Hazardous Effects of Hyperthermia on Brain and Testicular Responses in Rats

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Abstract: Hyperthermia was investigated in adult male albino rats exposed to high temperature (40 ± 1°C) for 12 hours. Twenty male rats 3 months old were used. They were divided into two groups and separated into two rooms. The rats in the first room were subjected to hyperthermia (40±1°C), while rats of the control group were maintained under normal environmental conditions (25±5°C). Neural response to heat exposure was assessed by determining the levels of dopamine, nor adrenaline and serotonin in the brain homogenate. Serum electrolytes (sodium, potassium, magnesium and calcium) were also evaluated. Testes response to heat exposure was also assessed by determining the levels of LH and testosterone by (EIA). Histopathological examination of brain and testes were evaluated after heat exposure. Brain content of dopamine, nor adrenaline and serotonin showed significant increase, there was an increased potassium and calcium levels while sodium and magnesium concentrations decreased. Also LH testosterone levels decreased after heat exposure.
Histopathological examination revealed hyperemic capillaries and blood vessels allover the cerebral and disorganization of semineferous tubules of the testes. In conclusion, avoidance of hyperthermia is very important, the body temperature must be maintained in a safe normothermic range. It is recommended to assess the role of nutritional supplementation to alleviate the hazardous effects of heat stress.

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1. Introduction

Hyperthermia is a condition of abnormal rise of core (intraperitoneal) body temperature resulting from exceeded heat gain over heat loss (Robergs and Roberts, 2000). They added that the increasing hyperthermia can lead to a series of system and cellular changes that increase risk for exhaustion, organ failure (especially the brain and testes), and death. Although hyperthermia can occur without severe dehydration, dehydration exacerbates the condition. Mickley et al., (1997) stated that hyperthermia or heat shock or hyperpyrexia is mostly achieved following prolonged exposure to high atmospheric temperature. This occurs usually in the tropic regions during summer. Heat generation is also occurred by injection of pyrogens or during exposure to hyperthermic agents as microwaves, ultrasonic and radiofrequency radiation.

Guyton and Hall (2006) noted that when the body temperature rises beyond a critical temperature into the range of 105°F to 108°F, the individual is likely to develop heatstroke. They added that the hyperpyrexia itself is also exceedingly damaging to the body tissues, especially the brain, and is responsible for most of the effects. In fact, even a few minutes of very high body temperature can sometimes be fatal. A complicating fact to achieve hyperthermia is the variety of normal body temperature between mammalian species, eg. 37°C in human, 38°C in rats, 39°C in pigs and 39°C in rabbits and sheep (Miller and Ziskin, 1989). Hyperthermia intensified the processes of lipid peroxidation in many organs (Kokuta et al., 2002).

Zaghloul (2009) reported that spermatozoa are subjected to different stresses during thawing, it should be slow enough to prevent intracellular ice formation which is lethal.

Several noxious effects on the central nervous system were induced by hyperthermia. It caused disruption of the blood brain barrier, increased intracranial pressure and induced an upregulation of nitric oxide synthases in brain which causing cell injury (Sharma and Alm, 2002). Gourine et al., (2004) reported that fever, which means a body temperature above the usual range of normal, can be caused by abnormalities in the brain itself or by toxic substances that affect the temperature regulating centers. Some causes of fever include bacterial diseases, brain tumors and environmental conditions that may terminate in heatstroke.

The mechanisms involved in cellular injuries caused by hyperthermia deserve more attention. Therefore, the purpose of this study was to elucidate the neural and testicular changes involved when adult male rats exposed to high temperature (40°C) for 12 hours.

2. Materials and Methods

Animals and treatment: Twenty adult male albino rats, aged 3 months, weighing 121±9 g. Rats were acclimatized for 3 days. The animals were housed, one per cage in wire bottomed stainless steel cages in a temperature controlled room (25±5°C) with relative humanity (50±10) and with 12 h. light/dark cycle. Rats were allowed to a standard commercial chow diet.

The rats were divided randomly into two groups each comprising 10 rats, a control group were left in a temperature controlled room (25±5°C) and the experimental group were subjected to high temperature (40±1°C) for 12 hours. During the time course of heat exposure rectal temperature was monitored using thermometer unit reached to 40°C.

The animals were sacrificed after overnight fasting under ether anesthesia. The relative humidity of experimental group was 90%. Blood samples were collected for estimation of serum LH and testosterone levels in control and heat exposed rats by (EIA) together with Calcium, Magnesium, Sodium and Potassium brain and testes samples were taken for histopathological examination.

Biochemical analysis of the brain:

1- Estimation of dopamine, noradrenaline and serotonin, the brain of experimental and control group were removed immediately and frozen in dry ice. The frozen tissues were weighed and homogenized in butanal acidified with 0.1 NHCl and centrifuged at 1500 rpm for 10 min. Catecholamines and serotonin were measured in the clear supernatant spectroflurometer as described by Jacabwitz and Richardson (1978).

