

## Does the Heat Stress Affect the Neurons Development in Some Central Nervous System Regions of Albino Rat Newborns?

<sup>1</sup>O.M. Ahmed, <sup>1</sup>R.G. Ahmed, <sup>2</sup>M.M.S. Nada and <sup>3</sup>M. Bahgat

<sup>1</sup>Department of Zoology, Faculty of Science, Beni Suef University, Egypt

<sup>2</sup>Department of Cell and Histology, Veterinary Medicine,

Cairo University, Beni-Suef Branch, Egypt

<sup>3</sup>Department of Zoology, Faculty of Science, Mansoura University, Egypt

**Abstract:** Because the heat stress is one of the most stressful factors on the biological systems, it was important to study its effect on the development of neurons in different Central Nervous System (CNS) regions of albino rat newborns. Development of neurons in cerebral cortex, cerebellar cortex and cervical and lumbar regions of the spinal cord was followed by using Golgi-copisch stain between days 7 and 21 after birth. The present study does not only illustrate the aspects of development processes of normal neurons in different regions of CNS, but also records the effects of heat stress ( $40\pm1^{\circ}\text{C}$ ) on them. The present study revealed that the development of the CNS is extremely sensitive to heat stress which led, in turn, to some harmful effects on the neurons development and caused delay of the dendritic arborization in all investigated CNS regions of the rat newborns. Taken together, further studies are required to determine if the beneficial effects of heat exposure result in changes of stress complications only or not. Thus, experiments will be required to solve these problems and to comprehend the actual role of heatstroke in neurodegeneration of CNS.

**Key words:** Heat stress-central nervous system-neurons

## INTRODUCTION

In view to the recent studies, the biological effects of 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. The external stimuli of a mechanical, thermal, or chemical nature are signalled by specialized primary afferents, whose cell bodies are in dorsal root (DRG) or trigeminal ganglia (Meyer *et al.*, 2005; Munns *et al.*, 2007). Also, the formation of the vertebrate nervous system involves a complex process of cell division, cellular rearrangement and differentiation, that has to be tightly coordinated in space and time (Ille *et al.*, 2007). Several reports have been published on the harmful effects of temperature and hyperthermia exposure (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; Sharma and Hoopes, 2003; Chang *et al.*, 2004; Ahmed, 2005; Ahmed *et al.*, 2005; 2006a, b; Yan *et al.*, 2006).

The cerebral cortex as in general mammals is divided into six layers and its pyramidal cells exhibit morphology unique to that particular region. These layers are molecular, external granular, external pyramidal, internal granular, internal pyramidal and polymorphic (Kelly *et al.*, 1984; Ross and Reith, 1985; Gartner and Hiatt, 1997). Some reports indicated that the local heating of the cerebral cortex of the cat (Tesch and Gellhorn, 1949) and rats (Dalia, 1998, 2002; Ahmed, 2005) and of the lung tissue (Reed, 1965) and liver (Reed *et al.*, 1964) of the dog to  $45^{\circ}\text{C}$  for between 30 and 60 min may not cause

**Corresponding Author:** M.M.S. Nada, Department of Cell and Histology, Veterinary Medicine, Cairo University, Beni-Suef Branch, Egypt

permanent damage to these animals. In a primate model, the heatstroke led to deterioration with depression of all cerebral functions, but the cause of death was the systemic homodynamic deterioration (Eshel and Safar, 2002).

The cerebellar cortex has received a great deal of attention from neuroscientists in order to understand its basic organization, neural circuitry and development (Lin *et al.*, 1994; Millen *et al.*, 1994; Wan *et al.*, 1994; Wilson, 1995; Mohammed *et al.*, 1997; Dalia, 1998, 2002; Ahmed *et al.*, 2005). The cerebellar cortex of all vertebrates is divided histologically into 3 regions: A deep granular layer (stratum granulosum) which has plenty of cells, a middle Purkinje (ganglionic) cell layer and a superficial molecular layer (stratum molecular) which has scattered cells (Burkitt *et al.*, 1993). The heat stress may be responsible for some growth reduction of neuron cells in different layers of cerebellar cortex (Altman, 1973; Herndon and Oster-Granite, 1975; Berry and Bradley, 1976; Johnson *et al.*, 1976; Dalia, 1998; Sharma *et al.*, 2003a, b; Ahmed, 2005).

The rostrocaudal gradient in the development of the spinal cord was recorded in some mammals including cats (Sechzer *et al.*, 1984), rats (Donatelle, 1977) and mice (Fox, 1965). Leong *et al.* (1984) revealed that the spinal cord of the rat receives a large number of descending projections from various brain stem nuclei and deep cerebellar and diencephalic nuclei. The morphologic maturation of spinal cord motoneurons can be enhanced by these descending fibers which develop in a rostrocaudal manner (Tanaka *et al.*, 1997). Their neurotransmitters, like serotonin and noradrenaline, are supposed to play a crucial role in the differentiation and proliferation of the target cells (Rajafetra *et al.*, 1989).

The relationship between the spinal cord hyperthermia, the incidence and severity of neurological symptoms was studied in detail. Sminia *et al.* (1987) investigated the histopathological changes of cervical region of spinal cord of rat after exposure to  $42.9 \pm 0.4^\circ\text{C}$  for 38 min and he found damage to myelin tracts and damage to the neurons and vasculature in both white and gray matter. Goffinet *et al.* (1977) showed that heat treatment of mouse thoracolumbar spinal cord at  $42^\circ\text{C}$  for 60 min led neither to neurological symptoms nor to significant spinal cord injury. In addition, the heat stress may retard partially the degree of the postnatal neurogenesis and the growth in the spinal cord (Ahmed *et al.*, 2005). In other word, Radmilovich *et al.* (2003) confirmed that, a warm environment increased cell proliferation in the CNS of turtles.

Here, we investigated the degree of neurogenesis and growth of the neurons of some CNS regions (number and size of the cells, the presence of spicules or spines which are one of the maturation features and the dendrites development): cerebral cortex, cerebellar cortex and also the cervical and lumbar regions of the spinal cord in the normal and exposed rat newborns at high temperature ( $40 \pm 1^\circ\text{C}$ ) for 7 and 21 days after birth. Furthermore, we sought to elucidate, (1) Whether the development of the CNS are sensitive to heat stress?, (2) Whether the development of the spinal cord of rat newborns will follow rostrocaudal gradient? and (3) whether the neurons-dysfunctions; as reduction in the cellular processes are associated with the heat stress or not?. Understanding these questions should help to clarify the beneficial effects of heat exposure on the neurons development.

