B-13.1 Effects of Heat Stress on Defence Reactions, Metabolic Activities and Heat Related Disorders

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Abstract Since global warming will have an increase heat stress in hot summer in some temperate big cities, various health risk caused by heat stress has been studied. According to the epidemiological survey, the incidence of heat-related illness significantly correlated to hot environment in Tokyo, Japan and in Nanjing, China. The epidemiological results showed that hyperthermia caused by heat stress induced many heat stroke patients in Tokyo, Japan and in Nanjing, China.

Hyperthermia developed histochemical degeneration in immune systems, such as spleen, thymus, lymphatic system. Hyperthermia also affected on biochemical function and intracellular components in hepatic cells.

Immune reactions, such as thymus lymphocyte reaction, spleen lymphocyte reaction, and humoral antibody reaction was markedly affected in hyperthermia. Therefore global warming may have profound impacts on human defence reactions against some diseases during heat stress in hot summer.

Since heat stress caused an increase in morbidity and mortality, oxygen radical damages in hyperthermia were studied. Since lipid peroxidation was greatly induced in liver, hyperthermia greatly developed hypertrophy and vacuolized degeneration in hepatic cells.

Protective enzymes, such as glutathione peroxidase activities were induced in hyperthermia. Heat stress also affected central nervous systems and changed the sleeping behaviour.

Key Words Heat stress, Immune system, Lymphocyte, Humoral antibody, heat stroke, Radicals

INTRODUCTION Since the human activities, such as combustion of fossil fuel, agricultural activity, and changes in land-use, are responsible for anthropogenic greenhouse gases(carbon dioxide, methane, and nitrous oxide) emissions, climate models predict an increase in the global surface temperature of 0.9 C to 4.0 C by the year 2100(IPCC, 1992, 1995; WMO/UNEP, 1994). These expected global temperature changes would be greater than natural fluctuations and would occur at a rate significantly faster than observed changes in the last 10,000 years, when modern society has evolved.

For human health, it is evaluated that global warming may have a critical issue on the increased periods of severe heat stress in summer throughout the world. In some temperate large cities, extreme heat stress associated with the increased heat island's effect. Global warming may cause an increase in morbidity and mortality in these cities(USEPA, 1989; IPCC,1995; WHO, 1990; Kalkstein, 1994). The incidence heat related mortality and morbidity, such as heat stroke of aged person increased according to extreme hot temperature in summer(Hawkins-Bell and Rankin, 1994; Donoghue et al., 1995; Tamura et al., 1995).

In animal and human, some physiological and biochemical adaptations could occur to protect essential cell functions against heat stress and to permit a rapid recovery from hyperthermic damage(Burdon, 1986; Ostermann et al., 1989). Furthermore, each tissue and organ has a different sensitivity for sustaining thermal injury(Freeman et al., 1985; Keatinge et al., 1986; Hales and Richards, 1987; Ando et. al., 1994). Therefore, it is necessary to study the biochemical mechanism of hyperthermic damage and age-related response under hot environment.

Cellular and intracellular membrane damage and denaturation of enzymes might be important in the pathogenesis of heat injury. The oxygen free radical damage of biological membrane and high molecules is a destructive phenomenon as associated with a variety of cellular damage(Hruszkewycz et al., 1978; Ando and Tappel, 1985-a).

Significant lipid peroxidation occurred in guinea pig liver in passive hyperthermia caused by hot environment. Since the peroxidation of lipids in biological membrane is a destructive phenomenon as associated with a variety of cellular damage, hyperthermia developed hypertrophy and vacuolated degeneration in hepatic cells.

For the protection of cell function from lipid peroxidation, two types of glutathione peroxidases(GSH peroxidase: EC 1.11.1.9), such as selenium GSH peroxidase and non selenium GSH peroxidase are very important (Lawrence and Burk, 1976; Burk and Lawrence, 1978). The activities of these enzymes are markedly different among animal species. Selenium GSH peroxidase activities in human liver are very low in comparison with that in rat liver. Moreover, selenium GSH peroxidase is not active in guinea pig liver(Lawrence and Burk, 1978).

Global warming may have a critical issue on the increased periods of severe heat stress that may have a potential impacts on aged persons. Damage on immune systems and peroxidation are markedly related to the adaptation to heat stress and protection for oxygen radicals. Therefore, epidemiological and oxicological aspects of heat stress on human health were carried out. The relationship between age-related change of the adaptation and the damage of heat stress on cellular and intracellular structure was also carried out.

