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Psychogenic fever, functional fever, or psychogenic hyperthermia?

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Psychogenic fever reflects a phenomenon where core body temperature is high (up to 41°C) or low-grade high (37–38°C) during either acute or chronic stress. Underlying mechanisms are distinct from infection-induced fever and involve the central and sympathetic nervous systems. Psychogenic fever appears a complex psychological, physiological and endocrinological phenomenon.

Oka[1] discusses an important issue dealing with consequences and mechanisms of psychological stress on core body temperature in humans and animals. In some human individuals (more in females than males) such stress may lead to 'psychogenic fever', which upon acute emotional stress leads to a high core body temperature (up to 41°C). Other individuals show a low-grade high core temperature (37–38°C) upon chronic stress.

Temperature can be used as an important read-out of stress-mediated phenomena. Every emotional stress leads to a (short-lasting) increase in core temperature, and this temperature increase is part of a complex of stress-related physiological and endocrinological parameters including increases in ACTH, cortisol, blood pressure, tachycardia, and others.[2] In literature, stress-induced hyperthermia or psychogenic fever has been mainly investigated in 'normal' functioning individuals and not, or rarely so, in pathological conditions. The anecdotic description of many psychogenic fever patients in literature indicates that this area needs fundamental research into the underlying mechanisms, larger cohorts of patients and understanding of the complex 'disease' patterns in individual patients. The stress-induced temperature research is a strong example of translational research. The high resemblance of the physiology and pharmacology of this parameter in rodents and man[2] strongly suggests the possibility to create a 'pathological' psychogenic fever animal model. Early research in stress-induced hyperthermia in mice[3] however, showed the difficulty to generate a pathologically enhanced hyperthermia after an emotional stress and to my knowledge so far no animal model of chronic emotional hyperthermia has been developed. The role of enhanced body temperature in pathophysiology has received limited attention. There is however, evidence for altered thermoregulation or stress-induced hyperthermia response in various stress-related disorders, e.g. in schizophrenia patients.[4] Moreover, circadian temperature abnormalities have been found in major depression and in insomnia. Interestingly, removal of the olfactory bulbs in rats, an animal model of depression, generates rapid, stable and persistent changes in basal and stress-induced temperature levels[5] suggesting that this olfactory bulbectomy model might be a potential animal model for stress-related disturbances in thermoregulation and depression.

Human body temperature is kept at a constant 37°C (ranging from 35.8 to 38.2°C) by regulating the balance between heat production and heat loss. It is challenging to determine the 'normal' body temperature, because that appears highly dependent on where the temperature is measured. There has been an ongoing debate which site of measurement most accurately reflects the true core temperature. In rest, metabolically active organs such as the liver produce most heat, whereas during exercise, skeletal muscles account for heat production. Body temperature is also regulated by environmental heat exchange. Different parts of the body have different temperatures; highest temperatures are found in the brain and in the thoracic and abdominal cavities (the 'core' temperature). The skin usually has the lowest temperature. Body temperature regulation is a complex process governed by the central nervous system (mainly in the hypothalamus). Emotional and psychological stress consistently activates the autonomic nervous system. The autonomic stress response is mediated by an increased activity of the sympatho-adrenomedullary system, resulting in increased heart rate and blood pressure, cutaneous vasoconstriction of the limbs or selective vasodilatation elsewhere, redistribution of organ blood flow, increased cardiac output and an increase in non-shivering thermogenesis.[6] Vinkers et al. [7] studied the effect of stress on core and peripheral body temperature in healthy humans. Using a standardized stress test (the Trier Social Stress Test), core temperature (intestinal and temporal artery) and peripheral temperature (facial and body skin) were measured. Compared to a

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control condition, stress exposure decreased intestinal temperature but did not affect temporal artery temperature. Skin temperature followed a gradient-like pattern upon stress, decreased at distal locations (finger, hand), and unchanged or marginally increased at proximal locations. No gender differences were present in contrast to facial temperatures; decreased nasal skin temperature in females, increased cheek temperature in males. The function of the differential facial temperature effects is not yet clear but creates an interesting puzzle. In this study, as expected, heart rate, blood pressure, respiration rate and cortisol levels increased after stress. This study shows the complexity of the human situation; the location of the temperature measurement is extremely important and may influence the interpretation of the underlying 'disease' in case of psychopathology. Many drugs have effects on different parts of the thermoregulatory circuit. Dependent on where temperature is measured, drug effects might vary. If a drug induces vasoconstriction or dilatation, false positive or negative effects may be found. It could be advised that apart from measuring temperature (and preferably at different body parts) other parameters also need to be determined. Moreover, a direct translation of the preclinical stress-induced hyperthermia paradigm[5,8] seems troublesome. In the preclinical model rectal and abdominal (via telemetry) temperature consistently increase after stress whereas in man no clear-cut pattern is evident.

Non-shivering thermogenesis in brown adipose tissue generates the heat for the stress-induced hyperthermia. The most likely explanation for a pathological hyperthermia lies in disturbed hypothalamic thermoregulation probably induced via higher (e.g., amygdala) mechanisms in the brain. However, it cannot be excluded that peripheral mechanism might be disturbed leading to aberrant hyperthermia during stress. More research is clearly needed to unravel such mechanisms, including genetic, metabolic and neuronal factors. To this end, genetic and genomic technology might contribute. Studies on emotional or febrile responses in genetically modified mice have supported the hypothesis that fever-induced or emotional-induced hyperthermia is caused by (partially) different mechanisms.[8]

Overall, body temperature increase upon a psychological stressor seems a universal principle, but needs close attention because it depends (in humans) where temperature is measured. Oka (*present issue*) proposes 'functional hyperthermia' instead of 'psychogenic fever' for pathological hyperthermia. I suggest avoiding 'fever' as there are big differences between infection/inflammation-induced fever and stress-induced hyperthermia. Why not 'psychogenic hyperthermia' in case of pathological response of patients to stress?

Disclosure of Potential Conflict of Interest

No potential conflicts of interest were disclosed.

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