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Hypothermia

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Glossary

g0005	*Cold-Induced Fibrillation*	Very rapid, irregular contractions of the muscle fibers of the heart resulting in a lack of synchronization between heartbeat and pulse, with a resultant lack of cardiac output.
g0010	*Cold Narcosis*	A state of stupor, unconsciousness, or arrested activity produced by cooling.
g0015	*Homeotherm*	A warm-blooded animal such as humans that regulates its core temperature at a constant temperature (usually 37°C, or 98.6°C) irrespective of environmental temperature.
g0020	*Ischemia*	Localized deprivation of oxygen (hypoxia) and nutrients to a tissue due to interruption of blood supply.
g0025	*Lipid Phase Transition*	A temperature-induced change of state of the lipid component of biological membranes involving a change from a gel phase to a liquid crystal phase. These physical changes of membrane fluidity often result in functional alterations of membrane properties.
g0030	*Thermogenesis*	The production of heat in the body, usually by metabolic oxidation of food substrates.

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Definitions

p0005 The prefix hypo means below or under, and therm means temperature, so hypothermia literally means below normal temperature. In humans and most other mammals, normal temperature is regarded as 37°C (98.6°F), but this single value belies the fact that normal temperature in healthy individuals varies within a degree or so, depending on factors such as the site of measurement (core or exterior) and time of day (circadian rhythm). Body temperature can be measured in a variety of ways. Exterior temperatures include sublingual (under the tongue), skin, or axillary (under the armpit) measurements. Core or interior temperatures reflect the mean temperatures of the vital organs and are approximated by esophageal, rectal, tympanic membranes, and pulmonary artery measurements. In humans, normal body temperature has traditionally been set at 37°C based upon 1 million axilliary measurements from 25 000 individuals carried out by the nineteenth century investigator Carl Wunderlich in 1868. Modern-day corroboration of these data has been provided by a study of 148 healthy men and women that showed a mean oral temperature of 36.8°C, with 37.7°C as the upper limit of normal.

p0010 Humans are homeothermic mammals (warm-blooded animals), which means that the core body temperature is precisely regulated and kept constant at about 37°C, irrespective of the ambient temperature. Even though core temperature is well maintained, the temperature of the peripheral shell (skin, fat, and muscle) ranges from 31°C to 35°C, with skin temperature at 28°C to 32°C. Thermoregulation impairment, prolonged exposure to an extreme environment, or both may lead to a decrease in core temperature and the onset of a pathological state. Nevertheless, under controlled conditions in a hospital setting, hypothermia can actually be used for therapeutic advantage in a variety of medical applications since cold can also be a protective modality. Hypothermia is defined in homeotherms as the reduction of core body temperature below 35°C (95°F), and clinically has been arbitrarily graded for convenience into degrees of hypothermia, as shown in **Table 1**.

Background to Hypothermia as a Stress

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p0015 Hypothermia is a double-edged sword in that cold has been both a friend and a foe to humanity. Historically, we know that cold can be a devastating stress, as illustrated by the nineteenth century records that Napoleon watched helplessly as his army was

Table 1 Classification of hypothermia

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Classification	*Temperature range (°C)*	*Temperature range (°F)*
Mild	32–35	90–95
Moderate	27–32	81–90
Deep or profound	10–27	50–81
Ultraprofound	<10	<50

This alkalosis is, however, gradually replaced by metabolic acidosis as cooling progresses, due to poor tissue perfusion and oxygenation, as discussed earlier. So, in general, respiration is depressed during hypothermia, but the rate is almost in proportion to metabolic needs until respiration becomes shallow and erratic and eventually stops in the region of 25–30°C.

s0045 p0055 **Effect of hypothermia on the blood** Hypothermia also results in marked hematological perturbations such as increased viscosity, leukopenia (abnormally low number of circulating leukocytes), and thrombocytopenia (reduced numbers of platelets leading to bleeding tendencies). Increasing blood viscosity, which changes by as much as 5% per degree Celsius, also contributes to an apparent rise in vascular resistance (decreased efficiency of vascular perfusion). Deep hypothermia also hinders clotting by slowing the enzyme-mediated coagulation cascade and by promoting fibrinolysis. Abnormalities in clotting mechanisms occur in 68–100% of patients subjected to clinical hypothermia, making bleeding tendencies a major concern in people subjected to prolonged hypothermia.

s0050 p0060 **Physiological signs and symptoms of cold exposure** Hypothermia is now recognized as the number one killer of outdoor recreationalists, and along with this has come the need for increasing awareness of the problem. As a consequence, many outdoor organizations are taking active measures to educate their members about hypothermia as an environmental hazard and are teaching emergency care for hypothermia. A critical part of this process is the ability to recognize the signs and symptoms of hypothermic exposure. **Table 2** illustrates some of the characteristic signs and symptoms at various stages of hypothermia.