## MATERIALS AND METHODS

### Experimental Animals

Fifty white albino rats (*Rattus rattus*) male and female ( $150 \pm 200$  g) were used in this study. The protocol was approved by the Committee of Ethics of Animal Experiments of the National Research Institute of Ophthalmology, Giza (Egypt) and accordance the general guidelines of animal care. All efforts were made to minimize the number of animals used and their suffering and this study was conducted at 2005. The adult rats were kept under observation in the department animal house for 2 weeks to exclude any intercurrent infection and to acclimatize the new conditions. They were given enough rat food and water *ad libitum* and maintained on a 12 h light and 12 h dark cycle (lights on at 06:00h). Males and females were allowed to meet for 2 consecutive days, then the pregnant females were transferred into separate cages.

### **Experimental Schedule**

Within 24 h after delivery, the newborns were assigned randomly selected and divided into the following groups:

- The newborns of the 1st group were maintained at room temperature ( $25^{\circ}\text{C}$ ) with their mothers.
- The individuals of the 2nd group were subjected to heat stress by housing the newborns in a separate woody perforated cage and placed in an incubator set at  $40\pm1^{\circ}\text{C}$  for 2 h daily for 7 days or 21 days; then the newborns were returned to the nursing mothers. Newborns were observed after 4 to 6 h, when the most severe behavioral seizures had usually ceased.

The normal and treated newborns were deeply anaesthetized with diethyl ether ( $100 \text{ mg kg}^{-1}$ , i.p.) and the decapitation was done at days 7 and 21. Then the brains removed and separated from the skull base after cutting all the cranial nerves quickly to verify the staining procedure by the Golgi-copsch stain (Tömböl, 1966) as a following:

The cerebral hemisphere, cerebellum and the two regions of the spinal cord were cut into slices. The slices were placed in 4:1 mixture of 5% potassium dichromate and concentrated formaldehyde (40%) for 4 days. The slices were transferred to 3.6% potassium dichromate for 4 days. They were washed in 0.75% silver nitrate and then placed in the same solution for 4 days. The last two steps were repeated once. The slices were dehydrated, then placed in xylene for 20 min. Embedding process was made in paraffin wax. After that, serial sections were made at  $25 \mu\text{m}$ . The de-waxed process was carried out by using xylene. The sections were mounted in canada balsam.

## **RESULTS**

### **The Neurons of Cerebral Cortex**

The layers of the cerebral cortex, in both normal and treated rats, are characterized by the presence of the pyramidal cells which are characterized by a pyramid-shaped perikaryon with an apical dendrite directed toward the surface of the brain and an axon leaving the base of the perikaryon to course into the white matter (Fig. 1 and 2).

In both normal and treated rats, the sections show four types of nerve cells in layers III, IV, V and VI of cerebral cortex as follows.

- The external pyramidal neurons layer containing large pyramidal cells which became increasingly larger from the external to the internal border of this layer.
- The internal granular layer containing larger pyramidal cells.
- The internal pyramidal layer containing the largest pyramidal cells.
- The polymorphic cell layer containing neurons with different shapes, while the pyramidal cells are absent.

The layer V pyramidal neurons had longer apical dendrites than those of layers III- IV neurons in normal rats due to the difference in their location (Fig. 1 and 2). The spicules appeared on the apical dendrites as projections on its shaft. Also, the distribution of the spine density over the different segments of apical dendrites show different patterns in layers III, IV and layer V (Fig. 1 and 2). For these reasons, the following description was based on findings from day 7 to day 21 in the cerebral cortex.

At day 7, the neurons in the different layers of the cerebral cortex are clearly visualized in both normal and treated rats (Fig. 1). The normal pyramidal cells of layer III had short apical dendrites when compared to the treated ones (Fig. 1A<sub>1</sub> and A<sub>2</sub>). Some lateral dendrites which originate from the lateral

