Physiology

LEC. 3

Homeostasis

Homeostasis: A Defining Feature of Physiology

Homeostasis **is a property of cells, tissues, and organisms that allows the maintenance and regulation of the stability and constancy needed to function properly. Homeostasis is a healthy state that is maintained by the constant adjustment of biochemical and physiological pathways**.for ex,it is ***a dynamic***, not a static, process ,consider swings in the concentration of glucose in the bloodover the course of a day. After a typical meal,carbohydrates in food are broken down in the intestines intoglucose molecules, which are then absorbed across the intestinal epithelium and released into the blood. What is important isthat once the concentration of glucose in the blood increases,compensatory mechanisms restore it toward the concentration it was before the meal.

These homeostatic compensatory mechanisms do not, however, **overshoot تتخطى to any significant degree** in the opposite direction. That is, the blood glucoseusually does not decrease below the pre-meal concentration,or does so only slightly.

In the case of glucose, the endocrine system is primarily responsible for this adjustment, but a widevariety of control systems may be initiated to regulate otherprocesses.

Homeostasis, therefore, does not imply that a given physiological function or variable is **rigidly constant** with respect to time but that it **fluctuates within a predictable andoften narrow range**. When disturbed above or below the normalrange, it is restored to normal.

Blood glucose concentrations, if the daily average glucose concentration was determined in the same person on many consecutive days, it would be much more predictable over days or even years than random, individual measurements of glucoseover the course of a single day. In other words, there maybe considerable variation in glucose values over short timeperiods, but less when they are averaged over long periods oftime.

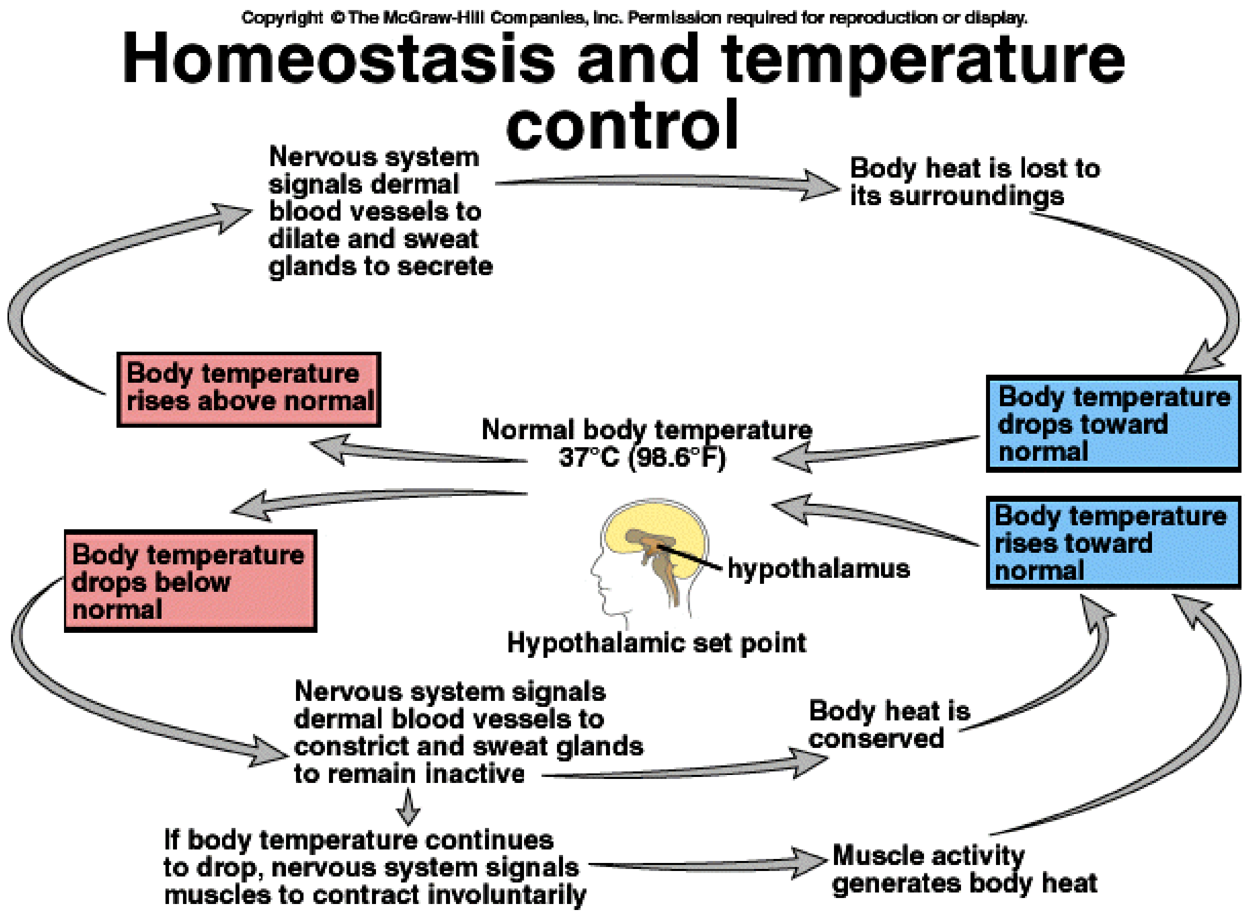
This has led to the concept that homeostasis is a state of **dynamic constancy ثبات ديناميكي .**In such a state, a given variable like blood glucose may vary in the short term but is stable and predictable when averaged over the long term.