2- Specimens of brain and testes were taken for histopathological examination, and after zenker fixation for 24 hours they were embedded in paraffin wax, sections were cut 5-8 µm thick and stained with hematoxylin and eosin.

Estimation of serum electrolytes:

Sodium and potassium were determined by using flame photometer according to Zilversmit (1965). Magnesium and calcium, were determined using spectrophotometer according to Grindler and Health (1971) and Grindler and King (1972).

Statistical analysis :

Data was expressed as means ± SD using Snedecor and Cochran (1990) statistical analysis.

3. Results

Hyperthermia induced by exposure to elevated temperature (40°C) for 12 hours, produced significant changes in the levels of dopamine, nor adrenaline and serotonin (Table 1), significant increases in the levels of neurotransmitters were recorded in brain homogenate. Features of diffuse hyperemic changes were prominent in brain tissues in examined samples (Fig. 1).

Serum electrolyte imbalance was observed in the hyperthermia group. There was marked hyperkalemia with decreased concentration of sodium and magnesium. Calcium level showed significant increases when compared to the control group (Table 2). Serum level of LH and testosterone were diminished in experimental rats compared with the control group (Table 3).

Semineferous tubules of experimental group showed disorganization and slight damage of germinal cells (Fig. 4).

Table (1) Effect of hyperthermia on the concentrations of Dopamine, Noradrenaline and sertonin (ng/g tissue) in the brain homogenate of rats

Parameters	Control group	Hyperthermic group
Dopamine	993±5.10	1068±5.4*
Noradrenaline	266±4.2	312±4.6*
Serotonin	232±2.9	259±2.4*

Values are expressed as means ± SE (n = 10)
* Significant different ($p < 0.05$)

Table (2) Effect of hyperthermia on the concentrations of electrolytes in rats

Parameters	Control group	Hyperthermic group
Sodium (mEq/L.)	138±7.4	106±5.2*
Potassium (mEq/L.)	4.18±0.30	5.9±0.42*
Magnesium (mg%)	4.56±0.51	3.09±0.22*
Calcium (mg%)	6.90±0.58	8.86±0.48*

Values are expressed as mean ± SE (n = 10)
* Significant different ($p < 0.05$)

Table (3) Effect of hyperthermia on testosterone and LH in rats.

Parameters	Control group	Hyperthermic group
Testosterone ng/ml	2.74±0.7	1.2±0.2*
LH mIU/ml	0.46	0.22*

Values are expressed as mean ± SE (n = 10)
* Significant different ($p < 0.05$)

Fig. (1) : Brain of heat exposed rat showing hyperemic capillaries and blood vessels allover the cerebral tissue (H & E X 40)

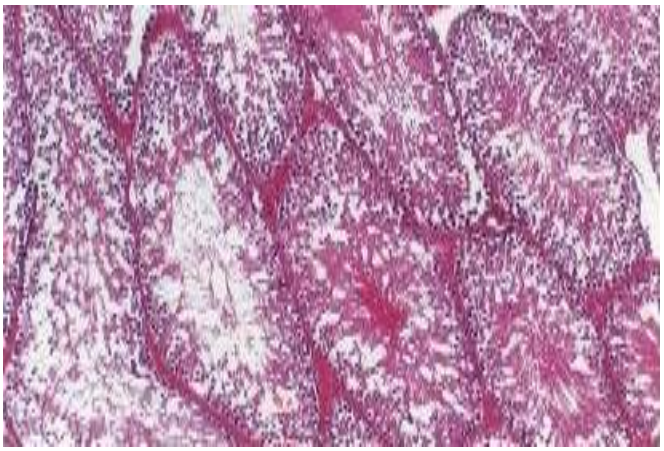

Fig. (2) : Transverse section in testis showing normal structure (H&E X 100)

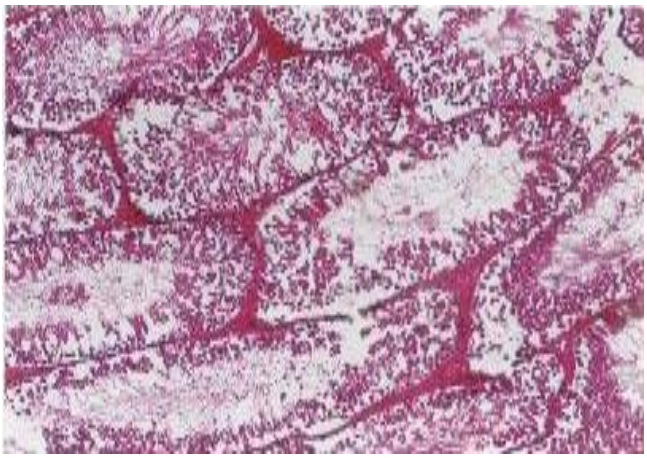

Fig. (3) : Transverse section in testis showing degenerative changes in all series of spermatogenic cells as well as some tubules are empty from spermatozoa. (H&E X 100)