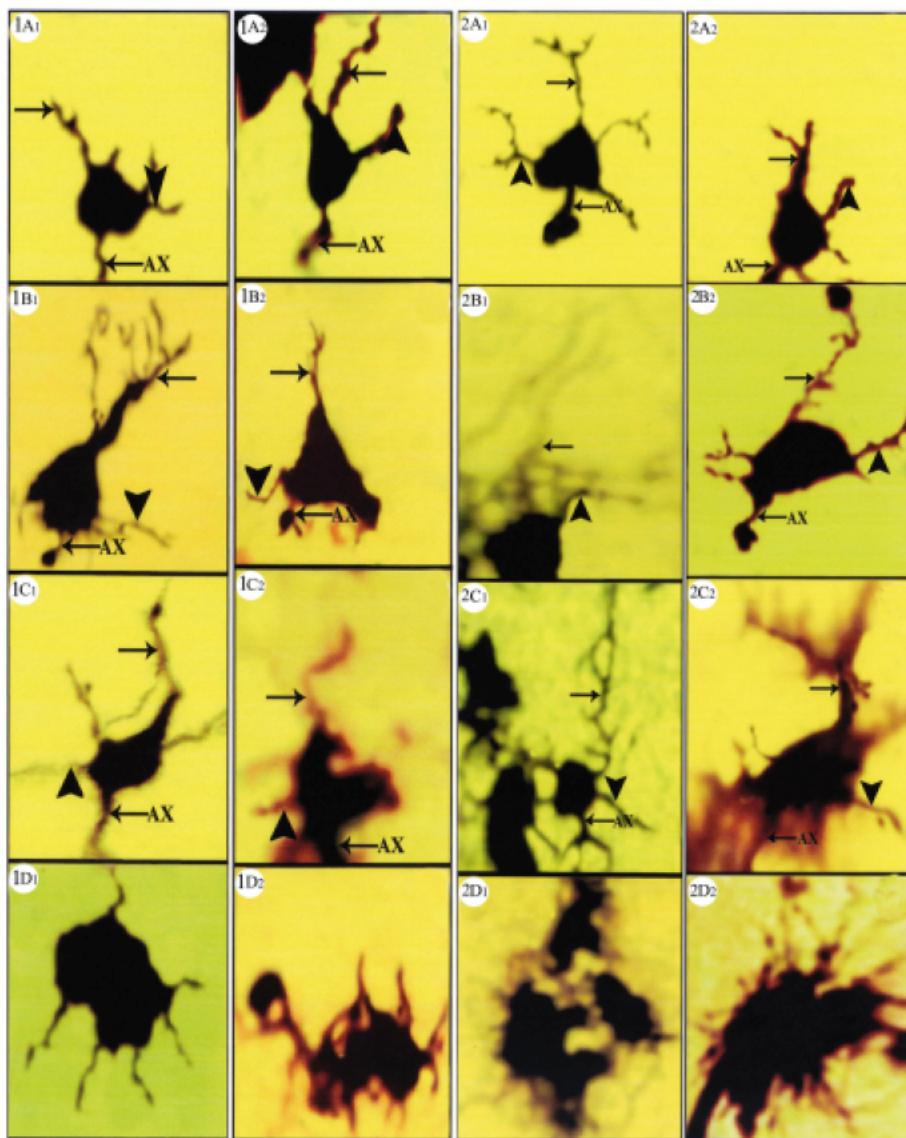


Fig. 1

Fig. 2

Fig. 1 and 2: Sagittal sections in the cerebral hemisphere at day 7 (Fig. 1) and day 21 (Fig. 2) in normal and treated rat newborns showing pyramidal cells in layer III (A<sub>1</sub>: Normal; A<sub>2</sub>: Treated), pyramidal cells in layer IV (B<sub>1</sub>: Normal; B<sub>2</sub>: Treated), pyramidal cells in layer V (C<sub>1</sub>: Normal; C<sub>2</sub>: Treated) and polymorphous cells in layer VI (D<sub>1</sub>: Normal; D<sub>2</sub>: Treated). The arrows, arrow heads and AX refer respectively to apical dendrites, lateral dendrites and axon

side of the pyramidal perikaryon of the layer III were noticed with few nodules in both normal and treated rats (Fig. 1A<sub>1</sub> and A<sub>2</sub>). Moreover, the same latter figures clearly show that, the axon of these cells in layer III was thick; originates from the base of the perikaryon and moves far from the pial surface in both normal and treated rats. In layers IV and V, the typical pyramidal cells appeared with their multipolar shape (Fig. 1B<sub>1</sub> and C<sub>1</sub>). These cells of layers IV and V became more complex in their

dendritic fields when compared to the cells of the third layer in normal rats (Fig. 3A<sub>1</sub>, B<sub>1</sub> and C<sub>1</sub>). The apical dendrites of the pyramidal cells in both IV and V layers were thick, long and having some nodules and spicules in normal rats if compared to the treated ones (Fig. 1B<sub>2</sub> and C<sub>2</sub>). Also, the axon and lateral dendrites of normal pyramidal cells in layers IV and V were long if compared with the treated rats (Fig. 1B<sub>1</sub>, B<sub>2</sub>, C<sub>1</sub> and C<sub>2</sub>). On the other hand, in the treated rats, the layer VI was observed owing to the presence of few polymorphic cells with short collaterals if compared to normal ones (Fig. 1D<sub>1</sub> and D<sub>2</sub>).

At day 21, the pyramidal cells in different layers attained long apical and lateral dendrites in normal rat newborns. The collaterals of dendrites arborization increased in its density and complexity much more than the collaterals of the comparable layers at day 7 (Fig. 1 and 2). The pyramidal cells of the layer III appeared with short and thick apical and lateral dendrites with few spicules in the treated rats when compared to the normal ones (Fig. 2A<sub>1</sub> and A<sub>2</sub>). In addition, the axon of these cells in layer III was long and thick in normal rats if compared to the treated ones (Fig. 2A<sub>1</sub> and A<sub>2</sub>). Moreover, the apical and lateral dendrites of the pyramidal cells in layer IV in normal rats were thin and long (Fig. 2A<sub>1</sub> and A<sub>2</sub>) when compared to the treated ones (Fig. 2B<sub>1</sub> and B<sub>2</sub>). The pyramidal cells of the layer V, in normal rats, reach their typical form; they had an ideal multipolar form with densely arborized apical and lateral dendrites whose collaterals were long and rich in the spicules (Fig. 2C<sub>1</sub>). In the treated newborns, these cells of the layer V had thick axon and short apical and lateral dendrites if compared to the normal ones (Fig. 2C<sub>1</sub> and C<sub>2</sub>). The dendrites of layer V had number of spicules in both normal and treated rats (Fig. 2C<sub>1</sub> and C<sub>2</sub>). Furthermore, the polymorphic cells of the layer VI have short dendrites with few spicules in the normal rats when compared to the treated ones (Fig. 2D<sub>1</sub> and D<sub>2</sub>).

### **The Neurons of the Cerebellar Cortex**

In both normal and treated newborns, five types of neuron cells in the layers of cerebellar cortex were recorded (Fig. 3-4).

#### **The Purkinje Cell Layer**

The Purkinje cells in both normal and treated rats appear possessing one main dendrite which arise from the upper end of the cell body and extending through the molecular layer at day 7. These main dendrites repeatedly branch to form a large dendritic arborization usually with innumerable tiny spicules at day 21 in normal rats and this arborization was confined to a plane perpendicular to the pia matter in normal rats. At day 7, these cells in normal rats were large in size and had long dendrites when compared to the treated ones. Also, at day 7, the dendrites of Purkinje cells had spicules in both normal and treated rats. At day 21, these cells of normal newborns increased in number and in their dendrites. Also, these primary dendrites branch repeatedly through the molecular layer into secondary and tertiary dendrites giving a rich dendritic tree at age 21 days. The density of this dendritic network in treated newborns was lesser and with few spicules than that seen in the normal ones with the age progress (Fig. 3-4 A<sub>1</sub> and A<sub>2</sub>).

#### **The Molecular Layer**

This layer has two types of neurons; the stellate and basket cells (Fig. 3-4 B<sub>1</sub>, B<sub>2</sub>, C<sub>1</sub> and C<sub>2</sub>).

