Published in final edited form as:
Spine (Phila Pa 1976). 2011 December 1; 36(25 Suppl): S226–S232. doi:10.1097/BRS.0b013e3182387fb4.

The Potential Contribution of Stress Systems to the Transition to Chronic WAD

Samuel A McLean, MD
Department of Anesthesiology, N2201 UNC Hospitals, Campus Box 7010, Chapel Hill, NC 27599-7010, USA. Tel.: +1 919 843-5931; fax: + 1 919 966-1470

Samuel A McLean: samclean@email.unc.edu

Abstract

Study Design—A narrative description highlighting preclinical and clinical evidence that physiologic stress systems contribute to WAD pathogenesis.

Objective—To present several lines of evidence supporting the hypothesis that physiologic stress systems contribute to WAD pathogenesis.

Summary of Background Data—In addition to subjecting soft tissue to biomechanical strain, a motor vehicle collision (MVC) event is also an acute stressor which activates physiologic stress systems. Increasing data from animal and human studies suggest that the activation of these stress systems may contribute to long lasting changes in pain sensitivity after tissue injury.

Methods—Non-systematic review of several lines of evidence that together suggest that physiologic systems involved in the stress response may contribute to the development of WAD.

Results—Stress systems which appear capable of producing hyperalgesia and allodynia include catecholaminergic systems, serotonin systems, and the hypothalamic-pituitary-adrenocortical (HPA) system. Evidence for the role of these systems comes, in part, from studies examining the association between genetic variants and chronic pain outcomes. For example, in a recent study of acute neck pain after MVC, patients with certain genotypes of an enzyme involved in catecholamine metabolism were more than twice as likely to report moderate or severe neck pain in the emergency department. Such pain vulnerability due to stress system function may interact with the effects of biomechanical injury and psychobehavioral responses to influence the development of WAD.

Conclusion—More research examining the influence of stress systems on WAD are needed. If these systems do influence WAD outcomes, then treatments which diminish the adverse effects of stress systems may be a useful component of multimodal therapeutic interventions for individuals at risk of chronic pain development after MVC.

Keywords

WAD; musculoskeletal pain; Stress; motor vehicle collision

Introduction

Several epidemiologic characteristics of Whiplash Associated Disorders (WAD) seem incompatible with a purely biomechanical pathogenesis. First, the incidence of chronic pain following motor vehicle collision (MVC) is strongly influenced by sociocultural factors.[1–3] In addition, collisions that occur in other non-threatening settings (e.g. in bumper cars) exert the same biomechanical stress as a low speed MVC,[4] yet prolonged WAD after bumper car collisions are rare[5]. The results of one small clinical study even suggest that physical

collision may not be necessary for WAD symptoms, as a minority of individuals exposed to a "sham" (placebo) rear-end collision reported whiplash symptoms three days after the event.[6]

In the broader pain field, chronic musculoskeletal pain pathogenesis is summarized in biopsychosocial models such as the well known cognitive-behavioral model of Vlaeyen et al.[7] In brief, according to this model patients with initial WAD symptoms who greatly fear the experience of pain (e.g. because of the belief that pain denotes permanent body damage being done) withdraw from activities, promoting disuse, disability, and increased pain. This further heightens fear, leading to a vicious cycle of disuse, disability, pain, and fear. Vlaeyen's model[7] and its application to WAD[8] exemplifies the progress that has been made in identifying psychobehavioral factors that may contribute to persistent pain development. However, the fear-avoidance model does not identify candidate neurobiological mechanisms which mediate the development of the pain symptoms which are the hallmark of WAD[9–12].

The purpose of this narrative review is to present several lines of evidence that together suggest that physiologic systems involved in the stress response may contribute to the development of WAD. Because this review is concerned with the potential influence of stress systems in total, and because the mechanisms by which stress systems may influence pain and other somatic symptoms are myriad and complex, this is not a comprehensive review of specific physiologic mechanisms. For the same reasons, stress systems are considered broadly. For example, there are a number of catecholaminergic systems which may be activated in response to stress exposure, including central catecholaminergic systems, the sympatho-adrenomedullary system, and sympatho-neural systems.[13] For the purposes of this discussion, all of these systems will together be referred to simply as "catecholaminergic systems".

Stress systems, such as these catecholaminergic systems, are extremely useful in optimizing the response of an organism to immediate environmental circumstances (e.g. by increasing vigilance and energy mobilization[14,15]). However, there is increasing appreciation that the activation of these systems can also have adverse biologic consequences. For example, the activation of catecholaminergic systems in the setting of a surgical stressor has been shown to increase both immediate and long term cardiovascular sequelae.[16,17] Interestingly, while less well appreciated, there is increasing evidence that the activation of these systems may also contribute to the development of post-stress pain and somatic symptoms.[18] Evidence suggesting that the activation of stress systems may contribute to pain and somatic symptoms after MVC will be described below. Several animal models of stress-induced hyperalgesia will be reviewed, and evidence regarding the potential influence of several specific stress system components on neurosensory processing will be presented. In the final sections, potential clinical implications of these findings will be discussed and current research needs and future directions will be described.

