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# Energy homeostasis: physiologic regulatory mechanisms for Ingestive behavior

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**Abstract**
This article discusses the mechanisms by which humans achieve homeostatic control of vital characteristics of extracellular fluid through ingestive behavior which includes ingestion of food, water and electrolytes. A physiological regulatory mechanism is a mechanism that has the capacity to maintain the constancy of some internal characteristics of the organism in the face of external variability. Ingestive behaviors are correctional mechanisms that replenish or provide the body's depleted stores of water and nutrients and may include eating and drinking behavior. Drinking behavior may be influenced by physiological make-up, environmental factors or underlying disease conditions. Atrial chamber baroreceptors and juxtaglomerular apparatus-response related mechanisms are some of the mechanisms in control of volumetric thirst. Osmometric thirst and eating behavior are more concerned with responses by the central nervous system with areas within the ventral portion of the third ventricle, the ventromedial and lateral hypothalamic nucleus. Without a basic understanding of the physiologic regulatory mechanisms of ingestion and ingestive behaviors, chances of finding an intervention in certain metabolic neurobehavioral disorders may be lost.

**Keywords:** Ingestive, Osmometric, volumetric, homeostatic, behavior

## Introduction

The goal of physiology is to explain the physical and chemical factors that are responsible for the origin, development, and progression of life [1]. In human physiology, attempt is made to explain the specific characteristics and mechanisms of the human body that makes it a living being. The very fact that humans remain alive is almost beyond self-control, for hunger induces us to seek or crave for food and fear makes us seek refuge, sensations of cold makes us look for warmth; the appeal to reproduce makes us seek for a mate. Other forces cause us to seek fellowship and to reproduce. Thus, the human being is actually an 'automated being', and the fact that humans are sensitive, resistive and knowledgeable beings is part of this automatic sequence of life; these special attributes allows humans to exist under highly variable conditions. All these capabilities are the reasons most notable scholars in metaphysics regard human beings as '*the good that is*' [2]. Human physiology should at least be able to explain with scientific mechanisms, the beginning and the end of live forms. In accordance to the French physiologist Claude Bernard (1813-1878), 'The constancy of the internal environment is a necessary condition for a free life'. This is a famous quotation that strictly reveals what living organisms must consider as priority in other to be able to exist in environments that are hostile to the living cells that they are composed of. To maintain an almost stable internal environment, there must be a barrier between the living cells that make up the internal environment and the external environment. In the case of humans, this barrier exists in form of skin and mucus membranes. The physiologic and anatomic characteristics of our body cells are constantly evolving [3]. The simplest cells floated freely in the ocean before they evolved to more complex cells. Due to evolution, cells no longer float freely in the ocean but rather a special fluid medium which carries nutrients and removes waste has been provided to bathe the body cells and maintain their functional and structural intergrity through-out period of life. Also, humans have developed systems which help in maintaining internal body conditions, keeping it in a state of 'dynamic equilibrium'. Some of these systems include respiratory, excretory, nervous and gastrointestinal systems. Humans, due to evolution, can exhibit certain behaviors that allow us to seek, find and ingest food and water. *Homeostasis* is the maintenance of an almost constant internal environment [4], and regulation of the constituent of the fluid that bathes body cells is part of this process.

This article discusses the mechanisms by which humans achieve homeostatic control of vital characteristics of extracellular fluid through ingestive behavior which includes ingestion of food, water and electrolytes. The clinical relevance of this article is that without a basic understanding of the physiologic regulatory mechanisms of ingestion, hope of finding an effective treatment against certain disorders like obesity (including hypothalamic obesity as well as obesity related to Prada Willi's syndrome) and anorexia nervosa may be lost.

### Physiological regulatory mechanisms

A physiological regulatory mechanism is a mechanism that has the capacity to maintain the constancy of some internal characteristics of the organism in the face of external variability-for example, keeping the body temperature constant despite changes in ambient temperature. A physiologic regulatory mechanism contains four (4) essential features.

- The system variable
- A set point

- A detector
- A correctional mechanism

The system variable is the characteristic to be regulated. A set point is the optimal value of the system variable. A detector monitors the value of the system variable and responds to its alterations or fluctuations. The correctional mechanism restores the system variable to the set point.

