

# Brain Hyperthermia During Physiological and Pathological Conditions: Causes, Mechanisms, and Functional Implications

Eugene A. Kiyatkin\*

*Behavioral Neuroscience Branch, National Institute on Drug Abuse – Intramural Research Program, National Institutes of Health, DHHS, 5500 Nathan Shock, Baltimore, Maryland 21224, USA*

**Abstract:** Although brain metabolism consumes high amounts of energy and is accompanied by intense heat production, brain temperature is usually considered a stable, tightly regulated homeostatic parameter. Current animal research, however, has shown that different forms of functional neural activation are accompanied by relatively large brain hyperthermia (2-3°C), which has an intra-brain origin; cerebral circulation plays a crucial role in dissipating this potentially dangerous metabolic heat from brain tissue. Brain hyperthermia, therefore, reflects enhanced brain metabolism and is a normal physiological phenomenon that can be enhanced by interaction with common elements of an organism's environment. There are, however, instances when brain hyperthermia becomes pathological. Both exposure to extreme environmental heat and intense physical activity in a hot, humid environment restrict heat dissipation from the brain and may push brain temperatures to the limits of physiological functions, resulting in acute life-threatening complications and destructive effects on neural cells and functions of the brain as a whole. Brain hyperthermia may also result from metabolic activation induced by various addictive drugs, such as heroin, cocaine, and meth-amphetamine (METH). In contrast to heroin and cocaine, whose stimulatory effects on brain metabolism invert with increases in dose, METH increases brain metabolism dose-dependently and diminishes heat dissipation because of peripheral vasoconstriction. The thermogenic effects of this drug, moreover, are enhanced during physiological activation, resulting in pathological brain hyperthermia. Since brain hyperthermia exacerbates drug-induced toxicity and is destructive to neural cells, uncontrollable use of amphetamine-like drugs under conditions restricting heat dissipation from the brain may result both in acute life-threatening complications and clinically latent but dangerous morphological and functional brain destruction.

**Key Words:** Brain, metabolism, cerebral blood flow, hyperthermia, metabolic neural activation, addictive drugs, emotional and physical activation, neurotoxicity.

## INTRODUCTION

Although the brain represents ~2% of the human body's mass, it accounts for ~20% of the total oxygen consumption, having a much greater metabolic rate than the rest of the body (Schmidt-Nielsen, 1997). Under resting conditions, neurons require several orders of magnitude more energy than other cells; the power consumption of a single central neuron is about 0.5-4.0 nW, 300-2500 times more than the average body cell (1.6 pW). The most energy used for neuronal metabolism is spent restoring membrane potentials after electrical discharges (Siesjo, 1978; Sokoloff, 1999), suggesting a basic relationship between electrical and metabolic neural activity. Significant energy, however, is spent by the CNS on neural processes not directly related to electrical activity of neurons, particularly for synthesis of macromolecules and transport of protons across mitochondrial membranes, which counteracts the proton leak in the opposite direction. Since all energy used for neural metabolism is finally transformed into heat (Siesjo, 1978), neural activity should be accompanied by heat release. This metabolic heat continuously dissipates from brain tissue, and brain

circulation appears to be the primary means of heat removal from the brain to the lungs and skin, and then to the external environment. While cerebral heat production and its removal are tightly balanced and brain temperature remains relatively stable under normal resting conditions, under several physiological and pathological conditions the balance may be shifted and brain hyperthermia may develop.

## BRAIN HYPERTHERMIA RESULTING FROM FUNCTIONAL NEURAL ACTIVATION: SOURCES, MECHANISMS, AND FUNCTIONAL ROLE

While it is generally believed that brain temperature is a stable, tightly regulated homeostatic parameter, relatively large temperature fluctuations ( $\pm 2-3^\circ\text{C}$ ) were found in animals exposed to various environmental challenges and engaged in different behaviors. Such fluctuations have been reported after exposure to various stressful, emotionally arousing, and even simply novel environmental stimuli (McElligott and Melzack, 1967; Moser *et al.*, 1993; Kiyatkin and Wise, 2001), during feeding (Abrams and Hammel, 1964) and sexual behavior (Blumberg *et al.*, 1987; Kiyatkin and Mitchum, 2003) and in the transition from sleep to wakefulness (Delgado and Hanai, 1966). Although several findings of early brain thermorecording studies support the idea that brain temperature fluctuations reflect primarily changes in metabolic neural activity (correlation

\*Address correspondence to this author at the Behavioral Neuroscience Branch, National Institute on Drug Abuse – Intramural Research Program, 5500 Nathan Shock, Baltimore, Maryland 21224, USA; Tel: (410) 550-5551; Fax: (410) 550-5553; E-mail: ekiyatki@intra.nida.nih.gov

between temperature fluctuations and biological significance of stimuli or behaviors, correlation between temperature and EEG changes, tight association of temperature change with sleep-wakefulness cycle, and localized temperature changes to visual and auditory stimuli in specific thalamic structures involved in processing of these stimuli), observed brain temperature fluctuations were generally correlative in different brain structures and associated with similar changes in body temperature. Therefore, the possible influence of body heat delivery to the brain in mediating brain hyperthermia could not be excluded.

