Temperature 2:3, 328–329; July/August/September 2015; Published with license by Taylor & Francis Group, LLC

Shaping our understanding of endothermic thermoregulation

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Dear Editor-in-Chief,

The paper by Kobayashi entitled "Temperature receptors in cutaneous nerve endings are thermostat molecules that induce thermoregulatory behaviors against thermal load"[1] summarizes a series of elegant studies conducted by Kobayashi and colleagues during the past 30 years. These studies have challenged the "hypothalamic proportional control" model which remains the most widely accepted approach for the functional architecture of endothermic thermoregulation over the past 50+ years.[2] Kobayashi opposes the dogma that receptors are sensors, arguing instead that receptors are "comparators."[1] He proposes that heat- and cold-sensitive neurons are comparators of temperature and evoke impulses when temperature surpasses a receptor activation threshold. In turn, these impulses are not a form of neural code (as assumed by the "hypothalamic proportional control" model) but they are *actually* triggers to activate target effector neurons in the brain. For instance, when skin temperature is below its threshold value, peripheral cold-sensitive neurons evoke impulses to stimulate target neurons in the brain responsible for appropriate heat-seeking responses. Consequently, skin coolness "*. . .only occurs in the sensation world in our mind.*"[3] Ergo, the "comparator" model suggests that effectors are triggered via sensory neurons *directly*, without the involvement/presence of a separate decision-making network or temperature code computations.

A number of scientists – including the author of this letter – that hope to unravel the functional architecture of endothermic thermoregulation have expressed concerns that the ability of the "hypothalamic proportional control" model to explain the phenomena of nature is limited.[2,4-6] The "comparator" model proposed by Kobayashi does explain some natural phenomena more eloquently and it is supported by the relatively recent discovery and nature of transient receptor potential ion channels. Indeed, for warm- and cold-sensitive neurons to be sensors – as proposed by the "hypothalamic proportional control" model – their firing rate (i.e., impulses·sec^{-1}) must be a code by which these neurons convey local temperature information. For this assumption to be correct the neural code of firing rate must be directly related to temperature and the receivers (i.e., inter-neurons in the central nervous system) of these impulses must possess the ability to decipher the code of firing rate and detect the local temperature information. Yet, as argued by Kobayashi,[1] no convincing evidence has been presented hitherto confirming either of these assumptions. The notion inherent in the "comparator" model that thermoregulatory effectors may be triggered via sensory neurons *directly* – without the involvement/presence of a separate decision-making network or temperature code computations – could be instrumental in our understanding of endothermic thermoregulation. However, the ability of the "comparator" model to explain the natural phenomena is questionable under conditions where conflicting commands are received from different areas of the body, or when autonomic and behavioral thermoeffector responses are pitted against each other. The latter was recently demonstrated in this Journal using an experimental model of chronic exposure to nitrous oxide-induced hypothermia.[2,7] The results showed that behavioral and autonomic thermoregulatory responses can act independently and, even, oppose each other under specific conditions.[2,7] In this scenario, the "comparator" model would be unable to explain the fact that the studied animals did not adopt the cost-effective behavioral strategy of moving to a warmer environment to counteract the nitrous oxide-induced hypothermia.[2,7]

A number of thermoregulation studies published each year make it increasingly clear that the "hypothalamic proportional control" model cannot effectively explain the functional architecture of endothermic thermoregulation. In this light, I believe that the "comparator" model proposed by Kobayashi is a step toward the right direction. Nevertheless, at this stage the arguments supporting this alternative theory are primarily philosophical and cannot effectively explain a number of results that appear in the literature. Moreover, support for the "comparator" model to date has mainly come from the research group that proposed it, while convincing evidence is yet to be presented by other research groups. It is my belief that, eventually, aspects of the "comparator" model as well as the "hypothalamic proportional control" model will be amalgamated together with elements from other

Letter on: Kobayashi S. Temperature receptors in cutaneous nerve endings are thermostat molecules that induce thermoregulatory behaviors against thermal load. Temperature 2015; 2(3):346-52; http://dx.doi.org/10.1080/23328940.2015.1039190

Keywords: comparator, homeostasis, set point, thermoregulation, thermoeffector responses

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Submitted: 06/01/2015

Accepted: 06/01/2015

http://dx.doi.org/10.1080/23328940.2015.1058321

prominent theories of endothermic thermoregulation in order to form a unifying – and complete – theory for the functional architecture of endothermic thermoregulation. As Albert Einstein wrote, "No fairer destiny could be allowed to any physical theory than that it should itself point out the way to introducing a more comprehensive theory in which it lives on as a limiting case." And it is in this regard that Kobayashi and his colleagues should be congratulated, as they have already been instrumental in shaping our understanding of endothermic thermoregulation.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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