Body's cold 'sensor' could hold key for frostbite and hypothermia treatments

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A cold 'sensor' which triggers the skin's vascular response to the cold could represent an exciting new therapeutic target for the treatment of frostbite and hypothermia, according to scientists at King's College London.

Known to be linked to pain sensitivity and currently used in the development of painkillers, this is the first time the TRPA1 gene has been implicated in the response of blood vessels in the skin to cold. Published today in *Nature Communications*, the research was funded by the British Heart Foundation and the Biotechnology and Biological Sciences Research Council.

The human body has several defence mechanisms to try and boost its core temperature in the face of cold weather. The skin responds by narrowing its blood vessels in order to constrict the supply of blood and retain body heat (vasoconstriction). The reverse of this activity then occurs, called vasodilatation, where blood vessels are widened and more blood flows to the surface of the skin. This process is important for rewarming the skin and keeping it healthy.

In extreme cold, and especially if bare skin is open to the elements, the cold is overpowering, disrupting blood flow leading to frostbite or swelling (chilblains). The lack of warm blood reaching the skin can enhance tissue freezing and injury.

Cold weather is also a concern for older people, with Age UK estimating that several thousand die every year from the cold, independent of infection, although recent figures suggest this has fallen in 2013/14 due to milder weather.

In the King's study, the skin of anaesthetised mice was exposed to cold by immersing a paw in water. Blood flow was measured prior to this exposure and following a cooling period. Researchers found that TRPA1 acted in two distinct ways – first by sensing the change in temperature, and then by stimulating the protective constriction of blood vessels. The subsequent vasodilatation phase was also dependent on TRPA1 activation and was crucial for restoring blood flow.

Although an early study, the results offer a new understanding of TRPA1's role in cold exposure and provide impetus for further research into how this gene could be targeted to enhance the body's protective response to cold.

Susan Brain, Professor of Pharmacology in the Cardiovascular Division at King's College London, said: 'In response to cold weather the body seeks first and foremost to keep the core warm, which means retaining blood close to the centre and constricting blood supply to the skin.

'Our findings highlight the crucial role TRPA1 plays in this physiological response and could pave the way to learn of new pathways that limit the adverse effects of exposure to cold, and potentially the whole body cooling process associated with hypothermia.'

Professor Brain added: 'Next steps are to build on these promising early findings to learn more about the extent of the role of other TRP receptors in the skin's response to cold, especially as there is a large family of these temperature sensitive

receptors and several of them have their own defined sensitivities to cold. Future research must also investigate the relationship between the vascular responses to cold exposure and the maintenance of skin and body temperatures.'

Professor Peter Weissberg, Medical Director at the British Heart Foundation, which part-funded the research, said: 'This study helps us to understand how and why our blood vessels contract and expand, and could help scientists develop treatments for many conditions where blood vessel or 'vascular' health is important, from Raynaud's to heart failure.

'Any research that helps to explain the complicated processes that control the circulatory system may have wide reaching implications in the future, as vascular health is involved in so many different diseases.'

Provided by King's College London