### The Brain Source of Functional Brain Hyperthermia

To verify the source of physiological brain hyperthermia, we recorded temperatures simultaneously in several brain structures and in arterial blood in freely moving rats exposed to various environmental challenges ranging from simple sensory to known stressful stimuli (Kiyatkin *et al.*, 2002). Our arterial electrode was located in the tip of a polyethylene catheter implanted in the abdominal aorta (at the level of renal arteries) via the caudal artery. Although the carotid artery offers greater proximity to the brain, electrode placement here is problematic in rats because of inevitable partial occlusion of the vessel by the catheter. Any decrease in blood flow at the point of measurement would bring the measured temperature closer to that of the surrounding tissues as well as affect the brain's arterial blood supply, compromising temperature measurements from the brain. Instead, we measured arterial blood temperature in the warmest part of the body ("core"), where our catheter did not have a significant effect on blood flow. The brain and our aortal recording site, moreover, were approximately equidistant from the heart, and the blood reaching either site has little time for heat exchange into surrounding tissues.

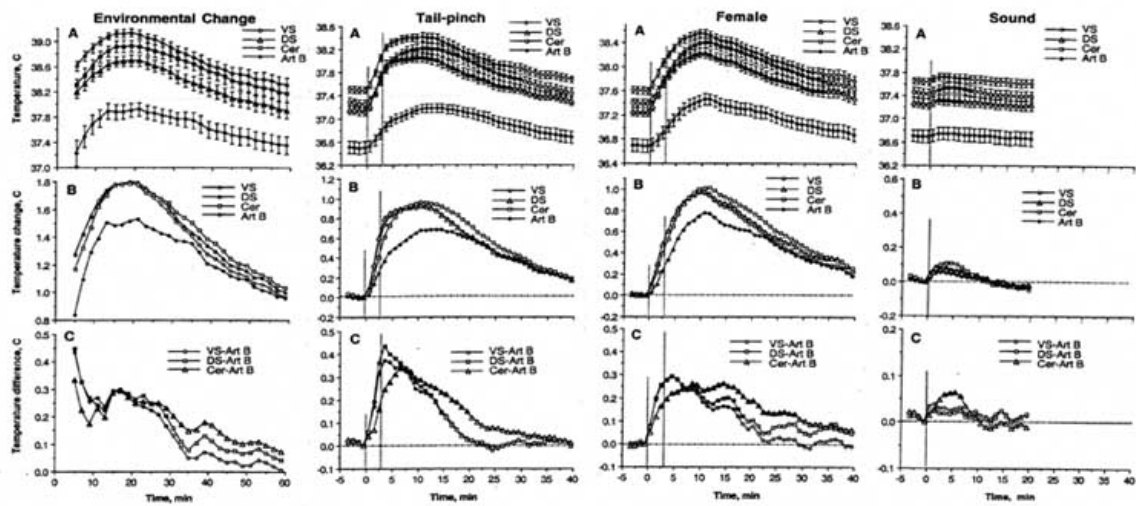
This study produced several findings summarized in (Fig. 1 and 2). First, each environmental challenge significantly affected brain temperature, inducing a unique, rapid, structure-specific, and relatively long elevation, which greatly exceeded the duration of stimulus presentation. Temperature elevation was minimal and shortest ( $\sim 0.1^\circ\text{C}$  for 6-7 min) after a 20-s sound stimulus, and maximal and most prolonged ( $\sim 1.8^\circ\text{C}$  for 2-4 hours) after the rat was placed in the testing chamber (environmental change). Social interaction between a recorded male and either male or female companions and 3-min tail-pinch were all accompanied by moderate temperature elevations ( $\sim 1^\circ\text{C}$  for 20-30 min). Second, the temperature of the arterial blood was consistently lower than that of any brain structure, and its increases were weaker and more delayed than those of any brain structure (Fig. 1A and B). This disparity resulted in a significant increase of the brain-arterial blood temperature differentials (C), which was especially evident in rapid time-course analysis. As shown in (Fig. 2), the increase in each brain structure occurs with shorter latencies (8-12 s until the change vs. baseline became significant) than that in arterial blood (30-40 s). Third, despite a general correlation, each brain structure had significantly different basal temperatures and showed a specific pattern of temperature response during different types of stimulation. Finally, brain temperature responses changed in consistent ways during repeated daily tests. While the elevation following tail-pinch, male-male,

and male-female social interactions remained relatively stable over 5 daily sessions, responses to sound showed a clear habituation with a complete disappearance of the response by the fifth day. The initial temperature increase associated with environmental change was relatively stable over repeated daily tests, but on each subsequent day temperatures decreased more quickly to lower levels, enhancing the relative response magnitude.

