].

A mini review conducted by Tammimaki A et al on Catechol-O-methyltransferase gene polymorphism and chronic human pain, studied the low COMT activity and its association with increased sensitivity to acute clinical preoperative or postoperative pain in human subjects. The

authors explored the association between COMT genotype and three chronic pain conditions: migranious headache, fibromyalgia or chronic widespread pain and chronic musculoskeletal pain. The meta-analyses showed that fibromyalgia or chronic widespread pain is the only type of chronic pain that could be associated with the COMT single nucleotide polymorphism rs4680 (Val158Met). Met158, which results in the low-activity variant of COMT, is the risk allele. Low COMT activity is not associated with migrainous headache or chronic musculoskeletal pain conditions, but it may increase the risk for fibromyalgia or chronic widespread pain. Low COMT activity increases opioid receptors and enhances opioid analgesia and adverse effects in some cancer pains[14].

A study by Kyle M et al on Contribution of COMT and BDNF Genotype and Expression to the Risk of Transition From Acute to Chronic Low Back Pain, studied a number of factors including hereditary and the environment contribution to risk of transition from acute lew back pain and its chronic version. The study aimed to compare the somatosensory function and pain ratings at low back pain onset between the acute and chronic variants of low back pain and also to evaluate the association between BDNF () and COMT () polymorphisms and expression levels at Low back pain onset to acute and chronic variants. CLBP refers to long-term pain in the lower back, typically lasting for 3 months or longer. Pain burden refers to the overall intensity or severity of pain someone is experiencing, and somatosensory hypersensitivity means an increased sensitivity to stimuli, like touch or temperature, which could make a person feel pain more intensely than usual. Chronic low back pain generally have higher pain levels and greater sensitivity to various sensations. COMT is a gene that codes for an enzyme that breaks down dopamine (a neurotransmitter). The rs4680 refers to a specific genetic variation (or SNP) within the COMT gene. People can have different genotypes at this SNP, with the GG genotype being one of them. The GG genotype is associated with acute cold pain sensitivity, meaning people with this genotype are more sensitive to pain from cold stimuli. COMT rs4680 (GG) genotype is also linked to a higher risk of transitioning from acute (short-term) low back pain (LBP) to chronic low back pain (CLBP). The study found that people with CLBP tend to report more severe pain and experience greater sensitivity to pain (especially at the time the pain first starts). The expression of the COMT gene (how much enzyme it produces) is also an important factor in whether a person is likely to develop chronic low back pain. COMT genotype (GG) is linked to being more sensitive to cold pain and having a higher chance of the pain transitioning from acute to chronic[15].

Another study by Daniel J. Clauw and James Witter on Pain and Rheumatology, demonstrated that, Psychological factors like anxiety and depression have been studied and found to contribute slightly to the variance in OA pain, but they don't fully explain the pain seen in many individuals. Recent research has explored the idea that genetic factors play a significant role in pain sensitivity. Specifically, the COMT (catechol-O-methyltransferase) gene has been implicated. A particular variant of the COMT gene (called 158Met) is linked to increased pain sensitivity, particularly in women. People with the 158Met variant of COMT are at a higher risk of experiencing pain in OA, even if their radiographs show similar joint damage to others who don't have this variant. The effect of the COMT gene on pain sensitivity is stronger in women, which aligns with known gender differences in pain perception (women often report more pain than men). Estrogen has been shown to influence COMT activity, contributing to these sex differences. Pain is ultimately perceived in the brain, not just in the damaged joint or tissue. Factors like pain processing systems and genetic pain sensitivity are key to understanding individual experiences of pain. There are heightened states of pain sensitivity, such as hyperalgesia (increased pain response) and allodynia (pain from normally non-painful stimuli), which can occur in chronic pain conditions, including OA. This research emphasizes the complexity of chronic pain, particularly in OA, where pain cannot solely be explained by joint damage. Genetic factors, such as the COMT gene, contribute significantly to pain perception, and these factors should be considered in both understanding and treating chronic pain. The passage advocates for a shift toward personalized and brain-centered approaches in pain management, moving beyond the joint and incorporating genetic and neurobiological insights[16].

5.2 TNF-α and Inflammatory Pain

Tumour Necrosis Factor-alpha (TNF-α) is a key pro-inflammatory cytokine involved in the initiation and maintenance of inflammatory pain. It is produced predominantly by activated macrophages, T-cells, and other immune cells in response to tissue injury, mechanical stress, or immune activation. In chronic musculoskeletal conditions, sustained TNF-α expression contributes to persistent inflammation and enhanced nociceptive signalling[17].

