Evidence for spinal cord hypersensitivity in chronic pain after whiplash injury and in fibromyalgia

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FROM ABSTRACT:

Patients with chronic pain after whiplash injury and fibromyalgia patients display exaggerated pain after sensory stimulation.

Because evident tissue damage is usually lacking, this exaggerated pain perception could be explained by hyperexcitability of the central nervous system.

The nociceptive withdrawal reflex (a spinal reflex) may be used to study the excitability state of spinal cord neurons.

We tested the hypothesis that patients with chronic whiplash pain and fibromyalgia display facilitated withdrawal reflex and therefore spinal cord hypersensitivity.

Three groups were studied: whiplash \((n=27)\), fibromyalgia \((n=22)\) and healthy controls \((n=29)\).

Two types of transcutaneous electrical stimulation of the sural nerve were applied: single stimulus and five repeated stimuli at 2 Hz. Electromyography was recorded from the biceps femoris muscle. The main outcome measurement was the minimum current intensity eliciting a spinal reflex (reflex threshold).

Reflex thresholds were significantly lower in the whiplash compared with the control group, after both single and repeated stimulation.

The same was observed for the fibromyalgia group, after both stimulation modalities.

We provide evidence for spinal cord hyperexcitability in patients with chronic pain after whiplash injury and in fibromyalgia patients.

This can cause exaggerated pain following low intensity nociceptive or innocuous peripheral stimulation.

Spinal hypersensitivity may explain, at least in part, pain in the absence of detectable tissue damage.
THESE AUTHORS ALSO NOTE:

“Peripheral injury and/or inflammation, induced experimentally in animals, cause plasticity changes in the central nervous system that result in neuronal hyperexcitability.”

“This central hypersensitivity causes exaggerated perception of painful stimuli (hyperalgesia) and a perception of innocuous stimuli as painful (allodynia).”

Patients with chronic pain after whiplash injury and with fibromyalgia have exaggerated pain responses following sensory stimulation of healthy tissues.

Central hypersensitivity causes the nociceptive signal to be amplified, even in the presence of minimal and undetectable soft tissue damage. [IMPORTANT]

These chronic pain patients could have irreversible plasticity changes in the central nervous system.

The nociceptive withdrawal reflex is a spinal reflex of the lower extremity that can be elicited by a painful stimulation of a sensory nerve. The minimal intensity of the stimulus that is sufficient to elicit a reflex can be electro-physiologically documented.

This method can be used to quantifying the excitability of spinal neurons.

All whiplash and fibromyalgia patients in this study had pain for more than 6 months.

In these patients, psychological assessment was performed by the self-report questionnaires:

1) The German versions of the NEO-FFI test (Neuroticism, Extraversion, Openness; Five Factor Inventory. The NEO-FFI test assesses five personality dimensions (neuroticism, extraversion, openness, agreeableness and conscientiousness), which are considered the major dimensions of the human personality. This inventory is reliable when retesting over time and is therefore independent of current life circumstances. It consists of 60 items (12 for each personality dimension). The item analysis yields a score for each personality dimension, which is transformed into t-value adjusted to gender.

2) The SCL-90-R (Symptom Check List-90, revised version. The SCL-90-R is used to assess psychological distress in patients, including patients with chronic pain. The SCL-90-R is a checklist with 90 items, each describing a physical or psychological symptom. The item analysis yields scores for nine
dimensions: somatization, obsession-compulsion, inter-personal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism. In addition, a score for the general psychological distress (general severity index) is calculated.

“The normal range of the scores of both NEO-FFI and SCL-90-R corresponds to $t$-values between 40 and 60. $t$-Values greater than 60 indicates a pathology of the corresponding psychological dimension.”

Pain intensity was quantified with a 10 cm visual analogue scale (VAS), where 0 indicates no pain and 10 corresponds to the worst pain imaginable.

Muscle tenderness was measured with an electronic pressure algometer.

Pain detection threshold was defined as the point at which the pressure sensation turned to pain.

Pain tolerance threshold was defined as the point at which the subject felt pain as intolerable.

RESULTS

Regarding personality traits, all three groups scored within the normal range (i.e. between 40 and 60).

“In contrast, both patient groups displayed considerably elevated scores on several dimensions of the SCL-90-R, indicating psychological distress. Particularly high scores were found in the fibromyalgia group.”

In the whiplash group, the median duration of pain was 22 months and the median pain intensity was 3.7.