Research Objective For human health, it is evaluated that global warming may have a critical issue on the increased periods of serious heat stress in summer throughout the world. In some temperate big cities, the extreme heat stress associated with the increased heat islands effect already causes in morbidity and mortality. Since there is an urgent need for risk evaluation of global warming, epidemiological and experimental research works on pathogenesis of heat related disorders were carried out.

Subjects and Methods To evaluate the health risk of extreme heat stress in hot summer, international cooperative work on epidemiology were carried out in Tokyo, Japan and in Nanjing, China. Since in these big cities, heat stress in summer is different year by year, epidemiological work has been carried out in summer season during 1993-1995.

To study the biochemical and physiological impacts of heat stress on human health, animals were kept at 25 + 0.5 °C, 30 + 0.5 °C, 32 + 0.5 °C, and 35 + 0.5 °C at 40 + 10 % relative humidity. After exposure to various temperature, tissue was prepared for histochemical and biochemical analysis.

Result and Discussion A serious heat stress occured in July to August, 1994 in Tokyo, Japan and in Nanjing, China. As shown in Fig. 1, the monthly mean temperature in Tokyo was 24.8 °C during August in 1993 and 28.9 °C during August in 1994, respectively. This hot summer produced heat stroke patients 386 persons in Tokyo. The incidence of heat stroke was remarkably high in elderly persons.

It has been evaluated the global warming may cause an increase in the global surface temperature of 0.9 °C to 4 °C by the year 2100(IPCC,1992). For human health,

it is evaluated that global warming may have a critical issue on the increased periods of severe heat stress in summer(USEPA, 1989; IPCC,1990, 1995; Kalkstein, 1994). The incidence of heat related mortality and morbidity, such as heat stroke of aged person increased according to hot temperature in summer(Marmor, 1978; Stephen et al., 1982; Khogali, 1987; Zhang and Mao, 1990; Hawkins-Bell and Rankin, 1994; Donoghue et al., 1995; Tamura et al., 1995). Therefore, it is necessary to evaluate whether heat stress can cause health impacts on human and animal as a result of global warming.

In animal and human, some physiological and biochemical adaptations could occur to protect essential cell functions against increased temperature and to permit a rapid recovery from heat stress(Burdon, 1986; Ostermann et al., 1989; Tytler and Ireland, 1995). Therefore, each tissue and organ in animal and human has a different sensitivity for sustaining thermal injury(Freeman et al., 1985; Keatinge et al., 1986; Hales and Richards, 1987).

In young rat, hepatic cytosolic GSH peroxidase activities especially selenium GSH peroxidase activities were greatly induced corresponding to the increased environmental temperature.(Fig.2-b) Induction of GSH peroxidase activities in liver continued during the long lasting heat exposure until 6 weeks. While in aged rat, GSH peroxidase activities were not induced, moreover slightly decreased.

In young rat, hepatic cytosolic GSH transferase activities were also slightly induced by hot temperature. Whereas, GSH transferase in aged rat were not induced, moreover decreased by hot environment. Furthermore, hepatic catalase activities in aged rat were markedly decreased by hot environment.

In young rat liver, it was proved that GSH peroxidase activities were induced not only in cytosols but also in mitochondria. Therefore, lipid peroxidation in intracellular structures, such as mitochondria were not affected in acute hyperthermia.

Hepatic cytosolic and mitochondrial GSH peroxidase activities in aged rat was markedly increased under usual temperature. In aged rat, GSH peroxidase activities was not induced, moreover slightly decreased by heat stress. Moreover, other protective enzymes for oxygen radicals, such as catalase and GSH-transferase were also decreased after heat exposure, therefore the lipid peroxidation in liver was seriously induced in aged rat. Lipid peroxidation was greatly induced not only in liver homogenate but also in intracellular structures, such as mitochondria and microsomes in hyperthermic aged rat.

Selenium GSH peroxidase activities in human liver are very low in comparison with those in rat liver(Lawrence and Burk, 1976; 1978; Halliwell and Gutteridge, 1985). Therefore, it is necessary to consider the age-related inducibility of GSH peroxidase when effects of acute heat stress on human health are evaluated.

