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Escape from homeostasis

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ABSTRACT

Many physiological systems, from gene networks to biochemistry to whole organism physiology, exhibit homeostatic mechanisms that keep certain variables within a fairly narrow range. Because homeostatic mechanisms buffer traits against environmental and genetic variation they allow the accumulation of cryptic genetic variation. Homeostatic mechanisms are never perfect and can be destabilized by mutations in genes that alter the kinetics of the underlying mechanism. We use mathematical models to study five diverse mechanisms of homeostasis: thermoregulation; maintenance of homocysteine concentration; neural control by a feed forward circuit; the myogenic response in the kidney; and regulation of extracellular dopamine levels in the brain. In all these cases there are homeostatic regions where the trait is relatively insensitive to genetic or environmental variation, flanked by regions where it is sensitive. Moreover, mutations or environmental changes can place an individual closer to the edge of the homeostatic region, thus predisposing that individual to deleterious effects caused by additional mutations or environmental changes. Mutations and environmental variables can also reduce the size of the homeostatic region, thus releasing potentially deleterious cryptic genetic variation. These considerations of mutations, environment, homeostasis, and escape from homeostasis help to explain why the etiology of so many diseases is complex.

1. Introduction

Humans, as all other organisms, are subject to a great deal of genetic and environmental variation. Yet our phenotypes are remarkably robust to those perturbations. The stability against environmental fluctuations is maintained dynamically by homeostatic mechanisms that activate a variety of compensatory processes. Homeostatic mechanisms therefore allow us to adapt to a large range of environments and to daily and seasonal fluctuations in environmental variables such as nutrition and temperature.

Homeostatic mechanisms also stabilize phenotypes against genetic variation [1–4]. These processes mask the deleterious effects of mutations and thus allow the accumulation of mutations that might otherwise cause disease. These continually accumulating mutations are referred to as cryptic genetic variation [5]. When a homeostasis mechanism is disrupted by a mutation, then environmental variation and cryptic genetic variation are no longer buffered and this can result in aberrant, variable and unstable phenotypes. Deleterious mutations are no longer masked, and this is believed to be the underlying cause of many complex diseases [5,6].

The mechanisms that stabilize phenotypes against environmental and genetic variation are diverse and operate at the genetic, biochemical, physiological and behavioral levels. All these mechanisms result in a chair-shaped response curve to environmental or genetic variation: the trait initially rises with increasing values of the independent variable, then there is a range over which the mechanism is able to stabilize the trait, but the trait then rises again with further increase of the genetic or environmental variable. Mutations in the homeostatic mechanism either reduce the range over which the trait is stable or make the trait less stable over the entire range of environmental or genetic variation.

Here we use mathematical models to explore the properties of five very different homeostatic mechanisms: mammalian thermoregulation, maintenance of homocysteine concentration in the liver, feed-forward inhibition in a neural circuit, the myogenic response in kidneys, and regulation of extracellular dopamine concentration + in the brain. In each case, there is a range of genetic or environmental variation in which the trait is stable and adjacent regions where it is not. In the case of dopamine we show that much of the standing genetic variation occurs within the homeostatic region where mutations have little effect on the

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dopamine concentration. We illustrate how the stable homeostatic region can be reduced or eliminated by simple changes in the underlying mechanism.

2. Results

2.1. Thermoregulation

This is the classical example of a homeostatic system. Experimental data show that body temperature in mammals remains quite constant over a large range of environmental temperatures. Body temperature is regulated by the hypothalamus, which receives information about blood temperature and skin temperature and regulates metabolic rate, peripheral vasoconstriction, piloerection, shivering and sweating, as appropriate, to bring temperature back to a set-point. These regulatory mechanisms are unable to buffer body temperature at both extremely low and extremely high environmental temperatures. A simple mathematical model of thermoregulation with saturating heating and cooling mechanisms is given by:

$$\frac{dBT}{dt} = k_1(envT - BT) + k_2 + \frac{k_3(setp - BT)^+}{k_4(setp - BT)^+} - \frac{k_5(BT - setp)^+}{k_6(BT - setp)^+} \qquad (1)$$

The first term gives the rate of heating or cooling as the difference between environmental temperature (*envT*) and body temperature (*BT*); the second term is the rate of endogenous metabolic heat production, the third and fourth terms are saturating functions that set the rates of heating and cooling, respectively, controlled by the difference between body temperature and a set-point (*setp*). The parameter k_1 sets the rate of conductive gain or loss and parameters k_2–k_5 determine the shape of the response. For each choice of *envT*, we solve the differential equation and let it relax to equilibrium. A graph of the equilibrium temperature *BT* as function of *envT* is shown in Fig. 1A, which we compare to experimental data from the brown opossum [7]. Parameters were chosen so that the curve fits the data well. If the heating and cooling terms were not there, then at steady state *BT* would be a linearly increasing function of *envT*. With the heating and cooling terms present, there is a wide plateau region because the heating and cooling terms automatically compensate for the changes in environmental temperature. This homeostatic mechanism works well over a wide range of environmental temperatures but breaks down below 12 °C and above 30 °C. Notice that the brown opossum tries to thermoregulate to 34 °C, but once the environmental temperature reaches 30 °C it begins to lose control due to metabolic heat production. Mutations that reduce the activity of the heating or cooling mechanism narrow the stability plateau of the chair curve (Fig. 1B).