#### **The Stellate Cells**

The stellate cells occupy the upper half of the molecular layer in both normal and treated rats. One of the characteristic features of the dendrites is the presence of spicules and nodules on its surface. At day 7, these cells had thick dendrites in normal and treated rats with the presence of spicules and nodules. These dendrites at day 7 in normal rats were originated from all parts of the cell body and

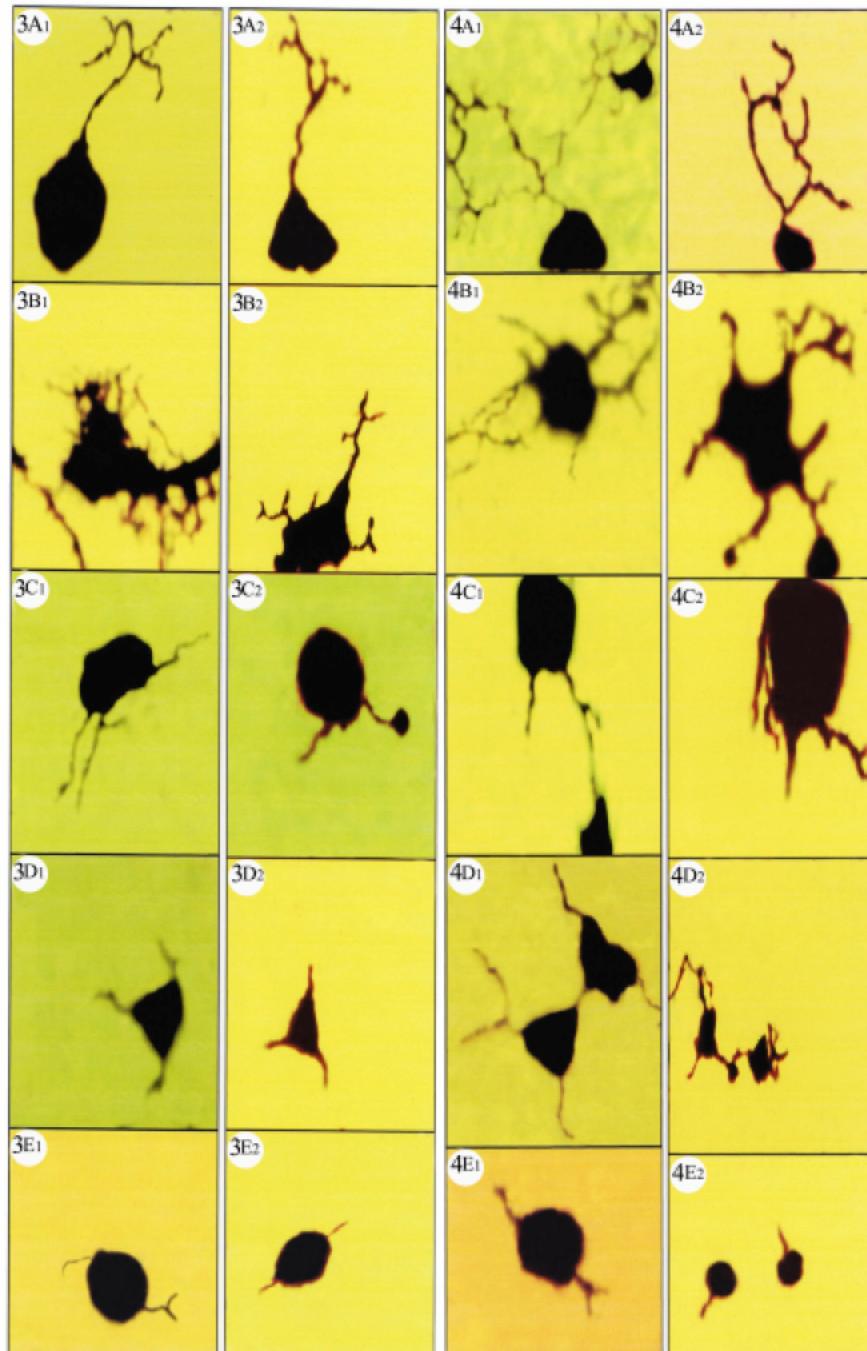


Fig. 3

Fig. 4

**Fig. 3 and 4:** Sagittal sections in the cerebellar cortex at day 7 (Fig. 3) and day 21 (Fig. 4) in normal and treated rat newborns showing Purkinje cells (A<sub>1</sub>: Normal; A<sub>2</sub>: Treated), stellate cells (B<sub>1</sub>: Normal; B<sub>2</sub>: Treated), basket cells (C<sub>1</sub>: Normal; C<sub>2</sub>: Treated), Golgi cells (D<sub>1</sub>: Normal; D<sub>2</sub>: Treated) and granule cells (E<sub>1</sub>: Normal; E<sub>2</sub>: Treated)

form tree if compared with those dendrites in the treated ones. These cells in normal rats at day 21 were found to have longer dendrites with some spicules when compared to the treated ones. The branching of these dendrites form interlacing network became more evident in normal newborns when compared to the treated ones. The stellate cells of the treated rats were increased in size at day 21 if compared to the normal ones (Fig. 3-4 B<sub>1</sub> and B<sub>2</sub>).

#### **The Basket Cells**

The basket cells in both normal and treated rats occupy the deep region in the molecular layer at different examined ages. They were rounded or oval, bipolar perikaryon and their branches moving parallel to the pial surface in both normal and treated newborns at day 7. These cells at day 21 appeared having shorter dendrites in treated rats if compared to the normal ones. Furthermore, these cells in treated newborns were large in size in all examined ages when compared to the normal ones (Fig. 3-4 C<sub>1</sub> and C<sub>2</sub>).

#### **The Internal Granular Layer**

There are two types of neurons: Golgi cells and the Granule cells (Fig. 3 - 4 D<sub>1</sub>, D<sub>2</sub>, E<sub>1</sub> and E<sub>2</sub>).

#### **The Golgi Cells**

The Golgi cells occupy the upper region of the internal granular layer in both normal and treated rats. These cells in both normal and treated newborns were triangular in shape at days 7 and 21. The dendrites of these cells were branching and extending in all directions. At day 7, these cells appeared to have short and thick branches of dendrites that were produced from the different parts of the cell body in normal and treated. Also, these dendrites usually move at different angles with the surface of the pia matter. Pertaining to the cell size at day 21, these cells were large and their dendritic branches became longer in normal rats when compared to the treated ones (Fig. 3D<sub>1</sub> and D<sub>2</sub> and 4D<sub>1</sub> and D<sub>2</sub>).