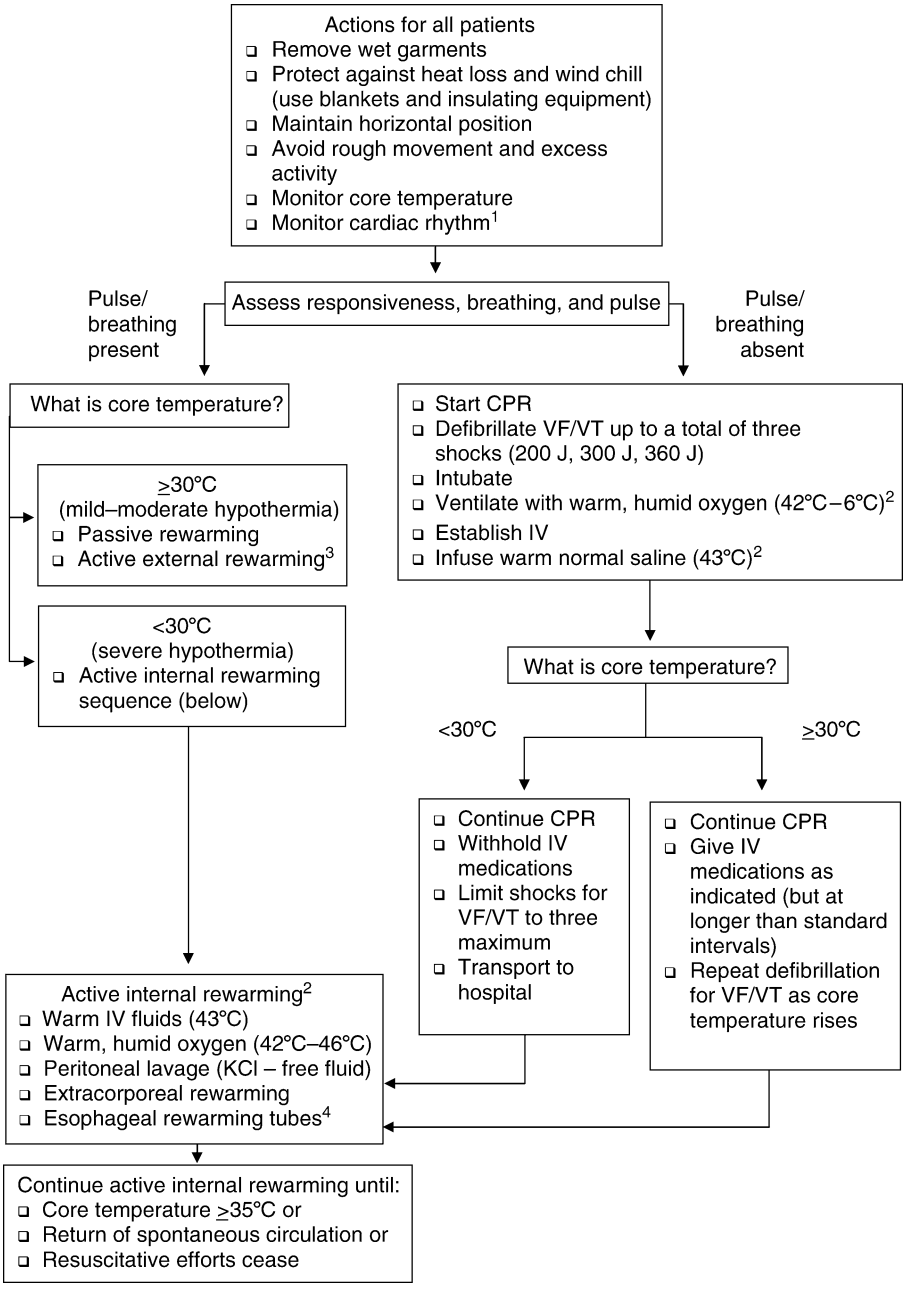
p0065 Because survival after cold exposure is critically dependent on early intervention to reverse the effects of hypothermia, emergency personnel have become increasingly skilled over the past several years at managing and treating victims of hypothermia. It is beyond the scope of this article to describe the recommended treatments for victims of accidental hypothermia, but **Figure 1**. illustrates an algorithm of recommended actions. It is noteworthy that some early interventions can be initiated in the field, while more aggressive treatments can not be considered until the patient is transferred to an adequately equipped emergency vehicle or hospital.