A good example of a physiologic regulatory mechanism includes the temperature regulatory activity of the hypothalamus. The system variable for this physiological regulatory mechanism is the core body temperature and the detector is the hypothalamic thermostatic centers that respond to changes in core body temperature. The set point is the optimal core body temperature maintained by the hypothalamus. Once there is a fluctuation in core body temperature from the set point, the thermostatic centers (heat loss and heat gain centers) located in the anterior and lateral hypothalamic nuclei are activated. This elicits series of events that ultimately restores the core body temperature back to its set point.

**Ingestive Behaviors**

Ingestive behaviors are correctional mechanisms that replenish or provide the body's depleted stores of water and nutrients. Ingestive behaviors include;

- Drinking behavior
- Eating behavior

Ingestive behaviors are controlled by physiologic regulatory mechanisms called the 'hunger and satiety mechanisms'. This mechanism, is composed of all the essential features of physiologic regulatory mechanisms. Ingestive behavior is controlled by signals arising from several systems of the human body like the gastrointestinal system. Soon after we ingest water or food after severe thirst or hunger, we gradually stop further ingestion even before the molecules we have ingested are absorbed into the circulation. Satiety aspect of this mechanism elicits the 'stop' signal in anticipation of the replenishment that will occur later. This proves the fact that the gastrointestinal system has a spectacular histologic make-up that allows it to function as a 'meter' over the food we eat or water we drink. This metering effect is to ensure that we do not ingest more than we actually need; enough to change or alter homeostasis.

**Drinking behavior**

We drink water daily in other to maintain the optimal state of our internal environment. The volume of water we ingest daily varies and is dependent on several factors, but its range is between 2 liters to 4 liters. Drinking behavior may be influenced by physiological make-up, environmental factors or underlying disease conditions. Water makes up a major part of our body fluid. The volume of water in the body has to be carefully regulated otherwise death will occur. If water intake is less than normal, the cells may shrink and then hypovolemia accompanied by circulatory shock may occur. If water intake is more than normal, the cells may swell and then hypervolemia accompanied by water intoxication may occur. Hence, it is of utmost importance that water ingestion is carefully regulated. The stimulus for drinking behavior is thirst.

**There are two (2) types of thirst**

- Osmometric thirst
- Volumetric thirst

Osmometric thirst is the thirst produced by an increase in osmotic pressure of the extracellular fluid relative to the intracellular fluid. It produces cellular dehydration. Volumetric thirst is the thirst produced by hypovolemia, during which there is a reduction in blood volume.

**Physiologic regulation of osmometric thirst**

In 1947, a scientist named Verney discovered the existence of neurons that respond to changes in the solute concentration of the extracellular fluid. These neurons are the detectors. Verney called these detectors the osmoreceptors. According to Verney, The intensity of stimulation and firing rate of these osmoreceptors was determined by the level of dehydration. Verney proposed the following mechanism which will be illustrated schematically.

- Osmometric thirst is elicited when there is an osmotic change in fluid surrounding the osmoreceptors.
- An ingestion of a salty meal or drink will cause increase in salt content of ECF.
- Increase in salt (NaCl) content in ECF (or ISF) causes increase in osmotically active electrolytes in the chamber.
- The osmotic pressure in ECF (or ISF) becomes greater than that in the intracellular fluid chamber. The osmotic equilibrium between the ECF and ICF is lost.
- The ICF within the osmoreceptors will become hyposmotic to ECF and there will be movement of fluid via osmosis from the ICF to ECF.
- This osmotic movement causes shrinking of osmoreceptor cells.
- The shrinking of these osmoreceptor cells is directly proportional to the extent of fluid movement and subsequent dehydration of the osmoreceptor cells.
- As these cells shrink, they send out impulses in form of action potentials to other brain areas that regulate thirst and drinking behavior.