#### **The Granule Cells**

The granule cells in both normal and treated rats occupy the deep region of the internal granular layer. These cells appeared rounded to ovoid in shape and were characterized by the presence of 1 or 2 dendrites at days 7 and 21 in both normal and treated rats. These main dendrites branch repeatedly into secondary dendrites at day 7 and day 21 in normal newborns. In addition, these cells had long dendrites in normal rats if compared to the treated ones in all investigated ages. Concerning the spicules, they were missing in both normal and treated newborns (Fig. 3E<sub>1</sub> and E<sub>2</sub> and E<sub>1</sub> and E<sub>2</sub>).

#### **The Neuron Cells of the Cervical Region of Spinal Cord**

In both normal and treated newborns, two types of nerve cells, motoneurons and astrocytes, in cervical region of spinal cord were recorded. Pertaining to the normal and treated rats, at day 7, a few number of motoneurons appeared solitary in their arrangement (Fig. 5A<sub>1</sub> and A<sub>2</sub>). Also, the motoneurons in normal rats were large in size and had thick dendrites if compared to the treated ones (Fig. 5A<sub>1</sub> and A<sub>2</sub>). At the same time, the astrocytes were stellate in shape and arranged in clusters with thick branches at day 7 in normal newborns if compared to the treated ones (Fig. 5B<sub>1</sub> and B<sub>2</sub>). At day 21, the normal motoneuron and astrocyte cells increased in their number and in the density of their dendrites (Fig. 6). The motoneuron cells of normal rats had longer and thicker dendrites at day 21 if compared to the treated ones (Fig. 6A<sub>1</sub> and A<sub>2</sub>). Also, the astrocyte cells in normal rats had thin and long dendrites with presence of spicules if compared to the treated ones (Fig. 6B<sub>1</sub> and B<sub>2</sub>).

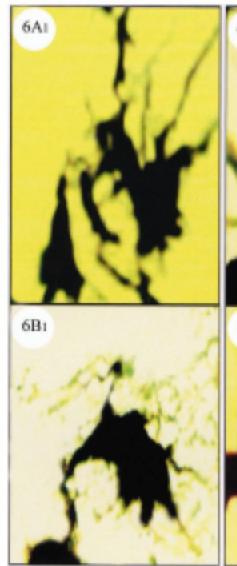
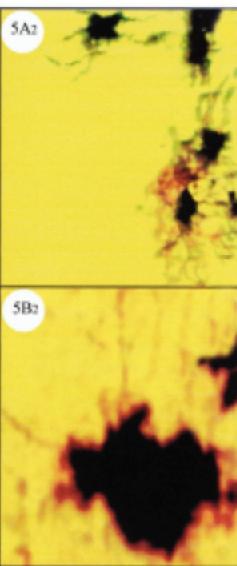
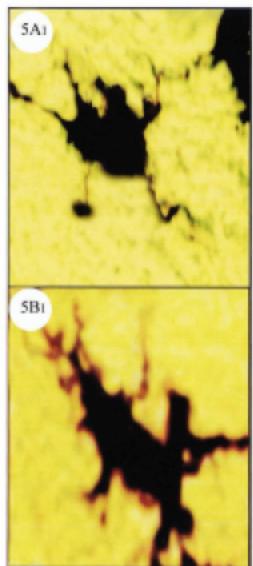


Fig. 5

Fig. 6

Fig. 5 and 6: Transverse sections in the cervical region of spinal cord at day 7 (Fig. 5) and day 21 (Fig. 6) in normal and treated rat newborns showing motoneuron cells (A<sub>1</sub>: Normal; A<sub>2</sub>: Treated) and astrocyte cells (B<sub>1</sub>: Normal; B<sub>2</sub>: Treated)

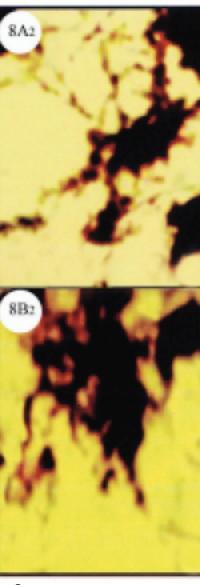
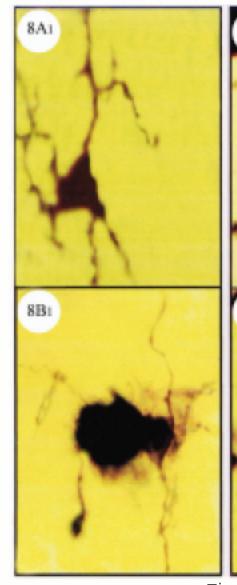
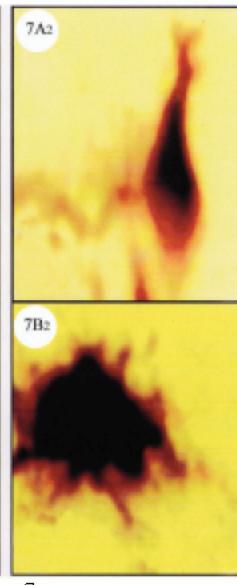


Fig. 7

Fig. 8

Fig. 7 and 8: Transverse sections in the lumbar region of spinal cord at day 7 (Fig. 7) and day 21 (Fig. 8) in normal and treated rat newborns showing motoneuron cells (A<sub>1</sub>: Normal; A<sub>2</sub>: Treated) and astrocyte cells (B<sub>1</sub>: Normal; B<sub>2</sub>: Treated)

### The Neuron Cells of the Lumbar Region of Spinal Cord

Also, in both normal and treated newborns, motoneurons and astrocytes were present in the lumbar region of the spinal cord. The morphological characteristics of these neurons in lumbar region were more or less similar to those of the cervical region of cord. At day 7, the motoneurons of the lumbar region in normal rats were always fewer and smaller than the corresponding cells of the cervical region of the spinal cord (Fig. 7 and 8, Fig. 5A<sub>1</sub> and 7A<sub>1</sub>).

At days 7 and 21, the motoneuron cells of normal rats have longer dendrites if compared with the treated ones (Fig. 7-8 A<sub>1</sub> and A<sub>2</sub>). The normal astrocyte cells possessed long and thin dendrites if compared to the treated rats at days 7 and 21 (Fig. 7-8 B<sub>1</sub> and 7B<sub>2</sub>).

