

The Relation between Biological Consequences and High Temperature in Mammals

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Abstract: Because of the temperature is one of the most encountered stressful factors in the environment, it was deemed important to survey the literature for reports on high temperatures or hyperthermia exposure durations at which biological effects occur. Since that time, several method of heating the entire body have evolved, including the artificial induction of fever, the wrapping of an anesthetized patient in plastic and dipping them in hot wax and heating the blood supply. The aim of this review was to determine the changes in tissue temperature and the duration of this effect. In general, the higher the temperature or the longer the hyperthermia, the greater the chance for observing a perturbation to the biological effects. It appears reasonably well established that, short exposure to sharply-elevated temperatures result in a protective effect against further thermal insult; the generation of heat shock proteins by cells coincides with the onset of such "thermal protection". It can be concluded that, thermal damage increases as the time at an elevated temperature increases.

Key words: Hyperthermia, thermogenesis, teratogenicity, development, cellular effect, thermal protection, lethality

Introduction

In view to the recent studies, the biological effect of high temperatures or hyperthermia exposure durations are mediated through both thermal and nonthermal mechanisms of interaction. Both mechanisms are important and either may be the predominant mechanism depending on the exposure conditions. Also, the effects of hyperthermia are strongly influenced by thermotolerance (Lepock and Kruuv, 1980).

In addition, mitochondrial respiratory chain activity is central to all hypothesis of cellular heat generation-thermogenesis (Nicholls and Locke, 1983). There is an association between the relative number of mitochondria per cell and homothermic and heterothermic organisms; the former having more mitochondria and the mitochondria having a greater surface area (Giardier and Stock, 1983).

On the other hand, several reports are listed on the harmful effect of high temperatures and hyperthermia exposure (Poswillo *et al.*, 1974; Johnson *et al.*, 1976; Fajardo, 1984; Sminia *et al.*, 1989; Sharma and Cervos-Navarro, 1990; Sharma *et al.*, 1992; Bongiovanni *et al.*, 1999; Lee *et al.*, 2000; Kay and Marino, 2000; Hirobumi *et al.*, 2002; Chou *et al.*, 2003; Edwards *et al.*, 2003; Radmilovich *et al.*, 2003; Sharma *et al.*, 2003; Chang *et al.*, 2004). The following is a brief concerted attempt to describe the backgrounds and recent findings which provide specific suggestions for explore the effect of high temperatures or hyperthermia exposure duration.

Effects on the Life Processes

There are a number of fascinating observations of living organisms maintained under a wide variety of temperatures. For example, *in vitro* mammalian cells retain their viability for nearly indefinite periods if kept in the vapor of liquid nitrogen (-79°C), will die if frozen at 0°C, have cell growth kinetics which appear maximal at 33-39°C and are generally lethally affected by temperatures of about 45°C; however, a very brief exposure to a very high temperature can confer "thermotolerance" and thus render the cell capable of surviving subsequent exposures to high temperature (Miller and Ziskin, 1989).

The temperature is not constant throughout the body. Core temperature is usually 37°C, but skin temperatures can range from a low of 31.5°C (calf) to 35.0°C (Olesen, 1984). During work a person's core temperature can rise to 38.4°C (Gas and Camp, 1984); a competitive marathon runner's temperature was 41°C (Dark and Edholm, 1985). During sunbathing, a person's skin can rise about 5°C on the 'sunny' side (Clark and Edholm, 1985), with dissipating mechanisms preventing further increase in temperature. Miller and Ziskin (1989) found that ultrasonically-induced heat is whether maternal temperature *per se* or fetal temperature specifically is the important parameter in attempting to establish some above-normal temperature below which no thermal effects are anticipated.

Also, there is a range of temperatures over which the body can function. A person's temperature can vary with type and duration of activity. DuBios (1948) has reported an estimate of the range of body temperature (rectal, oral) for various activities, from early morning (sleeping, nonactivity) to normal ranges to vigorous exercise and hard work. The temperatures range from slightly less than 36°C to about 40°C, with the usual range of normal roughly 36 to 38°C (Hardy, 1982).