TNF-α exerts its effects through binding to its receptors, TNFR1 and TNFR2, expressed on nociceptive neurons, immune cells, glial cells, and musculoskeletal tissues. Activation of these receptors initiates intracellular signalling cascades that increase the excitability of peripheral nociceptors and amplify pain transmission. TNF-α directly sensitizes nociceptors by increasing ion channel activity, lowering activation thresholds, and enhancing responsiveness to mechanical and chemical stimuli[17]. This sensitization leads to hyperalgesia and allodynia, hallmark features of chronic inflammatory pain.

A critical mechanism through which TNF-α amplifies pain is its interaction with transient receptor potential channels, particularly TRPV1. TNF-α upregulates TRPV1 expression and function on sensory neurons, increasing calcium influx and neuronal depolarization. This interaction potentiates pain responses to thermal, mechanical, and chemical stimuli, thereby reinforcing

peripheral sensitization[18]. In addition, TNF-α promotes the release of other pro-inflammatory mediators, creating a self-perpetuating inflammatory environment that sustains nociceptive signalling.

At the spinal and supraspinal levels, TNF-α contributes to central sensitization by activating microglia and astrocytes within the dorsal horn. Glial activation leads to increased release of cytokines, nitric oxide, and excitatory neurotransmitters, further enhancing synaptic transmission and reducing inhibitory control[17]. These changes strengthen pain signalling pathways and diminish the effectiveness of descending inhibitory mechanisms such as conditioned pain modulation.

Genetic polymorphisms in the TNF-α gene influence cytokine expression and inflammatory responses. Variants such as TNF-α −308 G/A, −238 G/A, and −857 C/T are associated with increased TNF-α production and heightened susceptibility to chronic inflammatory pain conditions, including chronic low back pain, osteoarthritis, and inflammatory spinal disorders. Individuals carrying high-expression alleles may exhibit exaggerated inflammatory responses and increased pain sensitivity, contributing to pain persistence and treatment resistance[19].

Beyond genetic variation, TNF-α is also regulated through epigenetic mechanisms. Chronic inflammation can induce sustained epigenetic modifications, such as altered DNA methylation and histone acetylation in immune and neural cells, leading to prolonged TNF-α expression even in the absence of ongoing tissue damage[20]. This epigenetic upregulation contributes to the maintenance of chronic pain states and explains the persistence of pain beyond structural healing.

From a rehabilitation perspective, TNF-α represents a critical molecular link between immune activation and pain modulation. Physiotherapy interventions such as exercise therapy and manual therapy have been shown to reduce systemic inflammation and modulate cytokine profiles, including downregulation of TNF-α[20]. By reducing inflammatory load and nociceptor sensitization, physiotherapy may indirectly influence epigenetic regulation of inflammatory genes, restoring more adaptive pain processing mechanisms. Understanding TNF-α–mediated inflammatory pain thus provides a strong biological foundation for integrating anti-inflammatory, movement-based rehabilitation strategies in chronic pain management.

5.3 TRPV1 and Nociceptor Sensitization

TRPV1 is a nociceptor involved in detecting heat, acidic conditions, chemical irritants, and mechanical stress. It is found in sensory neurons, dorsal horn of the spinal cord, brain regions, immune cells, and peripheral tissues. In chronic pain conditions, TRPV1 receptors become sensitized, lowering activation thresholds and increasing pain sensitivity. TRPV1 polymorphisms such as C1462T and I296V influence pain perception and predisposition to chronic pain conditions[21].

TRPV1 activation during mechanical injury leads to ion influx, neuronal depolarization, and pain transmission. Chronic inflammation results in upregulation of TRPV1 receptors, contributing to persistent sensitization[21]. TRPV1 (Transient Receptor Potential Vanilloid 1) is a type of ion channel found in the sensory nerve endings of the body, primarily involved in detecting and responding to temperature and pain. TRPV1 receptors are primarily located in various tissues and systems that are involved in pain, temperature, and sensory detection. They are predominantly found in sensory nerve endings (nociceptors) of the skin, muscles, joints, and internal organs, where they detect noxious stimuli like heat, pressure, and chemical irritants. These receptors are also present in the spinal cord, specifically in the dorsal horn, where they help modulate pain signals, as well as in certain areas of the brain such as the cortex, amygdala, and hypothalamus, where they contribute to the emotional and cognitive aspects of pain. TRPV1 can also be found in epithelial cells of the skin and mucosal membranes, and in the gastrointestinal tract, where they sense mechanical stress and irritants[22]. Additionally, these receptors are present in the bladder, blood vessels, and immune cells (like mast cells, macrophages, and T-cells), where they play roles in inflammation and pain hypersensitivity. TRPV1 is also located in the airways, where it responds to irritants, and in the cornea of the eye, contributing to pain perception in response to environmental stimuli.