It is also important to realize that a person may be homeostatic for one variable but not homeostatic for another.

Homeostasis must be described differently, therefore, for each variable. For example, as long as the concentration of sodium ions in the blood remains within a few percentage points of its normal range, sodium homeostasis exists.

In general, if all the major organ systems are operating in a homeostatic manner, a person is in good health. Certain kinds of disease, in fact, can be definedas the loss of homeostasis in one or more systems in the body.

To elaborate on our earlier definition of *physiology*, therefore,when homeostasis is maintained, we refer to physiology; whenit is not, we refer to pathophysiology (from the Greek *pathos*,meaning “suffering” or “disease”).



General Characteristics of Homeostatic Control Systems

The activities of cells, tissues, and organs must be regulatedand integrated with each other so that any change in the extracellular fluid initiates a reaction to correct the change.

The compensating mechanisms that mediate such responsesare performed by **homeostatic control systems**.

Consider an example of the regulation of body temperature. This time, our subject is a resting, man in a room having a temperature of 20 C and moderate humidity. His internal body temperature is 37 C, and he is losing heat to the external environment because it is at a lower temperature. However, the chemical reactions occurring within the cells of his body are producing heat at a rate equal to the rate of heat loss. Under these conditions, the body undergoesno *net* gain or loss of heat, and the body temperature remains constant. The system is in a **steady state ,** definedas a system in which a particular variable— temperature, in this case—is not changing but in which energy—in this case,heat—must be added continuously to maintain a constantcondition. (**Steady state differs from equilibrium,**in whicha particular variable is not changing but no input of energyis required to maintain the constancy.) The steady-state temperaturein our example is known as the **set point** of the thermoregulatorysystem.

This example illustrates a crucial generalization about homeostasis. Stability of an internal environmental variable isachieved by the balancing of inputs and outputs. In the previousexample, the variable (body temperature) remains constant because metabolic heat production (input) equals heatloss from the body (output). **مهم**

Now imagine that we rapidly reduce the temperature of theroom, say to 5 C, and keep it there. This immediately increases the loss of heat from our subject's warm skin, upsetting the balance between heat gain and loss. The body temperature thereof restarts to decrease. Very rapidly, however, a variety of homeostatic responses occur to limit the decrease.

The first homeostatic response is that blood vessels to the skin become constricted (narrowed), reducing the amount of blood flowing through the skin. This reduces heat loss from the blood to the environment and helps maintain body temperature.

At a room temperature of 5 C, however, blood vessel constriction cannot completely eliminate the extra heat loss from the skin. Clearly, then, if excessive heat loss (output) cannotbe prevented, the only way of restoring the balance between heat input and output is **to increase input**, and this is precisely what occurs. Our subject begins to shake, and the chemical reactions responsible for the skeletal muscle contractions that constitute shivering produce large quantities of heat.

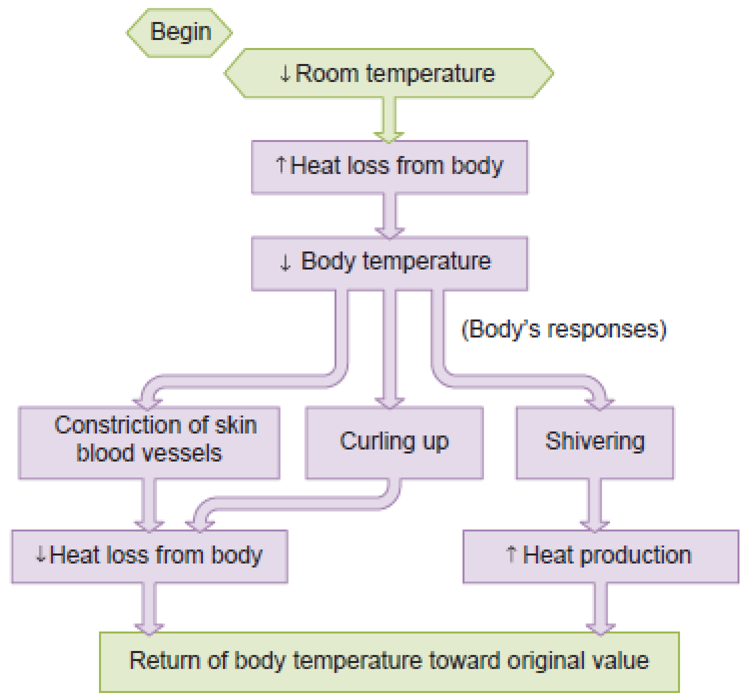


Figure 1.5 A homeostatic control system maintains body temperature when room temperature decreases. This flow diagram is typical of those used throughout this book to illustrate homeostatic systems, and several conventions should be noted. The "Begin" sign indicates where to start. The arrows next to each term within the boxes denote increases or decreases. The arrows connecting any two boxes in the figure denote cause and effect; that is, an arrow can be read as "causes" or "leads to." (For example, decreased room temperature "leads to" increased heat loss from the body.) In general, you should add the words "tends to" in thinking about these cause-and-effect relationships. For example, decreased room temperature tends to cause an increase in heat loss from the body, and curling up tends to cause a decrease in heat loss from the body. Qualifying the relationship in this way is necessary because variables like heat production and heat loss are under the influence of many factors, some of which oppose each other.