Teratogenic Effects in Mammals

Hyperthermia is thought to be a teratogen in many animal species including primates and also in humans (Smith, 1982; Shepard, 1982; Sasaki *et al.*, 1995). The retrospective human studies have a related hyperthermia to both neural tube and head defects (Layde *et al.*, 1980; Fisher and Smith, 1981; Spraggett and Fraser, 1982). Furthermore, Sasaki *et al.* (1995) reported that hyperthermia caused by sauna, hot tub, or fever during the early stages of pregnancy is related to an increased risk for neural tube defects. Also, Edward (1986) found that, the hyperthermia causes several congenital abnormalities in a number of domestic and laboratory species of mammals, including defects on the central nervous system.

Layde *et al.* (1980) proposed that hyperthermia in the pregnant woman is associated with neural tube defects in her offspring. Also, maternal hyperthermia in early pregnancy can cause neural tube defects in man, especially anencephaly (Shiota, 1982). Milunsky *et al.* (1992) found that exposure to heat in the form of hot tub, sauna, or fever in the first trimester of woman pregnancy was associated with an increased risk for neural tube defects (NTDs). Moreover, Edwards *et al.* (2003) found that hyperthermia during pregnancy can cause embryonic death, abortion, growth retardation and developmental defects. Furthermore, Arora *et al.* (1979) noticed that oedema, microencephaly and microphthalmia on day 4, 6, or 8 when rats exposed to ambient temperatures of 43-44°C at various stages of pregnancy. Berman *et al.* (1990) found that increasing ambient temperature was effective in decreasing maternal weight gain and fetal body weight and increasing fetal relative brain weight. In humans, epidemiological studies suggest that an elevation of maternal body temperature by 2°C for at least 24h during fever can cause a range of developmental defects, but there is little information on thresholds for shorter exposures (Edwards *et al.*, 2003). Also, Cronje (1977) noted that pregnant women with elevated intrauterine temperatures (38.8 vs 37.4°C for controls) had a higher incidence

of fetal tachycardia. Laurence *et al.* (1968) reported an excess of first trimester pyrexia in mothers delivering fetuses with anencephaly, memmigomyelocoele, or hydrocephalus. Fraser and Skelton (1978) recorded that possible teratogenicity of maternal fever were present. In limited study with pregnant baboons whose core temperature was raised to 42°C (39°C is normal) over 3 to 4 h, a variety of fetal disorders; metabolic acidosis, fetal cardiac arrest, fetal asphyxiation, rise in heart beat, fall in blood pressure, including abortion were noted (Morishima *et al.*, 1975).

Exposure of embryos to experimentally elevated temperature during organogenesis has long been known to be embryotoxic (Johnson *et al.*, 1975; Hutchinson and Bowler, 1984; Edwards, 1986; Upfold *et al.*, 1989). Hyperthermia at critical stages during embryonic development causes several developmental abnormalities (Edwards, 1986) including defects of the central nervous system. Experiments carried out on rat embryos cultured for 48 h at 40.5°C resulted in a significant microcephaly and oedema of the pericardium (Cockroft and New, 1978). From these observations, we can conclude that, the temperature may delay partially the development of the embryos.

The range of defects induced by hyperthermia in experimental animals includes: anencephaly/exencephaly, encephalocoele (Webster and Edwards, 1984; Cawdell-Smith *et al.*, 1992), micrencephaly (Edwards, 1969; Edwards *et al.*, 1984; Upfold *et al.*, 1989), microphthalmia, talipes, arthrogryposis, abdominal wall defects and limb reduction defects (Edwards, 1986). Such defects have been induced by heat in a variety of mammals, including guinea pigs, hamsters, rats, mice, rabbits, sheep, pigs, monkeys and humans (Edwards, 1986), though the confounding effects of the febrile illnesses themselves and their therapies remain problematic in the interpretation of the human data.

Furthermore, the central nervous system defects appear to be the most common consequence of hyperthermia in all species and cell death or delay in proliferation of neuroblasts is believed to be one major explanation for these effects (Edwards *et al.*, 1974; Wanner *et al.*, 1975; Upfold *et al.*, 1989). It is apparent from the above mentioned results that, the hyperthermia or temperature not only may a potential behavioral teratogen but also may obstruct the biological processes.

