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A unifying theory for the functional architecture of endothermic thermoregulation

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Developing a unifying theory for the functional architecture of endothermic thermoregulation has been proven to be a challenging endeavor. Three papers published in this issue of Temperature take a closer look at this problem and add interesting views to our knowledge about the way that endothermic thermoregulation works.

The importance of maintaining thermal balance has been acknowledged since the time of Aristotle. He was the first to propose the contribution of the brain in the maintenance of a "healthy body state" through the regulation of food intake and behavior related to body temperature.[1] Yet, thermoregulation was established as vital input for the practice of medicine through the work of Lavoisier, Carnot, and Mayer in the late 18th and early 19th century.[1] Since then, studies on thermoregulatory mechanisms have been an integral part of physiological research and have illuminated physiological mechanisms at all levels of biological organization. At the cellular and molecular levels, our understanding of mechanisms governing thermal balance is dramatically increasing aided by the continuous advances in technology. However, at the systems level (i.e., the level of architecture and organization) several fundamental questions remain unanswered. The most prominent of these questions involves the mechanism by which the thermoregulatory threshold is determined which, after numerous investigations, remains a mystery.[2] The elegant experiments by Douglas Ramsay, Stephen Woods and Karl Kaiyala[3-5] in this issue of Temperature take a closer look at this problem and add interesting views to our knowledge about the way that endothermic thermoregulation works.

The overarching aim in the 3 studies by Ramsay, Woods and Kaiyala[3-5] is to scrutinize the concept of homeostasis – thermal homeostasis in this case – by using an experimental model of chronic exposure to nitrous oxide-induced hypothermia. Acute administration of nitrous oxide via inhalation leads to a rapid increase in heat loss and, thus, attenuated core temperature. Tolerance to nitrous oxide can develop both acutely (during a single exposure) and – even more so – chronically (over subsequent administrations) manifested as enhanced metabolic heat production. By administering nitrous oxide in a gas-tight thermal gradient cooled at one end and heated at the other end – thereby creating a temperature continuum along the length – the authors were able to create a scenario where autonomic (i.e., heat production and loss) and behavioral (i.e., selected location along the temperature continuum) thermoeffector responses are pitted against each other. The aim of this Editorial comment is not to summarize the findings of the studies by Ramsay, Woods and Kaiyala[3-5] but, instead, to place this work in the context of our search for the mechanism by which the thermoregulatory threshold is determined. Thus, I will leave it to the reader to enjoy reading these 3 papers and I will elaborate somewhat on their implications.

Developing a unifying theory for the functional architecture of endothermic thermoregulation has proved to be an exceedingly challenging endeavor and the philosophical attempts to achieve it extend over millennia, at least as far back as Aristotle. Since the 1960s, there have been 4 major theoretical models of endothermic thermoregulation,[2,6] none of which has been unanimously accepted. These are: (i) the "hypothalamic proportional control with an adjustable set point," (ii) the "comparator model," (iii) "core temperature defense at a null zone," and (iv) the "model of heat regulation." Each concept presents with inherent advantages and limitations in its capacity to explain the various phenomena of endothermic thermoregulation. More importantly, each of them shows a clear lack of validity under specific conditions. Some argue that, as long as a model is valid under most "normal" circumstances, the fact that it cannot explain the observed thermoregulatory responses in some "experimental" or "artificial" conditions should not be used as evidence against its validity. However, as Hawking proposes,[7] the predictions of theoretical concepts must be able

Comment on: Lanza D, Vegetti M. Opere Biologiche di Aristotele. Torino: UTET, 1996. Romanovsky AA. Thermoregulation: some concepts have changed. Functional architecture of the thermoregulatory system. Am J Physiol Regul Integr Comp Physiol 2007; 292:R37-46; PMID:17008453; http://dx.doi.org/10.1152/ajpregu.00668.2006. Kaiyala KJ, Woods SC, Ramsay DS. Persistence of a hyperthermic sign-reversal during nitrous oxide inhalation despite cue-exposure treatment with and without a drug-onset cue. Temperature 2014; 1(3):267-74; http://dx.doi.org/10.4161/23328940.2014.944811

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to survive scrutiny against empirical observations. In cases where the predictions concur with specific observations, a theoretical concept should not be accepted but, instead, put through further scrutiny against additional observations until the researcher is certain that the theory can explain all relevant phenomena in an elegant and natural manner.[7] This suggests that all 4 major theoretical models of endothermic thermoregulation proposed to date are wrong or – at best – incomplete. Having written that, it would be a terrible mistake not to acknowledge that they all (and, maybe, some more than others) have been instrumental in stimulating new research and fresh inquiry that, most certainly, will lead to new and improved theories.

The studies by Ramsay, Woods and Kaiyala[3-5] clearly demonstrate that behavioral and autonomic thermoregulatory responses can act independently and, even, oppose each other under specific conditions. Indeed, the cost-effective behavioral strategy of moving to a warmer environment was never adopted by the studied animals to counteract the nitrous oxide-induced hypothermia. One may argue that nitrous oxide simply acted on both behavioral and autonomic brain centers leading to a selection of cooler areas inside the gas-tight thermal gradient as well as increased heat loss. Nevertheless, the animals demonstrated enhanced metabolic heat production within the first few minutes of nitrous oxide exposure – especially after the development of tolerance. This response was able to compensate for both the increased heat loss and the attenuated selected ambient temperature suggesting that the autonomic pathway (i) adapts to nitrous oxide-induced perturbations and (ii) has a greater capacity to maintain heat balance than previously thought, especially in relation to the behavioral pathway. On the other hand, the fact that animals continued to select cooler ambient temperatures even after 12 3-h administrations of 60% nitrous oxide suggests that the behavioral thermoregulation pathway may be less likely to develop tolerance to external stressors. Interestingly, afferent thermal input is simultaneously projected to the hypothalamus and the brainstem, providing an energy-efficient method for precise control of thermoregulation; hypothalamus being the center of autonomic thermal responses and the brainstem being responsible for emotional whole-body homeostasis, including behavioral thermoregulation.[8] This principle of "opponent organization" is well known throughout physiology[9] and may be implicated in the observations made by Ramsay, Woods and Kaiyala.[3-5]

This Journal views differences in opinion as a reason for discussion, not a reason for rejection. In their series of studies,[3-5] Ramsay, Woods and Kaiyala provide fresh and stimulating views about the way endothermic thermoregulation works. Whether their findings will be supported by other data and point the way toward a more comprehensive theory of endothermic thermoregulation remains to be seen. As Richard Feynman wrote, "we are trying to prove ourselves wrong as quickly as possible, because only in that way can we find progress." The studies by Ramsay, Woods and Kaiyala[3-5] in this issue of Temperature will certainly contribute to that.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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