s0055 p0070 **Enhancing tolerance to cold exposure** The risk of accidental hypothermia is ever present for people who live at high altitudes, and efforts to protect against cold exposure have focused on methods of decreasing heat loss by improving insulation. Nevertheless, some research has been devoted to finding ways of improving cold tolerance by modifying the thermoregulatory response to cold. The principal strategies employed have been thermal acclimation, physical exercise, dietary enhancement of thermogenesis, pharmacological enhancement of thermogenesis, and manipulation of the thermoregulatory set point. While none of these approaches have been accepted routinely to improve cold tolerance, it can be concluded from some studies that the pharmacological enhancement of cold thermogenesis using ephedrine in combination with methylxanthine represents the most promising method for delaying the onset of hypothermia in humans.

t0010 **Table 2** Characteristics of hypothermic stress at different stages of cooling

Stage	*Core temperature*	*Signs and symptoms*
Mild hypothermia	37–35°C (98–95°F)	Normal, shivering can begin, cold sensation, goose bumps, unable to perform complex tasks with hands, shiver can be mild to severe, hands numb
Mild–moderate hypothermia	35–33°C (95–93°F)	Shivering/intense, muscle incoordination becomes apparent, movements slow and labored, stumbling pace, mild confusion, may appear alert. Use sobriety test; if unable to walk a 30-foot straight line, the person is hypothermic
	33–32°C (93–90°F)	Violent shivering persists, difficulty speaking, sluggish thinking, amnesia starts to appear, gross muscle movements sluggish, unable to use hands, stumbles frequently, difficulty speaking, signs of depression, withdrawn
Moderate hypothermia	32–30°C (90–86°F)	Shivering stops, exposed skin blue or puffy, muscle coordination very poor, inability to walk, confusion, incoherent/irrational behavior, but may be able to maintain posture and appearance of awareness
	30–27°C (86–82°F)	Muscle rigidity, semiconscious, stupor, loss of awareness of others, pulse and respiration rate decrease, possible heart fibrillation
Deep hypothermia	27–25°C (82–78°F)	Unconscious, heart beat and respiration erratic, pulse may not be palpable
	<25°C (<77°F)	Pulmonary edema, cardiac and respiratory failure, death (death may occur before this temperature is reached)

Adapted from the Princeton University Outdoor Action Guide, with permission.



f0005 **Figure 1** Algorithm for treatment of hypothermia. Notes: (1) This may require needle electrodes through the skin. (2) Many experts think that these interventions should be done only in-hospital, though practices vary. (3) Methods include electric or charcoal warming devices, hot water bottles, heating pads, radiant heat sources, and warming beds. (4) Esophageal rewarming tubes are widely used internationally and should become available in the United States. Abbreviations: VF, ventricular fibrillation; VT, ventricular tachycardia; CPR, cardiopulmonary resuscitation; IV, intravenous. This algorithm is based on the Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiac Care published by the American Medical Association (*JAMA*, **268**, 2171, Copyright 1992, American Medical Association, all rights reserved) and is adapted from the article 'JAMA protocol for hypothermia' at http://hypothermia.org/jama.htm

s0060 p0075 **Contrasting outcome between victims of accidental hypothermia and patients experiencing clinical hypothermia** In considering the chances of survival after the stress of hypothermia, an important distinction has to be made between accidental hypothermia and clinical hypothermia. Even though the final core temperature of the individual may drop to the same level, the survival rate from clinically induced hypothermia is much higher than that of accidental hypothermia. In the latter case, homeotherms respond to hypothermic stress with immediate activation of heat production as well as inhibition of heat loss. The timing and intensity of the thermogenic response, as well as the duration over which the process can be

maintained, depend on factors such as sex, age, and health of the individual. Hypothermia ensues when maximum thermogenesis fails to balance minimum heat loss and heat deficit results. As hypothermia progresses, cold narcosis of the central nervous system supervenes and respiratory support declines. Heart rate also slows with decreasing temperature, but the heart may continue to beat for some time depending upon the cooling rate. Eventually, when the core temperature drops to a specific level (in the range 15–25°C [60–77°F]), the heart either goes into ventricular fibrillation or arrests. In the battle to maintain core temperature, the subject has exhausted itself.