8 Chapter 1

Feedback Systems

The thermo regulatory system just described is an example of a **negative feedback** system, in which an increase or decrease in the variable being regulated brings about responses that tend to move the variable in the direction opposite ("negative" to)the direction of the original change. Thus, in our example,a decrease in body temperature led to responses that tended to increase the body temperature—that is, move it toward itsoriginal value.

Without negative feedback, oscillations تذبذبlike some of those described would be much greater and, therefore,the variability in a given system would increase. Negative feedback also prevents the compensatory responses to a loss of homeostasis from continuing unabated بلا توقف.

Negative feedback may occur at the organ, cellular, o rmolecular level. For instance, negative feedback regulates many enzymatic processes, as shown in schematic form in**Figure 1.6** .

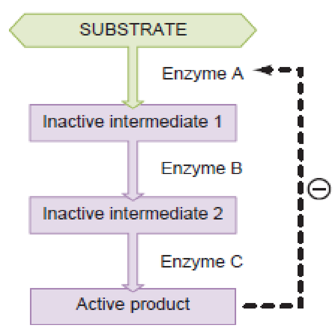


Figure 1.6 Hypothetical example of negative feedback (as denoted by the circled minus sign and dashed feedback line) occurring within a set of sequential chemical reactions. By inhibiting the activity of the first enzyme involved in the formation of a product, the product can regulate the rate of its own formation.

In this example, the product formed from a substrateby an enzyme negatively feeds back to inhibit further raction of the enzyme. This may occur by several processes,such as chemical modification of the enzyme by the productof the reaction. The production of adenosine triphosphate(ATP) within cells is a good example of a chemical processregulated by feedback. Normally, glucose molecules are enzymatically broken down inside cells to release some ofthe chemical energy that was contained in the bonds of themolecule. This energy is then stored in the bonds of ATP.

The energy from ATP can later be tapped by cells to power such functions as muscle contraction, cellular secretions,and transport of molecules across cell membranes. As ATP accumulates in the cell, however, it inhibits the activity of some of the enzymes involved in the breakdown of glucose.

Therefore, as ATP concentrations increase within a cell,further production of ATP slows down due to negative feedback.Conversely, if ATP concentrations decrease within acell, negative feedback is removed and more glucose is broken down so that more ATP can be produced.

Not all forms of feedback are negative. In some cases,**positive feedback** accelerates a process, leading to an “explosive”system. This is counter to the principle of homeostasis,because positive feedback has no obvious means of stopping.

Not surprisingly, therefore, positive feedback is much lesscommon in nature than negative feedback. Nonetheless, thereare examples in physiology in which positive feedback is veryimportant.

As the uterine muscles contract and a baby's head is pressed against the mother's cervix during labor, signals are relayed تترحل via nerves from the cervix to the mother's brain. The brain initiates the secretion into the blood of a molecule called oxytocin from the mother's pituitary gland. Oxytocin is a potent stimulator of further uterine contractions. As the uterus contracts even harder in response to oxytocin, the baby's head is pushed harder against the cervix, causing it to stretch more; this stimulates yet more nerve signals to the mother's brain, resulting in yet more oxytocin secretion. This self-perpetuating cycle continues untilfinally the baby pushes through the stretched cervix and is born.

Resetting of Set Points

As we have seen, changes in the external environment can displace a variable from its set point. In addition, the set points for many regulated variables can be physiologically reset to a new value. A common example is fever, the increase in body temperature that occurs in response to infection and that is somewhat analogous to raising the setting of a thermostat in a room. The homeostatic control systems regulating body temperature are still functioning during a fever, but they maintain the temperature at an increased value. This regulated increase in body temperatureis adaptive for fighting the infection, because elevated temperature inhibits proliferation of some pathogens. In fact,this is why a fever is often preceded by chills and shivering. The set point for body temperature has been reset to a higher value, and the body responds by shivering to generate heat.

The example of fever may have left the impression that set points are reset only in response to external stimuli, suchas the presence of pathogens, but this is not the case. Indeed,the set points for many regulated variables change on a rhythmic basis every day. For example, the set point for body temperature is higher during the day than at night.

Although the resetting of a set point is adaptive in somecases, in others it simply reflects the clashing demands of different regulatory systems. This brings us to one more generalization.It is not possible for everything to be held constantby homeostatic control systems. In our earlier example, body temperature was maintained despite large swings in ambient المحيطه temperature, but only because the homeostatic control system brought about large changes in skin blood flow and skeletal muscle contraction. Moreover, because so many properties of the internal environment are closely inter related, it is often possible to keep one property relatively stable only by moving others away from their usual set point. This is what we meanby "**clashing demands,**" which explains the phenomenon mentioned earlier about the interplay between body temperature and water balance during exercise.

The generalizations we have given about homeostatic controlsystems are summarized in **Table 1.2** .

TABLE 1.2 Some Important Generalizations About Homeostatic Control Systems
Stability of an internal environmental variable is achieved by balancing inputs and outputs. It is not the absolute magnitudes of the inputs and outputs that matter but the balance between them.
In negative feedback, a change in the variable being regulated brings about responses that tend to move the variable in the direction opposite the original change—that is, back toward the initial value (set point).
Homeostatic control systems cannot maintain complete constancy of any given feature of the internal environment. Therefore, any regulated variable will have a more or less narrow range of normal values depending on the external environmental conditions.
The set point of some variables regulated by homeostatic control systems can be reset—that is, physiologically raised or lowered.
It is not always possible for homeostatic control systems to maintain every variable within a narrow normal range in response to an environmental challenge. There is a hierarchy of importance, so that certain variables may be altered markedly to maintain others within their normal range.

