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Latent Modulation of Neuropathic Pain Intensity via Hypothalamus-pituitary-thyroid Axis of Psychogenic Stress

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Latent modulation of neuropathic pain intensity via hypothalamus-pituitary-thyroid axis of psychogenic stress.

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INTRODUCTION

Complex regional pain syndrome (CRPS) is a chronic pain syndrome characterized by autonomic changes and pain in an extremity which is out of proportion in intensity and duration to the inciting trauma.[1,2] Pain experienced by individuals with CRPS fluctuates over time and manifests episodic peaks.[1] Many factors, such as temperature, activity level, and stress may contribute to the appearance of pain flares.[2] Stress has been studied as a factor mediating pain intensity over time, yet a same-day relationship between perceived stress and pain intensity has not been supported.[3] However, recent studies have reported notable correlations between peak stress days and pain flares occurring ten days later in patients with fibromyalgia syndrome and CRPS.[3,4] The hypothesized mechanism involves delayed activation of the stress-related hormone thyroxine via the hypothalamus-pituitary-thyroid (HPT) axis of the stress response.[5] After secretion, thyroxine is bound by serum proteins then uncoupled over time into its active free state, producing peak systemic effects after approximately ten days.[6] Effects include increased peripheral nerve excitability, central nervous system sensitization, and insomnia, which may mediate both nociceptive input intensity and cognitive interpretation of pain.[5] While theoretically plausible, there is not yet evidence that the stress-related release of thyroxine temporally parallels changes in pain intensity for patients with chronic pain syndromes.[5] Providing some explanation for seemingly unpredictable pain flares may help patients and therapists discriminate between stress-related flares and those caused by factors such as poor activity pacing or intensity of therapeutic activity.

PURPOSE

The purpose of this study was to investigate a hypothesized psychophysiological mechanism for recent findings that psychogenic stress episodes precipitate delayed flares in pain intensity occurring ten days after the stressful event in patients with complex regional pain syndrome (CRPS). Specifically, this study assessed temporal relationships over a ten-week period between daily stress, perceived pain intensity, pain-related function, and serum levels of the stress-related hormone thyroxine in patients with CRPS.

METHODS

Three patients were assessed daily for ten weeks on stress, pain intensity, pain-related function, and serum thyroxine (T4) levels. Each day, for 70 consecutive days, patients completed a visual analog stress scale (VASS), visual analog pain scale (VAPS), an individualized visual analog function scale (VAFS), and the McGill pain questionnaire short form (SF-MPQ). Throughout the ten-week period patients submitted daily blood draws for T4 analysis. Free serum T4 levels were determined using microplate enzyme immunoassays. To assess daily reliability of T4 assays, each daily blood sample was split and analyzed twice by an independent laboratory, each time using separate procedures, separate technicians, and reagent kits from two separate manufacturers. Thyroxine assays yielded a free T4 index (FTI) and two independent assessments of free T4. Samples were maintained at 2-8º C until analysis and all assays were conducted within seven days of collection. Due to possible influences on pain and hormone activity, patients reported all daily medication usage and any menstrual activity.

ANALYSIS

Linear regression relationships between perceived stress, pain, and FTI were analyzed using serial lag correlations to determine occurrences of consistently delayed elevations in pain or free T4. Daily stress scores were correlated with pain and T4 measures for same-day as well as each consecutive day's pain and T4 scores up to a fourteen-day lag. Same-day product-moment correlation coefficients were calculated between pain and T4 scores.

RESULTS

Across patients, 14 peak stress episodes and 26 significant pain flares were reported. Each stress episode was followed ten days by a significant pain flare and free T_4 values exceeding normal adult range (2.4ng/dL). Serial lag correlations were strongest between stress and pain for pain experienced ten days after peak stress episodes ($r=+0.381$, $p< 0.05$). FTI correlated strongest with stress ten days following a stressful episode ($r =+0.454$, $p< 0.001$). Same-day pain and FTI correlated at $r=+0.643$, $p< 0.001$. Figures 1-4 illustrate the temporal responses of pain and thyroxine levels as a function of measured psychogenic stress for patient #1.

Figure 1. Visual analog stress scores (VASS) with visual analog pain scores (VAPS) from ten days later across ten weeks.

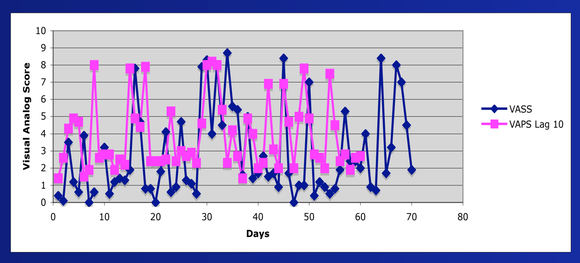


Figure 2. Serial lag correlations between daily visual analog stress scores and lagged pain up to a fourteen-day lag.

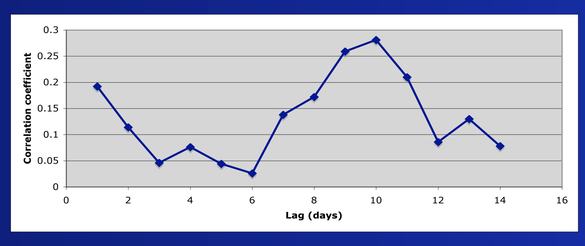


Figure 3. Visual analog stress scores (VASS) with free thyroxine index (FTI) ten days later across ten weeks.