p0080 In contrast to the preceding scenario, clinically induced hypothermia is a sedate, relatively nonstressful, and intensively monitored condition. The patient is initially anesthetized and rapidly cooled, often with the aid of cardiopulmonary bypass support, with little or no metabolic resistance. Moreover, the patient is monitored continuously throughout so that presenting complications can be corrected expeditiously or rewarming employed before they become lethal. It is important to explain why hypothermia is sometimes induced electively in patients for clinical benefit. As described in the next section, it has long been known that hypothermia is a highly effective modality for protecting cells against the deleterious effects of hypoxia and ischemia. In general, the extent of protection is directly related to the degree of hypothermia, with colder temperatures offering greater protection. This is based on the fundamental effect of cooling on biophysical and biochemical processes as molecular activity and mobility is slowed. In the fields of cardiovascular surgery, neurosurgery, and more recently in trauma medicine, there is often a need in complicated cases for the surgeon to implement a temporary cessation of blood flow to the heart or the brain. Adjunctive hypothermia is often used to protect the organs against hypoxia and ischemia. In recent years, there has been a renewed interest in the application of mild to moderate hypothermia as a potent neuroprotective modality, and consideration is being given to a potential therapeutic benefit of hypothermia to avert the complications of traumatic brain injury and stroke.

s0065 Cellular Responses to Hypothermic Stress

p0085 A complete understanding of the effects of hypothermia on the body calls for examination of the events at the cellular level, since this is where the pathophysiology of hypothermic stress is ultimately mediated. A great deal is known about the effects of cold on cells, since cooling has proved to be the foundation of nearly all effective methods of protecting and preserving cells and tissues for applications such as transplantation. Transplantation science calls for effective methods of preservation since donor cells, tissues, and organs are required to withstand a period of ischemia and hypoxia as part of any transplantation procedure when the blood supply is temporarily interrupted. The basis of this hypothermic protection is that cooling can help to combat the deleterious effects of ischemia, but the consequences of cooling are not exclusively beneficial, such that hypothermic storage is a compromise between the benefits and detriments of cooling. In the following, the detrimental effects only of hypothermic stress on cells is outlined.

General suppression of reaction rates The fundamental basis of all biological and chemical processes is molecular activity and mobility, which are governed by thermal energy such that as temperature is lowered, molecular motion is slowed. The removal of heat from a system slows down both physical and chemical processes in proportion to the loss of heat and therefore to the fall in temperature. Since the processes of deterioration associated with ischemia and anoxia are mediated by chemical reactions, it has proved well founded to attempt to prevent or attenuate these changes by cooling. Biochemical processes involve molecular interactions that are invariably catalyzed by enzymes in reactions that require energy input from cellular stores such as ATP or creatine phosphate. Cooling can affect all components of these reactions, including the energy status of the substrate molecules, the stability of the enzyme protein, and the capacity of the cell to supply biological energy. The rate of biophysical processes such as diffusion of ions and osmosis declines linearly with temperature by approximately 3% per 10°C. It is apparent, therefore, that biophysical events are relatively little affected by the comparatively modest temperature changes imposed during hypothermic storage of tissues for transplantation. It is only at much lower temperatures that the rates of biophysical processes become significantly important, especially at sub-zero temperatures, when phase changes lead to both ice formation and solute concentration changes. s0070 p0090

p0095 By comparison, the rate of chemical reactions, including the biochemical processes that constitute metabolic activity, is slowed significantly more by a given degree of hypothermic exposure. It is well established that within the temperature range 0–42°C, oxygen consumption in tissues decreases by at least 50% for each 10°C fall in temperature. The quantitative relationship between energy requirements for biochemical processes and temperature changes has been expressed mathematically in different ways:

1. The Arrhenius relationship: Biochemical processes, in common with all chemical reactions, occur only between activated molecules, the proportion of which in a given system is given by the Boltzmann expression, $\exp(-E/RT)$, where E is the activation energy, R is the gas constant, and T is the absolute temperature. According to the Arrhenius relationship, the logarithm of the reaction rate, k, is inversely proportional to the reciprocal of the absolute temperature:

$$-\log k = A(-E/2.3RT).$$

A graphical plot of log k against $1/T$ will yield a straight line with a slope of $E/2.3R$ if the relationship represents a single rate-limiting step.