The region in the brain within which the osmoreceptors responsible for osmometric thirst are located is called the *lamina terminalis*. The lamina terminalis is found just rostral to the ventral portion of the third ($3^{rd}$) ventricle. The lamina terminalis contains two (2) specialized circumventricular organs;

- The organum vasculosum or 'vascular organ' of lamina terminalis (OVLT)
- Subfornical organ (SFO)

These circumventricular organs are located in specialized regions of the brain along the ventricular system and have a rich blood supply. They are both located outside the blood brain barrier. Recent studies suggest that OVLT has more osmoreceptors than SFO. The SFO is located specifically at a region just below the commissure of the ventral fornix. Neurophysiologists after series of investigations have revealed that the electrical activity within the OVLT and SFO increases periods immediately after intravenous infusion of hypertonic saline. This electrical activity reflected by the rate of neuronal firing, decreases immediately hypotonic fluid is ingested. This reveals the importance of these regions in regulation of osmometric thirst. In 1991, McIver, reported that brain damage that affected the region of the lamina terminalis may cause complete suppression of the urge to drink, a condition referred to as *adipsia*. To survive this condition, there must be deliberate consumption of water at regular intervals each day, even though there is no urge to justify the behavior.

**Physiologic regulation of volumetric thirst**

Volumetric thirst occurs when blood volume decreases or in hypovolemia. When we lose water through evaporation (or sweating) we as well lose water from both the ECF and ICF. Thus, sweating produces both volumetric and osmometric thirst. Volumetric thirst can be caused by hemorrhage, vomiting and diarrhea. Loss of blood is the most obvious cause of volumetric thirst. There are two (2) sets of receptors that accomplish the initiation of volumetric thirst, they include;

- The juxtaglomerular apparatus (JGA)
- The atrial chamber baroreceptors

**Juxtaglomerular apparatus (JGA)**

The JGA is located in both kidneys. It is a specialized receptor organ situated near the glomerulus of each nephron. It is composed of macula densa, juxtaglomerular cells and extra glomerular mesangial cells. The receptor cells within the JGA are able to detect decreases in renal blood flow (RBF). The usual cause of decreased RBF is hypovolemia.

The cells of the JGA secrete renin in response to hypovolemia; this is renin secretion is caused by a decrease in blood flow to the kidneys. Renin is an enzyme hormone composed of 340 amino acids. Renin catalyzes the conversion of angiotensinogen, a plasma protein and an alpha 2 globulin, into angiotensin I (AI). The pulmonary capillaries of the lungs are suspected to be the source of the enzyme called 'angiotensin converting enzyme' (ACE) or simply converting enzyme. ACE catalyzes the conversion of angiotensin I to angiotensin II (AII). Angiotensin II or *hypertensin* is a potent vasoconstrictor. The physiologic effects of angiotensin II include;

- It stimulates the release of corticotropin (CRH) by the corticotropes of the anterior pituitary
- It stimulates the release of antidiuretic hormone (ADH) from the supraoptic nuclei of the anterior hypothalamus
- It induces thirst by stimulating the region of the lamina terminalis
- It stimulates the release of the mineralocorticoid called aldosterone from the adrenal cortex
- It causes hyperplasia of the zona glomerulosa of the adrenal cortex
- It is a ventricular growth factor
- It enhances release of catecholamines from sympathetic adrenergic nerve endings
- It causes peripheral vasoconstriction
- It promotes reabsorption of sodium and chloride (NaCl) from the proximal convoluted tubule (PCT) of the kidneys. This increases water reabsorption
- Through efferent arteriolar vasoconstriction, it causes an initial increase in glomerular filteration rate (GFR)
- It induces a salty appetite

Therefore, the behavioral effect of juxtaglomerular apparatus (JGA) stimulation is initiation of both drinking and salty appetite.

In 1978, Simpson, Epstein and Camardo discovered that a very low dose injection of angiotensin II directly into the subfornical organ (SFO) caused drinking behavior. Philips and Felix in 1976, through functional imaging, explained that the rate of firing of SFO neurons increased after administration of angiotensin II; evidently these neurons contain angiotensin II receptors.