TRPV1 (Transient Receptor Potential Vanilloid 1) is primarily activated during injury by noxious (harmful) stimuli, such as extreme heat, acidic conditions, or certain chemical compounds, and mechanical stimulation which is how it plays a role in sensing pain. In essence, TRPV1 receptors are found throughout the body, but they are most densely concentrated in regions involved in sensory perception, particularly in response to pain, temperature, and injury. Their widespread presence allows TRPV1 to serve as an important mediator in various physiological processes, especially in pain perception and inflammatory responses. Mechanical stimulation refers to the physical deformation or stretching of tissues, which could happen due to injury (e.g., trauma, pressure, or a stretching force). This includes things like a bruise, cut, or pinch that physically damages or deforms the tissue. Mechanical forces from this injury can be applied to the skin, muscles, organs, or other tissues. While TRPV1 is typically known for responding to heat, acid, and certain chemicals, it can also be activated by mechanical forces such as stretch or pressure. This activation occurs because of the mechanosensitivity of TRPV1. The proposed mechanism how TRPV1 is stimulated on mechanical stimulus is still unclear but, theories have been proposed for the same as below;

A. Through sensory neurons

Tissue damage/injury or stretch when subjected to mechanical forces

Activation of sensory neurons, which directly alter the mechanical properties of the ion channels embedded in the membrane.

This alteration can lead to opening of several ion channels one of which is TRPV1

B. Through Lipid Bilayer[24]

Mechanical stimulation stretches the lipid bilayer causing changes in its membrane tension

This mechanical tension can physically influence the confrontation of TRPV1 ion channel causing its opening.

TRPV1 ion channel opening leads to influx of cation ions (sodium (Na^+) and calcium (Ca^{2+})) into the neuron leading to it depolarization

Generation of action potential to pass further forward and this electrical impulse is carried to the brain and is recognized as pain.

C. Chronic sensitization[24]

Inflammation or injury from ongoing mechanical stress can also lead to upregulation of TRPV1 receptors on the surface of sensory nerve endings.

Thus, these sensory nerve endings further become more sensitive to mechanical, thermal and chemical stimuli

Pain fibers where they are present: TRPV1 receptors are found in both C fibers and Aδ fibers, with C fibers being more abundant and involved in transmitting slow, chronic pain (often related to burning sensations), and Aδ fibers responsible for transmitting sharp, acute pain[25]. These fibers together play a critical role in detecting and transmitting pain from heat, chemical irritants, and injuries to the brain[26].

5.4 GCH1, GTP and Pain Signalling

GTP (Guanosine Triphosphate) plays a critical role in cellular signalling, particularly in G-protein coupled receptor (GPCR) pathways. GPCR activation leads to exchange of GDP for GTP, initiating intracellular signalling cascades that amplify pain signals[27].

GCH1 is involved in the synthesis of tetrahydrobiopterin (BH4), a cofactor required for neurotransmitter synthesis and nitric oxide production. Increased BH4 levels following nerve injury enhance nitric oxide production and pain sensitivity. Low GCH1 activity is associated with reduced pain sensitivity[28].

GTP is involved in processes like:

2. **Protein synthesis –** It helps in the translation phase, where the ribosome uses GTP to add amino acids to a growing protein chain[29].

3. **Signal transduction –** GTP binds to G-proteins, which are involved in transmitting signals from outside the cell to inside, influencing various cellular activities[30].

4. **DNA and RNA synthesis –** GTP is one of the building blocks (along with ATP, CTP, and UTP) used to form RNA[31].

GTP is indirectly related to pain through its involvement in cellular signaling, particularly in the context of G-protein coupled receptors (GPCRs). These receptors are involved in transmitting pain signals[27].

1. **G-protein signaling:** When pain signals (like from inflammation or injury) are detected, certain receptors on nerve cells, known as GPCRs, get activated. GTP plays a crucial role here—when a receptor is activated, it binds to a G-protein, which then exchanges GDP (guanosine diphosphate) for GTP. This exchange triggers the G-protein to relay the pain signal inside the cell, influencing pathways that ultimately result in pain perception.
2. **Pain modulation:** GTP and G-proteins are involved in modulating pain signals in the nervous system. In some cases, the binding of GTP to certain proteins can either amplify or dampen pain signals, depending on the specific signaling pathway involved.
3. **Opioid receptors:** GTP is also involved in the action of opioid receptors. Opioid drugs, like morphine, interact with these receptors, which are GCPRs, and their activation leads to pain relief. GTP binding is part of how the receptor transmits a signal to reduce pain sensation.

So, while GTP isn't directly "causing" pain, it plays a crucial role in how pain signals are transmitted and regulated in the body.