One additional point is that, as is illustrated by the regulation of body temperature,multiple systems usually control a single parameter. The adaptive value of such redundancy is that it provides much greaterfine-tuning and also permits regulation to occur even when oneof the systems is not functioning properly because of disease.

Feed Forward Regulation

Another type of regulatory process often used in conjunction with a feedback system is *feed forward*. Let us give an example of feed forward and then define it. The temperature-sensitive neurons that trigger negative feedback regulation of body temperature when it begins to decrease are located inside the body. In addition,there are temperature-sensitive neurons in the skin; these cells, in effect, monitor outside temperature.

When **outside temperature decreases**, as in our example, these neurons immediately detect the change and relay this information to the brain. The brain then sends out signals to the blood vessels and muscles, resultingin heat conservation and increased heat production. In this manner, compensatory thermoregulatory responses are activating *before* the colder outside temperature can cause the internal body temperature to decrease.

In another familiar example, the smell of food triggers nerve responses from odor receptors in the nose tothe cells of the digestive system. The effect is to prepare the digestive system for the arrival of food before we even consume it, forexample by inducing saliva to be secreted in the mouth and causing the stomach to churn and produce acid. Thus, **feedforward**regulation anticipates changes in regulated variables such as internalbody temperature or energy availability, improves the speedof the body’s homeostatic responses, and minimizes fluctuations in the level of the variable being regulated—that is, it reduces theamount of deviation from the set point.

In our examples, feedforward regulation utilizes a set of external or internal environmental detectors. It is likely, however,that many examples of feedforward regulation are the result of a different phenomenon—learning. The first times they occur,early in life, perturbations in the external environment probably cause relatively large changes in regulated internal environmental factors, and in responding to these changes the central nervous system learns to anticipate them and resist them more effectively. A familiar form of this is the increased heart rate that occurs in an athlete just before a competition begins.

Components of HomeostaticControl Systems

- **Reflexes**

The thermo regulatory system we used as an example in the previous section and many of the other homeostatic control systems belong to the general category of stimulus–response sequences known as *reflexes.* Although in some reflexes we are aware ofthe stimulus and/or the response, many reflexes regulating the internal environment occur without our conscious awareness.

In the narrowest sense of the word, a **reflex** is a specific,involuntary, unpremeditated غير متعمد , "built-in" response to a particular stimulus. Examples of such reflexes include pulling your hand away from a hot object or shutting your eyes as an object rapidly approaches your face. Many responses,however, appear automatic and stereotyped but are actually the result of learning and practice. For example, an experienced driver performs many complicated acts in operating a car. To the driver, these motions are, in large part, automatic,stereotyped, and unpremeditated, but they occur only because a great deal of conscious effort was spent learning them. We term such reflexes **learned** or **acquired reflexes.**

In general, most reflexes, no matter how simple they may appear to be, are subject to alteration by learning.The pathway mediating a reflex is known as the **reflexarc** ,and its components are shown in **Figure 1.7** .

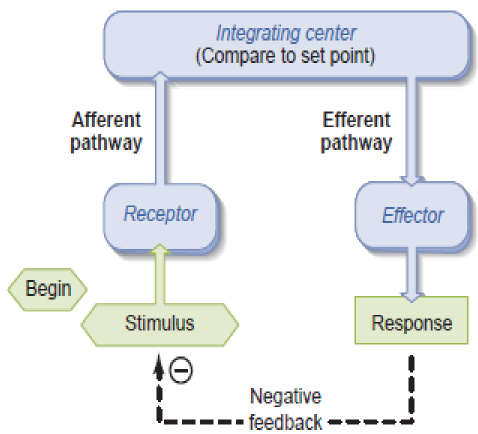


Figure 1.7 General components of a reflex arc that functions as a negative feedback control system. The response of the system has the effect of counteracting or eliminating the stimulus. This phenomenon of negative feedback is emphasized by the minus sign in the dashed feedback loop.

A **stimulus** is defined as a detectable change in the internal or external environment, such as a change in temperature, plasma potassium concentration, or blood pressure. A **receptor** detects the environmental change. A stimulus acts upon a receptor toproduce a signal that is relayed to an **integrating center.** Thesignal travels between the receptor and the integrating centeralong the **afferent pathway** (the general term *afferent* means“to carry to,” in this case, to the integrating center).

An integrating center often receives signals from many receptors, some of which may respond to quite different types of stimuli. Thus, the output of an integrating center reflectsthe net effect of the total afferent input; that is, it represents anintegration of numerous bits of information.

The output of an integrating center is sent to the last component of the system, whose change in activity constitutes the overall response of the system. This component isknown as an **effector.** The information going from an integrating center to an effector is like a command directing the effector to alter its activity. This information travels along the**efferent pathway** (the general term *efferent* means “to carryaway from,” in this case, away from the integrating center).

If the response produced by the effect or causes a decrease in the magnitude of the stimulus that triggered the sequence of events, then the reflex leads to negative feedback and we have a typical homeostatic control system. Not all reflexes areassociated with such feedback. For example, the smell of foodstimulates the stomach to secrete molecules that are importantfor digestion, but these molecules do not eliminate the smell of food (the stimulus).

