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Hyperthermia-induced Changes of Afferent Sensory Transmission to the SI Cortex of Anesthetized Rats

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ABSTRACT

The effects of hyperthermia on the afferent sensory transmission to neurons in the primary somatosensory (SI) cortex were determined in anesthetized rats. Afferent sensory transmission evoked by electrical stimulation to the forepaw area was not significantly changed during gradual heating to 42°C and subsequent recovery to normal body temperature. However, afferent transmission was significantly elevated (17~23%) when body temperature was maintained steadily at 42°C of hyperthermia. These results suggest that differential changes of afferent sensory transmission to the somatosensory cortex may occur between short period of body temperature elevation and sustained hyperthermia.

Key words: hyperthermia, SI cortex, sensory transmission

INTRODUCTION

Dramatically under-reported, heat-related pathology contributes to significant morbidity as well as occasional mortality in athletic, elderly, paediatric and disabled populations (Coris et al., 2004). Heat illness is a spectrum of illnesses from heat cramps to heat stroke (Dhainaut et al., 2004). Mortality for heat stroke ranges from 17% to 70%, depending on severity and age of the patient (Bytomski and Squire, 2003). During exercise with hyperthermia excessive accumulation of heat in the brain due to impeded heat removal by the cerebral circulation may elevate the brain temperature to above 40°C and impair the ability to sustain maximal motor activation (Nybo and Secher, 2004).

Whole body hyperthermia can be used for the treatment of metastatic cancer and human immunodeficiency virus infections. The therapeutic effects of hyperthermia are dependent upon the actual temperature of the target tissues (Vertrees, 1996). Central nervous system (CNS) hyperthermia is also induced therapeutically as an adjunct to anti-cancer (Hegewisch-Becker, 2003; Westermann et al., 2003) and anti-viral treatments (Carsillo, 2004; Conti, 1999).

Somatosensory evoked potentials (SEPs) reflect conduction of the afferent volley along the peripheral nerve, dorsal columns, and medial lemniscal pathways to the primary somatosensory (SI) cortex (Lee and Seyal, 1998). Hyperthermia reduced the latency and increased the conduction velocity of cortical SEPs. Cortical SEPs deteriorated above 42°C (Dubois et al., 1981; Oro and Haghighi,

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1992). The disappearance of SEPs to finger stimulation during sustained hyperthermia at 42°C indicates that a major neuronal dysfunction occurs under these circumstances (Dubois et al., 1981). These SEP studies suggest that corresponding changes may also occur at SI single neurons during hyperthermia. However actual experiment with single neurons has never been attempted previously.

In this study, therefore, we tested the degree and the polarity of hyperthermia-induced changes of afferent sensory transmission to single neurons in the SI cortex of anesthetized rats.

MATERIALS AND METHODS

Adult male Sprague-Dawley rats (250～300 g, n=12) were used in this study. All animals were succeeded in the experimental animal center of the Hallym University. The breeding room was maintained at 23±2°C and relative humidity was 55±10%. Artificial lighting was maintained 12 hours per day. Animals were transferred to laboratory just before experimentation and they were anesthetized with urethane (Sigma, USA, 20%, 7 ml/kg, i.p.) dissolved in saline, and transferred to a stereotaxic apparatus. Small supplementary injections of urethane were administered to maintain anesthesia during the experiments. After removal of the skin and soft tissue, a relatively large craniotomy (3～4 mm diameter) was made over the forepaw area of SI cortex of either hemisphere. A tungsten microelectrode (12 MΩ at 1 kHz, 125 μm diameter, A-M System, USA) was driven into the forepaw area (1.5 mm anterior from bregma～bregma, 3.5～4.5 mm lateral from midline) of the SI cortex with a microdrive. Further detailed methods for surgery and the recording of single neurons were described elsewhere (Shin and Chapin, 1990; Shin et al., 1993; Won et al., 1996). Cutaneous receptive fields were identified by listening to the recorded signal through an audio speaker while using a fine tipped probe to forepaw palm lightly, until the zone responding most intensely and reliably was defined on each channel of multi array electrode.