Given that the blood supply to the brain was cooler than the brain itself, and that brain temperatures rose more quickly and to a larger extent than arterial blood temperature in response to all challenges, intra-brain heat production appears to be the primary cause of functional brain hyperthermia. While arterial blood temperature also gradually increased in response to all challenges, brain vs. blood temperature differentials grew consistently during behavioral activation, showing an apparent increase in intra-brain heat production. Therefore, it seems that increased blood circulation removes heat from, rather than delivers heat to, the brain. Tail-pinch similar to that used in our study induced an almost two-fold increase in striatal blood flow (Fellows *et al.*, 1993), evidence that such a mechanism may exist. Similar to brain temperature, this increase was rapid and greatly exceeded the duration of stimulation. Phasic, large increases in striatal blood flow (80-120%) were also found to accompany grooming and eating (Fellows *et al.*, 1993), activities consistently associated with brain temperature increases (Kiyatkin and Wise, 2001). Brain circulation is therefore a significant factor in the redistribution of locally released heat within brain tissue, and a contributor to brain temperature fluctuations occurring under behavioral conditions.

Although numerous data suggest that increased brain metabolism is accompanied by increased brain circulation, and changes in general and local cerebral blood flow are widely used as a measure of functional brain activation, the relationships between brain metabolism and cerebral blood flow are complex and currently poorly understood (see Raichle, 2003; Mintun *et al.*, 2001 for review). While a discussion of these relationships are outside of the scope of our present review, changes in brain temperature may play an important role in coupling and adjusting local circulation to meet the demands of enhanced metabolism. While temperature is usually omitted from equations relating metabolism and blood flow (Yablonskiy *et al.*, 2000), direct relations between temperature and blood flow have been well established in peripheral tissues. An increase in local temperature was accompanied by linear and strong blood flow increases in skin (Charkoudian *et al.*, 2003; Ryan *et al.*, 1997), muscular tissue (Oobu, 1993), the intestine (Nagata *et al.*, 2000), and the liver (Nakajima *et al.*, 1992). This relationship has also been observed in brain tissue, as shown in monkeys (Moriyama *et al.*, 1990), rats (Uda and Tanaka, 1990), and humans (Nybo *et al.*, 2002). Increases in local brain temperature resulting from increased neural metabolism can therefore be understood as a factor that increases local blood flow.

The brain hyperthermia we observed was caused by a variety of stimuli. With the exception of sound, which caused only a momentary arousal response or no visible effect at all, behavioral activation always accompanied brain



**Fig. (1).** Changes in brain (VS, ventral striatum, DS, dorsal striatum, Cer, cerebellum) and arterial blood temperatures induced by various environmental challenges in freely moving rats. A, absolute temperatures; B, relative temperature change; and C, brain-blood differentials. Filled symbols indicate values significantly different from baseline.

hyperthermia. The present data, therefore, indicate that brain hyperthermia is not a response specific to stressful stimuli or events, unless, as has been proposed by Selye (1975), any stimulus successful in eliciting an arousal response is taken to be stressful to some degree. The “stress-induced” or “emotional” hyperthermia described both in animals (see Moltz, 1993 for review) and humans (Briese, 1995), and based largely on recording of “core” or rectal temperature, may best be viewed as a consequence of a more general phenomenon of “arousal-related” brain hyperthermia. On the other hand, arousal can be viewed not only as an electrophysiological phenomenon, but as a metabolic neural activation and functional brain hyperthermia.