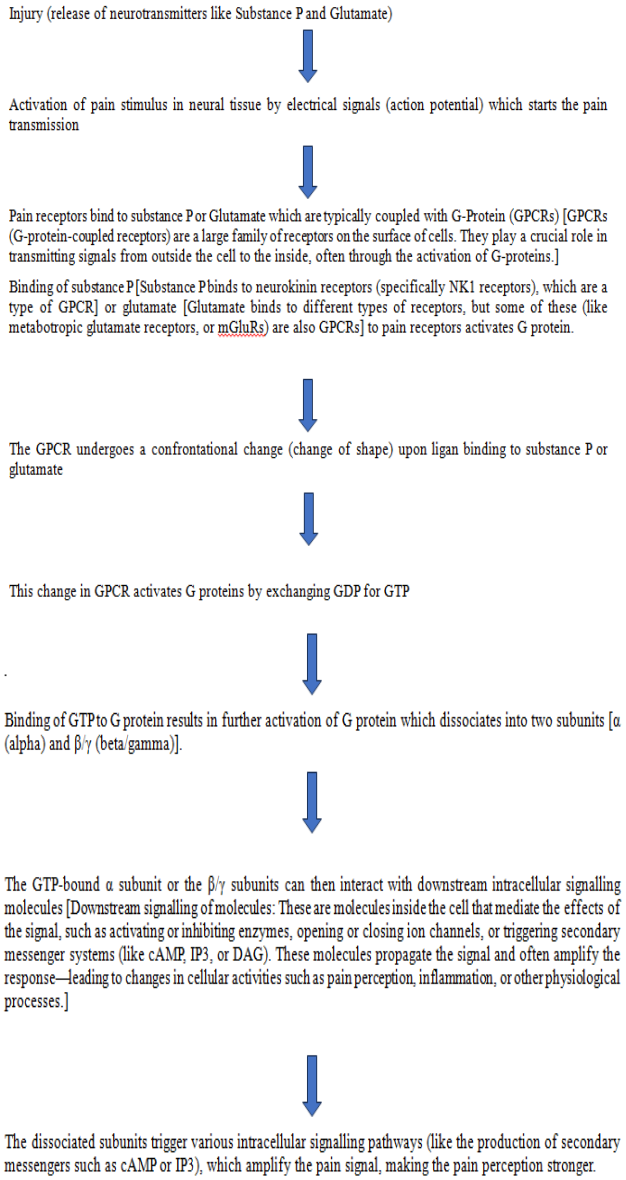
GTP plays a critical role in pain signaling, specifically in relation to signal transduction, which is how cells respond to external stimuli, like pain. It contains a guanine base, and three phosphate groups, which makes it high-energy like ATP. One of the primary roles of GTP in pain signaling is its involvement in G-protein-coupled receptors (GPCRs), which are critical for transmitting pain signals across nerve cells. G-proteins are intracellular signaling proteins that are activated when a receptor (such as a pain receptor) binds to its target, like a neurotransmitter or a stimulus. When a GPCR is activated by a pain signal (for example, the binding of substance P or glutamate, which are involved in pain transmission), it causes a change in the shape of the receptor. This change in the receptor then activates an associated G-protein (a type of protein inside the cell), which is normally bound to GDP (Guanosine diphosphate) in its inactive state. Upon activation, GTP is exchanged for GDP on the G-protein, turning it into its active form. The activated G-protein then disassociates into two subunits (α and β/γ), which can interact with other intracellular molecules to propagate the pain signal, often amplifying it to increase pain perception. Pain receptors on the nerve endings (such as nociceptors, which sense tissue damage and pain) are activated by various stimuli like heat, mechanical pressure, or chemical irritants. When these receptors are stimulated, they activate GPCRs, which then activate G-proteins by exchanging GDP for GTP.[27] The G-protein, now in its active form, will signal downstream proteins, such as adenylyl cyclase or phospholipase C, which will further

propagate the pain signal by producing secondary messengers like cAMP or IP3. These secondary messengers amplify the signal inside the cell, leading to the activation of ion channels (like calcium channels), which can further propagate the pain signal along nerves to the brain, where pain is perceived.

GTP (Guanosine Triphosphate) and GCH1 (GTP Cyclohydrolase 1) are involved in important biological processes, particularly in the synthesis of tetrahydrobiopterin (BH4), which is a crucial cofactor for various enzymes, including those involved in neurotransmitter synthesis and nitric oxide production.