## DISCUSSION

The cerebral cortex containing various types of the nerve cells assemblies organized to perform neural functions. In both normal and treated newborns, four types of the nerve cells were recorded in layers III, IV, V and VI of the present cerebral cortex by Golgi-copisch stain. Previous investigations furnished much insight into the distinctive types of neuron within the sixth layer of the cerebral cortex in mouse (Lorente DE Nô, 1933, 1949; Meller *et al.*, 1969), rat (Parnavelas *et al.*, 1977; Feldman and Peters, 1978; Peters and Proskauer, 1981), rabbit (Tömböl, 1978a, 1984; McMullen and Glaser, 1982), hedgehog (Valverde and Lopez-Mascaraque, 1981), cat (Tömböl, 1978a and 1984; dog (Miodonski, 1974), monkey (Tömböl, 1978b, 1984) and small mammals (Dalia, 2002).

In the present newborns, the typical pyramidal neurons appeared with a pyramidal perikaryon and their apical dendrites project toward the pial surface and some lateral dendrites emerging from its lateral and basal sides. At the same time, the axons leave the cells from the central base moving far from the pial surface. These results were recorded in human (Zhang, 1999), monkey (Kogan *et al.*, 2000) and small mammals (Dalia, 2002). Also, in the monkey, there is a marked increasing in the number of cells stained in each layer and likewise an increase in the complexity of the dendrites fields of these neurons (Kogan *et al.*, 2000).

The maturation process of pyramidal neurons involves many aspects. The increase in the dendrites arborization with the presence of spicules is one of the maturation features. The rate of neuron development in the present cerebral cortex is increased in its density and complexity with the age progress in normal rats as seen by Dalia (2002). Also, the present neurons of layer V in normal rats precede those of layers III and IV in the maturity of all investigated ages. In concomitant with the present results, Ahmed and Gabr (2000) who found that the pyramidal neurons of visual cortex in layer V were reached the maturity earlier at day 12 than those of the more superficial layers such as layer II and III at day 15. This could be explained by the inside outside gradient of migration of cortical neurons as seen by Angevine and Sidman (1961). However, at day 7, the present normal pyramidal cells of layer III had short dendrites if compared to the treated rats. Miller (1981) suggested that in the course of maturation, some dendrites might degenerate or fuse with adjacent ones thus reducing the total number of primary processes. A decrease in the number of neurons per unit volume of tissue has been reported in the brain of aged animals with advancing age by Terry *et al.* (1981) and Sturrock (1990). However, other investigators could not find evidence of neural loss, with aging, in several brain regions (Hinds and Mc Nelly, 1980). On the other hand, the interpretation in changes of the density of spicules and nodules during the development in the present normal and treated rats had to be considered in view of changes in the length of the shaft of the apical dendrites as well as its size. Similar observations were recorded by Ahmed and Gabr (2000). In the present treated newborns, the dendrites of the pyramidal cells of layers III, IV and V were short if compared to the normal ones at all investigated ages except at day 7 in layer III. Also, there was some degeneration in the dendrites of layer V between day 7 to day 21 in the treated rats. Sharma *et al.* (2003a and b) found the cell damage

in the brain regions of rats after heat stress. On the other hand, the present normal polymorphic cells of layer VI at day 7 had long collaterals of dendrites and short collaterals at day 21 if compared to the treated newborns. Sharma *et al.* (1997) said that the cell changes were noticed in hyperthermic brain injury of young rats as a result of exposure to heat stress at 38°C for 4 h.

Based on the above described results, the heat stress may be responsible for some reduction in the cellular processes that grow from the neuron cells in different layers of the cerebral cortex. These findings are concomitant with several investigators; (1) Lundgren *et al.* (1994) revealed that, the hyperthermia showed enhanced damage in the neocortex and neuronal necrosis; (2) Johnson *et al.* (1976) found that, the hyperthermia caused retarding of the degree of postnatal neurogenesis; (3) Westra and Dewey (1971) recorded that, the heat inhibits the activity of cells and (4) Eshel and Safer (2002) noticed in a primate model, the heatstroke led to depression of all the cerebral functions. Generally, Ahmed (2005) reported that the heat stress may retard partially the degree of the postnatal neurogenesis and growth of CNS.

On the other hand, the present normal and treated newborns have five types of neuron cells in the layers of cerebellar cortex. This result goes parallel with several studies. Bondok *et al.* (1991) found that the differentiating stellate, basket and granule cells were seen migrating through the molecular layer and their bulk was formed during the second and third weeks. This layer and its cell numbers were increased with time in the present normal rats. Similar observations were recorded by Bondok *et al.* (1991) who noticed that the cerebellar cortex showed a gradual increase in the depth of the molecular layer and gradual differentiation of cortical neurons.

The maturation process of the present cerebellar neurons involves many aspects. The increase in the number of the cells and the dendrites development is one of the maturation features. The present neurons examined at different postnatal ages showed an increase in the dendrites as they grow postnatally.

The present stellate cells occupy the upper half of the molecular layer with mainly thick horizontal dendrites. This evidence goes parallel with that of Bondok *et al.* (1991) and Dalia (1998 and 2002). Also, these cells increased in size and in their number of dendrites with age progress from day 7 to day 21 as in mammals (Getty, 1975), in human (Di Fiore, 1988 and Krause and Cutts, 1994) and in rat (Altman, 1969). Also, in mouse this layer reached its maximum at age 25 postnatal days by Noor El-Din (1966) and Haddara *et al.* (1975). On the other hand, the density of dendrites in stellate cells of the present normal newborns appeared more developed than the corresponding dendrites in the treated ones from day 7 to day 21. This observation agrees with Mohammed *et al.* (1997) who found a decrease in the dendritic length and number of the molecular cells in mice newborns exposed to gamma irradiation.