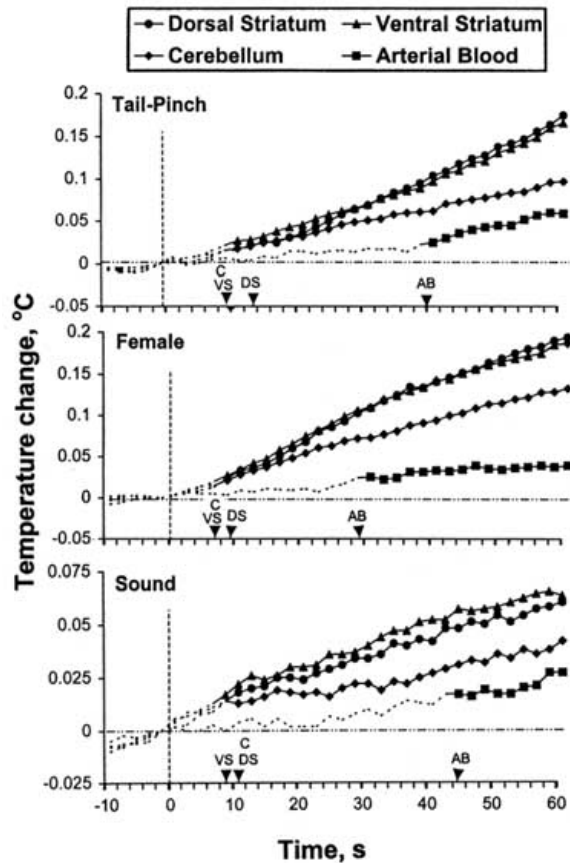
### Intra-Brain Temperature Gradients

Although different brain structures show a generally similar pattern of temperature fluctuations, their basal temperatures differ significantly. Temperatures recorded from more dorsally located structures (i.e., hippocampus) were up to 1°C lower than those of ventrally located structures (i.e., ventral striatum, ventral tegmentum of midbrain, hypothalamus), while the more centrally located thalamus and dorsal striatum had intermediate values (Kiyatkin and Wise, 2001; Kiyatkin *et al.*, 2002; Kiyatkin and Brown, 2003). Although these data support the dorso-ventral temperature gradient described in animal (Horvath *et al.*, 1999) and human brains (Schwab *et al.*, 1997; Mariack *et al.*, 2000), the reasons for this gradient are in dispute. One argument rests on the assumption that the blood, supplied to the brain from its basal arteries, is warmer than the brain (Andersen and Moser, 1995; Moltz, 1993; Moser and Mathiesen, 1996), and thus makes ventral structures warmer than more superficially located dorsal structures. This assumption, inferred from rectal or core body measurements is challenged by direct measurements of arterial blood

temperature, which, as discussed above, is always cooler than temperatures in any brain structure. Another point of view relates dorso-ventral temperature differences to the metabolic activity of neural tissue, specifically to the expression of brain uncoupling proteins that regulate uncoupling in mitochondria and local heat production (Horvath *et al.*, 1999). Structure-specific differences in brain metabolism may also manifest as known dorso-ventral differences in neuronal impulse activity. In the “cold” cortex, for example, a great majority of neural cells (>95-98%) are silent at rest, but show phasic activations as a result of either sensory or local glutamate-induced stimulations. The same is true for dorsal striatal cells, most of which (at least 90-95%) maintain electric silence in an awake, unrestrained rat at rest but show phasic stimuli- or glutamate-induced and movement-related excitations (Kiyatkin and Rebec, 1999). Additionally, most hypothalamic and ventral tegmental area neurons are spontaneously active at rest (Kiyatkin and Rebec, 1998) and maintain regular impulse activity even after being completely deprived from afferent inputs (pacemaker activity). It appears, therefore, that the difference in local brain metabolism (which may be reflected in neuronal activity) is the primary factor determining brain temperature gradients.

### Brain Temperature as a Factor Affecting Neural Functions

Although heat release is an obvious “by-product” of metabolic activation, the changes in brain temperature it triggers may play important adaptive and integrative roles, involving and uniting numerous central neurons within the brain. Heat that is locally generated within areas of high metabolism is rapidly distributed within the brain tissue via conduction and blood flow. Although this type of inter-neuronal communication is obviously not the main, nor the



**Fig. (2).** Onset of temperature responses induced by environmental challenges. Filled symbols show values significantly different from baseline.

most efficient, it may have adaptive significance. Since most physical and chemical processes governing neural activity are temperature-dependent, changes in brain temperature will not only reflect metabolic neural activity but also affect numerous neural functions. For example, dopamine uptake is known to double with a 3°C increase in temperature (Xie *et al.*, 2000), a range easily achieved in the brain under conditions of physiological activation. Since such a temperature increase affects the activity of ionic channels (particularly Na<sup>+</sup> and Ca<sup>++</sup>; Rosen, 1996, 2000), an increase in uptake should be compensated for by an increased dopamine release. By increasing both release and uptake, brain hyperthermia makes neurotransmission more efficient and neural functions more effective at reaching behavioral goals.