Animal Models Indicate that Stress Exposure without Injury Can Alter Pain Sensitivity

Data from animal models of stress exposure indicate that stress system activation is itself capable of altering pain processing, even in the absence of tissue trauma. These models will be briefly described; a more extensive review can be found in Imbe et al[19]. A number of experimental rat models have demonstrated that exposure to a single, brief, non-noxious stress can induce hyperalgesia.[20–23] Stress exposures used in these studies included placing the animal in a novel environment, holding the animal so that it cannot escape, and placing the animal on a vibrating plate.[20–23] The duration of hyperalgesia produced by these single brief stress exposures was relatively short.

Other models using repeated exposures (e.g. to cold[24], restraint[25–28], or swimming[29]) have produced more long-lasting changes in pain sensitivity. Cold exposure for several consecutive days has been shown to result in decreased mechanical pain threshold, which lasts for a number of days after the end of the exposure period.[24] Repeated swim stress exposure, in which rats must swim 10–20 minutes for 3 days (inescapable, non-painful, moderate swim stress) has been shown to produce hyperalgesia to both thermal and chemical stimuli.[29] When animals were tested 8 and 9 days after stress exposure, this hyperalgesia was still present.[29] Repeated restraint stress (for example, restraint of rats in a plastic tube 1 hour per day, 5 days a week for 40 days) has also been shown to produce long-lasting hyperalgesia.[25–28] Together, these animal studies provide support for the hypothesis that a stressful experience does not have to produce tissue injury in order to produce prolonged changes in pain sensitivity.

Influence of Stress Systems on Pain Sensitivity May Change over Time after Stress Exposure

When examining the influence of stress systems on pain after stress exposure, it is important to appreciate that the influence of stress systems on pain and somatic symptoms after stress exposure may change over time. For example, it has been shown that in order to form long-lasting memories (“flashbulb memories”) of a stressful event, the same set of stress response effectors produces a brief period of memory formation followed by a longer period of memory inhibition.[30,31] Such mechanisms may, in part, provide an explanation for discoveries regarding the opposing effects of catecholaminergic systems on pain.

Since the middle of the last century, it has been appreciated that the activation of catecholaminergic systems can produce immediate analgesia.[32,33] Indeed, it is part of common lay understanding that such immediate analgesia is a component of the “flight or flight” response. However, while the immediate influence of catecholaminergic systems is often to reduce pain, more recent evidence indicates that continued activation of these systems may result in hyperalgesia and allodynia[34–40]. These data, reviewed below, have prompted a renewed examination of the potential influence of catecholaminergic systems on chronic pain development after traumatic events such as MVC.

Evidence that Catecholaminergic Systems Influence Pain Sensitivity

In humans, the chronic administration of catecholamines has been shown to produce a painful arthritis-like syndrome.[41] Importantly, in addition to these direct effects on pain sensitivity, catecholamines have also been shown to enhance pain due to tissue injury and inflammation. For example, in animal models of rheumatoid arthritis, the sustained bioavailability of epinephrine (either released from the adrenal medulla or administered exogenously) substantially augments inflammatory mediator-induced hyperalgesia.[35,36] Similarly, increasing catecholamine levels have been shown to increase carrageenan-induced pain.[34]

Also, just as increased catecholamines have been shown to increase pain, a reduction in catecholamine effects has been shown to reduce pain and/or prevent enhanced pain sensitivity. Denervation of sympathetic noradrenergic fibers and the depletion of peripheral epinephrine have been found to attenuate arthritic responses.[37,38] In humans, sympathetic blockade or the administration of the β-adrenergic receptor antagonist propranolol have been observed to reduce the severity of arthritis and joint responses to injury, and to provide pain relief for patients with chronic musculoskeletal pain syndromes.[42–45] Together these studies provide substantial evidence that catecholamines may cause pain directly and/or increase pain caused by tissue injury. If this is the case, then it may be hypothesized that genetic

variations which influence catecholamine metabolism (and catecholamine levels) influence pain outcomes after MVC. Preliminary evidence supports this hypothesis.

Specific Catecholaminergic System Components: Catechol-o-methyltransferase enzyme

Catechol-o-methyltransferase (COMT) is the primary enzyme which degrades catecholamines. In animal studies, increasing catecholamine levels via the inhibition of this enzyme has been shown to produce allodynia and hyperalgesia.[34] The increase in pain sensitivity produced by elevated catecholamines has been found to be comparable in magnitude to that produced by the intraplantar injection of carrageenan (an inflammatory agent).[34]

Previous work has identified three common variations, or haplotypes, of the *COMT* gene that code for different levels of COMT enzymatic activity and influence an individual's pain sensitivity.[40] The *LPS* haplotype codes for the highest enzyme activity and is associated with the highest pain tolerance. The *APS* haplotype codes for comparably less enzyme activity and is associated with average pain tolerance. The *HPS* haplotype codes for the least enzyme activity and is associated with the lowest pain tolerance.[40] In a recent study of 89 patients presenting to the emergency department (ED) for evaluation in the hours after experiencing a MVC, individuals with a *COMT* pain vulnerable genotype (defined as genotypes that did not include at least one copy of the *LPS* haplotype) were more than twice as likely to report moderate-to-severe musculoskeletal neck pain in the ED (76% vs. 41%, RR = 2.1 (1.3–3.4)).[46] Individuals with a *COMT* pain vulnerable genotype were also more likely to report moderate or severe headache in the ED (61% versus 33%, RR = 3.15 (1.05–9.42)), and moderate or severe dizziness in the ED (26% versus 12%, RR = 1.97 (1.19–3.21)).[46] Individuals with a pain vulnerable genotype also experienced more dissociative symptoms in the ED, and estimated a longer time to physical recovery (median 14 versus 7 days, P = .002) and emotional recovery (median 8.5 versus 7 days, P = .038).[46] These findings support the hypothesis that genetic variations affecting stress system function influence the somatic and psychological response to MVC, and provided the first evidence of genetic risk for clinical symptoms after MVC. Because acute neck pain intensity is a strong risk factor for the development of WAD,[47] these data also suggest that genetic variations in COMT may predict chronic post-MVC pain.

