Blocking the body's response to cold

Lowering body temperature in patients suffering from stroke, heart attack and other conditions can have powerful therapeutic effects by reducing the body's demand for oxygen. A challenge of uniformly lowering body temperature, however, is the body's own cold-defense mechanisms, which are designed to maintain a warm body temperature in a cold environment. Induction of hypothermia therefore requires neutralizing the body's powerful thermoregulation system and overcoming what are called thermoeffector responses, including cold-avoidance behavior, constriction of blood vessels and generation of heat from fat cells. Anesthetized patients may be cooled artificially with an intravenous solution while the skin is warmed to prevent shivering, but it is difficult for physicians to precisely balance the necessary amounts of heat and cold.

Cold defenses use multiple processes in different tissues and are controlled by separate pathways, making them difficult to target. All thermoeffector responses, however, are initiated by signals from thermoreceptors, such as the temperature

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sensitive transient receptor potential channel TRPM8. These receptors are universal cold detectors, and they control all of the main cold defenses. The best way to prevent such responses is therefore to block cold signals from being transmitted.

Andrej A. Romanovsky's lab at St. Joseph's Hospital and Medical Center (Pheonix, AZ), in collaboration with researchers at Amgen (Thousand Oaks, CA) and University of California-Berkeley, have now found a new drug that blocks TRPM8, which is expressed in primary sensory neurons and is activated by cold and menthol. The drug, called M8-B, is a selective and potent antagonist of TRPM8 channel and can block activation of rat, human and mouse TRPM8 channels, including those on primary sensory neurons, from setting the body's cold defense mechanisms in motion. In mice that genetically lacked these receptors, on the other hand, M8-B failed to block cold-induced effects, confirming that TRPM8 receptors are the mechanism by which the drug affects body temperature (*J. Neurosci.* **32**, 2086–2099; 2012).

The study highlights the important role of TRPM8 receptors in thermoregulation. Deep body temperature maintenance depends on cold signals from the channels, which are found on nerve endings that form a dense network in the skin.

The authors suggest that selective pharmacological modulation of thermoreception can be used in the future to induce mild therapeutic hypothermia in unanesthetized patients and to maintain body temperature at the desired level. Furthermore, the ability to selectively control the body's temperature regulatory mechanisms by altering cell receptors may eventually lead to a new area of pharmaceutical development.

Kara Rosania

HUMAN Y CHROMOSOME ISN'T WASTING AWAY

Some time ago, the future of the human Y chromosome was called into question. After all, other species, such as mole voles and spiny rats, have lost their Y chromosomes, and sex-determination responsibilities have fallen to other chromosomes.

In fact, the human Y did not start off as a sex-determining chromosome either. Human X and Y chromosomes were once a pair of autosomes, like the 22 others we carry, and sex was determined by environmental factors rather than genetics. The ancient X and Y swapped gene copies during crossing-over, just like the other autosomes, to maintain genetic diversity and eliminate potentially harmful mutations. About 300 million years ago, however, one part of the X stopped swapping with the Y, then another, a third, a fourth and—about 30 million years ago—a fifth. As a result, the corresponding portions of the Y chromosome decayed, and it eventually lost ~97% of the genes that it once shared with its partner, the X chromosome. It seemed that the Y was disappearing. Some said this was happening at an unsustainable rate, that it would be gone altogether within 10 million years. Prospects seemed dim for the withered Y.

But new research from Jennifer F. Hughes, David C. Page (both of Whitehead Institute, Massachusetts Institute of Technology, Cambridge) and colleagues suggests that reports of the Y's demise may be exaggerated. Hughes and Page specifically looked at recent degeneration of the human Y chromosome by comparing it with the Y of the rhesus macaque (*Macaca mulatta*); the two species shared a common ancestor that lived about 25 million years ago. Since that time, the macaque Y has not lost a single gene, and the human Y has lost only one (*Nature* doi:10.1038/nature10843; published online 22 February 2012). The lost gene is located in an unstable portion that makes up only 3% of the chromosome.

Hughes stated in a press release, "With no loss of genes on the rhesus Y and one gene lost on the human Y, it's clear the Y isn't going anywhere." The results lead to a new understanding of the evolution of the human Y as a process featuring periods of decline separated by periods of stability. "We've been carefully developing this clearcut way of demystifying the evolution of the Y chromosome," Hughes said. Page explained, "The Y was in free fall early on, and genes were lost at an incredibly rapid rate. But then it leveled off, and it's been doing just fine since."

Monica Harrington