4. Discussion

Core temperature : the temperature of the deep tissues of the body, remains constant within ±1°F (±0.6°C). an individual can be exposed to temperature as low as 55°F or as high as 130°F in dry air and still maintain an almost constant core temperature (Guyton and Hall, 2006). They also added that experiments have been performed in which minute areas in the brain of an animal have been either heated or cooled by use of a thermode. The thermode affects body temperature, control the preoptic and anterior hypothalamic nuclei of the hypothalamus, they contain large numbers of heat-sensitive neurons and cold – sensitive neurons. These neurons function as temperature sensors for controlling body temperature. Xi et al., (2001) stated that whole body hyperthermia is a distinctive pathological condition with significant impact on tissue metabolism and organ function. Frosini et al., (2000) mentioned that, hyperthermia raise all inhibitory and excitatory neurotransmitters.

Table (1) revealed a significantly increased Dopamine, Noradrenaline and serotonin was mainly related to increased body temperature. Increased levels of these neurotransmitters could be due to their important role in temperature regulation. Noradrenaline and adrenaline are chemical transmitters at most sympathetic post ganglionic endings, stored in the synaptic knobs of adrenergic neurons. Dopamine is the immediate precursor of noradrenaline. It is found in the dopaminergic neurons in certain parts of the brain, particularly in the hypothalamus. Serotonin is a synaptic mediator formed from hydroxylation and decarboxylation of tryptophan. Distribution of nor adrenaline in the brain, parallels that of serotonin, it appears to be involved in the regulation of body temperature (Nylo and Nielsen, 2001).

The increased brain content of catecholamines and serotonin was in agreement with the findings of Zhao et al., (2001) and Blatteis et al., (2004). They found that the level of dopamine and serotonin were higher in hypothalamus and frontal cortex in heat stressed animals. However, there are marked species variations in the temperature responses to these amines. Ganong (2000) mentioned that increased catecholamine secretion is an important endocrine response. Drug have antidopaminergic properties and those capable of stimulating serotonin release are responsible for hyperthermia (Nimmo et al., 1993).

Fig. (1) revealed brain of heat exposed rat showing hyperemic capillaries and blood vessels and focal hemorrhage in cerebral tissue. Boulant (2004) reported that the pathological findings in cases that dies of hyperpyrexia are local hemorrhages and parenchymatous degeneration of cells throughout the entire body, but especially in the brain.

Table (2) revealed serum electrolyte variables in the hyperthermic group. There was a marked hyperkalemia with decreased concentration of sodium and magnesium, while calcium level showed a significant increase compared to control group. The marked potassium increase with decreased sodium concentration might be due to potassium that leak out the cells and the entrance of the sodium leading to dysfunction of the central nervous system and failure of the vital centers. In case of increased calcium quantities in extracellular fluid, this might cause stoppage of the heart in systole and act as a mental depressant (Chatterjea and Shinde, 2006) (Korner and Leibel, 2003), while magnesium which is about one sixth as plentiful in cells as potassium, it is required as catalyst for many intracellular enzymes, particularly those related to carbohydrate metabolism, and low magnesium concentration causes increased of the nervous system and cardiac arrhythmias and affects badly the brain (Guyton and Hall, 2006).

Table (3) revealed a decreased LH and testosterone concentrations after hyperthermia as compared with control rats. Histopathological examination (Fig. 2, 3) showed disorganization of semineferous tubules, with slight damage of germinal cells. The histological damage may also attribute to the biochemical alteration. Thoreux – Manlay et al., (1995) stated that a high level of exposure can impair testosterone production that could later have secondary reproductive consequence such as the impairment of spermatogenesis, because testosterone is clearly essential for the maintenance of established spermatogenesis. The reduced LH concentration may lead to leidig cell receptor inadequate and drop of secretory capacity after hyperthermia (Kemprinas et al., 1990). De Kretser (2004) reported that testosterone is secreted by the interstitial cells of Leydig in the testis, but only when they are stimulated by LH from the anterior pituitary gland. Furthermore, the quantity of testosterone secreted increases approximately in direct proportion to the amount of LH available.

Heat stress is one of the most challenging environmental conditions. Thus, substantial attention has been paid to the role of nutritional additives to minimize the effects of heat stress (Bollengier-Lee et al., 1998). Wilczek (2005) added that the physiological condition of an organism under stress can be assessed using different biochemical and molecular markers,

like stress protein expression and antioxidant activities.

Sahin et al. (2003) found that, dietary supplementation of vitamin C and E as a combination increased total protein but decreased corticosterone, glucose and cholesterol concentrations. El-Shaieb et al., (2009) concluded that ascorbic acid supplementation alleviate detrimental effects of heat stress.

It may be concluded that : avoidance of hyperthermia is very important, the body temperature must be maintained in a safe normothermic range. It is recommended to assess the role of nutritional supplementation to alleviate the hazardous effects of heat stress.

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