Specific Catecholaminergic System Components: Adrenergic receptors

Adrenergic receptors transduce the cellular response to catecholamines. If adrenergic pathways involved in the stress response influence pain sensitivity and vulnerability to develop persistent pain, then pain processing would also be expected to be influenced by the function of adrenergic receptors. Available evidence suggests that this is the case.

α_1-adrenoceptor activity has been shown to sensitize nociceptive neurotransmission at both peripheral and central nervous system sites[48] and to upregulate known pain and inflammatory mediators such as STAT and cytokines.[49] Consistent with these findings, α_1-adrenoceptor agonists such as phenylephrine generally have a pro-nociceptive effect.[50–56] α_1-adrenoceptors are subclassified as α_{1A}, α_{1B}, and α_{1D}. α_{1A} and α_{1D} receptors have been shown to contribute to inflammatory pain[50] and heat pain[57] sensitivity, respectively. In addition, the three α_1-adrenoceptor subtypes have been shown to be differentially expressed in response to painful nerve damage, suggesting that nociceptive stimulation likely regulates the expression of these genes.[58] In a recent prospective study, genetic variations in α_{1A} receptors were found to be associated with up to a 9-fold increase in vulnerability to develop a common musculoskeletal pain condition, myogenous TMD.[59] Further assessments of the influence of genetic variations in α_{1A} receptors on acute pain and vulnerability to persistent pain after motor vehicle collision (MVC) are needed.

α_2-adrenoceptor agonists such as clonidine are widely used as analgesics.[60] α_2-adrenoceptors are subclassified as α_{2A}, α_{2B}, and α_{2C}. α_{2A} receptors have received the most study, and have been shown to help mediate adrenergic antinociception.[61,62] Little work has been done examining the influence of specific α_2 genes on pain sensitivity, with the exception of a single study which found that variations in α_{2A} and α_{2C} receptors were associated with somatic symptom scores in irritable bowel disease patients.[63]

The β_2-adrenoceptor has received relatively more study, and has been associated with variation in nociceptive function.[39,64] Cardiovascular function, particularly arterial blood pressure, appears to be influenced by β_2-adrenoceptors,[39,65] and cardiovascular and pain regulatory systems are closely associated with one another.[66,67] A recent prospective study of the development of a common musculoskeletal pain disorder found that variation in the gene encoding the β_2-adrenoceptor is associated with vulnerability to develop persistent pain.[39] In addition, a recent report identified an association between clinical conditions characterized by musculoskeletal pain and somatic symptoms and the minor allele for the gene encoding the β_3-adrenoceptor.[68] The above data suggest that adrenergic receptor function may be associated with pain vulnerability, including vulnerability to WAD after MVC. Studies assessing the potential association between adrenergic receptor function and acute and persistent WAD symptoms after MVC are needed.

Evidence that hypothalamic-pituitary-adrenocortical (HPA) Axis Activity Influences Pain Sensitivity

Acute stressors trigger the release of corticotrophin-releasing factor, which initiates the activation of the hypothalamic-pituitary-adrenocortical (HPA) axis and the release of cortisol.[15] Variation in HPA axis function has been shown to predict the development of pain and somatic symptoms in large population-based studies,[69,70] in patients undergoing surgery,[71] and in experimental studies of patients exposed to standardized stressors.[72] It can be hypothesized that individual variation in cortisol levels after MVC may influence the balance of peripheral pro-inflammatory cytokines, which may contribute to pain symptoms via peripheral or central mechanisms.[73]

Variation in the function of glucocorticoid receptors may also influence vulnerability to pain after stress exposure. There is increasing appreciation that the physiology of glucocorticoid receptors is highly complex.[74] Glucocorticoid receptors are located throughout the central nervous system, including both the brain and spinal cord dorsal horn. The activation of central glucocorticoid receptors has been shown to reduce systemic mechanical pain thresholds.[75] Glucocorticoid receptors in the spinal cord dorsal horn respond to peripheral nociceptive stimulation [76,77] and are capable of inducing antinociception.[78–80] In addition, there appears to be substantial functional interactions between central glucocorticoid and opioid analgesic systems.[81] Several genetic variations in glucocorticoid receptors and associated regulatory elements have been associated with an altered HPA axis stress response.[82,83] More work examining associations between genetic polymorphisms related to HPA axis function and the development of acute and chronic WAD symptoms after MVC are needed.