2. The Van't Hoff rule relates the logarithm of a chemical reaction rate directly to temperature and is commonly expressed in the form of the respiratory quotient or temperature coefficient, Q_{10}, where Q_{10} is the ratio of reaction rates at two temperatures separated by 10°C. Accordingly,

$$Q_{10} = (K_2/K_1)10^{(T2-T1)}$$

For most reactions of biological interest, Q_{10} has a value between 2 and 3, but some complex, energy-dependent reactions have a Q_{10} between 4 and 6 and are more likely to stop completely at low temperatures. Both Q_{10} and Arrhenius plots have been used to quantitate changes in metabolic processes occurring in biological systems, whether they are enzyme reactions in single cells or the oxygen consumption of the entire human body. The Q_{10} for whole-body oxygen consumption is approximately 2, indicating that, in general, metabolic rate is halved for each 10°C drop in temperature.

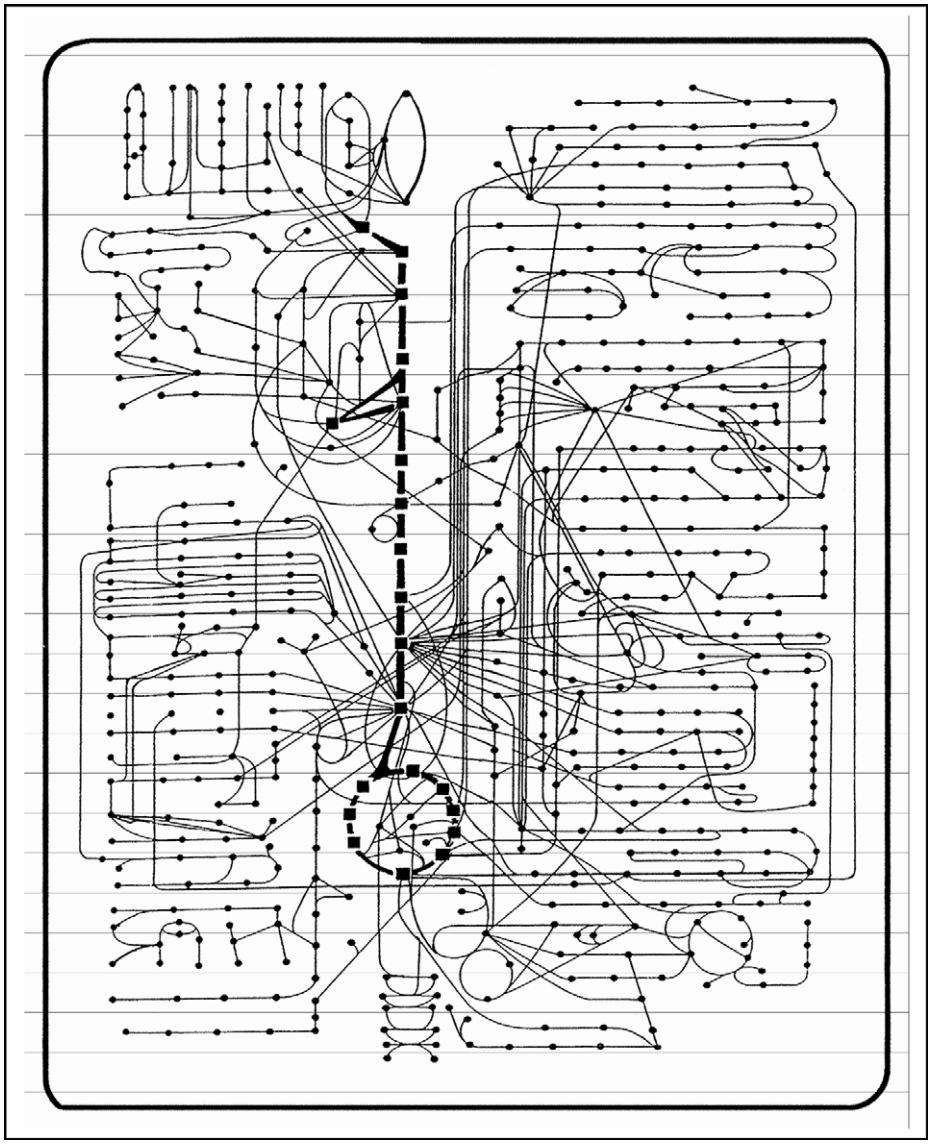
s0075 p0100 **Metabolic uncoupling** While it is clear that cooling has a profound effect on biochemical reaction rates and that this in turn can slow degradative processes and reduce the rate of substrate and energy depletion, it is important to realize that not all reaction rates are affected to the same degree, or even in the same manner, by cooling. One hypothesis of chilling injury states that at a certain critical temperature within the chilling injury range, the membrane lipids undergo a transition from a liquid-crystalline to a solid gel state. The two main consequences of the transition thought to eventually result in cell injury are an increase in membrane permeability and an increase in the activation energy of membrane-bound enzymes such as those controlling respiration in mitochondria. Thus, the result would be the accumulation or depletion of metabolites at the point of entry into mitochondria. Hence, the membrane phase transitions in subcellular membranes could cause metabolic imbalance and provide one component of injury sustained by homeothermic cells during cold exposure.