The distribution of locally generated heat within brain tissue results in global brain hyperthermia and a subsequent global circulatory response. Since this global temperature response may in most brain areas exceed local heat production, temperature can explain the well known but ill-understood phenomenon of excessive blood flow increase that exceeds metabolic activity of brain tissue (see Mintun *et al.*, 2001 for review). Thus, the brain is able to increase blood flow more and in advance of actual metabolic demands. This “anticipatory” metabolic activation therefore may provide a crucial advantage for successful goal-directed

behavior and the organism’s best adaptation to potential energetic demands. By increasing blood flow over its current demand, more oxygen and nutrients are delivered to the areas of potential demand and more potentially dangerous metabolic heat is removed from intensively working brain tissue.

### BRAIN HYPERTHERMIA RESULTING FROM A SHIFTED BALANCE BETWEEN HEAT PRODUCTION AND HEAT LOSS

While enhanced brain heat production associated with functional brain activation is accompanied by a compensatory increase in cerebral blood flow, limiting brain hyperthermia within physiological limits, brain hyperthermia may also develop during several situations associated with diminished ability to remove heat from the brain.

### Brain Hyperthermia During Intense Physical Exercise Under Harsh Environmental Conditions

Intense physical activity is associated with robust energy consumption and significant heat production in both animals and humans. Oxygen consumption in humans may increase up to 10-fold in the transition between quiet resting conditions and intense running (Schmidt-Nielson, 1997). This increase corresponds to whole-body metabolic heat production, which increases from ~1 W/kg at rest to ~10 W/kg during heavy exercise (Donaldson *et al.*, 2003). Enhanced heat production is typically compensated for by enhanced heat loss, resulting in a relatively stable body temperature. Yet under conditions of high environmental temperature and high humidity, restriction of heat loss from the organism may significantly increase body temperature. For example, individual body temperatures measured at the end of a marathon run on a warm day were found to be as high as 40°C and cases of fatigue during marathon running were associated with even higher temperatures (Chevront and Haymes, 2001). While 90-min of intense cycling in experienced cyclists at normal environmental temperatures increased body temperature less than 1°C, 2.0-2.5°C increases were found when participants cycled in water-impermeable suits that restricted heat loss via skin surfaces (Nybo *et al.*, 2002). The high effectiveness of heat loss mechanisms in humans depends on a well-developed ability to sweat and on a dynamic range of blood flow rates in the skin, which are much higher than those in other species. Skin blood flow in humans, for example, can increase from ~0.2-0.5 l/min in thermally neutral conditions, to 7-8 l/min under maximally tolerable heat stress (Rowell, 1983). Sweat rates under these conditions may reach up to 2.0 l/h, providing a potential evaporative rate of heat loss in excess of 1 kW (or ~14 W/kg). Thus, excessive heat production associated with intense physical activity may well be compensated for via adaptive mechanisms of heat loss. These mechanisms, however, become progressively less effective in hot, humid conditions.

Although robust body hyperthermia associated with intense physical activity under conditions that restrict heat loss is a known phenomenon, the impact of these conditions on the brain is a matter of intense speculation and controversy (Cabanac, 1998). Since the direct recording of

brain temperature in humans is usually impossible because of ethical considerations, tympanic temperature has been used as an indirect measure of brain temperature (Brinnet *et al.*, 1987; Cabanac *et al.*, 1987). From tympanic temperature measurements during exercise with and without active cooling of the head, it was concluded that brain temperatures during intense body heat production remain lower than body temperatures. This finding suggested selective brain cooling as a mechanism preventing brain over-heating under extreme body hyperthermia. While tympanic temperature was long considered to be a valid index of brain temperature, recent applications of more sophisticated physiological recordings called the existence of a brain cooling mechanism in humans into question (Nybo *et al.*, 2002; Nybo and Nielson, 2001). In these experiments, human volunteers were equipped with two thermosensor probes placed in arterial blood entering the brain (carotid artery) and venous blood exiting the brain (internal jugular vein). The temperature of venous blood exiting the brain should be equal or very close to brain temperature. At rest, a  $\sim +0.3^{\circ}\text{C}$  venous-arterial temperature difference was detected in these experiments. When the volunteers performed 40-min of cycling, both arterial and venous temperatures rapidly grew by about  $1^{\circ}\text{C}$  for the first 10-min and remained elevated for the entire period of exercise. Although the temperature of the arterial blood increased more strongly than venous temperature and the venous-arterial difference decreased, the difference always remained positive. This finding suggests that temperatures in the brain remain higher than those of arterial blood even under intense physical activity. When the cycling was done in water-impermeable suits, the increases were more dramatic (arterial from  $36.75$  to  $39.30^{\circ}\text{C}$ , venous from  $37.15$  to  $39.5^{\circ}\text{C}$  with individual changes up to  $40.4^{\circ}\text{C}$ ), but again the difference remained positive. After termination of exercise, arterial blood temperature rapidly dropped, while venous temperature decreased more slowly, and the venous-arterial difference reached  $0.9^{\circ}\text{C}$  before a slow return toward  $\sim 0.3^{\circ}\text{C}$  baseline values. Simultaneous measurements of tympanic temperatures in these experiments, moreover, revealed that their values are consistently lower than and independent of arterial and venous temperatures.