On the other hand, the signs of Malignant Hyperthermia (MH) are muscle spasm, rapid increase in temperature, tachycardia, increased blood pressure, increased oxygen demand, increased arterial PaCO₂ and acidosis (Harley *et al.*, 2005). This usually occurs on induction but its onset is, on rare occasions, delayed by a few hours. In generally, heatstroke is a multisystem disorder that can result in death (Flanagan *et al.*, 1995). So, from the pre-said studies, the temperature may cause some malformation in the pregnant, which may retard or delay partially the growth of its fetus and reduce its biological functions.

Effect of Temperature on the Protein Synthesis

Regarding to the Protein synthesis, the effect of hyperthermia, in general, on whole body leads to temporary cessation of normal synthesis of it (German, 1984). Also, Edwards *et al.* (1974) mentioned that heat causes protein denaturation in newborn guinea pigs. Heat causes a transient depression in overall protein synthesis (Lindquist and Craig, 1988). Moreover, Edwards *et al.* (1997) said that there was a reduction in normal protein synthesis of mammalian brain as a result of heat shock. The degradation of protein increased in rat brain as a result of hyperthermia (Bongiovanni *et al.*, 1999). According to the above results, it is worth mentioning that, the present overview may suggest the deleterious effect of temperature on the vital processes of the biological systems.

Metabolic Processes

The responses to heat are moderated by factors which influence on the metabolic heat production/heat loss, including the severity and duration of heat stimuli, accompanying exercise, the magnitude of the metabolic response and individual characteristics such as body composition, age and gender. Kay and Marino (2000) said there were alterations in the metabolic process as a result of exercise heat stress. Moreover, Wilmore *et al.* (1975) observed that the higher environmental temperature decreased metabolic rate in patients with large thermal injuries in whom the decrement in dry heat loss produced by higher ambient temperature exceeded the increase of wet heat loss. In other instance, Nilsen (1984) recorded that the hyperthermia distorts the small vessels and also produces irregularities of the microvascular pattern. Therefore, the above results presumed that, the distortion in blood vessels may cause the impairment of the metabolic processes (carbohydrates genesis) and thus, may reflex some delaying in the growth of the cellular processes.

Thermal Tolerance and Thermal Sensitivity

There is no known mechanism for explaining sensitivity of cells to heat (Miller and Ziskin, 1989). A variety of effects is known, including enhanced sensitivity of cells during stages S, G2 and M, perturbations to the cytoskeletal system, modulation of polyamine release and changes in DNA synthesis in hyperthermia treated cells (Leeper, 1985).

In addition, cells appear to be capable of developing nonheritable tolerance to heat treatments. Maximal tolerance develops during 3 to 4 h of exposure of cells to temperature below 42.5°C followed by 8 to 10 h of exposure of cells to greater than 43°C and then a return to 37°C (Leeper, 1985). The thermotolerance has been observed to occur in nearly every living biological system, including protozoan, slime molds, fungi, molluscs, nematodes, insects, echinoderms, fish, amphibian, birds, mammals and plants (Mover and Sharf, 1984). A notable exception to this appears to be the very early embryo stages (where only 8 or so cells are involved); it is possible that such cells are thermotolerance capable, but because there are so few of them it is difficult to demonstrate (Heikkila *et al.*, 1985). Later embryonic stages (e.g., blastula), which have many more cells, have been shown to be capable of induction of thermotolerance (Heikkila *et al.*, 1985). Thus, thermotolerance increases the resistance of surviving cells by several orders of magnitude, particularly if the heat fractions are given daily (Miller and Ziskin, 1989).