Evidence that Serotonin Activity Influences Pain Sensitivity

Serotonin is primarily located in nine clusters of cells in the brainstem, termed the raphe nuclei, which extend projections to almost all areas of the brain and spinal cord.[84,85] Some raphe nuclei are stimulated by corticotrophin releasing factor, and the activation of serotonin pathways is part of the acute stress response.[86] Serotonergic projections to the spinal cord are believed to play an important role in the inhibition and/or facilitation of nociceptive

inputs (reviewed in Millan[85]), and thus play an important role in enhancing/prolonging or extinguishing acute pain. This role is achieved, at least in part, via influencing the antinociceptive effects of opioids at the spinal cord level.[87,88] Serotonin reuptake inhibition is believed to be an important component of the analgesic efficacy of commonly used analgesic medications. A genetic variation in the serotonin transporter that results in relatively low levels of serotonin availability has been found to be associated with several chronic pain conditions, including fibromyalgia,[89] irritable bowel syndrome,[90] and tension headache.[91] More work examining associations between genetic polymorphisms influencing serotonin physiology and the development of acute and chronic WAD symptoms after MVC are needed.

Clinical Implications

The above examples support the hypothesis that that stress systems influence neurosensory processing. After a MVC, the influence of such systems is likely to interact with the effects of biomechanical injury and the psychological response to cause the alterations in neurosensory processing which are the hallmark of WAD. If this is indeed the case, then treatments that dampen the effect of these systems may provide another “arrow in our quiver” of multimodal therapeutic interventions to help individuals who are at risk of chronic symptom development.

In the animal model of stress-induced sensory changes mentioned in the introduction, it has been shown that the changes in sensory threshold and muscle hyperalgesia induced by stress exposure can be attenuated or prevented by pretreatment with medications which influence stress system biology.[29,92] For example, animal pretreatment with medications which augment central serotonin (e.g. fluoxetine) has been shown to attenuate sensory threshold changes and to reduce muscle hyperalgesia caused by stress exposure.[29,92] Whether the use of medications in humans which modify the influence of the stress response after stress exposure can improve WAD outcomes is unknown. However, it is possible that in selected patients such interventions may be useful adjuncts to current treatments and improve WAD outcomes.

Current Research Needs and Future Research Directions

This review has highlighted several lines of evidence supporting the potential influence of stress systems on neurosensory processing and the development of hyperalgesia and allodynia. Importantly, this review was not a comprehensive review of all stress systems potentially involved in WAD, nor of all mechanisms by which stress systems may influence neurosensory processing (e.g. little discussion was devoted to potential peripheral mechanisms). Most importantly, very little data was obtained from patient cohorts experiencing MVC. Research is needed which assesses the ability of measures of stress system function to predict persistent WAD symptom outcomes after MVC. Such studies would help determine whether stress system function influences WAD outcomes. Measures of stress system function assessed might include assessments of HPA axis function (e.g. cortisol levels) and/or autonomic nervous system function (e.g. heart rate variability assessment) collected around the time of MVC. Other studies which would provide useful information regarding the importance of stress systems in the pathophysiology of WAD are studies that assess whether genetic variations determining the function of important components of these systems are associated with risk of WAD symptom development. These studies should simultaneously examine a range of outcomes after MVC, including both regional and widespread pain and psychological sequelae, so that the potential influence of stress system function across a number of important patient outcomes can be assessed. Similarly, the potential interaction between stress system measures and other

patient characteristics (e.g. psychological and cognitive-behavioral characteristics) in shaping patient outcomes should also be examined.

If such observational studies indicate that stress systems may play an important role in the pathophysiology of WAD, either alone or via interactions with other factors, then studies providing interventions for selected high risk individuals which target one or more stress system components may be worthwhile. The identification of those high risk individuals most likely to benefit from the intervention is likely to be crucial in this regard. This is because WAD patients, like patients with other common musculoskeletal pain conditions, are likely to be heterogeneous. Thus the contribution of a particular etiologic factor or biologic pathway to patient outcomes may vary a great deal from patient to patient.

Acknowledgments

The author would like to thank the reviewers for their help in improving the manuscript, and would like to thank Lauren Ballina for her assistance with manuscript edits and formatting. The manuscript submitted does not contain information about medical device(s)/drug(s). Institutional funds were received to support this work. One or more of the author(s) has/have received or will receive benefits for personal or professional use from a commercial party related directly or indirectly to the subject of this manuscript: e.g., honoraria, gifts, consultancies, royalties, stocks, stock options, decision making position.