While diminished heat outflow from the brain appears to be the primary cause of intra-brain heat accumulation, physical exercise is also associated with increased brain metabolism (Ide and Secher, 2000; Ide *et al.*, 2000). Taking into account uptake of oxygen, glucose, and lactate, an almost two-fold increase in global brain metabolism was reported during 10-min intense cycling at normal environmental temperatures. Although cerebral blood flow increases during physical exercise and this increase is in excess of the increases in global cerebral metabolic activity (Ide *et al.*, 2000; Nybo *et al.*, 2002; Nybo and Nielson, 2001), cerebral blood flow gradually decreases during maximal exercise at hyperthermic conditions because of a hyperventilation-induced decrease in  $\text{CO}_2$  pressure (Nybo and Nielson, 2001). In contrast to more intense heat removal from the brain by blood flow during physical exercise under normal conditions, under hyperthermic conditions compromised cerebral blood flow is an additional and powerful factor restricting heat dissipation from the brain and determining intra-brain heat accumulation.

Although robust brain hyperthermia ( $\sim 39.5^{\circ}\text{C}$ ) did occur during intense cycling in harsh environmental conditions (Nybo *et al.*, 2002), such activity did not result in clear fatigue. Brain temperature associated with forced exercise-induced fatigue in rats was larger ( $40.1$ - $42.1^{\circ}\text{C}$ ; Walters *et al.*, 2000; latter value for hypothalamus) than that found in humans during self-motivated exercise ( $39.7$ - $40.3$ ; Nielson *et al.*, 2001). Thus, development of fatigue during intense exercise is an obvious protection against further brain overheating.

### Indirect Evaluations and Direct Measurements of Brain Temperature in Humans

While temperatures of venous blood exiting the brain have been viewed as the best indirect measure of brain temperature in humans, direct temperature measurements in the brain, jugular bulb, and core body in head-injured patients revealed unexpected differences between these areas (Rumana *et al.*, 1998). Temperatures in the brain (evaluated intraparenchymally at a depth of 1-2 cm from dura surface) were found to be  $\sim 1.1^{\circ}\text{C}$  higher than that in the jugular vein, which was similar to core body temperature. Although these data were obtained in neurological patients, they suggest that the use of jugular vein temperatures as an index of brain temperature (Nybo *et al.*, 2002) may in fact underestimate real brain temperatures. One cause of this underestimation is associated with the procedural features of jugular vein temperature measurement. Since venous blood flow is slow and the catheter with the thermosensor is in tight contact with the vessel's walls, the measured temperatures are influenced by cooler neighboring tissues and thus are lower than brain temperature.

A similar dissociation between jugular vein temperature and brain temperature was confirmed in another human study also made in patients with head injury (Mariak *et al.*, 1998). Like the study of Rumana *et al.*, this study confirmed that brain temperatures (both in brain surface and in ventricles) are higher than trunk temperatures, and showed that jugular temperatures correlate well with rectal temperature but weakly with brain temperature. Brain temperatures in humans remained higher than body temperature not only during normothermic conditions, but also during fever, suggesting that the human brain has no specific protection against thermal impact (Mariak *et al.*, 1998; 2000). On the other hand, brain temperatures decreased more sharply and became much lower than trunk temperatures during anesthesia (Mariak *et al.*, 1999), obviously reflecting metabolic brain inhibition induced by anesthetic drugs. Finally, these studies also demonstrated that insufficient heat outflow from the brain may result in robust brain hyperthermia even under conditions of strong decrease in brain metabolism.

If jugular venous measurements underestimate brain temperature, the real temperature difference between brain and arterial blood temperature under resting conditions may be greater than  $0.3^{\circ}\text{C}$  (Nybo *et al.*, 2002), as suggested by our measurements in rats (Kiyatkin *et al.*, 2002). The hippocampus, for example, was about  $0.6^{\circ}\text{C}$  warmer than arterial blood and this difference was about  $0.9^{\circ}\text{C}$  for the ventral striatum. A greater difference between brain and blood tem-

perature is also suggested by direct measurements of brain temperature in human patients (Mariak *et al.*, 1999). These data confirmed a  $\sim 0.6^\circ\text{C}$  dorso-ventral temperature gradient in the human brain and showed that temperatures in the most dorsally located brain site (subdural space) remain higher than those of the trunk during both normothermia and fever.

