E21 Pain Pathways

(308) Sympathetic hyperactivity, perceived pain, and anxiety in post-amputee pain

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Neurophysiologic adaptations after amputation predispose amputees to sympathetic hyperactivity. Anxiety is linked to increased catecholamine levels, which may exacerbate sympathetic activation of nociceptors. Sustained sympathetic discharge can further reduce efferent sympathetic action potential thresholds. This cyclic facilitation would expectedly result in increased signs of sympathetic hyperactivity over time, including hypoesthesia, epidermis color change, epidermis temperature change, edema, skin breakdown, allodynia, hyperalgesia, and contracture. Our study seeks to elucidate relationships between sympathetic hyperactivity, pain, anxiety and time since amputation. Thirty-four amputees recruited from an urban rehabilitation hospital underwent a physical exam, in which signs of sympathetic hyperactivity were recorded. Current pain levels were measured using the Visual Analog Scale (VAS) and the McGill Pain Questionnaire Short Form (MPQ), which included Affective and Sensory sub-scores. The Pain and Anxiety Symptoms Scale-20 (PASS) was used to measure pain anxiety, which included Cognitive, Fear, Escape/Avoidance, and Physiological sub-scores. Relationships between sympathetic hyperactivity, pain, anxiety and time since amputation were analyzed. Total number of sympathetic hyperactivity signs correlated with VAS Now, MPQ Total, MPQ Sensory, and MPQ Affective scores. Total number of sympathetic hyperactivity signs did not correlate with any PASS scores. Time since amputation did not correlate with epidermis color change, edema, tactile epidermis temperature, skin breakdown, hypoesthesia, allodynia, hyperalgesia, contracture, or total number of sympathetic hyperactivity signs. Correlations between pain levels and signs of sympathetic hyperactivity suggest that post-amputee pain is linked to sympathetic hyperactivity. Our results contrast prior findings, suggesting that anxiety in anticipation of pain does not increase sympathetic overdrive. This pilot work suggests several explanations, including that sympathetic hyperactivity in amputees stems from neurophysiologic adaptations, rather than psychological contributions. Finally sympathetic sensitization in post-amputee pain subjects does not appear to be present. This may be due to central nervous system reorganization after amputation, which could affect expected synaptic pathways.

(309) Sympathetic asymmetry in post amputation pain

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Striking numbers of amputees are plagued with chronic Post Amputation Pain (PAP), which can present as either Residual Limb Pain (RLP) or Phantom Limb Pain (PLP). Understanding the pathophysiology of RLP and PLP is central to establishing an acceptable standard of care. Disinhibition or activation of the sympathetic nervous system has been postulated to play a substantial role in patients' report of pain. This study aimed to understand the contribution of sympathetic mechanisms in PAP by directly examining the vasomotor sympathetic characteristics of phantom and residual limb pain. We hypothesized that compared to amputees without PAP (i.e. PLP and/or RLP), amputees with such pain will exhibit the following characteristics of sympathetically maintained pain in their residual limbs: decreased relative temperature (by Infra-Red Telethermography; IRT), discoloration, asymmetric sweating (vasomotor), and swelling or edema (sudomotor). Patients who reported PAP (i.e. PLP and/or RLP), PLP, or RLP were compared with patients who reported no pain (i.e. neither PLP or RLP). There was no significant difference in edema ($p=0.17$, $p=0.31$, $p=0.54$) or discoloration ($p=1.00$, $p=0.75$, $p=0.74$) of the residual limb between any cohort of patients. No patients showed signs of asymmetric sweating. Difference in temperature by IRT between the residual and unaffected limbs was similar between amputees reporting PAP, PLP, or RLP and not reporting any pain ($p=0.97$, $p=0.80$, $p=0.60$). These findings suggest no significant evidence of sympathetic activation or receptor up-regulation to 'maintain' PAP. A large definitive trial, including invasive manipulation of the SNS and more quantitative measurement of SNS function, should be conducted to ultimately resolve this question.

E22 Primary Afferents

(310) Group III mGluR-selective and mGluR8-selective agonists potentiate morphine-induced inhibition of sensitized peripheral nociceptors

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Opioids such as morphine are often used to treat acute and chronic pain. However, they cause significant side effects when taken in high doses or for long periods of time. Current studies aim to establish receptor groups and agonists that might potentiate analgesic efficacy of opioids, allowing treatment with lower doses in order to minimize side effects. One receptor family of interest is the metabotropic glutamate receptors (mGluRs). Current literature indicates that intrathecal and systemic applications of Group III agonists potentiate morphine analgesia. We have previously demonstrated that peripheral administration of the Group III-selective agonist L-AP-4 synergistically potentiates morphine anti-hyperalgesia. In this study, we employed the in vitro skin-nerve preparation to determine if the combination decreases sensitization at the single fiber level. Fibers were sensitized to heat via application of inflammatory soup and morphine, L-AP-4, or a Group III mGluR8-selective agonist (DCPG) was applied. Dose response curves for each drug were used to identify individual IC50s and to determine combination doses of morphine plus either L-AP-4 or DCPG. Further study will involve applying combinations and assessing responses to thermal stimuli to determine if Group III agonists potentiate morphine at the single fiber level. We also examined the anatomical basis of potentiation by double-labeling dorsal root ganglion (DRG) cells for Group III mGluR8 and the mu opioid receptor (μOR). Thus far, data indicate that the receptors are co-localized in 41% of nociceptors. This will be confirmed via triple-labeling DRG cells for mGluR8, μOR, and a nociceptor marker (TRPV1). Co-expression of mGluR8 and μOR on nociceptors suggests that potentiation occurs via an intracellular mechanism. Overall, we expect that peripheral Group III mGluR activation will potentiate morphine-induced inhibition of inflamed peripheral fibers via modulation of an intracellular pathway. Funding: NIH F30DA03229801 to ALB; NS027910/DA027460 to SMC.

(311) Molecular and electrophysiological changes induced by skin incision: implications for the development of chronic pain

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The development of chronic neuropathic pain (CNP) is a serious medical problem. Major etiological factors include damage to peripheral nerves and damage to peripheral tissue (even minor damage), particularly repeated tissue damage. Using skin incision as a model for tissue damage – one where axons are injured but remain in contact with their target tissue – we have determined that sensory neuron responses are similar, but not identical, to those evoked by injury to a peripheral nerve. Using qPCR and immunohistochemistry, we show that skin incision alters the expression of pain-related genes for ion channels, transduction channels, and regeneration growth-associated factors. In the condition of repeated tissue damage, these changes are either amplified or different from the changes evoked by single incision. Many of these effects are maintained long after the wound has healed and are resistant to standard clinical interventions, but can be modulated. Furthermore, using patch clamp electrophysiology, we have observed long-lasting altered electrophysiological characteristics in sensory neurons innervating the incised skin. Our results suggest that axonal injury responses may contribute to the development of CNP after tissue damage. This mechanism may be distinct from the sensory neuron responses to tissue damage-induced tissue inflammation, which is the current focus of treatment efforts. Repeated tissue injury is a lifelong condition for many patient communities, particularly those dealing with mobility issues. For communities such as those with spinal cord injury, traumatic brain injury, stroke, and other neurological disorders which themselves may constitute a "priming event," our findings may represent a new consideration for the impact that tissue damage may have on the health and well-being of individuals and on developing strategies for treatment. This study is funded through the Kentucky Spinal Cord and Head Injury Research Trust, Kentucky Spinal Cord Injury Research Center Traineeship, Paralyzed Veterans of America Fellowship, and NIH.