References

1. Cassidy JD, Carroll LJ, Cote P, et al. Effect of eliminating compensation for pain and suffering on the outcome of insurance claims for whiplash injury. New England Journal of Medicine. 2000; 342:1179–86. [PubMed: 10770984]
2. Obelieniene D, Bovim G, Schrader H, et al. Headache after whiplash: a historical cohort study outside the medico-legal context. Cephalalgia. 1998; 18:559–64. [PubMed: 9827248]
3. Partheni M, Constantoyannis C, Ferrari R, et al. A prospective cohort study of the outcome of acute whiplash injury in Greece. Clinical & Experimental Rheumatology. 2000; 18:67–70. [PubMed: 10728446]
4. Meyer S, Hugemann RE, Weber M. Zur Belastung der HWS dutch Auffahrkollisionen. Verkehrsunfall und Fahrzeugtechnik. 1994; 32:187–99.
5. Castro WH. Correlation between exposure to biomechanical stress and Whiplash Associated Disorders (WAD). Pain Res Manag. 2003; 8:76–8. [PubMed: 12879137]
6. Castro WH, Meyer SJ, Becke ME, et al. No stress--no whiplash? Prevalence of “whiplash” symptoms following exposure to a placebo rear-end collision. International Journal of Legal Medicine. 2001; 114:316–22. [PubMed: 11508796]
7. Vlaeyen JW, Linton SJ. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. Pain. 2000; 85:317–32. [PubMed: 10781906]
8. Nederhand MJ, Hermens HJ, IJzerman MJ, et al. Chronic neck pain disability due to an acute whiplash injury. Pain. 2003; 102:63–71. [PubMed: 12620597]
9. Sterling M, Jull G, Vicenzino B, et al. Characterization of acute whiplash-associated disorders. Spine. 2004; 29:182–8. [PubMed: 14722412]
10. Sterling M, Jull G, Vicenzino B, et al. Sensory hypersensitivity occurs soon after whiplash injury and is associated with poor recovery. Pain. 2003; 104:507–19.
11. Curatolo M, Petersen-Felix S, Arendt-Nielsen L, et al. Central hypersensitivity in chronic pain after whiplash injury. Clinical Journal of Pain. 2001; 17:306–15. [PubMed: 11783810]
12. Banic B, Petersen-Felix S, Andersen OK, et al. Evidence for spinal cord hypersensitivity in chronic pain after whiplash injury and in fibromyalgia. Pain. 2004; 107:7–15. [PubMed: 14715383]
13. Kvetnansky R, Sabban EL, Palkovits M. Catecholaminergic systems in stress: structural and molecular genetic approaches. Physiological reviews. 2009; 89:535–606. [PubMed: 19342614]
14. Goldstein DS. Catecholamines and stress. Endocr Regul. 2003; 37:69–80. [PubMed: 12932192]

15. Chrousos GP. Stressors, stress, and neuroendocrine integration of the adaptive response. The 1997 Hans Selye Memorial Lecture. Ann N Y Acad Sci. 1998; 851:311–35. [PubMed: 9668623]
16. Mangano DT, Layug EL, Wallace A, et al. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter Study of Perioperative Ischemia Research Group. N Engl J Med. 1996; 335:1713–20. [PubMed: 8929262]
17. Grassi G. Sympathetic overdrive and cardiovascular risk in the metabolic syndrome. Hypertens Res. 2006; 29:839–47. [PubMed: 17345783]
18. McLean SA, Clauw DJ, Abelson JL, et al. The development of persistent pain and psychological morbidity after motor vehicle collision: integrating the potential role of stress response systems into a biopsychosocial model. Psychosom Med. 2005; 67:783–90. [PubMed: 16204439]
19. Imbe H, Iwai-Liao Y, Senba E. Stress-induced hyperalgesia: animal models and putative mechanisms. Front Biosci. 2006; 11:2179–92. [PubMed: 16720304]
20. Vidal C, Jacob J. Hyperalgesia induced by non-noxious stress in the rat. Neurosci Lett. 1982; 32:75–80. [PubMed: 7145227]
21. Vidal C, Jacob JJ. Stress hyperalgesia in rats: an experimental animal model of anxiogenic hyperalgesia in human. Life Sci. 1982; 31:1241–4. [PubMed: 7144433]
22. Jorum E. Analgesia or hyperalgesia following stress correlates with emotional behavior in rats. Pain. 1988; 32:341–8. [PubMed: 3362568]
23. Jorum E. Noradrenergic mechanisms in mediation of stress-induced hyperalgesia in rats. Pain. 1988; 32:349–55. [PubMed: 2834686]
24. Satoh M, Kuraishi Y, Kawamura M. Effects of intrathecal antibodies to substance P, calcitonin gene-related peptide and galanin on repeated cold stress-induced hyperalgesia: comparison with carrageenan-induced hyperalgesia. Pain. 1992; 49:273–8. [PubMed: 1376888]
25. Gamaro GD, Xavier MH, Denardin JD, et al. The effects of acute and repeated restraint stress on the nociceptive response in rats. Physiol Behav. 1998; 63:693–7. [PubMed: 9523917]
26. da Silva Torres IL, Bonan CD, Crema L, et al. Effect of drugs active at adenosine receptors upon chronic stress-induced hyperalgesia in rats. Eur J Pharmacol. 2003; 481:197–201. [PubMed: 14642786]
27. da Silva Torres IL, Cucco SN, Bassani M, et al. Long-lasting delayed hyperalgesia after chronic restraint stress in rats-effect of morphine administration. Neurosci Res. 2003; 45:277–83. [PubMed: 12631463]
28. Imbe H, Murakami S, Okamoto K, et al. The effects of acute and chronic restraint stress on activation of ERK in the rostral ventromedial medulla and locus coeruleus. Pain. 2004; 112:361–71. [PubMed: 15561392]
29. Quintero L, Moreno M, Avila C, et al. Long-lasting delayed hyperalgesia after subchronic swim stress. Pharmacol Biochem Behav. 2000; 67:449–58. [PubMed: 11164071]
30. Diamond DM, Campbell AM, Park CR, et al. The temporal dynamics model of emotional memory processing: a synthesis on the neurobiological basis of stress-induced amnesia, flashbulb and traumatic memories, and the Yerkes-Dodson law. Neural Plast. 2007:60803. [PubMed: 17641736]
31. Joels M, Pu Z, Wiegert O, et al. Learning under stress: how does it work? Trends Cogn Sci. 2006; 10:152–8. [PubMed: 16513410]
32. Ivy AC, Gorrzl FR, Burmill DY. The analgesic effect of intracarotid and intravenous infection of epinephrine in dogs and of subcutaneous injection in man. Quart Bull Northw Univ med Sch. 1944; 18:298–306.
33. Leimdorfer A, Metzner WR. Analgesia and anesthesia induced by epinephrine. Am J Physiol. 1949; 157:116–21. [PubMed: 18144412]
34. Nackley AG, Tan KS, Fecho K, et al. Catechol-O-methyltransferase inhibition increases pain sensitivity through activation of both beta(2)-and beta(3)-adrenergic receptors. Pain. 2006; 128:199–208. [PubMed: 17084978]
35. Khasar SG, Green PG, Miao FJ, et al. Vagal modulation of nociception is mediated by adrenomedullary epinephrine in the rat. Eur J Neurosci. 2003; 17:909–15. [PubMed: 12603283]
36. Khasar SG, McCarter G, Levine JD. Epinephrine produces a beta-adrenergic receptor-mediated mechanical hyperalgesia and in vitro sensitization of rat nociceptors. J Neurophysiol. 1999; 81:1104–12. [PubMed: 10085337]