1. GTP is present in all cells of the body, particularly in neurons, muscle cells, and immune cells, due to its involvement in cellular energy and signalling processes. GTP (Guanosine Triphosphate) is a vital molecule in both sensory and motor neurons, playing essential roles in energy metabolism, cellular signalling, and neurotransmission. It is involved in a variety of cellular processes in these neurons due to its key functions in protein synthesis, signal transduction, and activation of G-proteins. They are present in several places like sensory neurons (G-protein Coupled Receptors (GPCRs), Sensory neurons rely on G-proteins for signal transduction, the release of neurotransmitters and involved in modulating synaptic plasticity and sensory adaptation in response to prolonged or repetitive stimuli), motor neurons (crucial for neurotransmitter release in motor neurons like acetylcholine at the neuromuscular junction is dependent on the activation of G-proteins, involved in G-protein coupled receptor (GPCR) signalling, which can modulate muscle tone, motor control, and neuroplasticity, regulating the cytoskeleton dynamics , which is necessary for axonal transport by involving in polymerization and depolymerization of microtubules and actin filaments, components of the muscle cytoskeleton.)[30].
2. GCH1 is present in Brain (particularly in dopaminergic neurons, where it plays a crucial role in the synthesis of dopamine and other catecholamine), motor neurons (particularly in areas that control movement, such as the brainstem and spinal cord which plays a role in motor control and movement coordination.), sensory neurons (responsible for detecting various stimuli, including pain, temperature, and touch), skeletal muscles (where BH4 is needed for the production of nitric oxide (NO)), neuromuscular junction (influence the release of neurotransmitters and neuromuscular signalling, which are essential for effective muscle contraction)[32].

C fibers and Aδ fibers, the primary pain fibers involved in transmitting nociceptive pain signals, are both influenced by GTP through G-protein-coupled receptor (GPCR) signalling. GCH1 is related to both C fibers and Aδ fibers because it is involved in the synthesis of tetrahydrobiopterin (BH4), which is essential for nitric oxide synthase (NOS) function and the production of nitric oxide (NO). Nitric oxide plays a key role in pain transmission, especially in inflammatory pain and pain sensitization[27].



GTPases: Apart from G-proteins, GTPases are enzymes that hydrolyze GTP to GDP. Some GTPases are involved in the cytoskeletal rearrangements in nerve cells, which are important for neuron growth and synaptic plasticity, processes that can contribute to chronic pain conditions. Neuroinflammation: In some pain-related diseases, GTP-binding proteins are involved in the activation of inflammatory pathways that increase pain sensitivity, such as in conditions like neuropathic pain. GTP is crucial in the activation of G-proteins involved in GPCR signaling, which is a key process in pain signal transduction. GTP facilitates the activation of intracellular signaling pathways that lead to pain perception and, in some cases, pain amplification. Additionally, GTP's role extends to the modulation of pain via changes in receptor activity, ion

channels, and inflammatory pathways. This complex role of GTP in pain signaling highlights its importance in how pain is perceived and processed in the nervous system[32]. Essentially, it acts as a molecular switch that helps to regulate the flow of pain signals. GTP cyclohydrolase 1 (GCH1) is an enzyme involved in the synthesis of tetrahydrobiopterin (BH4), a crucial cofactor for the production of neurotransmitters like dopamine, serotonin, and norepinephrine[33]. These neurotransmitters are important for regulating pain perception and mood. Low GCH1 activity, and thus lower levels of BH4, have been linked to increased pain sensitivity. This is because lower dopamine and serotonin levels can impair the body's ability to manage pain and stress. Changes in GCH1 expression or function may contribute to chronic pain conditions, such as neuropathic pain, by disrupting normal pain signaling pathways[34].

Irmgard Tegeder studied the GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence. The authors studied that GCH1 is the rate-limiting enzyme in the production of BH4. This means that GCH1 controls the amount of BH4 synthesized in the body, which is crucial for the production of several molecules involved in pain regulation. BH4 is required for producing catecholamines (dopamine, norepinephrine), serotonin, and nitric oxide, all of which play roles in modulating pain, mood, and inflammation. After axonal injury (damage to nerve fibers), the levels of BH4 increase in primary sensory neurons due to the upregulation (increase in activity) of GCH1. After peripheral inflammation, BH4 levels also rise in dorsal root ganglia (DRGs), which are clusters of nerve cell bodies involved in pain signaling. The increase in BH4 leads to enhanced production of nitric oxide in these areas, which is associated with pain, especially neuropathic (nerve-related) and inflammatory pain. The authors concluded that; Inhibiting BH4 synthesis in rats reduced both neuropathic and inflammatory pain. It also prevented the overproduction of nitric oxide in the DRG after nerve injury. On the other hand, administering BH4 (injecting it into the spinal cord) worsened pain, highlighting that excess BH4 can exacerbate pain sensitivity. In humans, a specific GCH1 gene haplotype (a genetic variation) is linked to lower pain sensitivity. This haplotype, which is found in 15.4% of the population, was associated with less pain after a procedure for persistent low back pain (diskectomy). People with this haplotype had reduced sensitivity to experimental pain compared to others. When looking at their immune cells (leukocytes), the carriers of the haplotype had less upregulation of GCH1 when stimulated, meaning their GCH1 enzyme was less active[34].