Figure 1.8 demonstrates the components of a negativefeedback homeostatic reflex arc in the process of thermoregulation.

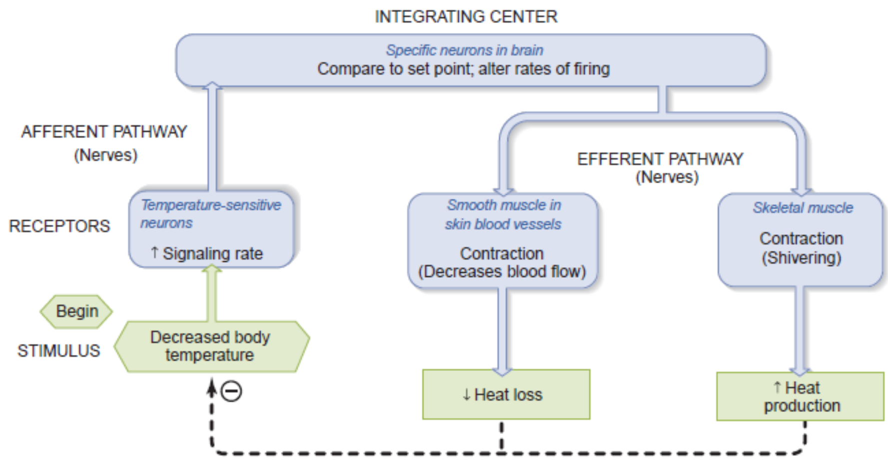


Figure 1.8 Reflex for minimizing the decrease in body temperature that occurs on exposure to a reduced external environmental temperature. This figure provides the internal components for the reflex shown in Figure 1.5. The dashed arrow and the ⊖ indicate the negative feedback nature of the reflex, denoting that the reflex responses cause the decreased body temperature to return toward normal. An additional flow-diagram convention is shown in this figure: blue boxes always denote events that are occurring in anatomical structures (labeled in blue italic type in the upper portion of the box).

The temperature receptors are the endings of certain neurons in various parts of the body. They generate electrical signals in the neurons at a rate determined by the temperature. These electrical signals are conducted by nerves containing processes from the neurons—the afferent pathway—to the brain, wherethe integrating center for temperature regulation is located. Theintegrating center, in turn, sends signals out along neurons that cause skeletal muscles and the muscles in skin blood vessels tocontract. The neurons to the muscles are the efferent pathway,and the muscles are the effectors. The dashed arrow and thenegative sign indicate the negative feedback nature of the reflex.

Almost all body cells can act as effectors in homeostatic reflexes. Muscles and glands, however, are the major effectorsof biological control systems. In the case of glands, for example,the effector may be a hormone secreted into the blood. A**hormone** is a type of chemical messenger secreted into theblood by cells of the endocrine system.

Hormones may act on many different cells simultaneously because they circulate throughout the body.Traditionally, the term *reflex* was restricted to situations in which the receptors, afferent pathway, integrating center,and efferent pathway were all parts of the nervous system, as in the thermoregulatory reflex. However, the principles are essentially the same when a blood-borne chemical messenger,rather than a nerve, serves as the efferent pathway, or whena hormone-secreting gland serves as the integrating center.

In our use of the term *reflex*, therefore, we include hormonesas reflex components. Moreover, depending on thespecific nature of the reflex, the integrating center may reside either in the nervous system or in a gland. In addition, a glandmay act as both receptor and integrating center in a reflex.

For example, the gland cells that secrete the hormone insulin,which *decreases* plasma glucose concentration, also detect*increases* in the plasma glucose concentration.

- **Local Homeostatic Responses**

In addition to reflexes, another group of biological responses,called **local homeostatic responses,**is of great importance for homeostasis. These responses are initiated by a change in the external or internal environment (that is, a stimulus), and theyinduce an alteration of cell activity with the net effect of counteracting the stimulus. Like a reflex, therefore, a local response is the result of a sequence of events proceeding from a stimulus. Unlike areflex, however, the entire sequence occurs only in the area of thestimulus. For example, when cells of a tissue become very metabolicallyactive, they secrete substances into the interstitial fluidthat dilate (widen) local blood vessels. The resulting increased blood flow increases the rate at which nutrients and oxygen are delivered to that area, and the rate at which wastes are removed.

The significance of local responses is that they provide individual areas of the body with mechanisms for local self-regulation.

- **The Role of Intercellular Chemical Messengers in Homeostasis**

Essential to reflexes and local homeostatic responses—and therefore to homeostasis—is the ability of cells to communicatewith one another. In this way, cells in the brain, for example, canbe made aware of the status of activities of structures outside thebrain, such as the heart, and help regulate those activities to meet new homeostatic challenges. In the majority of cases, intercellular communication is performed by chemical messengers. There are three categories of such messengers: hormones, neurotransmitters,and paracrine or autocrine substances (**Figure 1.9**).