In the fibromyalgia group, the median duration of pain was 138 months, and the median pain intensity was 4.6.

“Pressure pain detection and pressure pain tolerance thresholds were significantly lower in both patient groups compared with the control groups.”

15 whiplash patients and 16 fibromyalgia patients were not working because of their condition.

“Reflex thresholds after single and repeated electrical stimulation were significantly lower in both whiplash and fibromyalgia groups than in control groups.”

[IMPORTANT]

Median pain thresholds to electrical stimulation were lower in both patient groups compared to control groups.
DISCUSSION

“The stimulus intensity necessary to evoke a spinal reflex is significantly lower in patients with chronic pain after whiplash injury and in fibromyalgia patients than in healthy subjects.”

“This demonstrates a state of hypersensitivity of spinal neurons to peripheral stimulation.”

Seven cited previous studies on whiplash and fibromyalgia patients analyzed the stimulus intensity necessary to evoke a pain sensation, and in each, the pain threshold was lower in patients than in healthy subjects, which was attributed to a possible hypersensitivity of the central nervous system.

“Thus the present study is the first one clearly demonstrating [objectively] that spinal cord neurons are sensitized in chronic pain after whiplash injury and in fibromyalgia.”

These authors also found lower median pain thresholds in whiplash and fibromyalgia patients as compared to healthy subjects.

These authors found that reflex measurements may be more sensitive than pain threshold measurements for detecting central hypersensitivity.

“The presence of spinal cord hypersensitivity in these two very different pain syndromes suggests that this phenomenon may be present also in other chronic musculoskeletal pain states.” [IMPORTANT, synaptogenesis/neuroplasticity]

“Tissue damage and inflammation produce a variety of local biochemical events that sensitize the peripheral receptors and may activate normally inactive nociceptors.” [Prostaglandin E2 from the omega-6 arachidonic cascade]

“Peripheral inflammation induces a gene expression in the dorsal root ganglion resulting in an increased synthesis of peripheral receptors.” [Receptive Field Enlargement]

This causes a reduced threshold for pain within the injured area.

“Peripheral tissue damage is not detected in many patients with chronic pain after whiplash injury, although the available diagnostic tools may fail to identify the peripheral source of pain.” [IMPORTANT]

In this study, because the electrical stimulation bypasses peripheral receptors and activates directly the nerve fibers, the low reflex and pain thresholds observed was not the result of peripheral sensitization, but from altered spinal cord hypersensitivity.
“Tissue damage induces profound plasticity changes in the spinal cord that result in increased responsiveness to peripheral stimulation.”

Why is this hypersensitivity is observed at tissues that are not injured and distant from the site of pain?

An explanation is “expansion of receptive fields.” [IMPORTANT]

“As a result, a peripheral stimulus activates a higher number of dorsal horn neurons and hyperalgesia may also be evoked in healthy areas surrounding the injured region.” [IMPORTANT]

“Inflammation produces expression of cyclooxygenase-2 (COX-2) in the spinal cord, which leads to prostaglandin production and neuronal hyperexcitability.”

[Recall, COX-2 is an enzyme that converts the omega-6 fatty acid arachidonic acid into the pro-inflammatory eicosanoid prostaglandin E2. The pro-inflammatory eicosanoid prostaglandin E2 alters the thresholds of the nociceptive afferent system, sending more pain afferentation into the spinal cord.]

“Importantly, COX-2 expression is not confined to the neural structures connected to the site of inflammation, but is observed in the whole spinal cord and in supraspinal centers.”

“This may explain widespread spinal cord hyperexcitability after inflammation and tissue damage.” [IMPORTANT]

Why is hypersensitivity observed in the absence of evident tissue damage?

Research has shown the occurrence of irreversible changes in the central nervous system after tissue damage, such as “expression of gene products, destruction of inhibitory interneurons and aberrant excitatory connections.”

“These changes might persist after injury has healed, thereby explaining persistent pain.” [IMPORTANT]

“Absence of evident tissue damage does not necessarily mean that there is no tissue damage.” [VERY IMPORTANT]

“For instance, the zygapophysial joints have been identified as a frequent source of pain after a whiplash injury, even when clinical and radiological investigations do not show specific lesions of these joints.”

“Tissue damage, recognized or not by the available diagnostic methods, induces persistent hyperexcitability of spinal cord neurons of patients that are involved in persistent pain complaints.” [IMPORTANT]
“The underlying mechanism may be either a sustained central facilitation by nociceptive input from an unrecognized peripheral focus or spinal cord plasticity changes that persist after resolution of tissue damage.”