**Atrial chamber baroreceptors**

These receptors are located within the atrial chambers of the heart. The term '*baro-*' comes from a greek word *baros* meaning heavy weight or heavy pressure. These receptors within the atrial chambers are able to detect decrease in blood flow to the heart. In a case of excessive blood loss, there will be hypovolemia; this will reduce the volume of blood flow to the atrium. The atrium due to reduced blood flow will be less full than usual. This reduction in blood volume in atrium will be detected by the baroreceptors. Afferent impulses from these receptors are sent to the nucleus of solitary tract (NTS) in the brainstem and from this nucleus to many brain areas including the lamina terminalis to induce thirst. Therefore, the lamina terminalis is the integrating center for both osmometric and volumetric thirst that control drinking behavior.

In 1980, Fitzsimons and Moore-Gillon scientifically proved that sensory information from these receptors can induce thirst. They also discovered that when the nerve fibers connecting the atrial chamber baroreceptor with the brain is severed, the ingestion of water will be temporarily reduced.

**Eating behavior**

Without food survival will be impossible because we need nutrients from food in other to withstand life's requirements like growth, repair of worn out tissues, higher intellectual function and thermoregulation. Much of what an animal learns to do is motivated by the continuous struggle to obtain food. Clearly, eating is one of the most important things we do, and it can also be one of the most pleasurable. The need to ingest food undoubtedly shaped the evolutionary development of our own species. Control of ingestive behavior is more complex than control of drinking behavior.

**Control of Ingestive behavior includes**

- Metabolism
- Regulation of body weight
- Environmental and physiologic factors that begin and stop a meal
- Neural processes that monitor the nutrient state of the body and control Ingestive behavior.

Understanding the physiology of Ingestive behavior has been helpful in management of several disorders like obesity and anorexia nervosa.

After series of experimental research by various scientists, the following signals are believed to control Ingestive behaviors;

**Signals from the environment**

The environment our ancestors were exposed to shaped the evolution of these regulatory mechanisms. Starvation is by far a greater threat to survival than excessive feeding. Our ancestors had the habit of over feeding themselves in times of plenty in preparation for period of food scarcity. They gathered food, ate them and had enough energy reserved in them throughout the season of food scarcity. These environmental changes in availability of food shaped their ingestive behaviors.

**Signals from the stomach**

According to Kojima *et al* 1999, during hunger, the stomach releases a peptide hormone called ghrelin. Studies with laboratory animals have found that blood levels of ghrelin increases with fasting and are reduces after ingestion of a meal. Subcutaneous infusions of ghrelin into cerebral ventricles causes increase in weight by increasing food ingestion while decreasing fat metabolism. The use of ghrelin receptor antagonist inhibits eating.

**Signals from adipose tissues**

A large amount of energy in the body is stored as fats. The amount of fat varies amongst different individuals. Recent studies suggest that the hypothalamus receives signals from adipose tissues in form of a chemical messenger called 'leptin' which enables it to regulate feeding and satiety behavior. Leptin is a peptide hormone secreted by adipocytes. Leptin is an *adipokine,* as it has similar molecular make-up as a cytokine. In periods of positive energy balance i.e. when the amount of adipose tissue increases (signaling excess energy storage), the adipocytes produce increased amounts of leptin, which is released into the blood. Leptin then circulates to the brain, where it moves across the blood-brain barrier (BBB) by facilitated diffusion and occupies leptin receptors at multiple sites in the hypothalamus, especially the pro-opiomelanocortin (POMC) neurons of the arcuate nuclei and neurons of the paraventricular nuclei (PVN). Stimulation of leptin receptors in these hypothalamic nuclei initiates multiple reactions that suppress feeding and induce satiety thereby decreasing fat storage including [5];

- Decreased production in the hypothalamus of appetite stimulators, such as neuropeptide Y (NPY) and agouti-related peptide (AGRP).
- Activation of POMC neurons, causing release of alpha-melanocyte stimulating hormone (α-MSH) and activation of melanocortin receptors.
- Increased production in the hypothalamus of substances, such as corticotropin-releasing hormone (CRH), that decrease food intake.
- Increased sympathetic nerve activity (through neural projections from the hypothalamus to the vasomotor centers), which increases metabolic rate and energy expenditure.
- Decreased insulin secretion by the pancreatic beta cells, which decreases energy storage.