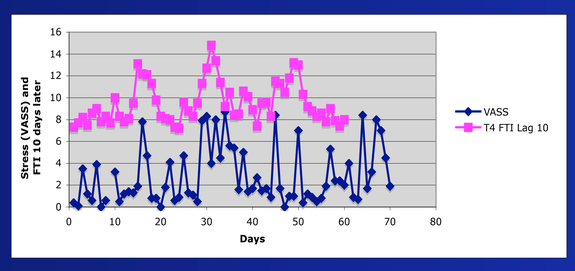
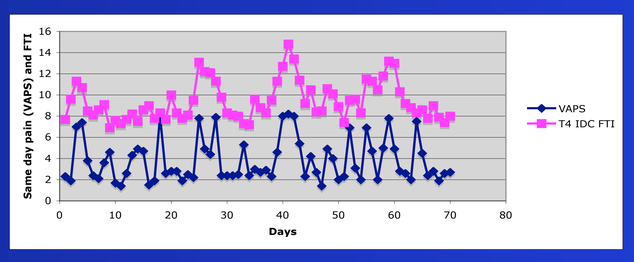


Figure 4. Same-day visual analog pain scores (VAPS) with free thyroxine index (FTI) across ten weeks.



Discussion

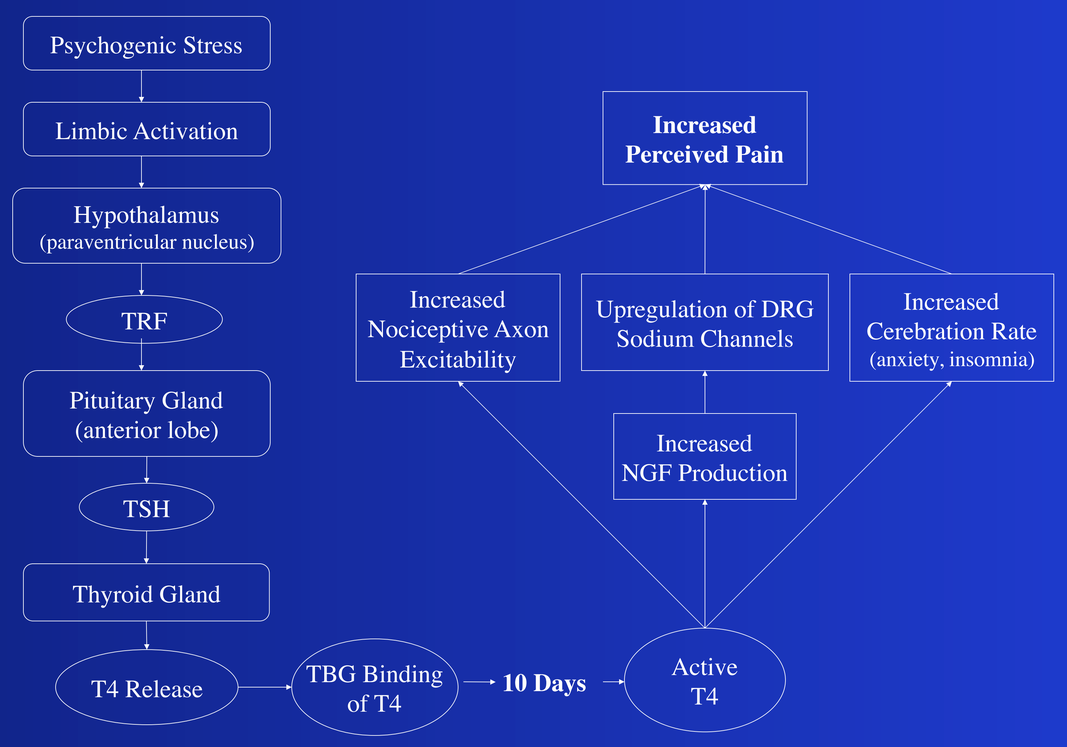
The findings of this investigation are consistent with prior research reporting a ten-day pain modulation effect due to psychogenic stress and lends support to the hypothesis that T4 release is at the root of the mechanism of pain modulation.

Via the HPT axis, thyoid hormones may modulate pain via several effects. First, by elevating peripheral nerve excitability, T4 increases peripheral nociceptive input to the dorsal horn without the necessity of an accompanying change at a distal lesion site. Second, via reticular core activation from increased spinoreticular input and direct CNS sensitization, cerebration rates increase, resulting in elevated cortical activity and anxiety. Further, high cerebration rates could lead to episodic insomnia and hence elevated pain perception secondary to sleep loss. Thyroxine could, therefore, increase the perceived intensity of pain by bringing a stronger pain signal into the CNS and ultimately deliver that message to a hyperaroused cortex that is more likely to interpret that message as severe, all without any change at the distal tissue level. Thyroxine may additionally induce hyperalgesia in patients with neuropathic pain through an indirect pathway, by increasing levels of neurotropic growth factor (NGF) resulting in an upregulation of sodium ion channels in the dorsal root ganglion (DRG). Intravenous injections of NGF in human patients have resulted in hyperalgesia and deep tissue pain, which occurs at the site of injection. Thyroxine's effect on the increase in NGF may, therefore, result in increased expression of sodium gated channels leading to a hypersensitivity to pain. [7]

Conclusion

Increased pain ten days following stressful events is related to psychogenic HPT activity in CRPS patients. Pain modulation by thyroxine may assist understanding pain fluctuation etiology and suggest new treatment avenues for managing neuropathic pain.

Figure 5. Summary of delayed pain modulation mechanism via T4 release and delayed influence on perceived pain intensity.



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IRB Approval
This study was granted approval for participation by human volunteers from the Institutional Review Board of the University of Puget Sound on 12/01/07;
IRB protocol #0607-007.

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