Thermal Protection

Pertaining to a genetic basis, the thermotolerance can be found in the development of Heat Shock Proteins (HSPs) (Hahnel *et al.*, 1986). Stressful stimuli activate the heat shock (stress) response in which a set of heat shock proteins is induced, which play roles in cellular repair and protective mechanisms (Bechtold and Brown, 2000). Also, the induction of stress response Heat Shock Proteins (HSPs) is a highly conserved response that protects many cell types from diverse physiological and environmental stressors (Kelly, 2002). There was an increase in the synthesis of a small set of proteins known as the heat shock proteins due to heat exposure (Lindquist and Craig, 1988). Also, the HSP72 synthesis significantly increased in the brain of the rats with hyperthermic treatment (Yang *et al.*, 1994). Recovering embryos mounted a heat shock response as evidenced by the induction of a 71 kilodalton heat shock protein (Walsh *et al.*, 1987). Activation of the heat shock response was not a teratogenic event in the developing embryo. Heat acclimation elevates the levels of HSP (Malyshev *et al.*, 2000). Moreover, when mouse exposed to environmental stress, cell survival is supported by the upregulation of stress proteins such as heat shock proteins or Glucose Regulated

Proteins (GRPs), which help prevent protein denaturation (Ostberg *et al.*, 2002). Yang and Lin (1999) revealed that, the neuronal HSP72 increases survival in rats exposed to heat stroke by attenuating arterial hypotension. The susceptibility of large neurons to stress induced cell death could be due, in part, to their inability to synthesize rapidly HSP70 in sufficient amounts to protect these cells from the initial molecular consequences of stress (Morrison-Bogorad *et al.*, 1994). Based on the above described results, the hyperthermia or heat may induce the secretion of the heat shock protein to make the protective mechanisms but this secretion depends not only on the duration of exposure but also on the type of tissue and the environmental conditions. Actually, it is not known if these proteins are truly protective, or if they are merely products of the process that provide the thermal tolerance (Miller and Ziskin, 1989).

Temperatures and Lethality

A general relationship between time and temperature for thermal death is given by Dickson and Calderwood (1980) *in vivo*, *in vitro* and some clinical studies. An important point in Dickson's presentation is that below about 40°C there was virtually no effect of temperature on organisms, but above that point less exposure duration is required with rise in temperature to cause an effect. Heat induced cell lethality has been shown to be dependent on both temperature and heating time (Haveman and Hart, 1989). Also, Dunn *et al.* (2004) reported that, in the zooxanthellae, both apoptosis-like and necrosis-like activity increased throughout the duration of the exposure to heat stress (6 days), dependent on temperature dose. Heat induced cell death by apoptosis is a feature of teratogenic damage to the developing brain (Edwards *et al.*, 1997). Apoptosis could be a by-product of a damaging heat exposure because of a priority favoring induction of the heat shock response over the normal gene program for organogenesis, survival being achieved at the expense of normal development (Edwards *et al.*, 1997). This effect depends on the age of the animals and their prior thermal experiences. In general, thresholds and exposure-response relationships vary between species and even between different strains of the same species, depending on genotypes. But, a thermal stress, which by itself is nonlethal (Kahraman and Thach, 2004).

Effect Temperature on the Balance Between Heat Gain and Heat Loss

The rise in deep body temperature of the rats during work is proportional to work intensity and that the enhanced heat production capacity can be compensated for by increasing the heat loss activities (Harri *et al.*, 1982). Also, Shih *et al.* (1984) found at $T_a = 40^\circ\text{C}$, heat gain exceeded heat loss and led to hyperthermia and heat stroke and the latency for the onset of heat stroke was found to be around 87 minutes. At the onset of heat stroke, the comatose animals showed higher levels of rectal temperature, ear skin blood flow, respiratory evaporative heat loss, metabolic rate, intracranial pressure (ICP) and cerebral water content as compared to those of control animals (kept at an ambient temperature of 24°C). Therefore, it can be inferred that, the temperature may cause some disturbance in the balance between the heat gain and heat loss. Furthermore, Hyperhydration or increasing body water content above normal (euhydration) level was thought to have some benefit during exercise heat-stress; however, attempts to overdrink have been minimized by a rapid diuretic response (Latzka and Sawka, 2000).