Elevated levels of substance P and excitatory amino acids [like glutamate] have been found in the cerebrospinal fluid of fibromyalgia patients, and they cause generalized spinal cord hyperexcitability. This may also occur in the cerebrospinal fluid in whiplash patients.

Supraspinal mechanisms may also explain spinal cord hyperexcitability and persistent pain.

“Spinal cord hyperexcitability elicited by trauma or inflammation is influenced by descending facilitatory and inhibitory pathways.”

Some patients have a genetic reduction in serotonin production.

These patients have higher levels of depression, psychological distress and pain.

Serotonin is known to modulate descending pain control and depression/psychological distress.

Consequently, “the psychological distress typical of chronic pain conditions is a determinant of spinal cord hyperexcitability via imbalance of descending modulatory mechanisms” [from a reduction of serotonin production].

CONCLUSIONS

“Using an objective assessment procedure, we found spinal cord hyperexcitability in chronic pain after whiplash injury and in fibromyalgia.”

“This finding can explain exaggerated pain following low intensity nociceptive stimulation arising from areas of minimal and undetectable tissue damage or pain after innocuous sensory stimulation.”

“Plasticity changes in the spinal cord excitability induced by peripheral mechanisms, genetically driven biochemical alterations in the neurotransmitter system and imbalance of descending modulatory pathways due to psychological factors may be responsible for the neuronal hypersensitivity.”

This “study demonstrates that both patient groups have neurobiological changes that are likely to alter the spinal nociceptive processing of peripheral stimuli.”
KEY POINTS FROM DAN MURPHY

1) Whiplash causes tissue damage.

2) This tissue damage is not recognized by available diagnostic procedures.

3) Whiplash tissue damage produces inflammation, [primarily from the conversion of the omega-6 fatty acid arachidonic acid into prostaglandin E2].

4) This inflammation alters the thresholds of the nociceptive afferent system, increasing pain.

5) This inflammation also induces a gene expression in the dorsal root ganglion resulting in increased peripheral receptor fields. [Receptive Field Enlargement] This also increases pain.

6) This inflammation also increases the expression (production) of cyclooxygenase-2 (COX-2) in the spinal cord, which is an enzyme that converts the omega-6 fatty acid arachidonic acid into the pro-inflammatory eicosanoid prostaglandin E2. The pro-inflammatory eicosanoid prostaglandin E2 further alters the thresholds of the nociceptive afferent system, sending more pain afferentation into the spinal cord.

7) This increased COX-2 expression is not confined to the neural structures connected to the site of inflammation, but is observed in the whole spinal cord and in supraspinal centers. This alters the pain sensitivity of the entire body, including non-injured regions.

8) All of this induces profound plasticity changes [synaptogenesis/neuroplasticity] in the spinal cord that result in increased pain that can persist after all possible tissue healing has occurred.

9) Some of these spinal plastic changes may be irreversible (permanent chronic pain syndromes).

10) This article objectively proves that patients with chronic pain have hypersensitivity of the spinal cord neurons.

11) This article suggests that important diagnostic efforts for the whiplash-injured patient include:
    A)) The nociceptive withdrawal reflex (flexor reflex afferents is what this is called in neurology diplomate class).
    B)) The NEO-FFI test (Neuroticism, Extraversion, Openness; Five Factor Inventory.
    C)) The SCL-90-R (Symptom Check List-90, revised version.
    D)) The visual analogue scale (VAS)
E) The pressure algometer.

12) The absence of evident tissue damage does not necessarily mean that there is no tissue damage.

13) Elevated levels of excitatory amino acids, like glutamate, are often found in the cerebrospinal fluid of chronic pain patients, and cause generalized spinal cord hyperexcitability. [Recall that glutamate is often added to foods to enhance taste, and it does cross the blood-brain barrier to enter the cerebral spinal fluid.]

14) Serotonin inhibits pain and inhibits depression. Reduced serotonin may explain while chronic pain patients often suffer from psychological distress.

COMMENT BY DAN MURPHY

I am currently involved in a whiplash case where the IME chiropractor states:

“The patient has been substantially over-treated and any treatment extending past the average 6-week expectation of recovery should not be reimbursed. The appropriate number of treatments would more approximately be 14 to 16 in the range of total cost of approximately $1,400.00.”

I believe this is wrong, and we will use this article as part of our rebuttal to her report.