In addition, the present basket cells were situated deep in the lower half of the molecular layer (Altman, 1969; Getty, 1975; Dalia, 1998 and 2002) or scattered among the Purkinje cells (Getty, 1975). The present normal basket cells are usually rounded or oval and bipolar perikaryon and their dendrites are seen moving parallel to the pial surface. The same findings were reported in human (Di Fiore, 1988; Krause and Cutts, 1994) and in rat (Altman, 1969). Furthermore, these present cells of normal rats were increased in their dendritic length and numbers if compared to the treated ones as the age progressed from day 7 to day 21. Mohammed *et al.* (1997) recorded that when mice newborns exposed to gamma irradiation, the dendritic length and number of the basket cells were decreased. In addition, Bondok *et al.* (1991) found increasing in number of the basket cells during development from the 1st to the 3rd weeks in rats. However, these cells in the present treated newborns were large in size if compared to normal ones in all examined ages. Dalia (1998) revealed that, the thickness of the molecular layer reached its maximum at 24 days old in rat newborns exposed to heat stress, but generally this thickness were decreased between 7 days and 24 days in treated rats if compared to normal ones.

The results of the current study in both normal and treated rats show that the Purkinje cell layer is situated between the molecular and the internal granular layers and its cells are scattered among the underlying granule cells and demarcated difficulty from them at day 7 of birth. This correlates well with Altman (1969) who showed that, the neurogenesis of Purkinje cell was formed before birth, whereas their differentiation and maturation occurred during postnatal life. These cells base on the granular layer and send large dendrites into the molecular layer and perpendicular to the longitudinal direction of the cerebellar folia (Altman, 1969). In addition, Getty (1975) found that, the mammalian Purkinje cells had sent two main dendrites into the molecular layer. Cajal (1911) and Mial and Sidman (1961) found at day 5 in mice, Purkinje cells can not be demarcated from the underlying granule cells. In the mean time, at days 21, the present Purkinje cells are increased in the size and formed a complex network of larger dendrites in normal rats and become clearly differentiated in rows. The same results are recorded in human (Gardner *et al.*, 1976 and Krause and Cutts, 1994). These findings coincide with those of other investigators; Miale and Sidman (1961) and Noor El-Din (1966) observed that, the Purkinje cells arranged in a single row at day 14 postnatally in mice. In addition, in normal rats, these cells appeared in one row at different ages as a following; (1) At 7-8 days (Altman, 1969a); (2) At 10 days (Saleh *et al.*, 1993); (3) At 14 days (Ibrahim, 1976 and Bondok *et al.*, 1991) and (4) At 24 days (Dalia, 1998). This arrangement in a single row explained by Altman and Winfree (1977) who found that, this arrangement is due to the pressure exerted on the growing Purkinje cells from below by the expanding granular layer and barrier formed above these cells by the pile of parallel fibers. However, The Purkinje cells in rat were arranged in several layers at 5 days old (Saleh *et al.*, 1993) and at 7 days old in mice (Noor El-Din, 1966) and in chick (El-Falaky, 1977). Furthermore, Mial and Sidman (1961) found that, the Purkinje cells gradually increased in size and become clearly differentiated with the age progress in mice. Di Fiore (1988) observed that, the Purkinje cells are pyriform in shape and give off one or more thick dendrites which in turn giving off complex branches through the molecular layer.

Regarding to the present treated newborns, the Purkinje cells decreased in their dendrites if compared to normal ones in all investigated ages. This attribution was confirmed by Dalia (1998) who revealed that after exposure of rats to high temperature, a reduction in the diameter of Purkinje cells between days 7 and 24 was noticed. Also, Mohammed *et al.* (1997) found a decrease in the dendritic length and number of the Purkinje cells in mice newborns exposed to gamma irradiation. The damage in the Purkinje cells may be due to the harmful effect of hyperthermia on granule cells; through the destruction of granule cells which stunts the growth of Purkinje cell dendrites and alters the final shape of the dendritic tree (Altman, 1973; Herndon and Oster-Granite, 1975; Woodward *et al.*, 1975; Berry and Bradley, 1976). Moreover, Lennox *et al.* (1954) reported that the hyperthermia-induced convulsions in kittens caused a loss of Purkinje cells in the cerebellum. In addition, these changes can be explained by other different ways; (1) heat may inhibit 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) and (3) the heat induced cell death is popularly believed to be due to protein denaturation (Edwards *et al.*, 1974). So, it is apparent from the present results that the heat stress may deteriorate Purkinje cell growth through affecting its activity.

The present internal granular layer, in both normal and treated rats, has two types of cells which are Golgi and granule cells. The present Golgi cells occupied the upper region of the internal granular layer as in human (Krause and Cutts, 1994) and in rats (Dalia, 1998, 2002). The present granule cells occupied the deep region of the internal granular layer, this goes parallel with Altman (1966, 1969 and 1972), Altman and Das (1966) and Dalia (1998 and 2002). This layer become more clearly differentiated with the age progress from day 7 to day 21 in the present normal and treated newborns. This suggestion is in a good agreement with Saleh *et al.* (1993) who mentioned that the granular layer was ill defined from the subjacent white matter at day 5 after birth in rats and it was well defined from white matter at day 10. However, Dalia (1998) found that rat newborns exposed to high temperature, the internal granular layer can not be demarcated from the underlying white matter at day 7 while at 14 and 24 days old, both layers are clearly differentiated in both normal and treated ones.

Regarding to the normal rats, the present Golgi cells contain different branches, which were produced from the different parts of the cell body. This result is supported by several authors; El-Sayad (1988) and Mohammed *et al.* (1997) who recorded that the dendrites of the adult Golgi cells were branching and extending in all directions. Cajal (1911) reported that many dendrites of Golgi cells are passing through the molecular layer at the right angle with the surface of the molecular layer. On the other hand, these cells had shorter dendrites in the present treated rats if compared to normal ones between days 7 and 21. Similar observations were recorded in rat newborns exposed to high temperature through its effect on the dendrites and the spicules of Golgi cells between ages 14 and 24 days (Dalia, 1998).

Moreover, in the present treated newborns, the dendrites of the granule cells were short at all examined ages when compared to normal ones. Consistent with this result, Dalia (1998) found that, the heat stress has some effects on the dendrites and the spicules of granule cells between day 14 and 24 day. Also, there were some degenerated dendrites in the present treated newborns with age progress as a result of exposure to high temperature. The hyperthermia caused the destruction of the granule cells (Altman, 1973; Herndon and Oster-Granite, 1975; Woodward *et al.*, 1975; Berry and Bradley, 1976). Furthermore the retarded growth and the degenerative changes of the granule cells were observed by Kornguth *et al.* (1979) who found that during the cerebellar histogenesis in rat, mainly granule cell maturation was deeply affected by chronic alcohol consumption. In addition, the rate of granule cell division in the external granular layer may be controlled by the nearby Purkinje cells (Mallet *et al.*, 1977; Herrup and Mullen, 1979; Fedderen *et al.*, 1992). In other instance, Dalia (1998) reported that, any damage in the granule cells may be appeared as a result of heat stress on the Purkinje cells of rat newborns.