p0105 **Figure 2** shows schematically the large number of different, integrated chemical reactions that constitute common metabolic pathways within a cell. Each of these reactions will be affected by cooling in a different manner and to a different degree such that the possibility exists for uncoupling reaction pathways and producing harmful consequences. In preservation, cooling prolongs *in vitro* survival because it slows metabolism, reduces the demand for oxygen and other metabolites, and conserves chemical energy. However, it does not affect all reactions to the same extent, and the net result of cooling on an integrated, metabolizing system is complex, not entirely predictable, and not completely understood.

p0110 Studies of the effects of pure hypothermia on cell viability in the absence of any prior hypoxia have shown that the inactivation (killing) rates of cells exposed to reduced temperatures change slope at approximately 7–8°C, implying that there are distinct mechanisms of hypothermic inactivation above and below this transition temperature. These values have been interpreted as suggesting that unbalanced metabolism is probably the rate-limiting step for hypothermic inactivation in the higher temperature range (8–25°C), and membrane lipid phase transition or cold denaturation of a critical protein is likely to be responsible for the strong temperature dependence in the lower range (<8°C).

s0080 p0115 **Effect upon energy metabolism** Under normal circumstances the supply of energy-rich compounds to fuel a cell's requirement for homeostatic control is continuously replenished by oxidative phosphorylation in the mitochondria. During cooling, however, there is a progressive exhaustion of chemical energy reserves in a cell despite the general suppressive effect of cooling on metabolism. The effect of cooling on metabolism is complex and should not be regarded as causing a simple uniform retardation of all biochemical reactions. For example, the complexity of low temperature effects on mitochondrial respiration is not limited to the impairment of translocase enzymes. It has been shown that other enzymes that control reactions of the tricarboxylic acid (TCA) cycle and the electron transport chain are affected differently by cold storage.

s0085 p0120 **Effect upon ion transport and cell swelling** Intracellular ionic composition and volume regulation of a cell are maintained by a pump-leak mechanism in which membrane-bound enzymes transport various



f0010 **Figure 2** Schematic diagram illustrating the complexity of integrated biochemical pathways responsible for the structural and functional integrity of a typical cell. A healthy cell depends upon the synthesis and degradation of a wide variety of molecules. These processes are controlled by a complex series of biochemical reactions that produce and consume energy in a highly regulated manner. The diagram portrays schematically the complex integrated pathways that constitute the biochemical machinery of a typical cell. About 500 common metabolic reactions are shown by the connecting lines, with each metabolite represented as a filled circle. The centrally placed reactions of the main energy-producing pathways (glycolysis and tricarboxylic acid cycle) are shown as bold. A typical mammalian cell synthesizes more than 10 000 different proteins, a major proportion of which is enzymes. Each of these pathways can be affected differently by reduced temperatures such that the possibility exists for disruption of the normal metabolic processes, with harmful consequences as described in the text. Adapted from Alberts et al. (1994). *Molecular biology of the cell* (3rd edn.), Garland Publishing, with permission.