Other Effects of Hyperthermia

Normal temperature maintenance requires an intact autonomic nervous system (Landsberg and Young, 1983). The body has adaptive capabilities for maintaining homeothermic

condition; when the body temperature begins to rise, heat dissipating mechanisms come into play the peripheral blood vessels dilate, cardiac pulse rate increases (Gross *et al.*, 1986) and sweating occurs. When the body temperature begins to drop "below normal" then shivering occurs, a mechanism designed to increase heat generation. On the other hand, the environmental stress as hyperthermia is generally believed to modify autonomic function through well-known classical pathways involving alternation in the cardiovascular function (Black *et al.*, 1976). These changes in the cardiovascular function vary in severity and direction depending upon the degree of temperature change as well as the duration of the exposure (Tveita *et al.*, 1991). Elazar *et al.* (1981) found that, the hyperthermia reduced the activity of the enkephalinergic system in the brain of rat; this reduced due to acceleration of the activity of peptidases involved in its breakdown. Furthermore, Arieli *et al.* (2003) reported that, the long term of heat acclimation prolongs the time to the development of the oxygen toxicity in the Central Nervous System (CNS-OT). Furthermore, Mirochnitchenko *et al.* (1995) suggested that, the hyperthermia may increase oxidative stress in tissues to form the reactive oxygen species with harmful to cellular functions and Chang *et al.* (2004) found that, the heatstroke increased the hydroxyl radicals and striatal neuronal damage in the brain of rats.

Summary of the Biological Effects of Hyperthermia

The elevated temperatures described in this report produce a wide range of significant biological effects as shown below:

Thermal effects	Temp (°C)	Exposure duration (min)	Species	References
Abnormal closure of anterior neuropore	43.0	7.5	Rat	Walsh (1985b)
Abortion	40.6	72	Monkey	Hendrickx <i>et al.</i> (1979)
Absence of optical vesicles	43.0	7.5	Rat	Walsh (1985b)
Agenesis	43.3	60	Guinea Pig	Edwards (1971)
Agnathia	43.0	60	Mouse	Pennycook (1965)
Anophthalmia	43.6	72	Monkey	Hendrickx (1979)
Arthrogyposis	42.9	60	Guinea Pig	Edwards (1971)
Beak defects	41.0	1440	Chicken	Nielsen (1969)
Behavioral abnormalities	41.5	60	Marmoset	Poswillo <i>et al.</i> (1974)
Blebbing of cell membrane	43.0	180	Chin. Hamster	Bass <i>et al.</i> (1978)
Brain cavitation	40.0	540	Sheep	Hartley <i>et al.</i> (1974)
Brain growth retardation	40.0	2880	Rat	Cockcroft and New (1978)
Brain weight reduction	40.0	540	Sheep	Alexander and Williams (1971)
Cardiac and vascular abnormalities	41.0	3180	Chick	Nielsen (1969)
Carpus distortion	43.3	60	Guinea Pig	Edwards (1971)
Cataract	42.5	60	Guinea Pig	Edwards (1967)
Central blindness	42.5	60	Guinea Pig	Edwards (1967)
Cleft lip	43.5	60	Rat	Webster <i>et al.</i> (1985)
Cleft palate	43.0	40	Rat	Edwards (1968)
Conc. of organelles in juxtannuclear position	43.0	180	Chin. Hamster	Bass <i>et al.</i> (1978)
cytoplasmic debris leaked in ventricle	43.0	60	Guinea Pigs	Upfold <i>et al.</i> (1986)
Developmental abnormalities	42.0	40	Rat	Skreb and Frank (1963)
Ear defects	43.5	60	Rat	Webster <i>et al.</i> (1985)
Embryonic resorptions	40.0	540	Sheep	Alexander and Williams (1971)
Encephalocele	43.5	60	Rat	Webster <i>et al.</i> (1985)
Exencephaly	42.3	5	Mouse	Webster and Edwards (1984)
Eye	41.0	1440	Chicken	Nielsen (1969)
Facial clefting	42.0	30	Rat	Germain <i>et al.</i> (1985)
Fibula hypoplasia	43.3	60	Guinea Pig	Edwards (1971)
Fragile sclera	42.5	60	Guinea Pig	Edwards (1967)

