Chapter

Introductory Chapter: Homeostasis – A Brief Description and Scope for Recent Advances in the Medical Field

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1. Introduction

Homeostasis is described as the balanced stage in a living system (internal chemical physical and social state or conditions) that does not change with time or negligibly [1]. As a result of a certain set of conditions, the organism has optimal functioning, including keeping certain variables within a certain range (homeostatic range). Moreover, there are other variables that need to be regulated despite changes in environment, diet, or activity level, such as the pH of extracellular fluid, sodium, potassium, and calcium ions concentrations, and blood sugar levels. A single regulator or homeostatic mechanism controls each of these variables, which together maintain life.

A state of homeostasis occurs when optimum conditions prevail [2]. The central motivation for organic action is equilibrium, which is maintained by many regulatory mechanisms. There are three parts to all homeostasis control mechanisms: receptors, control centers, and effectors [3]. In addition to monitoring and responding to changes in the environment, the receptor is also responsible for sensing changes within the body. A thermoreceptor and a mechanoreceptor are examples of receptors. Respiratory centers and renin-angiotensin systems are two of the control centers. In order to change back to a normal state, an effector must be acted upon. A nuclear receptor causes gene expression to change at the cellular level by upregulating or downregulating and acts as a negative feedback device. Controlling bile acids in the liver is one example [4].

Homeostasis was coined by Walter Bradford Cannon in 1926 after English physiologist Claude Bernard defined it in 1849 [5, 6]. In 1932, British physiologist Joseph Barcroft proposed that the most stable internal environment was necessary for higher brain function. Barcroft interpreted homeostasis as a service to the brain, rather than one that it organized [7]. The concept of homeostasis refers to the constant environment in which cells live and survive within the body, as described by Bernard and Cannon [8]. Homeostasis is defined as the state of being in balance on a physiological level, but cybernetics describes technological control systems such as thermostats that act as homeostasis but are often defined much more broadly than biological homeostasis [9–12].

All organisms are dependent on very specific chemical and physical environments for their metabolic processes to take place. Chemical processes vary by organism

and depending on whether they occur inside or outside the cells. Humans and other mammals possess one of the most widely known homeostatic mechanisms which are responsible for maintaining the constant composition of the extracellular fluid (also known as the internal environment). These mechanisms control the temperature, pH, osmolality, sodium, potassium, glucose, carbon dioxide, and oxygen concentrations in the extracellular fluid (or internal environment). However, a great many other homeostatic mechanisms, encompassing many aspects of human physiology, control other entities in the body. Where the levels of variables are higher or lower than those needed, they are often prefixed with hyper- and hypo-, respectively such as hyperthermia and hypothermia or hypertension and hypotension.

In the morning, the body temperature rises to about 37.5°C, then falls to about 36.4°C in the evening, before again rising to approximately 37.5°C in the morning. Having homeostatic control does not mean the value of an entity is always constant in health. The hypothalamus, among others, regulates the core body temperature via a homeostatic mechanism [13]. Regular resets are performed on the regulator's set point, however [14]. People's core body temperatures vary throughout the day (a circadian rhythm), with a low temperature at night and a high temperature in the afternoon. A woman's menstrual cycle can also cause variations in temperature [15, 16]. Infections cause a fever by resetting the temperature regulator [17]. Through the process of acclimatization, organisms can adjust somewhat to different conditions such as temperature or oxygen level changes. Body activities are not all governed by homeostasis [18, 19].