A review conducted by S. Han on Osteoarthritis in biology, studied several molecular mechanisms which was largely divided into the intracellular signalling mechanism and intercomponent interaction in chondrocyte homeostasis occurring in Osteoarthritis and its progression. The authors concluded that GPCR-Gα subunit-cAMP signalling promotes anabolic effects in chondrocytes by preventing hypertrophy. GPCR activation is terminated by GRK2-mediated phosphorylation, leading to internalization. Carlson et al. found that GRK2 expression increased in the articular cartilage of a DMM OA model, which reduced cAMP production. Deleting GRK2 specifically in cartilage or inhibiting it with the antidepressant paroxetine prevented OA progression and promoted cartilage regeneration. This suggests that GRK2 signalling contributes to OA chondrocyte hypertrophy by inhibiting GPCR-cAMP signalling[35].

Author Seong-Kyu Kim et al studied on association of Guanosine Triphosphate Cyclohydrolase- 1 with pain sensitivity in subjects with Fibromyalgia syndrome. They conducted GCH1 SNP to check for susceptibility and clinical measures in recruited subjects. The authors concluded that “NO” is responsible for pain sensitivity in the pathogenesis of Fibromyalgia. “NO” is Nitric Oxide a molecule that acts as a signalling molecule including pain in the nervous system, which occurs during processing of pain, substance P (a neurotransmitter of pain) and excitatory amino acid (which activates neurons) released from pre-synaptic afferent terminals include the activation of NMDA receptor (a receptor present on nerve cell) which result in increased NO production by NO synthase causing hyperexcitation of the dorsal horn (overly sensitive to pain). NO was reported to be a potent signalling molecule in pain processing in patients with FM, because the tender point index (a measure of pain sensitivity in Fibromyalgia subjects) was positively correlated with NO precursors and byproducts in cerebrospinal fluid (CSF) suggesting that NO plays a significant role in the pain experiences of individuals with fibromyalgia[36].

Richardson, Kayla K conducted an experimental study to determine the genetic factor associated with response to osteopathic manipulative treatment in individuals with chronic low back pain. This study effectively highlighted the connection between genetic factors and the response to OMT. Samples (n=230) were previously genotyped for 41 polymorphisms (Table 2) using the SNPlex^{TM} (Applied Biosystems, Carlsbad, CA) assay, which is a multiplex Polymerase chain reaction (PCR) oligonucletotide ligation assay (OLA) that has the ability to analyze up to 48 polymorphisms simultaneously. Authors studied SNP Minor Allele Frequencies of ADRB2, COMT, GCH1, IL1A, IL1B, IL1RN, IL8 and LARGE. Authors concluded that polymorphism in IL-8 (rs2227543), GCH1 (rs998259), and LARGE (rs240070) were significantly associated with treatment response and also defined as at least 30% pain reduction ($\alpha \leq 0.05$). An intergenic interaction was found in the GCH1 gene (rs998259/rs3783641), and a multivariate model incorporating these GCH1 polymorphisms explained approximately 76% of the variability in response to OMT[37].

Gene–Gene Interactions and Individualized Pain Phenotypes

Individual pain-related genetic polymorphisms do not act in isolation; rather, gene–gene interactions (epistasis) critically shape individual pain phenotypes. Interactions among genes involved in neurotransmitter metabolism, inflammatory signalling, and nociceptor excitability—such as COMT, GCH1, TNF-α, and TRPV1—modulate pain sensitivity and susceptibility to chronicity. For example, polymorphisms in *GCH1* can modify the functional impact of the COMT *val158met* variant, influencing enzyme activity and mechanical pain thresholds, demonstrating that catecholamine metabolism is regulated by parallel biochemical pathways[38]. Similarly, inflammatory gene variants such as TNF-α may interact with ion channel genes like TRPV1, altering nociceptor responsiveness in immune-sensitized environments. Together, these interactions support a polygenic model of chronic musculoskeletal pain, in which the combined effects of multiple interacting genes better explain inter-individual variability in pain persistence and treatment response than single-gene effects alone[39].