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ions and solutes to counter the passive diffusion driven by chemical potential gradients. These active pumps are inhibited by hypothermia both by its direct effect on enzyme activity and by the depletion of high-energy reserves as mitochondrial energy transduction fails. Nevertheless, the resultant passive redistribution of ions and water across the cell membrane and the concomitant change in the membrane potential have been demonstrated to be rapidly and fully reversible in the short term and may not be a source of permanent injury. Cells are known to have interrelated cation transport systems depending on energy supply and are thereby affected by reduced temperatures. Moreover, it is recognized that changes in the distribution of divalent cations (Ca^{2+}, Mg^{2+}) as a consequence of ischemia, hypoxia, and even cooling are especially important in cellular injury. The belief that calcium, in particular, is a mediator of cell death is based upon evidence accumulated over several decades from observations in a wide variety of tissues

AU1 and pertains to cell death from a variety of causes. Cytosolic calcium concentration is 10 000-fold lower than extracellular concentrations, and it is now postulated that enhanced or unbalanced calcium influx across the plasma membrane represents a final common pathway in cell death mediated by various conditions that share the tendency to induce an abnormal membrane permeability for calcium. In recent years, the recognition of the central role of calcium-mediated effects in the death of cells of ischemically sensitive tissues such as heart and brain has led to intense scrutiny of the effects of perturbations in divalent cation homeostasis. Calcium functions as a second messenger in the regulation of numerous biochemical and physiological processes, often by activating regulatory proteins, which, in turn, can activate many intracellular enzymes, including protein kinases. It has recently been proposed that the significant protective effect of mild hypothermia against ischemic brain injury might be mediated in part by inhibition of calcium-induced effects and the prevention of inactivation of important Ca-dependent enzyme systems such as the kinases. However, it is generally recognized that cooling has no beneficial effect in preventing, and may even accentuate, inhibition of the (Ca^{2+}, Mg^{2+})-ATPase pump mechanism, which in general is the most important factor in controlling intracellular Ca^{2+} concentrations. The effects of cooling on calcium homeostasis result not only from the inhibition of transmembrane pumping, but also from the inhibition of calcium sequestration by intracellular organelles, particularly the endoplasmic reticulum and mitochondria.

s0090 p0125 **Proton activity changes** The principal events of the ischemic cascade show that elevation of the concentration of protons, i.e., increasing acidity, is regarded as a contributory central event in the process of cellular injury ensuing from O_2 deprivation and energy depletion. Moreover, reduced temperatures are also known to influence pH regulation, which is another important homeostatic mechanism for cell survival. It has frequently been reported that hydrogen ion concentration increases in a variety of mammalian cells during hypothermic storage such that tissue pH has been recorded to fall to 6.5–6.8 within a few hours of cold. Acidity is widely recognized as a hazard for cells, with the accumulation of protons contributing to a variety of deleterious processes, including metabolic block of glycolysis and structural damage. Destabilization of lysozomes releasing harmful proteases and catalysis of oxidative stress by mobilization of free heavy metals have been implicated as mechanisms of cellular tissue injury during acidosis.

s0095 p0130 **Effect of hypothermia on the generation of oxygen free radicals** The emerging role of oxygen-derived free radicals (ODFRs) in tissue injury and their participation in reperfusion injury is well established. In essence, it is recognized that cooling increases the susceptibility of cells to produce free radicals and attenuates the natural defense mechanisms by which cells normally deal with the low-level free radical production in metabolism. Due to a lower activation energy, free radical reactions are depressed less by temperature reduction than the enzymatic processes used to scavenge them. It is the balance between production and removal of free radicals that is crucial to the cell such that a combination of excessive radical generation and hindrance of normal defense mechanisms can redirect the processes in favor of injury. There is evidence that some of the natural defense mechanisms against free radicals become depleted during cold storage and that the addition of natural pharmacological scavengers including superoxide dismutase (SOD), catalase, or mannitol to cold storage media may improve the viability of hypothermically stored organs. It is clear, therefore, that in tissues exposed to cold there is potential for unbalanced free radical reactivity and elevated intracellular free calcium levels, and subsequent warming and reperfusion is likely to greatly potentiate these adverse events.

s0100 p0135 **Structural changes** The interrelationship between structure and function is fundamentally important for cellular homeostasis, which is governed by an intricate array of biochemical, physiological, and biophysical processes. Moreover, these processes are compartmentalized within the cell such that the structure of biological membranes and the cytoskeleton are integral components of cell viability and vitality.

p0140 The sensitivity of biological structures to temperature change is well known, and the thermal denaturation of proteins in particular is well documented. Thus, most proteins, as well as nucleic acids and many polysaccharides, are able to exist in their biologically active states only within a limited temperature range that is characteristic of the macromolecule and its environmental conditions such as ionic strength and pH. While a great deal more is known about heat denaturation of proteins at elevated temperatures, there are well-described examples of cold denaturation involving spontaneously unfolding of proteins or dissociation of the multisubunit structure into biologically inactive species that may or may not reassemble on rewarming to normal temperatures.