The induction of lipid peroxidation in liver was also very sensitive biochemical indicator in hyperthermia. The induced formation of TBARS in liver progressively increased in passive hyperthermia resulting from the hot environment.(Fig.2-a) It was evaluated that cellular and intracellular membrane damage and denaturation of enzymes might be important in the pathogenesis of heat injury. The oxygen free radical damage of biological membrane and high molecules is a destructive phenomenon as associated with a variety of cellular damage(Hruszkewycz et al., 1978). Since the peroxidation of lipids in biological membrane is a destructive phenomenon as associated with a variety of cellular damage, hyperthermia greatly developed hypertrophy and vacuolated degeneration in hepatic cells.

It has been reported that the peroxidation of lipids in biological membranes can damage cellular redox state, intracellular structure, and some membrane bound enzymes(Hruszkewycz et al., 1978; Ando and Tappel, 1985-b; Kennedy et al., 1992; Pryor et al., 1992). Since endoplasmic reticulumn of the hepatic cells in aged rat showed the distorted shape under hot temperature, microsomal electron transport system, such as cytochrome P450 monooxygenase activities were seriously affected in hyperthermia.

Since liver should be one of the target organs of heat stress, the biochemical impacts of heat stress on liver functions need to be evaluated. In this study, heat stress seriously injured hepatic endoplasmic reticulumn and inhibit some microsomal monooxygenase activities in aged rat. Hepatic microsomal monooxygenase is vital for the metabolism of endogenous and exogenous lipophilic substrates, such as steroids and xenobiotics(Omura et al., 1993). Since hot environment greatly damages on hepatic microsomal electron transport systems in aged rat, it seems reasonable that heat stress has a potential peroxidative damage on aged animals including human.

Since distortion of hepatic mitochondria was slight under hot temperature, the activities of hepatic mitochondrial electron transport system, such as cytochrome c oxidase and cytochrome c reductase system were not inhibited in acute hyperthermia. While in cronic exposure to heat stress, cytochrome c oxidase and cytochrome c reductase system were simultaneously inhibited.

Since hepatic GSH-peroxidase activities were also not induced in guinea pig, lipid peroxidation was greatly induced not only in liver homogenate but also in intracellular structures, such as mitochondria and microsomes. Therefore, the activities of hepatic mitochondrial electron transport system were simultaneously inhibited in hyperthermic guinea pig(Ando et al., 1994).

It is well known that heat shock response activates heat shock proteins and protects the cellular function from destabilization(Denis and Gustafsson, 1989; Pratt et al., 1989; Welch, 1990; Morimoto et al., 1990). In previous study, 90-kDa heat shock inducible proteins markedly expressed in hyperthermic guinea pig. In this study, 70-kDa heat shock inducible protein synthesis was markedly enhanced in isolated hepatic cell.

In aged rat, GSH peroxidase in kidney was not affected by hot temperature, whereas catalase activities were markedly decreased. Therefore, lipid peroxidation in kidney in aged rat was also significantly induced by heat stress.

Since physiological and biochemical adaptation against heat stress is essential for sustaining thermal injury in aged humans and animals, further study is necessary to clarify the biochemical relationship between the protective enzyme activities, such as GSH peroxidase activities and the adaptability to hyperthermia according to aging.