37. Levine JD, Dardick SJ, Roizen MF, et al. Contribution of sensory afferents and sympathetic efferents to joint injury in experimental arthritis. J Neurosci. 1986; 6:3423–9. [PubMed: 3794780]
38. Coderre TJ, Basbaum AI, Dallman MF, et al. Epinephrine exacerbates arthritis by an action at presynaptic B2-adrenoceptors. Neuroscience. 1990; 34:521–3. [PubMed: 2159131]
39. Diatchenko L, Anderson AD, Slade GD, et al. Three major haplotypes of the β2 adrenergic receptor define psychological profile, blood pressure, and the risk for development of a common musculoskeletal pain disorder. American journal of molecular genetics. 2006; 141:449–62.
40. Diatchenko L, Slade GD, Nackley AG, et al. Genetic basis for individual variations in pain perception and the development of a chronic pain condition. Hum Med Genet. 2005; 14:135–43.
41. Vyden, J.; Groseth-Dittrich, M.; Callis, G.; Laks, M.; Weinberger, H. Arthritis & Rheumatism (abstract). 1971. p. 14
42. Baerwald CG, Laufenberg M, Specht T, et al. Impaired sympathetic influence on the immune response in patients with rheumatoid arthritis due to lymphocyte subset-specific modulation of beta 2-adrenergic receptors. Br J Rheumatol. 1997; 36:1262–9. [PubMed: 9448586]
43. Kaplan R, Robinson CA, Scavulli JF, et al. Propranolol and the treatment of rheumatoid arthritis. Arthritis Rheum. 1980; 23:253–5. [PubMed: 7362673]
44. Levine JD, Fye K, Heller P, et al. Clinical response to regional intravenous guanethidine in patients with rheumatoid arthritis. J Rheumatol. 1986; 13:1040–3. [PubMed: 3550071]
45. Tchivileva, IE.; Lim, PF.; Kasravi, P., et al. Propranolol in Temporomandibular Joint Disorder Treatment. American Pain Society; San Diego, CA: 2009.
46. McLean SA, Diatchenko L, Lee YM, et al. Catechol O-methyltransferase haplotype predicts immediate musculoskeletal neck pain and psychological symptoms after motor vehicle collision. J Pain. 2011; 12:101–7. [PubMed: 20688576]
47. Carroll LJ, Holm LW, Hogg-Johnson S, et al. Course and prognostic factors for neck pain in whiplash-associated disorders (WAD): results of the Bone and Joint Decade 2000–2010 Task Force on Neck Pain and Its Associated Disorders. Spine (Phila Pa 1976). 2008; 33:S83–92. [PubMed: 18204405]
48. Pertovaara A. Noradrenergic pain modulation. Prog Neurobiol. 2006; 80:53–83. [PubMed: 17030082]
49. Gonzalez-Cabrera PJ, Gaivin RJ, Yun J, et al. Genetic profiling of alpha 1-adrenergic receptor subtypes by oligonucleotide microarrays: coupling to interleukin-6 secretion but differences in STAT3 phosphorylation and gp-130. Mol Pharmacol. 2003; 63:1104–16. [PubMed: 12695539]
50. Hong Y, Abbott FV. Contribution of peripheral alpha 1A-adrenoceptors to pain induced by formalin or by alpha-methyl-5-hydroxytryptamine plus noradrenaline. Eur J Pharmacol. 1996; 301:41–8. [PubMed: 8773445]
51. Mailis-Gagnon A, Bennett GJ. Abnormal contralateral pain responses from an intradermal injection of phenylephrine in a subset of patients with complex regional pain syndrome (CRPS). Pain. 2004; 111:378–84. [PubMed: 15363882]
52. Ali Z, Ringkamp M, Hartke TV, et al. Uninjured C-fiber nociceptors develop spontaneous activity and alpha-adrenergic sensitivity following L6 spinal nerve ligation in monkey. J Neurophysiol. 1999; 81:455–66. [PubMed: 10036297]
53. Pluteanu F, Ristoiu V, Flonta ML, et al. Alpha(1)-adrenoceptor-mediated depolarization and beta-mediated hyperpolarization in cultured rat dorsal root ganglion neurones. Neurosci Lett. 2002; 329:277–80. [PubMed: 12183030]
54. Sagen J, Proudfit HK. Evidence for pain modulation by pre- and postsynaptic noradrenergic receptors in the medulla oblongata. Brain Res. 1985; 331:285–93. [PubMed: 2859092]
55. Hedo G, Lopez-Garcia JA. Alpha-1A adrenoceptors modulate potentiation of spinal nociceptive pathways in the rat spinal cord in vitro. Neuropharmacology. 2001; 41:862–9. [PubMed: 11684150]
56. Kingery WS, Guo TZ, Davies MF, et al. The alpha(2A) adrenoceptor and the sympathetic postganglionic neuron contribute to the development of neuropathic heat hyperalgesia in mice. Pain. 2000; 85:345–58. [PubMed: 10781908]
57. Harasawa I, Honda K, Tanoue A, et al. Responses to noxious stimuli in mice lacking alpha(1d)-adrenergic receptors. Neuroreport. 2003; 14:1857–60. [PubMed: 14534435]