Thus, leptin may be an important means by which the adipose tissue signals the brain that enough energy has been stored and that intake of food is no longer necessary.

In laboratory mice or humans with genetic mutations that render their adipocytes unable to produce leptin or mutations that cause defective or less responsive leptin receptors in the hypothalamus, marked hyperphagia and obesity occurs.

**Neuroendocrine signals**

There are two distinct types of neural clusters in the arcuate nuclei of the hypothalamus that are especially important as controllers of both hunger and satiety.

- Pro-opiomelanocortin (POMC) neurons that produce α-melanocyte stimulating hormone (α-MSH) together with cocaine and amphetamine-related transcript (CART).
- Neuronal clusters that produce the hypocretinergic or orexinergic chemical agent's neuropeptide Y (NPY) and agouti-related protein (AGRP).

Activation of the POMC neurons decreases food intake and increases energy expenditure, whereas activation of the NPY-AGRP neurons increases food intake and reduces energy expenditure. These neuronal clusters appear to be the major targets for the actions of several neuroendocrine hormones that regulate hunger and satiety.

Some of these neuroendocrine chemical transmitters include [6];

**Table 1**

| Satiety hormones | Hunger hormones |
|---|---|
| Leptin | Ghrelin |
| α-Melanocyte-stimulating hormone (a-MSH) | Orexin A and B |
| Norepinephrine | Galanin |
| Serotonin | Gamma amino butyric acid (GABA) |
| Corticotropin releasing hormone (CRH) | Glutamate |
| Glucagon-like peptide (GLP) Cortisol | Agouti-related protein (AGRP) |
| Cocaine- and amphetamine-regulated transcript (CART) | Melanin-concentrating hormone (MCH) |
| Peptide YY (PYY) | Endorphins |
| Cholecystokinin (CCK) | Cortisol |
| Insulin | |

**Higher center regulation of hunger and satiety**

Within the hypothalamus are two centers involved in coordination of hunger and satiety, these centers are [7];

- The ventromedial hypothalamic nucleus (VMH)
- The lateral hypothalamic nucleus (LH)

The *lateral hypothalamus nucleus* serves as a *feeding center,* and stimulation of this center causes an animal to eat voraciously; a condition called *hyperphagia.* Conversely, destruction of the lateral hypothalamic nucleus causes suppression of desire for food and progressive *inanition,* a condition characterized by marked muscle weakness, weight loss and decreased metabolism. The lateral hypothalamic feeding center operates by exciting the motor drives to search for food.

*The ventromedial nucleus of the hypothalamus* serves as the *satiety center.* This center is believed to give a sense of nutritional satisfaction that inhibits the feeding center. Electrical stimulation of this region can cause complete satiety, and even in the presence of highly appetizing food, the animal refuses to eat; a condition called *aphagia*. Conversely, destruction of the ventromedial nuclei causes voracious and continued eating until the animal becomes extremely obese, sometimes as large as four times normal.

There is much neurochemical cross-talk among the neurons in the hypothalamus, and together, these centers coordinate the mechanisms that control ingestive behavior and the perception of satiety. These nuclei of the hypothalamus also influence the secretion of several chemical messengers that are important in energy homeostasis, including those from the thyroid and adrenal glands, as well as the pancreatic islet cells. The hypothalamus receives neural signals from the gastrointestinal tract that provide sensory information about stomach filling, chemical signals from nutrients in the blood (glucose, amino acids, and fatty acids) that signify satiety, signals from gastrointestinal hormones, signals from hormones released by adipose tissue, and signals from the cerebral cortex (sight, smell and taste) that influence feeding behavior.

**Conclusion**

Humans, due to evolution, can exhibit certain behaviors that allow us to seek, find and ingest food and water. Ingestive behaviors are controlled by physiologic regulatory mechanisms called the ‘hunger and satiety mechanism’. This mechanism is composed of all the essential features of physiologic regulatory mechanisms. Ingestive behavior is controlled by signals arising from several systems of the human body like the gastrointestinal system, circulatory system and nervous system. The healthy state of these systems is necessary to ensure energy homeostasis.

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