A bipolar concentric stimulating electrode (50 μm tip, 100 μm o.d., 0.5 mm tip separation, David Kopf, Tujunga, CA) was inserted under the center of the receptive field and the electrode was fixed firmly to prevent any movement. A head stage plug was used to connect the inserted and fixed microwires to a preamplifier whose outputs were sent to a main amplifier and 1,401 plus (CED, UK, 8 Ch ADC) for on-line multichannel spike sorting and acquisition. Neural spikes of the SI cortex evoked by electrical stimulation (single 0.1 ms pulse, 1 Hz, 50～500 μA) through inserted electrode on the forepaw area, were sorted with voltage-time windows of the Spike2 software (CED, UK).

Post-stimulus time histograms (PSTHs) were generated to determine the quantitative changes of sensory transmission during hyperthermia. After verifying stability of the RFs, evoked unit responses (EURs, latency 8～17 ms) were recorded for 10～30 min at normal body temperature. In one group of animals body temperature was gradually increased up to 42°C and then temperature was gradually decreased to 37°C by peltier device and fine temperature regulator (accuracy=±0.1°C, DAGAN, USA). In other group of animals body temperature was abruptly increased to 42°C and maintained (42°C). Neural responses were continuously monitored up to 60 min. Modulation of sensory transmission was expressed in terms of the percentage change from the averaged EUR value calculated during the control period. Statistical analysis was undertaken with the unpaired Student's t-test. All results were presented as means±SEM.

RESULTS

In a group of animals (n=4) body temperature was gradually increased to 42°C for 30 min of period, subsequently, body temperature was allowed to be recovered to 37°C for 30 min of period. During control period of normal body temperature afferent sensory transmission was stably maintained (−5 to 0 min: 0.71±0.5%, −10～−6 min: 0.78±0.5%, −15 to −11 min: −0.94±0.44%). The afferent sensory transmission to neurons (n=13) of the SI cortex was not significantly altered during gradual heating to 42°C and subsequent cooling to 37°C (Fig. 1).

In another group of animals (n=4), sensory transmission was monitored for 15 min at normal body temperature and then continuous heating was

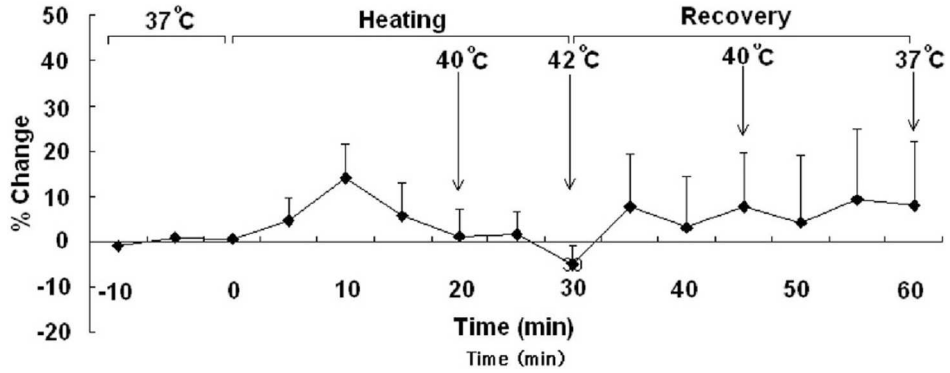

Fig. 1. Temporal changes of afferent sensory transmission to neurons in the SI cortex. Heating was done continuously for up to 30 min till reaching to body temperature of 42°C and subsequently cooling was done to regain normal body temperature. Evoked unit responses (EURs) were recorded from the SI single neurons every 5 min. Percentage changes of afferent transmission was expressed in reference to the degree of sensory transmission during the 15 min of control period at 37°C.