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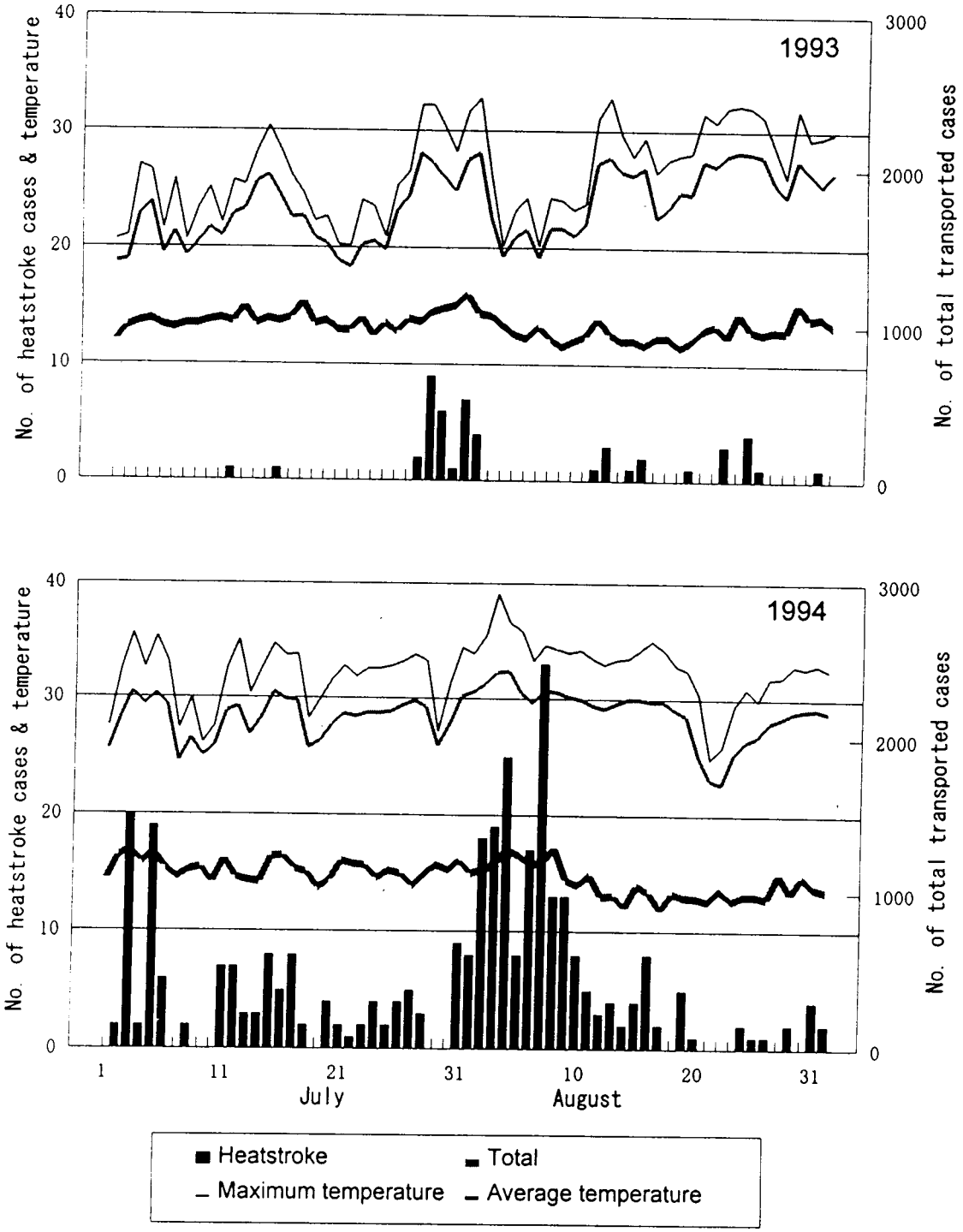
Fig.1 Maximum( ), mean temperature( ), severe heat stroke( ) and total emergent patients( ) during hot summer in Tokyo at July and August in 1993 and 1994.

Fig.2 Effects of heat exposure on lipid peroxidation(2-a:upper) and glutathione peroxidase activities(2-b:lower) in liver.

