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Heat stress induced histopathology and pathophysiology of the central nervous system

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Abstract

The number of reports on the effects of heat stress is still increasing on account of the temperature is one of the most encountered stressful factors on the different biological systems. Because the heat stress (HS) considered a model of thermal injury to the central nervous system (CNS), the purpose of this review was to assess the histopathological changes of HS on CNS. Also, this review emphasized that the heat stress may retard partially the degree of the postnatal neurogenesis and growth of CNS. Taken together, owing to one of the most important functions of heat shock protein is to protect the organisms from the deleterious effects of temperature, thus, it can be hypothesized that the formation of heat shock proteins may be related to the deleterious effect of HS. On the other hands, the alterations of neurotransmitters in the central nervous system might be involved in the physiological and biochemical responses that occur during heat stress. The hypothalamic monoaminergic systems play an important role in the thermoregulation through regulate the heat production and heat dissipation. In addition, the disturbance in the biochemical variables due to the high temperature may be the cause of the histopathological changes and the partial retardation in CNS and the reverse is true. Thus, further studies need to be done to emphasize this concept.

Keywords: Heat stress; CNS; Ages; Neurons; Heat shock protein; Recovery; Cholinergic enzymes; Monoamines

1. Introduction

Because of there are several reports have been published on the effects of the temperature exposure (Johnson et al., 1975, 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), this review appeared the deleterious effects of heat stress on the central nervous system (CNS) as a follows.

1.1. Age differences in the effects of temperature

In humans, epidemiological studies suggested that an elevation of maternal body temperature by 2 °C for at least 24 h during fever can cause a range of developmental defects, but there is little information on thresholds for shorter exposures (Edwards et al., 2003). 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 increasing the risk of neural tube defects (NTDs). Moreover, Edwards et al. (2003) reported that hyperthermia during pregnancy can cause embryonic death, abortion, growth retardation and developmental defects. Furthermore, Berman et al. (1990) recorded that increasing ambient temperature was effective in decreasing maternal weight gain and fetal body weight and increasing fetal relative brain weight. Also, 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). Exposure of embryos to long elevated temperature during organogenesis has been known to be embryotoxic (Johnson et al., 1975; Hutchinson and Bowler, 1984; Edwards, 1986; Upfold et al., 1989). In addition, Walsh et al. (1987) demonstrated that after rat embryos exposed to an elevated temperature (43 °C for 7.5 min), the gross reduction of the forebrain region was observed.

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Johnson et al. (1976) depicted that the hyperthermia caused retarding the degree of the postnatal neurogenesis and the brain growth. Yitzhakie et al. (1999) suggested that the tolerance of mouse embryos to a heat shock-induced teratogenic insult may, to some extent, depend on the character of the maternal immune responses. Furthermore, Arora et al. (1979) reported that, the oedema, microencephaly and microphthalmia were recorded at days 4, 6, or 8 when rats exposed to ambient temperatures of 43–44 °C at various stages of pregnancy.

1.2. Histopathological changes

1.2.1. The brain

There are several histopathological changes, oedema, focal hemorrhages and spotty infarction, after heating the hemispheres of dog brain above 42–43 °C for 30 min (Harris et al., 1962). However, Silberman et al. (1982) showed that normal rabbit brain could endure 42.4 °C for 60 min without apparent histopathological or clinical damaged. Also, acute histological effects of ultrasound hyperthermia applied to the cortex of one of the brain hemispheres in cats and dogs were studied by Britt et al. (1983) and Lyons et al. (1984) respectively. Thermal damage was observed immediately after treatment at 43 °C for 50 min to neurons in the gray matter and to myelin tracts in the white matter of the brains. In addition, Sneed et al. (1986) observed that a single heat treatment at 43–44 °C for 30 min produced a large cerebral lesion that consisted of central coagulation necrosis surrounded by a sharply demarcated hypervascular zone.

