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The thermostat concept – significant for mechanical temperature control systems, but irrelevant to mammalian thermoregulatory networks

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Keywords: brain temperature, thermostat, thermoregulation, thermoTRP channels, thermoregulatory behavior

Abbreviations: CNS, central nervous system; DRG, dorsal root ganglion; TRP, transient receptor potential.

Dear Editor-in-Chief:

The Challenge Article entitled "Temperature receptors in cutaneous nerve endings are thermostat molecules that induce thermoregulatory behaviors against thermal load" by Dr. Shigeo Kobayashi[1] reviews experiments on dorsal root ganglion (DRG) neuronal responses to reductions in bath temperature and summarizes his arguments that the transient receptor potential (TRP) channels in DRG thermosensory neurons are "physiological thermostats." The author sets up some of the earliest (nearly 50 years ago), and now antiquated,[2,3] "classical models" of central thermoregulation as 'straw men' which his "new model of thermostats" will replace. Indeed, since such models have been supplanted for some time, it would have been more relevant for Dr. Kobayashi to place his views in the context of a more updated, and anatomically- and physiologically-defined model of central thermoregulatory control (e.g., ref. 4).

The author takes the illogical position that since animals can't measure temperature, but they still exhibit behavioral thermoregulation, the thermal signals entering the central nervous system (CNS) must not be "decoded" into a temperature for comparison by a "physiological thermostat" to generate a behavioral thermoregulatory response to a cold ambient. This is another 'straw man' – no thermoregulatory neurobiologist would suggest that absolute temperature values are encoded within the CNS, so the 'model' criticized by the author does not exist. Not to mention the fact that it's not just animals - the vast majority of humans cannot measure temperature either. The bigger question, however, is whether the entire premise of this paper has any validity. The author's main contention, as stated in the Introduction, is that "physiological thermostats perform behavioral thermoregulation, and it is very important to identify the thermostats in temperature physiology." As with most of the arguments in this paper, this one is also not substantiated by any neurobiological evidence. There are 2 aspects to this contention.

Firstly, we do not know, in fact, how behavioral thermoregulatory responses are elaborated by the CNS. The author's title is correct in that cutaneous thermal receptors, rather than central ones, appear to be more important in initiating these motor behaviors. For instance, peripheral thermal signals reaching spinothalamic and spinoparabrachial neurons (and some of these may be a population of bifurcating dorsal horn neurons) in the dorsal horn appear to drive sensory cortical activation and autonomic thermoregulatory responses, respectively.[4] The spinothalamic pathway is presumed to mediate conscious thermal sensation, allowing for somatotopic localization of the thermal stimulation, and perhaps of its intensity. However, the neural networks generating the 'emotionally unpleasant' sensation of being cold or hot, likely involving limbic circuits and perhaps providing the 'motivation' to perform thermoregulatory behaviors, remains unknown. Indeed, this 'emotion' may be uniquely human.[5] Also unknown is how thermoregulatory behavioral responses are generated or whether, as the author suggests, they are a consequence of (i.e., in series with) the 'emotion' of being cold or hot. In this regard, these behaviors could be triggered in parallel with autonomic ones, by parabrachial neurons responding to a thermal sensory input, but not those projecting to the preoptic area;[6] or by thalamic or cortical neurons responding to thermal sensory inputs; or perhaps by neurons in limbic circuits that also underlie the emotional component.

Secondly, there is no mandate, besides what the author has written, to "identify the thermostats in temperature physiology." Indeed, the very concept of trying to find a neural counterpart for a piece of electronics in the mechanical systems humans have designed to control their environmental temperature, seems misguided. The brain is sometimes compared to a computer, but what would be the point of looking for the brain counterpart of a transistor? Defending the existence of a "physiological thermostat," or the now-defunct "set point,"[2] merely buys into the old circuit models that the author argues against. Both of these concepts seem to have been invoked to provide a simplistic

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and easily understood explanation of the overall function of central thermoregulation to a non-scientist audience. Furthermore, I would contend that neither of these concepts, nor the models that feature them, has provided any insight into the neurobiology of central thermoregulation.

In the context of thermostats, a significant and unaddressed question in the field of thermoregulation is how (and why) mammalian brain temperature is maintained at the value of ~37°C. Is this due, as one might extrapolate from the point of view expressed in this paper, to the specific thermal responsiveness of the TRP channels in peripheral thermoreceptors? This seems unlikely for several reasons, including, if the author's recordings are at all relevant to the *in vivo* behavior of thermoTRP channels, his finding that they only generate action potentials during a change in temperature. Thus, in a constant thermoneutral ambient for instance, they are not playing any role in effecting the balance between metabolic heat production and heat loss that establishes brain and core temperatures. Since brain temperature is the output of the central thermoregulatory network, one could argue that a brain temperature of ~37°C is simply the sum of the multitude of influences[7] on the core thermoregulatory pathways controlling thermal effectors, but this is axiomatic and does not address the question of how or why the specific value of ~37°C is the evolutionary choice for mammalian brain temperature. Ultimately, the brain is responsible for maintaining its optimal functioning temperature, and so one must focus on some central thermal sensor – but what aspect of its neurobiology results in a sustained brain temperature of ~37°C?

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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