Serial Numb	Gene	Name	Function	Pain function	Why physiotherapy?
1.	**COMT**	**(Catechol-O-Methyltransferase**	involved in the breakdown (regulate) of catecholamines, including neurotransmitters such as dopamine, norepinephrine, and epinephrine.	pain perception and sensitivity. The **val158 met** polymorphism in the COMT gene, where the amino acid valine (Val) is replaced by methionine (Met) at position 158, has been particularly well-researched. [Val/Val (high activity) and Met/Met (low activity)]	COMT can be tested through SNP analysis or DNA markers to identify genetic variants like **val158met** polymorphism which is commonly found variant related to pain perception.
2.	**TNF-α**	**Tumour Necrosis Factor-alpha**	regulating immune responses and inflammation.	**TNF-α** is one of the key cytokines involved in the inflammatory response. In conditions like **chronic back pain**, **degenerative disc disease**, or **osteoarthritis.** TNF-α can directly sensitize **nociceptors** (pain receptors), which increases pain perception. This can lead to **hyperalgesia** (an increased sensitivity to pain) and **allodyn**	Genetic variants: 1. **TNF-α -308 G/A (rs1800629)** 2. TNF-α -238 G/A (rs361525) 3. TNF-α -857 C/T (rs1799724)

				ia (pain due to stimuli that normally do not cause pain). TNF-α interacts with **TRPV1** receptors (like those found in sensory neurons), amplifying pain sensations and making the nervous system more responsive to STIMULI.	
3.	**TRPV1**	**Transient Receptor Potential Vanilloid 1**	receptor that plays a significant role in the sensation of pain, particularly in response to heat, capsaicin and other noxious stimuli. It is a part of the **TRP (Transient Receptor Potential)** channel family and is found primarily in **sensory neurons**, especially those involved in pain and thermosensation.	TRPV1 is a **nociceptor**, meaning it detects harmful stimuli such as heat, acidic conditions, and mechanical stress, which can lead to the sensation of pain. In chronic pain conditions, such as **back pain**, **arthritis**, and **neuropathic pain**, TRPV1 channels may become **sensitized (central sensitization).** This means that the threshold for activation is lowered, leading to heightened pain sensitivity (hyperalgesia).	**TRPV1 C1462T**: This variant has been linked to altered pain perception and a possible predisposition to conditions like **fibromyalgia** and **chronic low back pain**. **TRPV1 I296V**: Another polymorphism that may influence the receptor's response to stimuli and contribute to pain sensitivity.

6. INTRACELLULAR PAIN SIGNALLING PATHWAYS

Pain transmission involves activation of G-protein-coupled receptors (GPCRs) by neurotransmitters such as substance P and glutamate released following tissue injury or inflammation. Ligand binding induces conformational changes in GPCRs, leading to activation of heterotrimeric G-proteins through GDP–GTP exchange. The dissociated G-protein subunits (Gα and Gβγ) initiate intracellular signalling cascades involving secondary messengers such as cyclic adenosine monophosphate (cAMP), inositol trisphosphate (IP3), and diacylglycerol (DAG), which amplify nociceptive signalling and enhance neuronal excitability[40].

Persistent activation of these intracellular pathways contributes to long-term changes in gene expression within nociceptive neurons and central pain-processing regions. GTPases play a crucial role in regulating cytoskeletal dynamics, synaptic plasticity, and intracellular transport, all of which are essential for neuronal adaptation. In chronic pain states, excessive GTPase activity is associated with maladaptive neuroplasticity, facilitating sustained pain transmission and central sensitization[40].

Importantly, prolonged intracellular signalling is closely linked to epigenetic modifications, including DNA methylation, histone acetylation, and regulation by non-coding RNAs. These epigenetic mechanisms alter transcriptional activity of pain-related genes without changing the DNA sequence. Repeated nociceptive input and chronic inflammation can induce epigenetic upregulation of genes involved in neurotransmitter release, receptor sensitivity, and inflammatory mediator production, thereby reinforcing chronic pain states. Thus, intracellular signalling pathways act not only as immediate pain amplifiers but also as long-term regulators of pain through epigenetic reprogramming of neural and immune cells.

7. PAIN FIBERS AND NEUROINFLAMMATION

TRPV1 receptors are expressed predominantly in C fibers and Aδ fibers, the primary afferent fibers responsible for nociceptive transmission. C fibers mediate slow, dull, and burning pain, while Aδ fibers transmit sharp, fast pain. Activation of TRPV1 receptors by thermal, chemical, or mechanical stimuli leads to cation influx, neuronal depolarization, and action potential propagation toward the central nervous system[41].

Neuroinflammation plays a critical role in sensitizing these pain fibers. Immune-mediated release of cytokines, nitric oxide, and inflammatory mediators increases membrane excitability and lowers activation thresholds of nociceptors. Nitric oxide, produced through GCH1-dependent pathways, further enhances synaptic transmission and dorsal horn excitability, contributing to persistent pain and hyperalgesia[41].