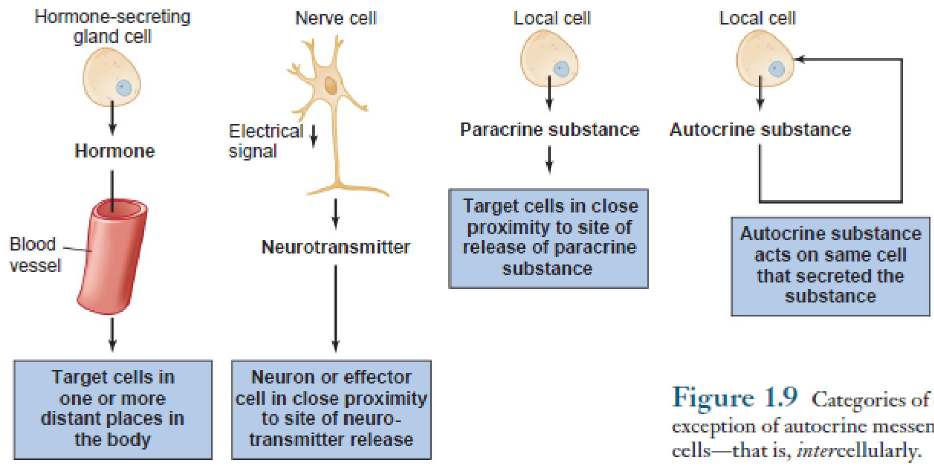


Figure 1.9 Categories of chemical messengers. With the exception of autocrine messengers, all messengers act between cells—that is, *inter*cellularly.

As noted earlier, a hormone functions as a chemicalmessenger that enables the hormone-secreting cell to communicate with cells acted upon by the hormone—its **target cells** —with the blood acting as the delivery system. Hormones are produced in and secreted from **endocrine glands**or in scattered cells that are distributed throughout anotherorgan. They play key roles in essentially all physiological processes,including growth, reproduction, metabolism, mineralbalance, and blood pressure, and are often produced wheneverhomeostasis is threatened.

In contrast to hormones, **neurotransmitters** are chemicalmessengers that are released from the endings of neurons onto other neurons, muscle cells, or gland cells. A neurotransmitter diffuses through the extracellular fluid separating the neuron and its target cell; it is not released into the blood likea hormone. In the context of homeostasis, they form the signaling basis of some reflexes, as well as playing a vital role in the compensatory responses to a wide variety of challenges, such as the requirementfor increased heart and lung function during exercise.

Chemical messengers participate not only in reflexesbut also in local responses. Chemical messengers involved inlocal communication between cells are known as **paracrinesubstances** (or agents). Paracrine substances are synthesizedby cells and released, once given the appropriate stimulus,into the extracellular fluid. They then diffuse to neighboringcells, some of which are their target cells. Given thisbroad definition, neurotransmitters could be classified asa subgroup of paracrine substances, but by convention theyare not. Once they have performed their functions, paracrinesubstances are generally inactivated by locally existingenzymes and therefore they do not enter the bloodstream inlarge quantities.

There is one category of local chemical messengers thatare not *inter*cellular messengers—that is, they do not communicate*between* cells. Rather, the chemical is secreted by a cellinto the extracellular fluid and then acts upon the very cell that secreted it. Such messengers are called **autocrine substances** (oragents) (see Figure 1.9). Frequently, a messenger may serve both paracrine and autocrine functions simultaneously—that is, molecules of the messenger released by a cell may act locally on adjacent cells as well as on the same cell that released the messenger.

A point of great importance must be emphasized here to avoid later confusion. A neuron, endocrine gland cell, andother cell type may all secrete the same chemical messenger.

In some cases, a particular messenger may sometimes functionas a neurotransmitter, a hormone, or a paracrine or autocrinesubstance. Norepinephrine, for example, is not only aneurotransmitter in the brain; it is also produced as a hormoneby cells of the adrenal glands.

All types of intercellular communication described thus far in this section involve secretion of a chemical messengerinto the extracellular fluid. However, there are two importanttypes of chemical communication between cells that do notrequire such secretion. In the first type, which occurs via gap junctions, molecules move from one cell to an adjacentcell without entering the extracellular fluid. In the secondtype, the chemical messenger is not actually released from thecell producing it but rather is located in the plasma membrane of that cell. When the cell encounters another cell type capableof responding to the message, the two cells link up via the membrane-bound messenger. This type of signaling, sometimestermed *juxtacrine*,is of particular importance in the growth anddifferentiation of tissues as well as in the functioning of cellsthat protect the body against pathogens.

Processes Related to Homeostasis

- **Adaptation and Acclimatization**

The term **adaptation** denotes a characteristic that favors survival in specific environments. Homeostatic control systems are inherited biological adaptations. The ability to respond to a particular environmental stress is not fixed,however, but can be enhanced by prolonged exposure tothat stress. This type of adaptation—the improved functioningof an already existing homeostatic system—isknown as **acclimatization**.

Let us take sweating in response to heat exposure as an example and perform a simple experiment. On day 1, we expose a person for 30 minutes (min) to an elevated temperature and ask her to do a standardized exercise test. Body temperature increases, and sweating begins after a certain period of time. The sweating provides a mechanism for increasing heat loss from the body and therefore tends to minimize the increase in body temperature in a hot environment. The volume of sweat produced under these conditions is measured.

Then, for a week, our subject enters the heat chamber for 1 or2 hours (h) per day and exercises. On day 8, her body temperature and sweating rate are again measured during the sameexercise test performed on day 1. The striking finding is thatthe subject begins to sweat sooner and much more profusely than she did on day 1. As a consequence, her body temperature does not increase to nearly the same degree. The subject as become acclimatized to the heat. She has undergone anadaptive change induced by repeated exposure to the heat and is now better able to respond to heat exposure.

