

Letter on Kobayashi's view of cutaneous thermoreceptors and their role in thermoregulation

Douglas S Ramsay^{1,2,3,*}, Karl J Kaiyala¹, and Stephen C Woods⁴

¹Department of Oral Health Sciences; University of Washington; Seattle, WA USA; ²Department of Orthodontics; University of Washington; Seattle, WA USA;

³Department of Pediatric Dentistry; University of Washington; Seattle, WA USA; ⁴Department of Psychiatry and Behavioral Neuroscience; University of Cincinnati Medical Center; Cincinnati, OH USA

Dear Editor-in-Chief,

The article by Shigeo Kobayashi¹ reiterates^{2,3} a novel concept for thermoregulation. The concept is provocative, as Kobayashi and colleagues argue against a fundamental protocol of the canonical thermoregulatory control scheme, namely that temperature is measured and encoded by thermal sensors to provide input for the homeostatic control of body temperature. Classical models of thermoregulation are envisioned in terms of an “engineering-style” central controller that receives, decodes and compares afferent temperature information to a reference signal (set-point) as a basis for actuating a coordinated set of effector responses that efficiently, even “wisely,” defend normothermia in the face of thermal challenges. This classical model localizes the

“comparator” to the central nervous system (CNS). By contrast, Kobayashi proposes that temperature-sensitive receptor molecules (thermo-TRP channels) located in cutaneous nerve endings are the actual comparators, being triggered at characteristic threshold temperatures so as to generate error inputs that actuate CNS-mediated effector responses. This model both precludes requirements for temperature encoding-decoding and thermoeffector coordination via a discrete CNS comparator. Accordingly, Kobayashi has repositioned the ‘thermostat’ from the brain to myriad ‘thermostats’ residing in the interface with the thermal environment. Moreover, according to this model, input from the thermoreceptors is conveyed to other brain areas to evoke temperature sensation (e.g., “cold in the skin”).

While Kobayashi's model is focused on thermoregulation, in a broader sense it also challenges the dominant model of how homeostasis orchestrates the seemingly well-coordinated and energetically efficient effector responses that stabilize a wide variety of regulated variables, at least in the context of “naturalistic” challenges. However, we contend that the accelerating presence of “non-naturalistic” challenges such as drugs of abuse and hyper-palatable refined calories has unmasked the truer nature of biobehavioral regulation.

According to the homeostatic perspective, when experimental evidence or clinical data reveal persistent effector states that are poorly coordinated, inefficient or maladaptive, the problem reflects one or more defects located somewhere along the homeostatic negative feedback-CNS controller-actuator-effector axis. Yet even when “broken,” this scheme would actually tend to favor a coordinated set of effector states; i.e., behavioral and autonomic effectors would promote the same

outcome. We have argued⁴ that a host of pathological regulatory states (drug addiction, obesity, type-2 diabetes, depression) are more readily interpreted in terms of a regulatory model that involves a scheme of distributed control whose elements are relatively independent. Effector independence would be masked in the face of the evolutionarily-based homeostatic challenges that selected for overall system behavior, yet provide a basis for the elaboration of dis-coordinated actions in the face of challenges that were rare or non-existent during the evolutionary selection for biobehavioral control systems such as persistently excess calories, cocaine and unremitting psychological stress.⁴ The allostatic alternative⁴ takes into account seminal work, including Satinoff's model⁵ that recast thermoregulatory control in terms of widely distributed semi-autonomous control elements subject to higher CNS-level refinement, and Romanovsky's model,⁶ which compellingly explains ‘set-point-like’ control as an emergent property of the summated action of independent thermoeffector loops having differing activation thresholds and gains. Importantly, these models^{5,6} were developed in response to experimental evidence for effector dis-coordination under non-naturalistic circumstances, and we have obtained such evidence as well.⁷ Kobayashi's model both complements and extends the ideas presented above, albeit in ways that await critical verification.