Moreover, Lyons et al. (1986) recorded a definite destructive degenerative changes after local ultrasound hyperthermia on the normal dog brain. Actually, Lundgren et al. (1994) summarized that, the hyperthermia aggravated the epileptic brain damage of rat. Furthermore, Sharma and Cervos-Navarro (1990) noticed that, in the brain of young rats, as a result of exposure to heat stress at 38 °C for 4 h, the perivascular oedema, vacuolation and collapsed microvessels were observed. Indeed, in the brain of rats heated to 41, 42 and 43 °C for 30 min, a cellular shrinkage and a vacuolation with nuclear pyknosis were noted at 4 h after this exposure (Lee et al., 2000).

Clearly, Sharma et al. (2003) reported that, as a result of exposure of rats to heat stress at 38 °C for 4 h, a disturbance and breakdown in the blood–brain barrier (BBB), and the brain oedema formation were noticed. The heatstroke induced cerebral ischemia insults and brain hypoxia in rat (Chou et al., 2003; Chang et al., 2004), and the hippocampus shows less responsiveness to hyperthermia than the cerebellum (Maroni et al., 2003). Also, Yaqub et al. (1986) depicted that a compatible degree of temperature to brain death is 43.5 °C. Hence, together with the previous studies, the current review suggests that, the exposure to high temperature caused some malformation in the CNS.

1.2.2. The spinal cord

There are only few publications on the effects of heat on the spinal cord. Goffinet et al. (1977) showed that heat treatment of mouse thoracolumbar spinal cord at 42 °C for 60 min led neither to neurological symptoms nor to significant spinal cord injury. Edwards (1971) reported that, the abnormal development of the gray-white architecture around multiple or misplaced central canal of the spinal cord of heating guinea pigs were noted. Furthermore, Godlewski et al. (1986) demonstrated that, in the lumbar region of the spinal cord, the cell nuclei oedema in neurocytes, oligodendrocytes and astrocytes was associated with a decrease in the relative DNA level and changes in the density and concentration of nuclear chromatin as a result of exposure of rat to 43 °C for 4 h. Radmilovich et al. (2003) confirmed that, a warm environment increased cell proliferation in the CNS of turtles. In addition, Noble and Wrathall (1989) found that, the development of both histopathological changes and functional deficits was quantitatively assessed after mild, moderate, and severe spinal cord contusive injuries through appeared areas of hemorrhage and lesion. It is generally, believed that the exposure to heat stress may cause some retardation in the growth of the spinal cord.

On the other hand, the relationship between spinal cord temperature and the incidence and severity of neurological symptoms was studied in detailed by Sminia et al. (1987). Also, Sminia et al. (1989) studied the time course of thermal damage to the rat spinal cord (cervical-5-thoracic-2) and the histology was examined at different intervals after 42.9 ± 0.4 °C for 38 min as in Table 1.

In other words, the thermal damage differs from radiation damage of the spinal cord in several aspects. Firstly, thermal damage appears immediately after treatment. ‘‘Early’’ radiation damage and ‘‘late’’ radiation damage appear after treatment between 4 and 7 months, and from 8 months to the end of life of the rats, respectively (Van der Kogel, 1979). Secondly, the histopathological changes are different. Thermal damage is characterized by neuronal death, demyelination and damage to the vasculature, indicating

Table 1
Time course of histopathological changes observed in the rat spinal cord (cervical-5-thoracic-2) (Sminia et al., 1989)