To the best of our knowledge, these results represent the process of growth and remodeling of cerebellar neurons and dendritic trees may be delayed partially under the effect of the heat stress. These results run in agreement with many authors; Johnson *et al.* (1976) found that the hyperthermia caused retarding the degree of postnatal neurogenesis. Heat induced cell death by apoptosis is a feature of teratogenic damage to the developing brain (Edwards *et al.*, 1997). Also, Bustó *et al.* (1987) noticed that the neocortical damage was evident in the hyperthermic ischemic animals and infarction occurred in the cerebellum. Sharma *et al.* (2003a and b) noticed that, there was cell damage in several brain regions of rats as a result of exposure to 38°C for 4 h. 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 (Ahmed, 2005).

The present motoneurons of both cervical and lumbar regions are increased in its dendritic branching and have increased in the size of dendritic territories with the age progress; this goes parallel with Dalia (2002). On the other hand, the present heat stress caused some degenerated symptoms in the dendrites of both spinal cord regions between day 7 and day 21. These results were found and explained by Sminia *et al.* (1989) who revealed some damage and degeneration in the neurons of cervical region of spinal cord of rat after exposure to  $42.9 \pm 0.4^\circ\text{C}$  for 38 min. The motoneuron and astrocyte cells of the present lumbar region appeared fewer and less developed if compared with those of the cervical region at day 7. Also, Dalia (2002) found that the motoneurons of the brachial spinal cord have larger diameter than the lumbar motoneurons and this difference is significant with age progress in rat. These results presumed that there is a rostrocaudal gradient in the development of the spinal cord which was also elucidated in some mammals like cats (Sechzer *et al.*, 1984), rats (Donatelle, 1977; Dalia, 2002) and mice (Fox, 1965). Takahashi *et al.* (1999) recorded that in rat, the dendrites elongated mainly during the first five postnatal days and they were longer and more extensive in cervical motoneurons than in the lumbar motoneurons. Also, they added that the age at which the neurite process index reached the maximum value was earlier in cervical motoneurons at the first five postnatal days than in lumbar motoneurons at day 14. Regarding the morphologic maturation of spinal cord, motoneurons can be enhanced by these descending fibers which develop in a rostrocaudal manner

(Tanaka *et al.*, 1997). The neurotransmitters, like serotonin and noradrenaline, which increased gradually with the age progress as indicated by Ahmed *et al.* (2005) were supposed to play a crucial role in the differentiation and proliferation of the target cells (Rajaofetra *et al.*, 1989). In addition, the first corticospinal tract fibers reach the cervical cord at postnatal day 1, the thoracic cord at postnatal day 3 and the lumbar cord at postnatal day 5 (Donatelle, 1977; Schreyer and Jones, 1982). However, Cabana *et al.* (1993) revealed that gerbils show no clear rostrocaudal gradient of maturation of the spinal cord.

Regarding to the present normal and treated rats, astrocyte cells in the cervical and lumbar spinal cord were detected at day 7. Also, in normal rats, at 14, 21 and 28 days old in both two regions of cord, these cells appeared more developed than the corresponding cells in the previous age. These results confirmed the work of Dalia (2002) who observed that, the astrocytes have a higher arborized dendritic field and the branches form a net like structures at day 21. Moreover, in human, the glial cells provide both structural and metabolic support for the neurons (Kelly *et al.*, 1984). They added that certain glial cells invest axons with a myelin sheath, dramatically increasing the speed of impulse conduction. the present astrocytes in the treated rats in both two regions of spinal cord, had less dendritic trees than the corresponding cells in the normal ones. These findings are concomitant with several authors; Gilmore (1963) and Heard and Gilmore (1985) found the irradiation exposure led to a depletion of the macroglial population (astrocytes and oligodendrocytes) and an accompanying state of hypomyelination in the rodent spinal cord. Godlewski *et al.* (1986) noticed that in the lumbar region of the spinal cord, degenerative alterations of neurocytes and oligodendroglia proliferation as a result of exposure of rat to 43°C. Furthermore, Shiota (1988) said that as a result of exposure of mice embryos to high temperature (42°C for 12.5-15 min or to 43°C for 7.5-10 min), a temporary cessation of cell proliferation was observed. However, Sminia *et al.* (1989) found that as a reaction to the thermal injury, gliosis was observed; reactive astrocytes were found in the gray matter. In general, Borzan *et al.* (2005) speculated that the number of dorsal horn neurons may shift from the non-responsive or inhibitory category to the excitatory category in response to graded heat stimuli. This shift may contribute to thermal hyperalgesia or thermal allodynia following tissue injury. So, it can be suggested that the heat stress may be responsible for some reduction in the cellular processes of neurons in both cervical and lumbar regions.

According to the present effects of heat stress on the central nervous system, the current study evidenced the following important findings: the development of the CNS are extremely sensitive to heat stress; this may lead, in turn, to some harmful effects on the neurons formation in all investigated CNS regions of the rat newborns. This drastic effect may be responsible for the delay of the neurons vital activity and dendritic arborization. Present results are in accordance with those of the previous investigators: Sharma and Hoopes (2003) observed that, the morphological changes in the axons, nerve cells, glial cells and vascular endothelium are seen at the cellular and the molecular levels in rats subjected to heat exposure at 38°C for 4 h. Also, Edwards *et al.* (2003) found that, hyperthermia during pregnancy can cause embryonic death, abortion, growth retardation and developmental defects. Processes critical to embryonic development, such as cell proliferation, migration, differentiation and programmed cell death (apoptosis) are adversely affected by elevated maternal temperatures these are confirmed by the same previous authors. Furthermore, there were developmental abnormalities and severe growth retardation in rats after exposure to heat stress (Skreb and Frank, 1963; Edwards, 1968). Finally, these results emphasized the present heat stress may retard partially the degree of postnatal neurogenesis and the growth in all investigated CNS regions. 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 CNS. But, a thermal stress, which by itself is non-lethal (Kahraman and Thach 2004). Therefore, we need to estimate if the beneficial effects of heat exposure result in changes of stress complications only or not.

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