Kobayashi's model for thermoregulation is not without some puzzling conjectures and debatable adherences to tradition. How do thermoreceptor potentials that exhibit transient states evoke sustained effector responses? Is skin temperature a primary regulated variable, as proposed by the model, or is it instead a feed-forward trigger for effector

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: allostasis, comparator, homeostasis, set-point, thermostat

© Douglas S Ramsay, Karl J Kaiyala, and Stephen C Woods

*Correspondence to: Douglas S Ramsay; Email: ramsay@uw.edu

Submitted: 05/05/2015

Accepted: 05/05/2015

<http://dx.doi.org/10.1080/23328940.2015.1050157>

This is an Open Access article distributed under the terms of the Creative Commons Attribution-Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited. The moral rights of the named author(s) have been asserted.

responses that primarily defend core temperature as an essential step in “saving one’s skin?” Kobayashi also persists in the tradition of applying control theory terminology to his model, which may impede its acceptance by unintentionally implying inaccurate mechanistic similarities between biology and engineering. Specifically, he refers to the temperature-activation thresholds of thermo-TRP channels as “set-points” and positions these entities as “physiological thermostats.” Similarly, he refers to “error correction” as a consequence of effector activation, in analogy with the standard model. Perpetuating normative engineering control terminology begs a number of important questions. If, as proposed, thermo-TRPs are the comparators, then how are the comparisons implemented? It is likely not via an internal reference signal, but more likely via a temperature-dependent phase transition. Is a phase transition the biological equivalent of an engineered “set-point”? Perhaps not, because an engineered thermostat implies symmetry, as a comparator integrates temperatures both above and below its operating point to generate coordinated signals that stimulate or inhibit effector activity. The Kobayashi entity seems more a switch whose output,

once triggered, exhibits some degree of gradation related to temperature.

An important unknown concerns the role of thermo-TRP channels in deep body and CNS tissues. Indeed, biobehavioral thermoeffectors are somehow coupled to local temperatures at many sites along the neuraxis as well as in non-CNS deep-body compartments. Might regulation emerge from a galaxy of relatively autonomous biological switches whose on-off thresholds are widely distributed along a temperature continuum? What would be the critical tests of such a model?

In any event, we believe that the Kobayashi model is congruent in important respects with emerging theoretical frameworks that better explain a wider range of experimental and clinical findings than does the standard homeostatic model. Moreover, we emphasize that this theoretical debate is not merely an issue of academic interest, given the epidemics of chronic disease states that are “dysregulatory” in nature. Rather, we argue that more attention should be given to the implications inherent in the concept of distributed and relatively independent control loops, including the inefficient concurrent activation of competing effectors.⁷ Refining and critically testing

concepts of distributed control and allostasis would seem vitally important steps in this process.

In summary, we believe that the model proposed by Kobayashi and colleagues is a provocative contribution with important implications for the debate centered on understanding the nature of biobehavioral regulation, and how to translate this understanding into more effective initiatives targeted at some of humankind’s most intractable diseases.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

1. Kobayashi S. *Temperature* 2015; 2(3):346-52; <http://dx.doi.org/10.1080/23328940.2015.1039190>
2. Kobayashi S, et al. *J Therm Biol* 2006; 31:19–23; <http://dx.doi.org/10.1016/j.jtherbio.2005.11.011>
3. Tajino K, et al. *PLoS One* 2011; 6:e17504; <http://dx.doi.org/10.1371/journal.pone.0017504>
4. Ramsay DS, et al. *Psychol Rev* 2014; 121:225–47; PMID:24730599; <http://dx.doi.org/10.1037/a0035942>
5. Satinoff E. *Science* 1978; 201:16–22; <http://dx.doi.org/10.1126/science.351802>
6. Romanovsky AA. *Am J Physiol Regul Integr Comp Physiol* 2007; 292:R37–R46; <http://dx.doi.org/10.1152/ajpregu.00668.2006>
7. Ramsay DS, et al. *Temperature* 2014; 1:151–61; <http://dx.doi.org/10.4161/23328940.2014.944809>