Characterization of Molecular Pattern in Sensory Pain Signaling and Its Neurotransmitters on Mouse Skin following Mustard Exposure

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Sulfur mustard (Sulfur mustard (SM, bis(2-chloroethyl sulfide))) is a warfare chemical which causes inflammation, epidermal blistering, and the characteristic but the unique effect of delayed skin pain. However, the underlying mechanisms mediating sensory pain following mustard exposure remain unclear. We have previously demonstrated activation of cannabinoid signaling following exposure of skin to mustards. Therefore, we hypothesized that downstream signaling following activation of cannabinoid receptors by mustards may modulate the sensory pain following mustard exposure in the skin and mediate the 4-12 hour delay in pain often experienced. In the present study, we investigated reprogramming of dermal sensory pain receptors by chemokines following mustard exposure utilizing mouse skin models. In these studies, we investigated correlations between cell proliferation and cellular responses important in pain, we measured differences in cell proliferation and pro-inflammatory gene expression in keratinocytes following mustard exposure. Mustard exposure mediated a distinct pattern of cell proliferation (PCNA mRNA) that was altered in a time-sensitive manner; in contrast, mRNA levels for Keratinocyte marker protein (Krt10) following mustard exposure, exhibited distinct redox patterns. A four-fold induction NQO1 and NQO2 including GST-1beta expression in in the early phase was observed. Contrarily, the pattern of NOXs (NOX1, NOX4 and NOX5) expression in response to SM was upregulated by two or three-fold in the later phases (at 48hr) compared to early (24 hr) responses. Of note, the tropism of pain receptors in mouse skin was distinctly altered from kappa (OPRK) to delta opioid receptor (OPRD) in a time-dependent manner. In addition, we found that NGF mRNA may play a role in the early phase responses in contrast to other neurotransmitters including BDNF, GDNF, and PDYN. Interestingly, SM triggered transient receptors by up- /down- (to TRPV1 mRNA) or down-/up- (TRPV3 mRNA) in a time-dependent manner. In general, these results indicate that sensitivity to Cannabinoid receptors in mouse skin was diminished in later time periods when compared to early responses. We speculate that those opioid receptors may implement cannabinoid signaling by promoting TRPV1 signaling, a process effected by mustard exposure dependent manner in the dermal lesion.