58. Xie J, Ho Lee Y, Wang C, et al. Differential expression of alpha1-adrenoceptor subtype mRNAs in the dorsal root ganglion after spinal nerve ligation. Brain Res Mol Brain Res. 2001; 93:164–72. [PubMed: 11589993]

59. Smith, S.; Slade, G.; Belfer, I., et al. ADRA1A polymorphisms associated with multiple psychological and nociceptive phenotypes predict vulnerability to an idiopathic pain condition. American Pain Society; Washington, D.C: 2007.

60. Crassous PA, Denis C, Paris H, et al. Interest of alpha2-adrenergic agonists and antagonists in clinical practice: background, facts and perspectives. Curr Top Med Chem. 2007; 7:187–94. [PubMed: 17266605]

61. Millan MJ, Bervoets K, Rivet JM, et al. Multiple alpha-2 adrenergic receptor subtypes. II. Evidence for a role of rat R alpha-2A adrenergic receptors in the control of nociception, motor behavior and hippocampal synthesis of noradrenaline. J Pharmacol Exp Ther. 1994; 270:958–72. [PubMed: 7932208]

62. Graham BA, Hammond DL, Proudfit HK. Differences in the antinociceptive effects of alpha-2 adrenoceptor agonists in two substrains of Sprague-Dawley rats. J Pharmacol Exp Ther. 1997; 283:511–9. [PubMed: 9353364]

63. Kim HJ, Camilleri M, Carlson PJ, et al. Association of distinct alpha(2) adrenoceptor and serotonin transporter polymorphisms with constipation and somatic symptoms in functional gastrointestinal disorders. Gut. 2004; 53:829–37. [PubMed: 15138209]

64. Small KM, McGraw DW, Liggett SB. Pharmacology and physiology of human adrenergic receptor polymorphisms. Annu Rev Pharmacol Toxicol. 2003; 43:381–411. [PubMed: 12540746]

65. Vardeny O, Peppard PE, Finn LA, et al. beta2 adrenergic receptor polymorphisms and nocturnal blood pressure dipping status in the Wisconsin Sleep Cohort Study. J Am Soc Hypertens. 2011; 5:114–22. [PubMed: 21414566]

66. Bruehl S, Chung OY. Interactions between the cardiovascular and pain regulatory systems: an updated review of mechanisms and possible alterations in chronic pain. Neurosci Biobehav Rev. 2004; 28:395–414. [PubMed: 15341037]

67. Hagen K, Zwart JA, Holmen J, et al. Does hypertension protect against chronic musculoskeletal complaints? The Nord-Trondelag Health Study. Arch Intern Med. 2005; 165:916–22. [PubMed: 15851644]

68. Clauw, DJ.; Belfer, I.; Max, MB., et al. Increased Frequency of the Minor Allele for beta-3 Adrenergic Receptors in Individuals with Fibromyalgia and Related Syndromes. American College of Rheumatology; Boston, MA: 2007.

69. McBeth J, Silman AJ, Gupta A, et al. Moderation of psychosocial risk factors through dysfunction of the hypothalamic-pituitary-adrenal stress axis in the onset of chronic widespread musculoskeletal pain: findings of a population-based prospective cohort study. Arthritis Rheum. 2007; 56:360–71. [PubMed: 17195240]

70. Holliday KL, Nicholl BI, Macfarlane GJ, et al. Genetic variation in the hypothalamic-pituitary-adrenal stress axis influences susceptibility to musculoskeletal pain: results from the EPIFUND study. Ann Rheum Dis. 2010; 69:556–60. [PubMed: 19723618]

71. Geiss A, Rohleder N, Kirschbaum C, et al. Predicting the failure of disc surgery by a hypofunctional HPA axis: evidence from a prospective study on patients undergoing disc surgery. Pain. 2005; 114:104–17. [PubMed: 15733636]

72. Glass JM, Lyden AK, Petzke F, et al. The effect of brief exercise cessation on pain, fatigue, and mood symptom development in healthy, fit individuals. J Psychosom Res. 2004; 57:391–8. [PubMed: 15518675]