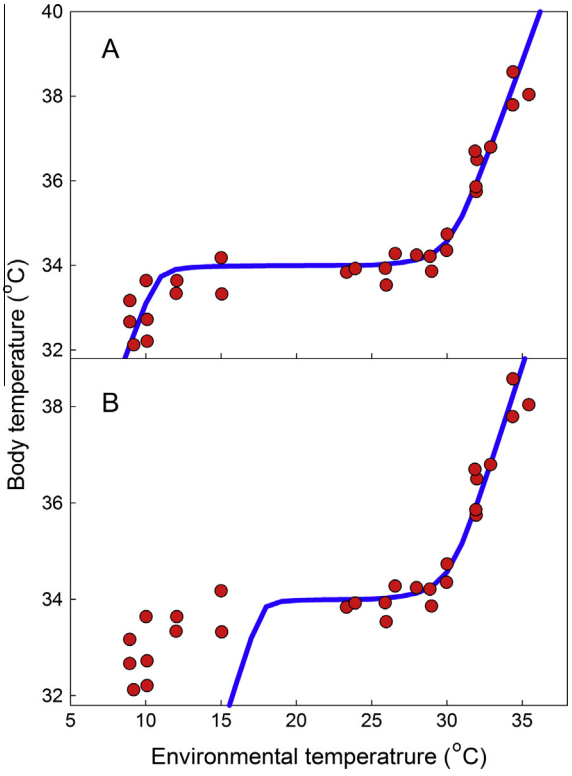

Fig. 1. Thermoregulatory homeostasis in the brown opossum. A. Data are shown by circles and the model calculations from Eq. (1) are shown by the chair-shaped curve. Parameter values were: *setp* = 34, k_1 = 2.15, k_2 = 20, k_3 = 30, k_4 = 0.01, k_5 = 12, k_6 = 0.1. B. A reduction in the efficacy of the heater (k_3 = 15) narrows the range of environmental temperatures over which body temperature can be maintained.

2.2. Homeostasis of homocysteine concentrations

Homocysteine (Hcy) is a metabolite that is produced from methionine in the methionine cycle (see Fig. 2). Some homocysteine is remethylated to form methionine and some enters the transsulfuration pathway (CBS reaction) that manufactures glutathione (GSH), the major anti-oxidant in cells. The importance of Hcy is that high levels of Hcy in the plasma or the urine have been clearly associated with adverse cardio-vascular events, though the exact causal mechanisms have not been determined [8]. The concentration of Hcy in the liver is affected by the input of methionine, which varies with each protein meal, and is also affected by folate (vitamin B9) because folate, in the form of 5-methyltetrahydrofolate (5mTHF), is a substrate for the reaction that remethylates Hcy to methionine [9]. Thus elevated input of methionine tends to raise Hcy and an elevated level of folate tends to reduce the concentration of Hcy.

The concentration of Hcy is stabilized by interesting homeostatic mechanisms that are due to long-range allosteric interactions (shown in red[2] in Fig. 2) between the folate cycle and the methionine cycle. That is, there are substrates in each cycle that inhibit enzymes in the other cycle. In [10], we showed that these long range interactions stabilize the flux of DNA methylation in the methionine cycle against fluctuations in methionine input due to meals. Here we use the mathematical model, corresponding to Fig. 2 and described in [11], to show that these same long-range interactions also stabilize the concentration of Hcy. When methionine input goes up, this increases the concentration of S-adenosylmethionine (SAM). Elevated levels of SAM have several consequences. SAM increases the activity of cystathionine-β-synthase (CBS), which increases removal of Hcy. SAM also inhibits the enzyme methylene tetrahydrofolate reductase (MTHFR), which reduces the concentration of 5mTHF. Since 5mTHF is a co-substrate for methionine synthase (MS) this reduces the rate of transformation of Hcy to methionine. A decrease in 5mTHF also increases the rate of the glycine methyltransferase (GNMT) reaction, which speeds up the production of Hcy. SAM also inhibits betaine-hydroxymethyltransferase (BHMT), which also reduces the rate at which Hcy is transformed into methionine. Together these reactions serve to increase the removal of Hcy from the system when methionine input goes up, and stabilize the Hcy concentration against fluctuations in methionine input.

[2] For interpretation of color in Fig. 2, the reader is referred to the web version of this article.