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# Thermoregulatory Dysfunction

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## SUMMARY

Patients with Parkinson's disease (PD) must maintain core body temperature in a narrow range despite fluctuations in both endogenous heat production and environmental conditions. The hypothalamus and peripheral autonomic nervous system are essential neuroanatomical substrates for thermoregulation. In the preoptic/anterior hypothalamus, dopamine excites warm-sensitive neurons and inhibits cold-sensitive neurons. Hypothalamic dopamine deficiency may perturb normal thermoregulatory responses. Several features of both the neuroleptic malignant syndrome (NMS) and the NMS-like syndrome associated with levodopa withdrawal are likely the result of inadequate stimulation of hypothalamic dopamine receptors. In PD, thermoregulatory dysfunction can also manifest as heat and cold intolerance, paroxysmal head and neck hyperhidrosis, and dry skin in the lower extremities. Tests of sudomotor function, such as the sympathetic skin response, quantitative sudomotor axon reflex test, thermoregulatory sweat test, silastic sweat imprint, and quantitative thermoregulatory sweat test, are often abnormal in PD, particularly in its more advanced stages. Therefore, clinicians should be cautious when using thermoregulatory testing to differentiate PD from other neurodegenerative disorders (e.g., multiple system atrophy [MSA]). In early PD, thermoregulatory dysfunction is mostly consistent with central and preganglionic autonomic dysfunction. As PD progresses, an increasing percentage of patients will also show evidence of postganglionic sympathetic abnormalities.

**Key Words:** Thermoregulation; Parkinson's disease (PD); hypothalamus; exothermic; radiation; conduction; sweat; dopamine; temperature; sudomotor; sympathetic; postganglionic; hyperhidrosis; neuroleptic malignant syndrome; seborrhea; xerosis.

## 1. INTRODUCTION

### *1.1. Normal Thermoregulatory Mechanisms*

Patients with Parkinson's disease (PD) have cells that need energy to do their work. Energy exists in forms like light, heat, and chemical bonds. Most types of energy can be classified as either kinetic or potential. Thermal (heat) and radiant (light) are two major kinds of kinetic energy. The first law of thermodynamics states that the various types of energy can be changed from one form to another. The process of photosynthesis, for example, converts the kinetic energy of light into the potential energy of covalent bonds. Concentration and charge gradients are other forms of potential energy that are critical to biological systems.

Biological systems continuously require energy for the performance of mechanical work, active transport of molecules and ions, and synthesis of macromolecules. Chemotrophs (e.g., humans) obtain free energy by the oxidation of foods, a process in which adenosine diphosphate (ADP) is converted to adenosine triphosphate (ATP). ATP serves as the principal carrier of free energy in biological systems.

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ATP contains two energy-rich phosphoanhydride bonds, and a large amount of energy is liberated when ATP is hydrolyzed to ADP.

The sequences of reactions required for the production of ATP are exothermic. In exothermic reactions, the products contain less bond energy than the reactants, and the excess energy is usually liberated as heat. On average, one third of the potential energy contained in foods is converted to heat during the process of ATP generation. Heat is also generated in the body during the turnover of cellular macromolecules, such as proteins. Heat production by the body is normally expressed in terms of metabolic rate, which is governed by basal cellular metabolism, muscular activity, thyroid hormones, and levels of circulating epinephrine and norepinephrine. Metabolic rate can be quantified by direct calorimetry, which measures the total quantity of heat liberated from the body during a fixed period of time.

In addition to endogenous production, heat may also be gained from exogenous sources via mechanisms like radiation and conduction. Radiation is the transfer of heat by electromagnetic radiation. When environmental temperatures are greater than body temperatures, a thermal gradient is present, and heat can be transferred to humans by radiation. Conduction is heat exchange between objects that are in contact with one another. For instance, a person can gain heat by conduction while sitting on asphalt pavement on a scorching summer day.

Homeotherms, like humans, must maintain core body temperature in a narrow range, despite fluctuations in environmental conditions and endogenous heat production. Humans have a variety of mechanisms for heat loss that can be used to prevent core temperature elevations. The vast majority of heat in humans is generated by deep tissues (e.g., brain, liver, heart, and skeletal muscles). For effective elimination, this heat must be first transferred to the skin, then from the skin to the surroundings. A robust microvascular network is present in the dermis and subdermal connective tissues. Draining veins from skin capillaries are directly connected to a venous plexus located in the lower dermis and subdermal connective tissue. In the hands, feet, and ears, muscular arteriovenous anastomoses directly link small arteries to this venous plexus. When necessary, blood flow to the skin venous plexus can increase to one fourth of cardiac output.

At an ambient temperature of 22°C, most heat is lost from the skin surface by radiation and conduction. Conduction of heat to the air layer surrounding the body is greatly augmented by convection. Heat from the skin that is conducted to the surrounding air is carried away by convection air currents.

Evaporation is the final major mechanism for heat loss and becomes critical when environmental temperatures exceed body temperature. Evaporation of 1 g of water removes 0.58 kcal of heat from the body. Most of this water is derived from sweat, but insensible losses from the lungs, upper airways, and skin average 50 mL per hour. During strenuous physical activity in a hot environment, sweat secretion can exceed 1600 mL per hour. Urination, defecation, and respiration only account for 2 to 3% of heat loss in normal circumstances.

### *1.2. Neuroanatomical Substrates of Thermoregulation*

An array of autonomic, behavioral, endocrine, and somatic thermoregulatory responses is involved in the maintenance of core temperature within a narrow range. Mechanisms activated by heat include sweating, cutaneous vasodilatation, and movement to a cooler environment. Mechanisms catalyzed by cold include vasoconstriction, piloerection, movement to a warmer environment, shivering, and possibly, increased output of thyroxine. The hypothalamus has a central role in these thermoregulatory responses.

The anterior/preoptic hypothalamus contains both warm- and cold-sensitive neurons. Warm-sensitive neurons outnumber cold-sensitive neurons by a 3:1 ratio. Increased core temperatures are associated with increased firing rates of warm-sensitive neurons, whereas cold-sensitive neurons increase their firing rates when core temperatures fall *(1)*. Although much less significant in the maintenance of core temperature, temperature sensors are also present in the skin and deep visceral tissues. In the skin, there are ten times more cold receptors than heat receptors. Afferent pathways for thermal receptors in the skin begin in the dorsal roots and ascend predominantly in the spinothalamic tract. Thermal receptors in deep