### **BRAIN TEMPERATURE AS A FACTOR INDUCING OR POTENTIATING NEURONAL DAMAGE**

Similar to systemic hyperthermia (fever), which is adaptive within some limits but may rise to pathological levels, it is quite difficult to draw the line between physiological and pathological brain hyperthermia. It is important, however, to realize that brain temperature increase above some limit has a direct destructive action on brain cells, which will increase exponentially with even slight increases above this limit. For example, 79% of bovine endothelial cells survived in culture at  $37^\circ\text{C}$  incubation temperature, but survival dropped to 9.0 and 0.2% at 41 and  $43^\circ\text{C}$ , respectively (Lin *et al.*, 1991). In another model, normal pulmonary fibroblasts completely stopped proliferation at  $41.0^\circ\text{C}$  (Iwagami, 1996). Finally, in lung cells morphologically verified onset of hyperthermic cell death occurred between  $40\text{--}41.5^\circ\text{C}$  (Lepock *et al.*, 1983). While all tissues are sensitive to hyperthermia, the brain and testicles are among the most sensitive organs (Dewhirst *et al.*, 2003). The most temperature-sensitive cellular elements are mitochondrial and plasma membranes, in which irreversible transitions in protein structure or arrangements begin to occur at temperatures higher than  $40^\circ\text{C}$  (Lepock *et al.* 1983; Iwagami, 1996; Lepock, 2003). Thus, brain temperature increase above  $40\text{--}41.0^\circ\text{C}$  may be considered as a threshold of pathological hyperthermia.

This threshold, however, is different in animals of different species ( $\sim 0.5^\circ\text{C}$  lower in rodent than human cells; Dewhirst *et al.*, 2003) and depends on animal age (lower in younger and higher in older animals). Although all brain tissue cells were affected by high temperature, destruction of endothelial cells of the brain and spinal cord and leakage of serum proteins across the brain-blood barrier (Sharma and Hoopes, 2003) are the most important factors determining brain edema, the most dangerous acute complication of pathological brain hyperthermia (Dewhirst *et al.*, 2003; Kalant, 2001). Heat-induced damage occurred in the cerebral cortex, hippocampus, cerebellum, thalamus, hypothalamus and brain stem; the damage was usually stronger within the edematous areas of the brain, suggesting edematous swelling as an important co-factor of heat-induced damage of brain tissue. Heat-induced brain injury is not limited to neural cells and includes glial cells and cerebral microvessels. While these changes occur within the whole brain, some brain areas are especially vulnerable to damage. For example, heat-induced increase in blood-brain barrier permeability was maximal in cingulate and occipital cortex and cerebellum (where edema was also maximal), but less in hypothalamus and thalamus. In contrast, maximal axonal damage, detected by myelin basic protein staining, was prominent in brain stem reticular formation, pons, medulla, and the spinal cord (Sharma *et al.*, 1998). Along with myelin basic protein, an index of axonal damage, several other immunomarkers were recently identified as factors activated by extreme brain

hyperthermia. It is not always clear, however, whether these factors induce brain damage or they are an index of occurred brain damage, or a part of adaptive mechanisms of heat-induced brain repair. For example, excessive body hyperthermia ( $\sim 41^\circ\text{C}$ ) induced by environmental heat induces marked alterations in carbon monoxide (CO) and nitric oxide (NO), detected by nitric oxide synthase and heme oxygenase immunoreactivity (Sharma *et al.*, 1998); up-regulation of these enzymes was found in many brain areas, including the cortex, hippocampus, cerebellum, thalamus, hypothalamus and spinal cord, which do not normally exhibit activity of these enzymes. The immunoreactivity was mainly confined with the cytoplasm of the neurons and dendrites. The functional role of these factors, however, is not well characterized. Excessive hyperthermia also results in expression of heat shock proteins (Welsh, 1992) that is a reliable index of thermal injury in a form of denatured protein (Lepock, 2003). These proteins appear to play an important role as endogenous neuroprotectors by binding partially folded and misfolded proteins, thus preventing their irreversible denaturation (Bouchama and Knochel, 2002). These proteins also play an important role in thermotolerance (King *et al.*, 2002). Since these proteins are also expressed during hypoxia, ischemia, heat trauma, neurodegenerative disease, and epilepsy (Reynolds and Allen, 2003), they are obviously a non-specific marker of neural damage and important part of endogenous neuroprotective mechanisms activated by all these pathological conditions.