73. Watkins LR, Maier SF, Goehler LE. Immune activation: the role of pro-inflammatory cytokines in inflammation, illness responses and pathological pain states. Pain. 1995; 63:289–302. [PubMed: 8719529]

74. Biddie SC, Hager GL. Glucocorticoid receptor dynamics and gene regulation. Stress. 2009; 12:193–205. [PubMed: 19051126]

75. Myers B, Greenwood-Van Meerveld B. Divergent Effects of Amygdala Glucocorticoid and Mineralocorticoid Receptors in the Regulation of Visceral and Somatic Pain. Am J Physiol Gastrointest Liver Physiol. 2010; 298:G295–303. [PubMed: 19875699]

76. De Nicola AF, Moses DF, Gonzalez S, et al. Adrenocorticoid action in the spinal cord: some unique molecular properties of glucocorticoid receptors. Cell Mol Neurobiol. 1989; 9:179–92. [PubMed: 2663168]
77. Cintra A, Molander C, Fuxe K. Colocalization of Fos- and glucocorticoid receptor-immunoreactivities is present only in a very restricted population of dorsal horn neurons of the rat spinal cord after nociceptive stimulation. Brain Res. 1993; 632:334–8. [PubMed: 8149241]
78. Capasso A, Di Giannuario A, Loizzo A, et al. Central interaction of dexamethasone and RU-38486 on morphine antinociception in mice. Life Sci. 1992; 51:PL139–43. [PubMed: 1518370]
79. Pieretti S, Capasso A, Di Giannuario A, et al. The interaction of peripherally and centrally administered dexamethasone and RU 38486 on morphine analgesia in mice. Gen Pharmacol. 1991; 22:929–33. [PubMed: 1761197]
80. Lim G, Wang S, Zeng Q, et al. Evidence for a long-term influence on morphine tolerance after previous morphine exposure: role of neuronal glucocorticoid receptors. Pain. 2005; 114:81–92. [PubMed: 15733634]
81. Capasso A, Loizzo A. Functional interference of dexamethasone on some morphine effects: hypothesis for the steroid-opioid interaction. Recent Pat CNS Drug Discov. 2008; 3:138–50. [PubMed: 18537773]
82. van Rossum EF, Lamberts SW. Polymorphisms in the glucocorticoid receptor gene and their associations with metabolic parameters and body composition. Recent Prog Horm Res. 2004; 59:333–57. [PubMed: 14749509]
83. Wust S, Van Rossum EF, Federenko IS, et al. Common polymorphisms in the glucocorticoid receptor gene are associated with adrenocortical responses to psychosocial stress. J Clin Endocrinol Metab. 2004; 89:565–73. [PubMed: 14764763]
84. Filip M, Bader M. Overview on 5-HT receptors and their role in physiology and pathology of the central nervous system. Pharmacol Rep. 2009; 61:761–77. [PubMed: 19903999]
85. Millan MJ. Descending control of pain. Prog Neurobiol. 2002; 66:355–474. [PubMed: 12034378]
86. Chaouloff F. Serotonin, stress and corticoids. J Psychopharmacol. 2000; 14:139–51. [PubMed: 10890308]
87. Hain HS, Belknap JK, Mogil JS. Pharmacogenetic evidence for the involvement of 5-hydroxytryptamine (Serotonin)-1B receptors in the mediation of morphine antinociceptive sensitivity. J Pharmacol Exp Ther. 1999; 291:444–9. [PubMed: 10525057]
88. Song B, Chen W, Marvizon JC. Inhibition of opioid release in the rat spinal cord by serotonin 5-HT(1A) receptors. Brain Res. 2007; 1158:57–62. [PubMed: 17555728]
89. Buskila D, Neumann L. Genetics of fibromyalgia. Curr Pain Headache Rep. 2005; 9:313–5. [PubMed: 16157058]
90. Yeo A, Boyd P, Lumsden S, et al. Association between a functional polymorphism in the serotonin transporter gene and diarrhoea predominant irritable bowel syndrome in women. Gut. 2004; 53:1452–8. [PubMed: 15361494]
91. Park JW, Kim JS, Lee HK, et al. Serotonin transporter polymorphism and harm avoidance personality in chronic tension-type headache. Headache. 2004; 44:1005–9. [PubMed: 15546263]
92. Suarez-Roca H, Quintero L, Arcaya JL, et al. Stress-induced muscle and cutaneous hyperalgesia: differential effect of milnacipran. Physiol Behav. 2006; 88:82–7. [PubMed: 16624346]

Key Points

1. Data from animal and human studies demonstrate that physiologic stress systems modulate pain sensitivity.
2. Several animal models of stress exposure have shown that stress exposure itself, in the absence of tissue injury, is capable of producing long lasting changes in pain sensitivity.
3. A genetic variant influencing the metabolism of catecholamines, hormones central to the endocrine response to stress, has been shown to predict acute pain and psychological symptoms in the aftermath of motor vehicle collision (MVC). This type of genetic vulnerability may interact with the effects of biomechanical injury and psychobehavioral responses to influence the development of WAD.
4. Treatments which diminish the adverse effects of stress systems may be a useful component of multimodal therapeutic interventions for individuals at risk of chronic pain development after MVC.