Time after hyperthermia	Histopathology
Immediately	Central chromatolysis in neurons, nuclear changes
4 h	Axonal swelling, vacuolization, pyknotic neurons
24 h	Vascular damage, myelin pallor, degenerated neurons
3 days	Necrotic areas, reactive astrocytes
7 days	Clearance reaction by macrophage and lymphocytes
14 days	Clearance reaction, scar formation, capillary outgrowth
28 days	Glial scar formation completed, demyelinated and necrotic areas

the involvement of neurons, oligodendrocytes as well as endothelial cells. The sequence of events in the damage after hyperthermia is too quick to disentangle primary and secondary targets. Early radiation damage (after a dose of 20 Gy or more) is characterized by demyelination and the possible target involved is the oligodendrocyte (Van der Kogel, 1986; Hubbard and Hopewell, 1978). Other authors (Blakemore and Palmer, 1982; Myers et al., 1986) have questioned this view. These latter authors conclude that white matter necrosis in the irradiated spinal cord results from vascular disturbance that may lead to focal or regional ischemia. Late radiation damage (after 15–20 Gy) is characterized by telangiectasia and hemorrhages, indicating that vascular endothelial cells are involved (Van der Kogel, 1983, 1986). Direct neuronal damage apparently does not occur after irradiation. Thirdly, after hyperthermia functional recovery is observed in all animals that do not die as a result of the treatment. Although for both types of radiation damage, early and late, some recovery was demonstrated, this recovery cannot compensate in time for the loss of functional cells, and thus the lesions progress (Van der Kogel, 1986).

1.3. Cellular changes

Heat induced cell death by apoptosis which is a feature of teratogenic damage to the developing brain (Edwards et al., 1997). Thermal cellular injury and circulatory changes, associated with acute heat stroke, resulted in widespread tissue injury to the heart, kidney, liver, blood coagulation system, but, most dramatically to the central nervous system (Malamud et al., 1946). The mediation of metabolic changes and tissue damage is not fully understood. 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 (Edwards et al., 1974; Wanner et al., 1975; Upfold et al., 1989).

Sharma and Hoopes (2003) observed that, the morphological changes in the axons, nerve cells, glial cells and vascular endothelium were seen at the cellular and the molecular levels in rats subjected to the heat exposure at 38 °C for 4 h. Also, Sharma et al. (1997) said that, the cell changes were examined in hyperthermic brain injury of young rats as a result of exposure to heat stress at 38 °C for 4 h. Edwards et al. (2003) found that, hyperthermia during the pregnancy can cause abortion, growth retardation and developmental defects. In addition, the neocortical damage was an evident in the hyperthermic ischemic animals and the infraction occurred in the cortex, thalamus, cerebellum and substantia nigra (Busto et al., 1987). Furthermore, there were developmental abnormalities and severe growth retardation in rats after exposing to heat stress (Skreb and Frank, 1963 and Edwards, 1968). Sharma et al. (2003) recorded that, there was cell damage in several brain regions of rats as a result of exposing to 38 °C for 4 h. In addition, Lundgren et al. (1994) revealed that, the hyperthermia showed enhanced damage in the neocortex and neuronal necrosis. Eshel and Safar (2002) noticed in a primate model, the heatstroke led to depression of all the cerebral functions. The thermal insult to the cerebellum leads to degeneration of purkinje cells with the pyknotic nuclei, chromolytic changes and swollen dendrites (Lin et al., 1994). Moreover, a damage in the neurons of the cervical region of the spinal cord of rat after exposing to 42.9 ± 0.4 °C for 38 min was noted (Sminia et al., 1987).

Based on the above findings, the heat stress may be responsible for some reduction in the cellular processes that grow from the neuron cells in different regions of the CNS. Also, these changes can be explained by other different ways: (1) Heat inhibits the activity of cells (Westra and Dewey, 1971); (2) The temporary cessation of normal protein synthesis which made by hyperthermia might be the cause of some developmental errors (German, 1984); (3) The degradation of protein increased in rat brain as a result of hyperthermia (Bongiovanni et al., 1999); and (4) The heat induced cell death by apoptosis (Edwards et al., 1997) or may by protein denaturation (Edwards et al., 1974). From the presaid studies, it is also worth mentioning that, these results emphasize the heat stress may retard partially the degree of the postnatal neurogenesis and the growth in all CNS regions.