In order to convey information about the direction and magnitude of the error detected by the sensor, the signal from the sensor to the effector is, of necessity, highly variable [11, 20, 21]. A similar mechanism is needed to reverse the effector's error—in fact, it should be in proportion (but in the opposite direction) to the error that threatens the environment within [12]. During the growth of the internal carotid arteries, stretch receptors in the aortic arch and carotid sinuses measure arterial blood pressure [13]. Blood pressure sensor signals are sent through sensory nerves to the medulla oblongata of the brain according to whether it has dropped or risen. Motor or efferent nerves of the autonomic nervous system then carry messages from the medulla oblongata to a variety of effector organs, whose activity is changed accordingly to correct the blood pressure error. When arterial blood pressure drops, the heart's rate increases (tachycardia), and when pressure rises above the set point, it slows down (bradycardia) [13]. As a result, the heart rate (for which the body does not have a sensor) does not function as a homeostatic control, but rather as an effector response to arterial blood pressure errors. Sweating is another example of sweating regulated by the hypothalamus of the brain. The hypothalamus is equipped with a sensor for measuring this effector, which helps to control body temperature by regulating heat load at home. Recent advances in understanding body weight homeostasis in humans.

There is no consensus framework for body weight homeostasis today, despite the assumption of control over body weight. The set point of body weight suggests that (i) it is more or less tightly controlled and (ii) it is symmetric or asymmetrically controlled biologically. This is the result of feedback loops between peripheral organs and tissues (e.g. leptin secreted by adipose tissue) and a central system. It is also possible that metabolic adaptations to energy imbalance occur without feedback control by reaching a "settling point" rather than a set point. An alternative method that combines both paradigms is the "dual intervention point" model, which introduces two set points and a settling point between them. Biological control of body weight is

not consistently demonstrated in observational studies on large populations, which may be overridden by obesogenic environments and cultures that affect behavior and experiences. A focused protocol based on sound principles is needed to address the issue of weight homeostasis, such as examining lean rather than overweight subjects before, during, and after weight loss. The association between the mass of individual body components (i) and mass and metabolic function (ii) in contexts of cerebrohumoral control and systemic effects need to be addressed with improved methods and a multi-level–multi-systemic approach. A greater effort should be made to avoid simplifications and non-biologic phenotypes (e.g. body mass index and waist circumference). Control (or a set point) will have more to do with energy expenditure than body weight, as changes in body weight are the result of mismatches between tightly controlled energy expenditure and loosely controlled energy intake [22]. Overall, body weight control is currently offered in three different forms. It is true that all models have limitations and cannot fully explain human weight fluctuations, despite their striking appearance. A tight control system might be invalidated in the short term due to the lack of autocorrelation between EI and EE. The settling point model might be suitable for long-term control of body weight. Based on the evidence presented, normal-weight subjects are more likely to show signs of biological control and to lose weight when calorie restriction is implemented. It is imperative to discuss the limitations of current research and to suggest better concepts, methods, and studies to improve body weight homeostasis in the future [22].

2. Iron homeostasis and modulation as an example of future studies to treat various diseases like stroke

Redox properties are characteristic of iron. A number of enzymes use it as an active site, and it plays a key role in various cellular and biological functions, such as the production of ATP and DNA. Redox-active iron causes oxidative stress and cell death by generating free radicals and lipid peroxidation. Apoptosis and necrosis are different types of cell death processes, and iron-mediated oxidation plays a central role in ferroptosis. The regulation of iron metabolism and homeostasis is sophisticated. Since hepcidin was identified as the main regulator of iron homeostasis, there have been exciting advances in understanding iron metabolism and regulation. Mammalian cells produce only one iron exporter, ferroportin, which is regulated by hepcidin. Ferroportin is a ferrous iron permease that exports iron to the outside. Recently, iron homeostasis has focused particularly on epigenetics. Iron metabolism is modulated by epigenetic processes including hepcidin. Reviewing recent advances in epigenetic regulation of hepcidin, ferritin, and ferroptosis, we focus on the rapid progress in understanding molecular mechanisms of iron homeostasis. Also discussed is the interaction between iron and methionine oxidation. In addition, several studies have demonstrated that accumulation of brain iron correlates with neuronal damage following stroke. It is briefly discussed how iron metabolism may play a role in strokes. It may be possible to treat various intractable diseases, such as stroke, by understanding the mechanisms behind iron regulation [23].

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