

Oxidized Linoleic Acid Metabolites and Their Role as Endo-Capsaicins in Pain

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Pain, both chronic and acute is experienced by millions of Americans and is a multi-billion dollar industry. Currently, the pain medications that are available for use have a narrow spectrum of action and a multitude of adverse effects. Prior studies have identified Transient Receptor Potential Vanilloid 1 to be one of the well characterized voltage-gated ion channels in the peripheral nervous system. Expressed on nociceptors, it is a principle detector of noxious heat as well as inflammatory pain. We now know that Oxidized Linoleic Acid Metabolites (OLAMs) are specific TRPV1 agonists, and therefore potentiate pain and act as endocapsaicins. OLAMs such as 9-HODE, 9-oxoODE, 13-HODE and 13-oxoODE are shown to be released peripherally in response to heat and centrally during inflammation and activate TRPV1 leading to a pain perception. Additionally, OLAMs are also found at elevated levels in burned human skin compared to normal human skin. However, the mechanism by which linoleic acid is converted to the OLAMs is unknown. Recent results from our lab show the involvement of cytochrome P450 (CYPs) enzymes in the formation of these OLAMs. Importantly, treatment of animals with drugs that inhibit CYPs at peripheral sites results in reversal of thermal allodynia in a rat model of burn pain as well as inhibit metabolism of C¹⁴ Linoleic acid from burned skin tissue. To further narrow down on specific CYP isoforms that may play a role in OLAM-mediated burn pain, we hypothesized changes in gene expression of CYP isoforms in burn skin compared with normal skin. Specifically, we speculate higher levels of expression of potential Cytochrome P450 isoforms in skin from burn patients compared to skin from normal patients. We used the Glue Grant Trauma Related Database to identify burn patient microarrays and selected for the Cytochrome P450 enzymes, Lipoxygenase and Epoxide genes. A total of 86 burn patients were identified with 238 microarray time points, and 58 Cytochrome P450, 4 Epoxide and 8 Lipoxygenase genes were isolated. The gene expression data collected from the burn patients was analyzed against 41 Control patients. Preliminary data suggests there are 7 CYP isoforms, 3 Lipoxygenases and 1 Epoxide genes that were expressed at increased levels when compared to the controls.