p0145 It has been postulated on the basis of measurements in both model systems and intact cells that a phase separation occurs within the plane of the membrane

as cooling proceeds. Such cold-induced changes in the degree of membrane fluidity render it thermodynamically unfavorable for membrane proteins to remain in the gel phase such that they may be redistributed laterally into regions of low melting point lipids that remain in the liquid crystalline phase. This process is thought to result in packing faults due to the development of lipid-rich and protein-rich microdomains in a membrane undergoing phase transitions. One consequence of this could be a change in membrane permeability and alteration in the solute barrier function of the membrane. Phase separation of mammalian membranes has been demonstrated at temperatures in the region of 10°C and below, and this correlates with the trend toward increased permeabilities to both ions and even large molecules such as proteins during cooling. In addition to phase separations, other forms of cold-induced membrane damage include the actual loss of membrane phospholipids, which is intuitively more deleterious than phase changes, which may in large part be reversible.

p0150 Cold-induced changes of cellular structural proteins that constitute cytoskeletal components such as microtubules have been known since the mid 1970s. This cold sensitivity appears to be mediated by depolymerization of component polypeptide units and in general is readily reversible upon rewarming. Nevertheless, the possibility exists for reassembly of the microtubules in a way that results in cellular abnormalities.

s0105 p0155 **Thermal shock** It has been discovered in some cells that the rate of cooling is also a determinant of injury; the phenomenon, which is not well understood, is referred to as thermal shock (cold shock) or chilling injury. The effects are thought to be related to the thermotropic properties of cell membranes involving phase transitions, as discussed briefly earlier. It has been proposed that rapid cooling in the absence of freezing can cause mechanical stresses on membranes induced by differential thermal contraction.

s0110 p0160 **Cold shock proteins** Changes in the structure of proteins are a common response to stress such that cells accumulate incorrectly folded proteins as a consequence of stresses such as hypoxia or temperature change. Proteins that experience unfolding or conformational changes do not remain soluble and are transformed into denatured proteins. It is now well established that one of the defense mechanisms adopted by cells to counteract such effects of stress is to synthesize new proteins commonly referred to as stress proteins or heat shock proteins (HSPs) because of their increased synthesis by many cell types after exposure to elevated temperatures. The general role of this group of highly conserved stress proteins is believed to be homeostatic in that they protect the cell against the harmful consequences of traumas and help promote a quick return to normal cellular activities once the shock has terminated.

p0165 The induction of stress proteins in response to cold (cold shock proteins) has been identified in invertebrate species such as bacteria and yeast, but it was not known until recently that similar families of cold shock proteins are also induced in mammalian cells.

s0115 p0170 **Apoptosis vs. necrosis in cold-induced cell death** It is now known that there are two distinct ways in which cells may die. Necrosis is caused by a general failure of cellular homeostatic regulation following injury induced by a variety of deleterious stimuli, including hypoxia, toxins, radiation, and temperature changes. Apoptosis (programmed cell death) by contrast, is a regulated process that has been distinguished from necrosis by numerous morphological biochemical and physiological differences. While many of the diverse stresses known to cause necrotic cell death have also been reported to induce apoptosis in a variety of cells, the role of low temperatures as a possible stimulus of programmed cell death has yet to be investigated in depth. Nevertheless, it has been shown that cultured mammalian fibroblast cells at the transition from logarithmic to stationary growth were killed by brief exposures to 0°C and rewarming at 37°C. Moreover, the kinetics of cell death served to distinguish cold-induced apoptosis from the lethal effects of longer-term cold storage (hours or day), and also showed characteristics inconsistent with direct chilling injury (cold shock). It is possible, therefore, that apoptosis may represent another manifestation of cold injury. Susceptibility to cold-induced apoptosis seems to depend critically upon cell growth cycle and the temperature of exposure. Recent studies in cultured hepatocytes and liver endothelial cells have indicated that reactive oxygen species (free radicals) might play a key role in mediating cold-induced apoptosis.

p0175 Finally, it is important to emphasize that both the severity and the reversibility of the catalog of effects outlined here are highly dependent upon both the duration and the extent of hypothermic exposure. Many of the consequences of hypothermic stress manifest in cells subjected to prolonged exposure during cold storage do not develop during brief exposure to mild or moderate hypothermia.

See Also the Following Articles

Heat Resistance (00189); Heat Shock Proteins: HSP60 Family Genes (00191); Hyperthermia (00205).

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