1.4. Summary of the regional differences of CNS exposure to temperature (Table 2)

The following table shows clearly that the elevation on the temperatures produce a wide range of the histopathological changes in the CNS. Thus, in general, the higher the temperature or the longer the hyperthermia, the greater the chance for observing a perturbation to the biological effects on the different regions of CNS. Although the data of the literatures, involve different species of experimental animals, different sites of treatment, different techniques etc. (see Table 2), they all seem to justify the conclusion that the maximum tolerated heated dose is in the range of 42.0–42.5 °C for 60 min or 43 °C for 10–20 min.

1.5. Molecular changes (heat shock proteins)

When living organisms exposed to thermal and non-thermal stressors, the synthesis of most proteins is retarded, but a group of highly conserved proteins known as heat shock protein (hsp) are rapidly synthesized (Etches et al., 1995). One of the most important functions of hsp is protecting organisms from the toxic effects of heating (Barbe et al., 1988). Furthermore, hsp may play roles in protein assembling and disassembling (Pelham, 1986), protein folding and unfolding (Randall and Hardy, 1986) and protein translocation (Murukami et al., 1988).

Indeed, heat shock proteins or stress proteins serve as biomarkers to identify the contribution of stress situations underlying the pathogenesis of degenerative diseases of the

Table 2

Authors	Animal	Tissue	Heating technique	Temperature and duration treatment	Follow up period	Neurological observation	Pathological findings
Harris et al. (1962)	Dog	One of the hemispheres	Warm blood	(a) 42–43 °C: 30 min (b) 44–46 °C: 30 min	68 days –	No changes hemiparesis, death within 36 h	No gross changes, oedema, haemorrhages
Goffinet et al. (1977)	Mouse	Thoracolumbar cord	Water-bath	42 °C: 60 min	1 year	No changes	–
Silberman et al. (1982)	Rabbit	Whole brain	Radiofrequency 13.56	(a) 42–43 °C: 30 min (b) 45 °C: few min	5 months –	No changes, death	No changes
Britt et al. (1983)	Cat	Part of occipital cortex	Ultrasound 2.06 MHz	42–48 °C: 50 min	–	–	Damage to gray and white matter after 50 min at 43 °C
Lyons et al. (1984)	Dog	Part of occipital cortex	Interstitial microwave heating 915 MHz	42–43.5 °C: 50–70 min	–	–	Damage to gray and white matter after 50 min at 43 °C
Sneed et al. (1986)	Dog	Part of one of the hemispheres	Interstitial microwave heating 915, 2450 MHz	43–44 °C: 30 min	16 week	Hemiparesis in all animals	Necrosis, inflammation
Lyons et al. (1986)	Cat	Part of occipital cortex	Ultrasound 2.06 MHz	41–48 °C: 50 min	56 days	Minor symptoms in few animals	Necrosis, inflammation
Sminia et al. (1987)	Rat	Cervical cord	Microwave heating 434 MHz	41.2–43.2 °C: 30–120 min	60 days	Uncoordinated use of forelegs to paralysis, death, above 60 min 42.3 °C	–
Shiota (1988)	Utero-mice	Anterior neural tube	Hot water	42 °C: 12.5–15 min, 43 °C: 7.5–10 min	12 h	–	Pyknotic cells
Sminia et al. (1989)	Rat	Cervical spinal cord	Microwave heating 434 MHZ	42.9 ± 0.4 °C: 38 min	28 days	Uncoordinated use of forelegs to paralysis and death in 90% (28/31)of rats	Vacuolation, neuronal degeneration and myelin pallor
Sharma and Cervos-Navarro (1990)	Rat	Brain	Biological oxygen demand incubator	38 °C for 4 h	–	–	Perivascular oedema
Sharma et al. (1997)	Young rat	Brain	Biological oxygen demand incubator	38 °C: 4 h	–	–	Oedema, disturbance in blood brain barrier and cerebral blood flow
Lee et al. (2000)	Rat	Brain	Interstitial heating (sham-heating)	39, 40, 41, 42, 43 °C: 30 min	168 h	–	Vacuolation, cellular shrinkage, petechiae and necrosis
Sharma et al. (2003)	Rat	Several brain regions	Biological oxygen demand incubator	38 °C: 4 h	–	–	Cellular damage, oedema and breakdown blood brain barrier