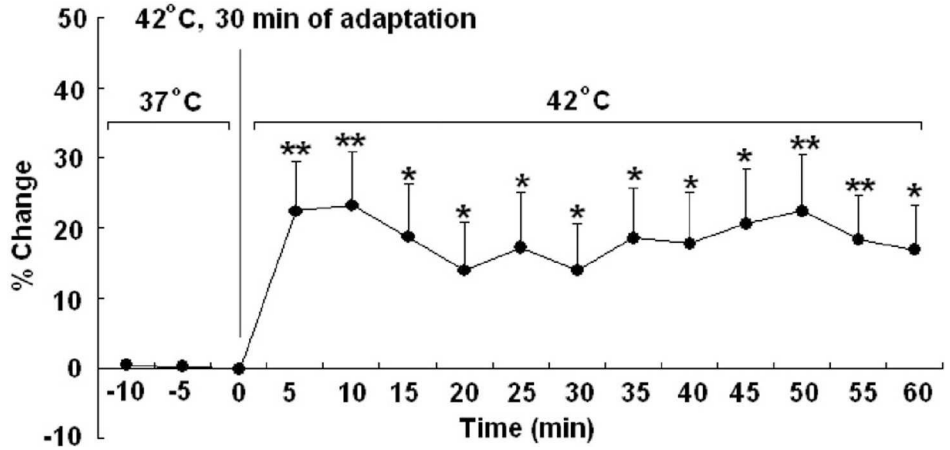

Fig. 2. Temporal changes of afferent sensory transmission to neurons in the SI cortex during sustained hyperthermic condition at 42°C for 60 min following 30 min of adaptation period.

done until body temperature was reaching to 42°C. Thereafter, body temperature was maintained at 42°C for 30 min. Recording of the evoked unit responses were resumed for subsequent 60 min of hyperthermic period with 42°C of body temperature. As shown in Fig. 2, afferent transmission to neurons (n=21) in the SI cortex was significantly increased (17～23%) during hyperthermia when compared to that at normal body temperature.

DISCUSSION

The results of this study clearly demonstrate that afferent transmission to the SI cortex neuron was significantly elevated during sustained hyperthermic condition with body temperature at 42°C. This study also showed that no change of sensory transmission during acute gradual increase of body temperature up to 42°C. These results suggest that normal function of afferent transmission was maintained during gradual increase of body temperature up to 42°C. However, during sustained hyperthermic condition, afferent transmission to the SI cortex was out of normal state.

Previously, Dubois et al. (1981) reported the disappearance of SEP components later than 160 ms during the early part of elevating body temperature up to 42°C for 2 hrs in human and the total disappearance of SEPs to finger stimulation during sustained hyperthermia at 42°C. This sug-

gests that early part of the SEP might have been intact during the initial heating period. In our study, gradual increase of body temperature in a group of rats did not affect the afferent sensory transmission for 30 min of heating up to 42°C of body temperature. A significant elevation of afferent sensory transmission observed in another group of animal during sustained hyperthermia for 90 min appeared to be not consistent with the total disappearance of the SEPs. This discrepancy may be related to the species difference between human and rat. It appears that the duration of the hyperthermia may not count for the discrepancy. Our results found in two groups of rats may suggest that rat's adaptation capacity to hyperthermia is superior than human's. In the rat heat stroke model, established by heating to a climatic chamber temperature of 42°C, the brain temperature was found to be consistently lower than the rectal temperature, suggesting efficient brain cooling mechanisms in the rat (Panjwani et al., 1991).

Rat's strong ability to adapt to adversive temperature change is much more prominent in cold environment than in hyperthermic condition. In our previous study with rats, we reported that during gradual lowering of body temperature to 27°C rats did not show any change of afferent sensory transmission to the SI cortex (Won et al., 1996). This sort of strong preservation of normal sensory capacity in extreme environment is also true in hyperthermia. In the current study, with gradual increase of body temperature up to 42°C, there was no change of afferent sensory transmission to the SI cortex. Expression of thermotolerance after a 'conditioning' heat dose was clearly observed in the spinal cord of rodents (Haveman, 2005; Sminia, 1994). However, steep suppression of sensory transmission was occurred wile lowering body temperature from 26°C to 23°C. Total failure of the sensory transmission was observed below 22°C (Won et al., 1996). In the current study, about 20% increase of afferent transmission during the steady hyperthermic condition at body temperature 42°C may reflect the transition state from normality of somatosensory perception to total failure.

Previously we have reported the occurrence of tonic facilitation of afferent sensory transmission in the dorsal column-lemniscal pathwy to the SI cortex in several different conditions. Interleukin-1 beta exerted phasic facilitation of afferent sensory transmission in anethetized rat (Won et al., 1995). This was interpreted as an alteration of sensory inflow during immune activation. We have also provided an evidence that a disinhibition of the GABAergic system may be involved in the facilitation of afferent transmission during peripheral deafferentation (Jung and Shin, 2002). In the current study, the observed tonic facilitation during sustained hyperthermic condition may reflect a dysfunction of the GABAergic inhibitory system to regulate normal inflow of sensory information when the rat was subject to just below the total collapse of the system. In other point of view, the maintenance of tonic sensory facilitation may be considered of sustained counteraction to the imminent system failure by acquiring more sensory information from the environment.

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