Thermal effects	Temp (°C)	Exposure duration (min)	Species	References
Fragile tibia	43.3	60	Guinea Pig	Edwards (1971)
Growth retardation	41.5	60	Marmoset	Poswillo <i>et al.</i> (1974)
Head defects	43.0	40	Rat	Edwards (1968)
Hydrocephalus	43.0	40	Rat	Edwards (1968)
Hypertonas of gastrocnemius	43.3	60	Guinea Pig	Edwards (1971)
Hypoplasia	40.6	72	Monkey	Hendrickx <i>et al.</i> (1979)
Hypoplastic adrenals and Kidneys	40.6	72	Monkey	Hendrickx <i>et al.</i> (1979)
Limb, toe and tail defects	43.0	40	Rat	Edwards (1968)
Loss of microvilli	43.0	180	Chin. Hamster	Bass <i>et al.</i> (1978)
Lower protein content in head	40.0	2880	Rat	Cockcroft and New (1978)
Maxillary Hypoplasia	43.5	60	Rat	Webster <i>et al.</i> (1985)
Meroanencephaly	40.6	72	Monkey	Hendrickx <i>et al.</i> (1979)
Micrencephaly	42.5	60	Guinea Pig	Edwards (1969a, 1969b)
Microphthalmia	41.0	60	Rat	Germain <i>et al.</i> (1985)
Necrotic cells in neuroepithelium	43.0	30	Rat	Mirkes (1985)
Neural tube	39.1	1440	Chicken	Alsop (1919)
Neurogenic talipes	42.5	60	Guinea Pig	Edwards (1971)
Neuropore closure defect	41.0	2880	Rat	Cockcroft and New (1978)
Pericardial edema	41.0	2880	Rat	Cockcroft and New (1978)
Perinatal mortality	40.0	540	Sheep	Alexander and Williams (1971)
rostenor paralysis	43.0	60	Mouse	Penny cuik (1965)
Prenatal growth retardation	40.0	540	Sheep	Alexander and Williams (1971)
Proencephalon size reduction	43.0	7.5	Rat	Walsh (1985)
Pyknosis in ventricular	42.0	60	Guinea Pig	Wanner <i>et al.</i> (1976)
Reduced maxilla	43.0	60	Mouse	Penny cuik (1965)
Reduced number of toes	43.0	60	Mouse	Penny cuik (1965)
Reduced protein per embryo	43.0	7.5	Rat	Walsh (1985a)
Reduced protein synthesis	42.0	10	Rat	Walsh (1985b)
Resorption	42.9	60	Guinea pig	Edwards (1967)
Rounded up of the cell	43.0	180	Chin.Hamster	Bass <i>et al.</i> (1978)
Scoliosis	40.6	72	Monkey	Hendrickx <i>et al.</i> (1979)
Severe growth retardation	43.6	40	Rat	Edwards (1968)
Skeletal defects	41.5	60	Marmoset	Poswillo <i>et al.</i> (1974)
Spine	41.0	1440	Chicken	Nielsen (1969)
Strabismus	42.5	60	Guinea pig	Edwards (1967)
Tail and limb defects	43.0	40	Rat	Edwards (1967)
Talipes	40.6	72	Monkey	Hendrickx <i>et al.</i> (1979)
Tarsus distortion	43.3	60	Guinea Pig	Edwards (1971)
Testicular degeneration	40.0	540	Sheep	Alexander and Williams (1974)
Tetralogy of fallot	40.6	72	Monkey	Hendrickx <i>et al.</i> (1979)
Tooth defects	38.9	720	Rat	Kreshover and Clough (1953)
Tubercalcanei displacement	43.3	60	Guinea Pig	Edwards (1971)
Ventral body wall defect	41.0	1440	Chicken	Nielsen (1969)
Vertebral defects	43.0	1200	Mouse	Lecyk (1966)

Finally, in view to the recent studies on the effects of heat and hyperthermia on the biological consequences, the current overview throw up important findings, the biological consequences are extremely sensitive to the heat and hyperthermia exposure; this may lead to some harmful effects on them.

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