CNS (Goldbaum and Richter-Landsberg, 2001). As with other tissues, exposing the mammalian CNS to non-lethal heat stress (i.e., thermal preconditioning) increases levels of heat shock proteins (hsps) such as hsp70 and enhances the viability of neurons under subsequent stress (Kelty et al., 2002). Stressful stimuli activate the heat shock proteins which play roles in cellular repair and protective mechanisms (Bechtold and Brown, 2000). 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 rats with hyperthermic treatment (Yang et al., 1994). Hyperthermia causes neuronal expression of hsp70, particularly under strong heat stress, and may be sustained till death (Tan et al., 1997). Moreover, Satoh and Kim (1994) observed that the stress induces a predominant expression of hsp72 in astrocytes and microglia, and more limited in oligodendrocytes and neurons of fetal human neural cells cultures. The differential patterns of hsp72 induction in human neural cells were regulated by different among various cell types in the central nervous system (Satoh and Kim, 1994). Heat acclimation also elevates the level of hsp in different organs (Prosser, 1986; Horowitz et al., 1997; Maloyan et al., 1999; Malyshev et al., 2000). Neuronal hsp72 increases survival in rats exposed to heat stroke by attenuating arterial hypotension (Yang et al., 1998; Yang and Lin, 1999), and may play a role in processes that enhance neuron survival during transient focal cerebral ischemia (Yenari et al., 1998; Yang and Lin, 1999). The hsp70 may attenuate the overproduction of nitric oxide (NO) in the brain of rats adapted to heat, preventing deleterious alterations in cerebral blood pressure (Malyshev et al., 2000). Other researchers have shown that the cellular defense response to either oxidative or hyperthermia-induced or increased the intracellular antioxidant enzyme activities, particularly superoxide dismutase, in addition to induce hsp synthesis (Freeman and Crapo, 1982). In fact, the role that hsp70 plays in influencing thermal tolerance of a whole animal is not clearly understood (Parsell and Lindquist, 1993).

From the previous studies, this review hypothesized that the overexpression of hsp plays an important role in enhancing the survival of neuronal cells. Further studies need to be done to find the duration period of exposure to heat stress, which induce the synthesis of hsps and reduce the inhibition of synthesis of normal proteins for protecting factors.

1.6. Recovery and temperature exposure

Appearance of thermal injury and time course of repair did not seem to be very different from that observed with other types of acute injury (e.g. ischemic infarction, mechanical damage). Normally, one of the most common responses to injury is a reactive inflammatory process. The inflammatory response leads to a complex series of reactions resulting in healing and repair of damaged tissue. The inflammatory process may lead to a proliferation of astrocytes and the formation of large amounts of glial scar (La Via and Hill, 1975).

In the repair of tissue, either the area becomes replaced with a scar, or the tissue is restored to its original state by regenerative capacities of that tissue (Schilling, 1968). Repair in the central nervous system is seen primarily in the form of scar tissue formation because neuronal elements have little or no capacity to regenerate (Schilling, 1968). Furthermore, Johnson et al. (1976) reported that, some degree of the postnatal neurogenesis and the brain growth had occurred this was not sufficient to compensate for the retarding influence of hyperthermia. Frank (1982) found that, the spinal axons may have some capacity to regenerate, regrowth by scar formation at the lesion site. In disagreement with this study, Upfold et al. (1989) who recorded a recovery process after exposing a pregnant guinea pig to 44 °C for 1 h and a complete inhibition of the mitotic activity for 4–8 h after heat exposure and dramatic effect on cells within the ventricular zones were observed. Then, mitotic index returned to the control values within 1 h after mitotic resurgence occurred. Results from another histological study (Lyons et al., 1986) indicated that the appearance and time course of repair of thermal injury are analogous to those observed after acute brain necrosis as a result of cerebral infarction, except that no significant hemorrhages were observed.