At the epigenetic level, chronic neuroinflammation induces sustained transcriptional changes in nociceptive neurons and glial cells. Epigenetic modifications promote prolonged expression of TRPV1 receptors, inflammatory cytokines, and excitatory neurotransmitters, maintaining sensitization even after the initial tissue insult has resolved. This epigenetic “memory” of pain explains why chronic pain can persist despite structural healing and why pain becomes increasingly resistant to conventional interventions.

8. IMPLICATIONS FOR PHYSIOTHERAPY AND MANUAL THERAPY

Understanding the epigenetic consequences of altered pain modulation, immune activation, mitochondrial dysfunction, and intracellular signalling provides a strong biological rationale for physiotherapy interventions in chronic pain management. Physiotherapy does not merely act at a biomechanical level but has the potential to influence molecular and epigenetic pathways associated with pain processing.

Exercise therapy has been shown to modulate neurotransmitter metabolism, including COMT activity, thereby influencing dopamine availability and pain perception. Regular physical activity can downregulate pro-inflammatory cytokines such as TNF-α and IL-6, indirectly modifying epigenetic regulation of inflammatory genes. Exercise also enhances mitochondrial biogenesis and oxidative phosphorylation, improving cellular energy availability and reducing metabolic stress that contributes to pain sensitization[42].

Manual therapy and movement-based interventions may influence GPCR signalling and nociceptor sensitivity by altering afferent input, reducing sustained nociceptive signalling, and modulating central pain processing. Reduced nociceptive drive may, over time, reverse maladaptive epigenetic changes associated with chronic pain. Neuromodulatory effects of physiotherapy interventions can therefore be understood as mechanisms that promote favorable epigenetic reprogramming of neural and immune cells, restoring more adaptive pain modulation[42].

Physiotherapy and COMT Dose

The search results of the review confirmed that defining a precise exercise dose is difficult due to heterogeneity among sample and protocol. Therefore, the best reference should be a review that attempts to correlate *any* dose with molecular changes.

Point	Suggested Reference and Explanation
Dose (Intensity, Type, Frequency) of Exercise to Reduce S-COMT Activity	This review synthesizes the mechanistic effects of exercise on pain, including central pathways. This reference supports the general concept of exercise-induced hypoalgesia (EIH) being mediated by catecholamine metabolism and descending inhibitory pathways, thereby providing the necessary foundation for discussing the dose-response relationship in COMT[43].

Manual Therapy and Mechanotransduction

The search results for review strongly validate the role of TRPV1 in nociception and sympathetic activity. The core challenge is linking manual therapy to this *specific* mechanism.

Point	Suggested Reference and Explanation
Manual Therapy as a Mechanotransducer	This is a foundational model paper proposed that manual therapy works via mechanotransduction and *explicitly* includes autonomic

(TRPV1, SNS output)	responses and local effects on peripheral receptors (A-delta and C fibers, which contain TRPV1) as key mechanisms[44].

Biomarkers and Personalization

The search results for this review strongly support using COMT and GCH1 variants for personalized medicine.

Point	Suggested Reference and Explanation
Genetic Biomarkers (COMT/GCH1) and Personalization	This is a highly specific review focusing on the practical application of COMT and other genetic markers (GCH1 included) to tailor treatment. It directly supports the argument that genetic stratification (e.g., COMT Met/Met vs. Val/Val) can make the clinician's choose between centrally acting therapies (like CBT/mindfulness) and peripheral/anti-inflammatory treatments[45, 46, 47]

From an epigenetic perspective, physiotherapy interventions represent non-pharmacological strategies capable of influencing gene expression related to pain, inflammation, and neural plasticity. This supports a shift toward personalized, mechanism-based rehabilitation approaches tailored to individual pain phenotypes and genetic susceptibility.

9. CONCLUSION

Chronic low back pain is a multifactorial condition characterized by impaired conditioned pain modulation, persistent immune-mediated inflammation, mitochondrial dysfunction, altered intracellular signalling, and genetic and epigenetic susceptibility. Dysregulated GPCR-mediated signalling, GTP-dependent pathways, and sustained neuroinflammation drive maladaptive neuroplasticity and epigenetic changes that maintain pain sensitization beyond tissue healing. Recognition of these interconnected mechanisms emphasizes the need to move beyond purely structural explanations of pain. Physiotherapy interventions, through their influence on neural, immune, metabolic, and epigenetic pathways, offer a scientifically grounded approach to pain modulation and long-term rehabilitation. Integrating epigenetic understanding into physiotherapy practice provides a foundation for personalized, mechanism-based management of chronic low back pain.

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