Acclimatization is usually reversible. If, in the examplejust described, the daily exposures to heat are discontinued, oursubject's sweating rate will revert to the pre acclimatized value within a relatively short time.The precise anatomical and physiological changes thatbring about increased capacity to withstand change duringacclimatization are highly varied. Typically, they involve anincrease in the number, size, or sensitivity of one or more ofthe cell types in the homeostatic control system that mediatesthe basic response.

- **Biological Rhythms**

As noted earlier, a striking characteristic of many body functions is the rhythmic changes they manifest. The most common type is the **circadian rhythm,** which cycles approximately once every 24 h. waking, and sleeping, body temperature,hormone concentrations in the blood, the excretion ofions into the urine, and many other functions undergo circadianvariation

What do biological rhythms have to do with homeostasis?They add an anticipatory component to homeostatic control systems, in effect, a feedforward system operating without detectors. The negative feedback homeostatic responses we described earlier in this chapter are *corrective* responses. They are initiated *after* the steady state of the individualhas been perturbed. In contrast, biological rhythmsenable homeostatic mechanisms to be utilized immediately and automatically by activating them at times when a challenge is *likely* to occur but before it actually does occur.

For example, body temperature increases prior to waking in a person on a typical sleep–wake cycle. This allows the metabolic machinery of the body to operate most efficiently immediately upon waking, because metabolism (chemical reactions) is to some extent temperature dependent. Duringsleep, metabolism is slower than during the active hours, and therefore body temperature decreases at that time. A crucialpoint concerning most body rhythms is that they are internally driven. Environmental factors do not drive the rhythmbut rather provide the timing cues important for **entrainment**‘or setting of the actual hours of the rhythm. A classicexperiment will clarify this distinction.

Subjects were put in experimental chambers that completely isolated them from their usual external environment,including knowledge of the time of day. For the first few days,they were exposed to a 24 h rest–activity cycle in which the room lights were turned on and off at the same times eachday. Under these conditions, their sleep–wake cycles were24 h long. Then, all environmental time cues were eliminated,and the subjects were allowed to control the lights themselves.

Immediately, their sleep–wake patterns began to change. Onaverage, bedtime began about 30 min later each day, and so didwake-up time. Thus, a sleep–wake cycle persisted in the complete absence of environmental cues. Such a rhythm is called a **free-running rhythm.** In this case, it was approximately24.5 h rather than 24. This indicates that cues are required toentrain or set a circadian rhythm to 24 h.

The light–dark cycle is the most important environmentaltime cue in our lives—but not the only one. Othersinclude external environmental temperature, meal timing, andmany social cues. Thus, if several people were undergoing theexperiment just described in isolation from each other, theirfree-running rhythms would be somewhat different, but ifthey were all in the same room, social cues would entrain all ofthem to the same rhythm.

Environmental time cues also function to **phase-shift rh**ythms—in other words, to reset the internal clock. Thus, ifyou fly west or east to a different time zone, your sleep–wakecycle and other circadian rhythms slowly shift to the newlight–dark cycle. These shifts take time, however, and the disparitybetween external time and internal time is one of thecauses of the symptoms of jet lag—a disruption of homeostasisthat leads to gastrointestinal disturbances, decreasedvigilance and attention span, sleep problems, and a generalfeeling of malaise.

Similar symptoms occur in workers on permanent orrotating night shifts. These people generally do not adapt to their schedules even after several years because they areexposed to the usual outdoor light–dark cycle (normal indoorlighting is too dim to function as a good entrainer). In recent experiments, night-shift workers were exposed to extremelybright indoor lighting while they worked and they were exposed to 8 h of total darkness during the day when they slept. This schedule produced total adaptation to night-shiftwork within 5 days.

What is the neural basis of body rhythms? In the partof the brain called the hypothalamus, a specific collectionof neurons (the suprachiasmatic nucleus) functions as theprincipal **pacemaker,**or time clock, for circadian rhythms.How it keeps time independent of any external environmentalcues is not fully understood, but it appears to involve therhythmic turning on and off of critical genes in the pacemakercells.

The pacemaker receives input from the eyes and manyother parts of the nervous system, and these inputs mediatethe entrainment effects exerted by the external environment.

In turn, the pacemaker sends out neural signals toother parts of the brain, which then influence the variousbody systems, activating some and inhibiting others.

Oneoutput of the pacemaker goes to the **pineal gland ,**a glandwithin the brain that secretes the hormone **melatonin .**These neural signals from the pacemaker cause the pinealgland to secrete melatonin during darkness but not duringdaylight. It has been hypothesized; therefore, that melatoninmay act as an important mediator to influence other organseither directly or by altering the activity of the parts of thebrain that control these organs.

Balance of Chemical Substances in the Body

Many homeostatic systems regulate the balance between addition and removal of a chemical substance from the body.