1.7. Pathophysiological changes (neurotransmitter system)

1.7.1. The cholinergic enzymes change

An important aspect in this study on central nervous system (CNS) of rats is the measurement of the activity of enzymes associated with CNS functions as cholinesterase enzyme. Moreover, the control of body temperature uses cholinergic pathways in the integration and central processing of thermal information, as well as in the control of thermoeffector responses (Gordon, 1996).

The developmental studies of the cholinergic innervations in the nervous system have been concerned with changes in the levels of acetylcholine (Ach), Choline acetyltransferase and acetylcholinesterase (Bull et al., 1970; Ladinsky et al., 1972; Burt, 1975; McGeer et al., 1976). The specific activity of acetylcholinesterase and choline acetyltransferase associated with the Ach system and increased during the development of the vertebrate central nervous system (Burt, 1968). Sharpe et al. (1979) recorded that central cholinergic system appear to function in heat gain and possibly in heat loss mechanisms in rabbit.

Changes in acetylcholine (Ach) content could be produced by the change in the temperature (Lagerspetz, 1974; Kornyushenko, 1976), electrical stimulation (Richter and Crossland, 1949), electric shock (Artemenko, 1967),

traumatic shock (Kovach et al., 1957). In addition, in rat brain, Menon and Dandiya (1969) showed that, the activity of cholinesterase (chE) was significantly increased when the animals were kept at a higher ambient temperature (40 °C). Aly et al. (1986) found that, the heat stress provoked a decrease in the acetylcholinestrase activity of the cerebrum region of the gerbil (*Gerbillus Pyramidum*).

Therefore, the heat stress may cause the disturbance on the synthesis and release of the cholinergic enzymes and on their functions. These changes caused the impairment in the development of neurons, oligodendrocytes and the tissues of the CNS (Rao et al., 1990).

1.7.2. The monoamines concentration changes

The monoamines are one of the earliest developing neurotransmitter systems in the mammalian brain (Lauder et al., 1982). Yuan et al. (1989) found that in mice, the exposure to 45 °C for 15 min reduced the brain content of norepinepherine (NE) and serotonin (5-HT). Moreover, the NE and dopamine contents in the basal hypothalamus were found by Merritt et al. (1977) to be reduced as a concomitant of microwave-induced brain hyperthermia. Bliss et al. (1968) and Abdel Hamid et al. (1994) reported that, a variety of acute stresses (food, shock, cold, anoxia, aggregation and radiation) caused a decrease in level of norepinepherine in brains of mice, rats, guinea pigs, dogs, rabbits and monkeys. However, Myers and Chinn (1973) and Yaksh and Myers (1972) noticed that, when the rats, cats and monkeys exposed to heat, the secretion and turnover of catecholamine are increased. Kao et al. (1994) reported an increase in hypothalamic dopamine release and a decrease in local cerebral blood flow during heat stroke.

