Biofreeze Ingredient Ilex Increases Skin Blood Flow Through Endothelium-Derived Hyperpolarizing Factor Mechanisms

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Biofreeze gel is clinically utilized as a topical analgesic to relieve pain through gate-control theory mechanism. Menthol is the primary active ingredient in Biofreeze which activates TRPM8 receptors in nerve and vascular tissue and decreases blood flow through large conduit arteries after topical application. Ilex is a plant-derived additive in Biofreeze thought to increase permeability of menthol through the skin. In this double blind, placebo control study the aim was to examine the separate and combined effects of menthol and ilex on the control of microvascular skin blood flow after topical application. In 10 healthy young men and women (age 24±2 years) experimental sites were treated with (1) placebo, (2) menthol only, (3) ilex only, and (4) Biofreeze gels on the ventral forearm in the presence and absence of topical anesthetic to block sensory nerve perception. In two separate protocol days (with sensory nerve blockade and without) red blood cell flux was measured with laser speckle contrast imaging (LSCI) at each site at thermoneurtral baseline, during (1) post-occlusive reactive hyperemia (RH: 5 min arterial occlusion) which increases skin blood flow through sensory nerve and endothelium-derived hyperpolarizing factor (EDHF)-mediated mechanisms and (2) during slow local heating (0.5°C* 5 sec-1 to 42°C) of the skin to increase skin blood flow through endothelial nitric oxide (NO)-dependent mechanisms. Following these separate skin-specific protocols maximal cutaneous vasodilation was achieved (heating to 43^{o}C). Cutaneous vascular conductance (CVC=flux/MAP) was calculated to normalize for changes in blood pressure and expressed as a percentage of maximum CVC (%CVCmax). Resting skin blood flow during thermoneutral conditions (33°C) was increased in sites treated with Biofreeze (58 %CVCmax: $p<0.001$) and ilex (63 %CVCmax: $p<0.0001$) sites compared to placebo (20%CVCmax). The total hyperemic response (THR) following arterial occlusion was similarly elevated in the Biofreeze (18,942 %CVCmax*sec: $p<0.0001$) and ilex (18,760 %CVCmax*sec: $p<0.0001$) sites compared to placebo (5,912 %CVCmax*sec). The THR was partially attenuated after sensory nerve blockade in the Biofreeze (14,019 %CVCmax*sec: $p=0.04$) and Ilex (9991 %CVCmax*sec: $p=0.0004$) sites. During local heating Biofreeze (86 %CVCmax: $p<0.0001$) and Ilex (88 %CVCmax: $p<0.0001$) augmented the NO-dependent plateau only in the presence of sensory nerve blockade compared to placebo (65 %CVCmax). Together these data suggest that the ingredient Ilex in Biofreeze augments thermoneutral cutaneous blood flow and improves cutaneous vasodilation through EDHF-dependent mechanisms. Further Biofreeze may also improve NO-dependent vasodilation in the cutaneous microcirculation.