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EDITORIAL

Postulate of the Existence of a 'Nocistat': Rationale and Implications for Novel Analgesics

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In a controlled system, such as room temperature, adjusting the input in one branch of the loop (eg, the heater) only transiently alters the temperature, because the change in temperature is detected, and the opposing branch (eg, the air conditioner) is activated in order to return the temperature to the pre-set value, which is set and maintained by the "thermostat". This type of control system is well known as "homeostasis" in physiological systems. We have previously proposed, consistent with the original 1965 gate-control theory of Melzack and Wall[1] and later modifications, that the ascending and descending pain pathways must be connected in a way that forms a controlled system.[2] In place of the nomenclature "thermostat" to indicate control of temperature, we use the term "nocistat" for control of pain.[2] Just as a thermostat controls the temperature set-point and necessary adjustment to changes, a "nocistat" would control the set-point of pain sensitivity and control any necessary adjustment. This concept is actually a natural extension of gate-control theory (Figure 1).

Although the concept of a basal level of pain is not well appreciated outside of the pain specialist community, a basal level of pain is thought to be present due to the usual wear-and-tear of joint movement and anatomical imperfections that develop over aging.[3] An example is osteoarthritis (OA), the most common joint disease. OA is characterized by cartilage degeneration.[4] However, up to 40% of OA patients that display clear radiologic evidence of joint damage are asymptomatic.[5] Inglis et al[6] showed that the reason is not some genetic absence of or injury to pain transmission pathways but rather is the result of increased activity of the endogenous opioid system[7] that "masks" the pain signals, which demonstrates in these patients a basal level of (unperceived) pain.

Exciting research goals/opportunities and questions that emerge from this construct are determination if there is a "nocistat" or perhaps more than one, identification of the anatomical site(s) of a "nocistat", whether it is localized

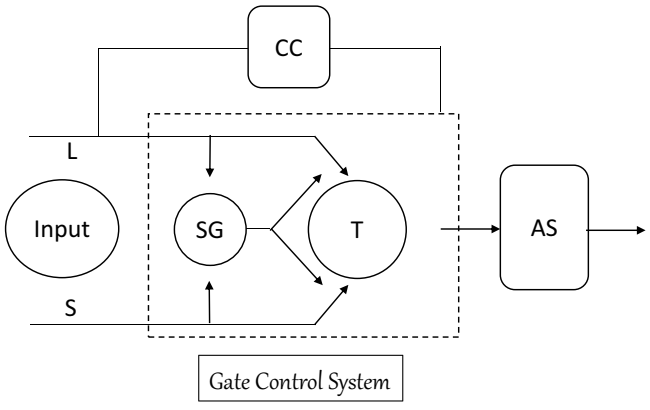

Figure 1 The original gate-control system representation. From Melzack R, Wall PD. Pain mechanisms: a new theory. *Science*. 1965;150(3699):971–979. Adapted with permission from AAAS.[1]

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within a compact brain and/or peripheral region or distributed throughout several regions (in a way similar to memory),[8] and what are its properties.

The properties of a "nocistat" might be informed by the design of thermostats. A thermostat senses the existing room temperature and compares it to the set-point temperature (Figure 2). If there is a disparity, thermostatically controlled loads (TCLs), ie, devices that convert electricity into heating or cooling energy (eg, heaters and air conditioners) are turned ON or OFF. Thus, standard thermostats[9] are feedback controllers that switch the control element between two states and, as such, are an example of *bang-bang controllers*[10] (ie, the heater or air conditioner is either running or not, depending on whether the room temperature is below or above the set-point). Thermostat *sensitivity* is the term used to describe how closely a thermostat attempts to maintain the desired set temperature within preestablished bounds. Thermostats do this by sensing the current room temperature and then signaling components of the control system if the temperature falls outside the range of the desired set-point bounds. This range is called the *swing* (among other names). Too narrow a swing will initiate a signal in response to too small a deviation in room temperature and will inefficiently oscillate back-and-forth around the set-point. A less sensitive thermostat has a wider swing and will allow greater fluctuation in room temperature before signaling the system to make an adjustment. Altering the sensitivity of the thermostat changes the width of this swing. Thermostats also need to avoid "overshoot" (exceeding the boundaries of the swing). Because there is a delay in the ON/OFF switching of the TLCs, innovations in thermostats employ thermal *anticipators* which cause the control system to send its signal earlier than waiting for the threshold to be reached. This improves the control performance of the thermostat and avoids overshoot in the temperature control.

It would be intriguing to determine if a "nocistat" employs similar strategies as a modern thermostat. It is easy to appreciate that a defective or improperly set thermostat results in a too-high or too-low room temperature or in inappropriate swings in temperature. Likewise, we envision that a "nocistat" could be defective due to some genetic predisposition or environmental insult or due to some drug-induced effect, resulting in inappropriate pain sensitivity or inhibitory control.

As a corollary to the above analogy to temperature control, when a change in desired or target room temperature is needed, the first thought is not to alter the wiring in the heater or air conditioner. Instead, we adjust the thermostat. This allows the heater and the air conditioner to smoothly and reliably reestablish the new equilibrium (homeostasis), without: excess overshoot (swings in temperature); disruption of either component of the loop (viz, heater or air conditioner); tolerance (the effect of resetting the thermostat does not diminish with time); or rebound (an opposite swing in temperature).

We conclude that: (i) our postulate of a "nocistat" is a natural extension of the gate-control theory and the control-system nature of the ascending-descending pain pathway loops; (ii) identification of the anatomical location(s) of a "nocistat" (whether localized in one region or distributed among regions) represents an important research goal; (iii) the operational/functional characteristics of thermostats might direct searches for similar properties of a "nocistat"; (iv) some atypical pain sensitivities or clinical pain conditions might result from some fault with a "nocistat" rather than a receptor, 2nd-messenger transduction system, or dysfunction of the pain transmitting or inhibiting pathways; and (v) a "nocistat" could represent a new target for the design of novel analgesic agents and/or therapeutic strategies.

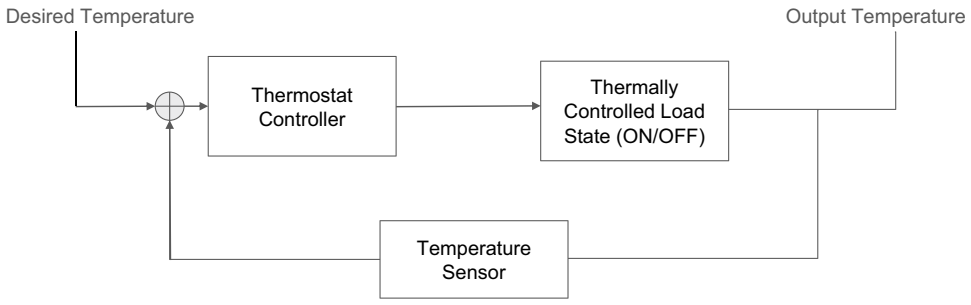

Figure 2 A generalized control system representation of temperature control by a thermostat.

Disclosure

The authors report no conflicts of interest in this work.

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