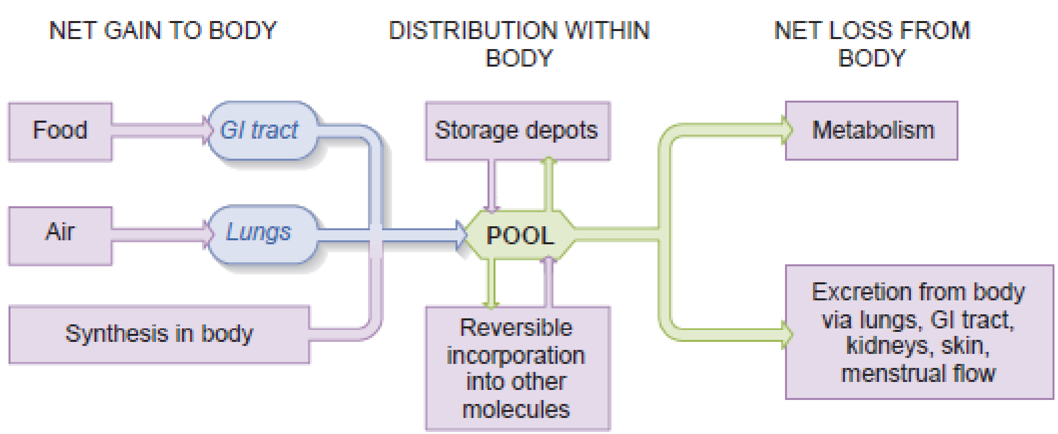


Figure 1.11 Balance diagram for a chemical substance.

. The **pool** occupies aposition of central importance in the balance sheet. It is the body's readily available quantity of the substance and is often identical to the amount present in the extracellular fluid.

The pool receives substances and redistributes them to allthe pathways.

The pathways on the right of the figure are causes of netloss from the body. A substance may be lost in the urine, feces,expired air, or menstrual fluid, as well as from the surface ofthe body as skin, hair, nails, sweat, or tears. The substancemay also be chemically altered by enzymes and thus removedby metabolism.

The central portion of the figure illustrates the distributionof the substance within the body. The substance may betaken from the pool and accumulated in storage depots—suchas the accumulation of fat in adipose tissue. Conversely, it mayleave the storage depots to reenter the pool. Finally, the substancemay be incorporated reversibly into some other molecularstructure, such as fatty acids into plasma membranes.

Incorporation is reversible because the substance is liberatedagain whenever the more complex structure is broken down.This pathway is distinguished from storage in that the incorporationof the substance into other molecules produces newmolecules with specific functions.

Substances do not necessarily follow all pathways of this generalized schema. For example, minerals such as Na cannotbe synthesized, do not normally enter through the lungs,and cannot be removed by metabolism.

Two important generalizations concerning the balance concept:

(1) During any period of time, total-body balance depends upon therelative rates of net gain and net loss to the body

(2) Thepool concentration depends not only upon the total amountof the substance in the body but also upon exchanges of thesubstance *within* the body.

For any substance, three states of total-body balanceare possible:

(1) Loss exceeds gain, so that the total amountof the substance in the body is decreasing, and the person isin **negative balance.**

(2) Gain exceeds loss, so that the totalamount of the substance in the body is increasing, and theperson is in **positive balance.**

(3) Gain equals loss, andthe person is in **stable balance.**

Clearly, a stable balance can be upset by a change inthe amount being gained or lost in any single pathway in theschema. For example, increased sweating can cause severe negativewater balance. Conversely, stable balance can be restoredby homeostatic control of water intake and output.

Let us take the balance of calcium ionsas another example. The concentration ofcalcium ions (Ca) in the extracellular fluidis critical for normal cellular functioning,notably muscle cells and neurons, but also forthe formation and maintenance of the skeleton.

The vast majority of the body's Ca is present in bone. The control systems forCa balance target the intestines and kidneyssuch that the amount of Ca absorbedfrom the diet is balanced with the amountexcreted in the urine. During infancy andchildhood, however, the net balance of Ca is positive, and Ca is deposited in growingbone. In later life, especially in women aftermenopause,Ca is released from bones fasterthan it can be deposited, and that extra Ca is lost in theurine. Consequently, the bone pool of Ca becomes smaller,the rate of Ca loss from the body exceeds the rate of intake,and Ca balance is negative.

In summary, homeostasis is a complex, dynamic processthat regulates the adaptive responses of the body tochanges in the external and internal environments. To workproperly, homeostatic systems require a sensor to detect theenvironmental change, and a means to produce a compensatoryresponse. Because compensatory responses requiremuscle activity, behavioral changes, or synthesis of chemicalmessengers such as hormones, homeostasis is achieved by theexpenditure of energy. The nutrients that provide this energy,as well as the cellular structures and chemical reactions thatrelease the energy stored in the chemical bonds of the nutrientsare described in the following two chapters.

General Principles of Physiology

When you undertake a detailed study of the functions ofthe human body, several fundamental, general principlesare repeatedly observed. Recognizing these principles andhow they manifest in the different organ systems can providea deeper understanding of the integrated function of thehuman body.

1. Homeostasis is essential for health and survival.

2. The functions of organ systems are coordinated witheach other.

3. Most physiological functions are controlled by multipleregulatory systems, often working in opposition.

4. Information flow between cells, tissues, and organsis an essential feature of homeostasis and allowsfor integration of physiological processes.

5. Controlled exchange of materials occurs betweencompartments and across cellular membranes.

6. Physiological processes are dictated by the laws ofchemistry and physics.

7. Physiological processes require the transfer andbalance of matter and energy.

8. Structure is a determinant of(and has coevolvedwith) function.