Fig.1



Daily number of cases and temperature
July and August

Fig.2-a

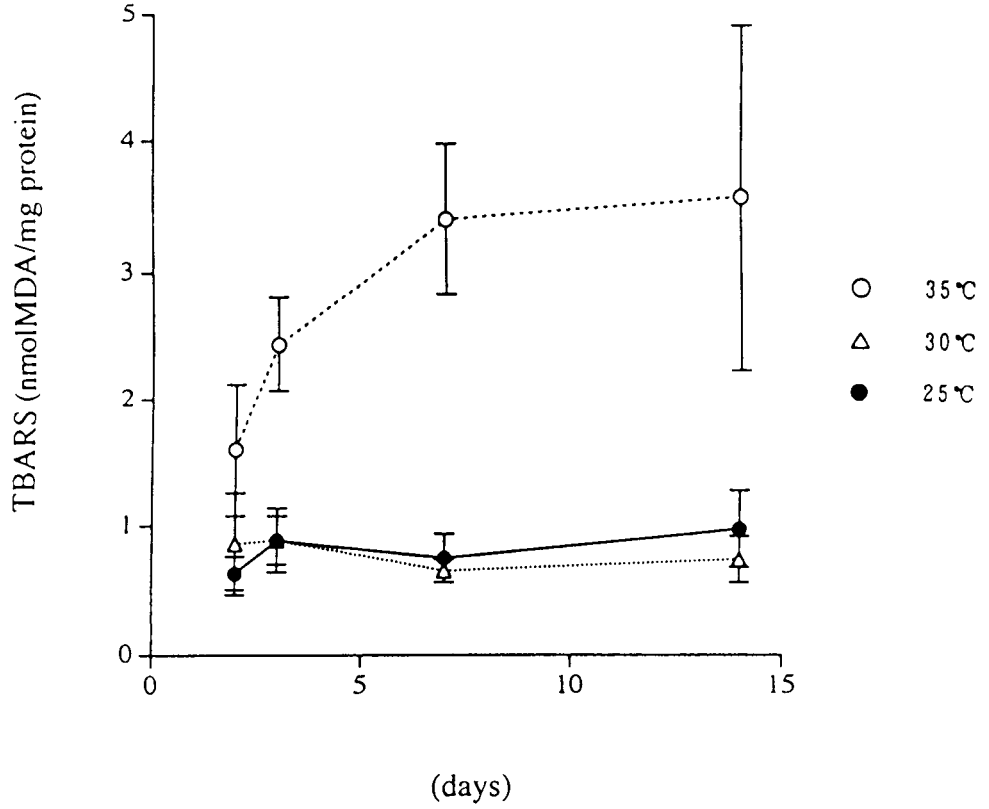
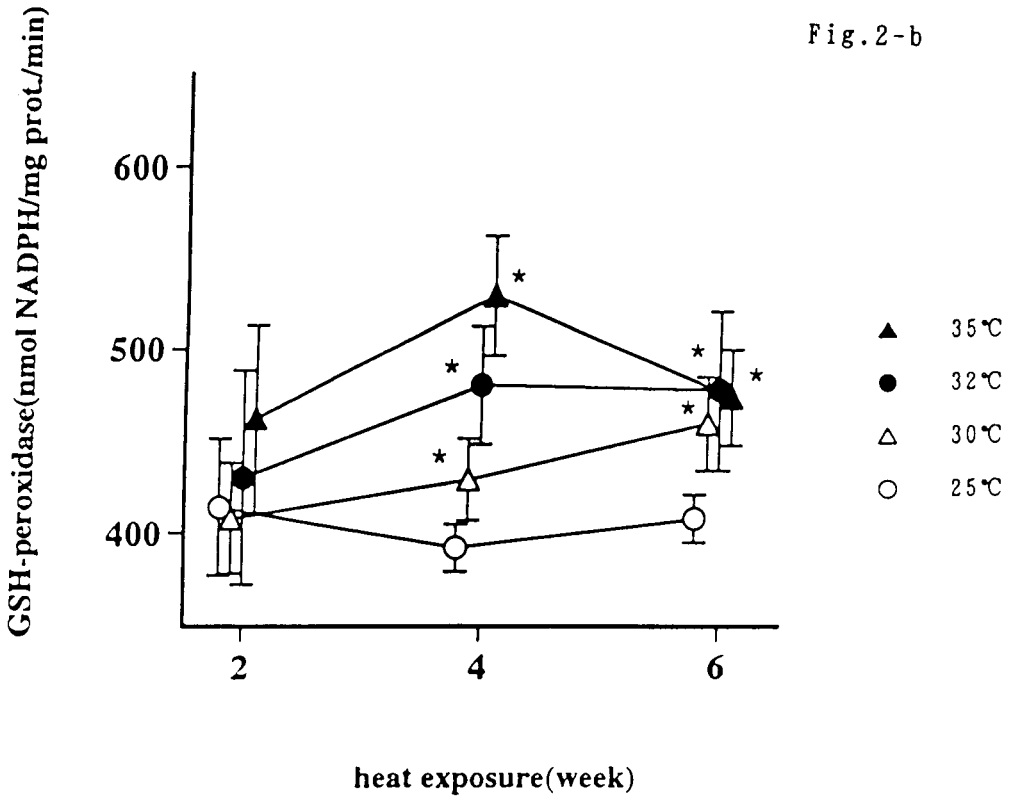

TBARS (nmolMDA/mg protein)
0
1
2
3
4
5
0
5
10
15
(days)
35℃
30℃
25℃

Fig.2-b


GSH-peroxidase(nmol NADPH/mg prot./min)
400
500
600
2
4
6
heat exposure(week)
35℃
32℃
30℃
25℃