On the other hand, the alterations of hypothalamic 5-HT and NE contents during thermal acclimation would participate in regulating the heat production and dissipation. In fish, heating and cooling the anterior brainstem changes the latency of escape from warm water in arctic and Antarctic fish (Green and Lomax, 1976). The graded increases in the temperature of anterior brainstem induce the fish to select the cooler water temperature (Crawshaw and Hammel, 1974). This thermoregulatory behavior is severely disrupted by the lesion of the preoptic area of goldfish and sunfish (Nelson and Prosser, 1979). These reports suggest that the hypothalamus is an important neural integration center in the behavioral thermoregulation of teleosts. Moreover, cholinergic stimulation lowers escape temperatures, whereas an increased level of catecholamine raises them (Green and Lomax, 1976). 5-HT and NE increases the selected temperature in fish (Gryer and Ogilvie, 1978; Wollmuth et al., 1987, 1988). These evidences indicate that the neurotransmitters are involved in the temperature selection of fish. The temperature selection is important in the maintenance of temperature for the optimal metabolic activity in fish (Norris, 1963). This behavioral thermoregulation of fish is activated in seconds and minutes after thermal stress (Crawshaw, 1980). However, during thermal acclimation, the heat production and dissipation should be varied with the brain temperature of fish. The alterations of heat production and dissipation should be mediated by the biochemical and physiological processes to maintain the optimal metabolic rate rather than by the behavior for selecting temperature (Tsai and Wang, 1997). The hypothalamic monoaminergic systems play an important mediator of environmental influences on endocrine and physiological functions (De Vlaming and Vodicnik, 1975; Peter and Crim, 1979; Olcese and De Vlaming, 1980; Andresson et al., 1992). It is suggested that the hypothalamic 5-HT and NE should participate in the physiological and biochemical responses that occur during thermal acclimation in fish. The biochemical and physiological responses are mediated during the elevated temperature acclimation by regulating the cardiovascular, respiratory, metabolic, ionic and osmotic functions (Crawshaw, 1980). In heat acclimated rat, the levels of stored NE in the preoptic area are increased (Christman and Gisolfi, 1985). Moreover, in endothermic vertebrates, the central serotonergic and noradrenergic systems are involved in the autonomous functions and the hypothalamo-pituitary-adrenal axis to regulate their body temperature during thermal acclimation (Arancibia et al., 1996). The hypothalamic serotonergic and noradrenergic neurons play a primary role in the control of energy metabolism and caloric intake to regulate the heat production and dissipation (Myer et al., 1996). In addition, in ectothermic teleosts, the physiological and biochemical functions of central serotonergic and noradrenergic systems during thermal acclimation needs to be investigated further.

Furthermore, the level of neurotransmitter in the brain is controlled by its synthesis, release, reuptake and metabolism. The monoamine oxidase (MAO) is a rate-limiting enzyme for the metabolism of biogenic amines (Berry et al., 1994). The MAO activity in the goldfish brain displays several changes in the functional activity during response to thermal acclimation (Hall et al., 1982). The changes of MAO activity after the elevated temperature acclimation should be involved in the alterations of the 5-HT and NE contents (Tsai and Wang, 1997).

Overall, the heat stress caused a disturbance in the secretion and turnover of the monoamine contents in different CNS regions. This deleterious effect in the monoamines may reflect the CNS damage and the histopathological changes in CNS, which in turn, affects on the vital processes of neurons to growth. Sharma et al. (1992) found after exposing of young rats to 4 h heat stress at 38 °C in a biological oxygen demand (BOD) incubator, a profound increase in the levels of serotonin (5-HT) in the brain and a pronounced reduction in the cerebral blood flow (CBF) were observed. Sharma et al. (2003) recorded that a disturbance and breakdown in the blood–brain barrier and the brain oedema formation were noticed in rats after heat stress. On the other hand, the daily exposure of rat newborns to 41 °C for 2 h, from birth to 3 weeks, induced deteriorated

effects on monoamines content and chE activity in different CNS regions (Osama et al., 2005). Also, the same latter authors reported that the withdrawal period for 7 days, from 3 to 4 weeks after birth and exposure, failed to return these altered variables to normal levels. Thus, the thermoregulatory responses to heat stress are key biomarkers that may provide insight into heat stroke pathophysiology (Leon et al., 2004).

Finally, it is also worth mentioning that, together with the previous studies, the current review suggests that, the exposure to high temperature caused some malformation, and from these observations, I can conclude that, the heat stress may delay partially the development of the architecture of the CNS. Thus, there is good reason to suppose that the pathological changes may due to the disturbance in the biochemical variables in CNS regions and the reverse is true.

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