Although most data on thermal damage of neural cells were obtained either *in vitro* or in animals exposed to extreme environmental heat, its damaging effect on brain functions significantly depends on brain's activity state. With the same exposure to environmental heat ( $38^\circ\text{C}$  for 4 hours), body hyperthermia and breakdown of brain-blood barrier (evaluated by edema) were much stronger in conscious than in anesthetized rats (Sharma and Hoopes, 2003). Therefore, metabolic neural activation induced by exposure to a hot environment is a significant contributor of the adverse outcome of environmental heat. This factor may be also important for "heat-induced" brain injury and subsequent neurological complications in professional athletes and military recruits.

Although high temperature *per se* may be a factor in cellular damage, more often it is a potentiating factor. An increased temperature strongly increases neural damage induced by experimental hypoxia, ischemia, and cerebral trauma in animals and hypothermia has a neuroprotective action (see Maier and Steinberg, 2003; Miyazawa *et al.*, 2003; Olsen, 2003 for review). Animal research also suggests that temperature is a strong potentiating factor for several mechanisms involved in neurotoxic damage occurring during ischemia, hypoxia, and brain trauma. For example, hyperthermia strongly potentiates the cytotoxic effects of reactive oxygen species *in vitro* (Lin *et al.*, 1991) and glutamate-induced neurotoxicity (Suehiro *et al.*, 1999). While prevention of fever and mild hypothermia may be important therapeutic tools to minimize the extent and severity of neural damage associated with these pathological conditions (see Maier and Steinberg, 2003 for review), it is unknown how brain temperature is changed during these situations. Without this crucial information, it is quite

difficult to establish the role of brain temperature as a contributing factor of neurotoxicity. The changes in temperature, however, may be an important factor for neuroprotective action of various pharmacological drugs. For example, HU-210, a synthetic cannabinoid agonist that decreased body temperature, effectively diminished ischemic damage induced by middle cerebral artery occlusion; this brain-protective effect was completely abolished by warming of the animals to the levels observed in control conditions (Leker *et al.*, 2003). The same was true for MK-801, a non-competitive NMDA receptor antagonist, another putative neuroprotective drug (DeBow and Colbourne, 2003). Temperature is also a known factor determining neurotoxic effects of some addictive drugs. These effects will be considered in detail in the next section.

### **BRAIN HYPERTHERMIA INDUCED BY ADDICTIVE DRUGS AS A REFLECTION OF DRUG-INDUCED METABOLIC ACTIVATION**

All addictive drugs induce behavioral, autonomic, and psycho-emotional stimulation (Wise and Bozarth, 1987; Wise, 2002), which may reflect metabolic neural activation, a presumed common feature of all addictive drugs. Opiates at low doses, for example, increased whole-body oxygen consumption and heat production (Lynch *et al.*, 1990; Pavlov and Epstein, 2003), parameters that point to metabolic activation, while they decreased these parameters at higher doses (Endoh *et al.*, 1999). Large doses of opiates also decrease cerebral blood flow (Zamani *et al.*, 2000), but either no changes or increases were induced by morphine and heroin at low doses (Fuller and Stein, 1991; Schlaepfer *et al.*, 1998). Cocaine used in drug-naïve animals also increased cerebral oxygen consumption (Robinson *et al.*, 2000), body temperatures (Ansah *et al.*, 1996), and cerebral blood flow (Robinson *et al.*, 2000; Howell *et al.*, 2002; Marota *et al.*, 2000), although preferential decreases in cerebral blood flow were reported in experienced drug users expecting drug administration (Gollub *et al.*, 1998; Li *et al.*, 2000). Metabolic activation is also typical to amphetamine-like substances (i.e., amphetamine, meth-amphetamine (METH), and MDMA) (Green *et al.*, 2003), nicotine (Perkins *et al.*, 1996; Jessen *et al.*, 2003), cannabinoids (Cota *et al.*, 2003), and ketamine (Langsjo *et al.*, 2003), an anesthetic abused by humans as a recreational drug.

### **Pathological Brain Hyperthermia Induced by METH and Its Modulation by Environmental Conditions**

METH and related amphetamine-like compounds (i.e., 3,4-methylenedioxymethamphetamine or MDMA) are addictive drugs that can cause serious health problems ranging from acute toxicity and mortality to brain damage with chronic use (Davidson *et al.*, 2001; Green *et al.*, 2003; Kalant, 2001; Rawson *et al.*, 2002). Since these substances induce abnormal release of various endogenous transmitters, including glutamate and catecholamines (Stephens and Yamamoto, 1994; Ohmori *et al.*, 1996; Seiden and Sabol, 1996), some toxic products of their metabolism (i.e., nitric oxide, catechol-quinones, peroxy-nitrite, and arachidonic acid) are usually considered primary contributors to neural cell damage via oxidative stress (Spina and Cohen, 1989; Lipton and Rosenberg, 1994; Kuhn and Geddes, 2000; Cadet *et al.*,

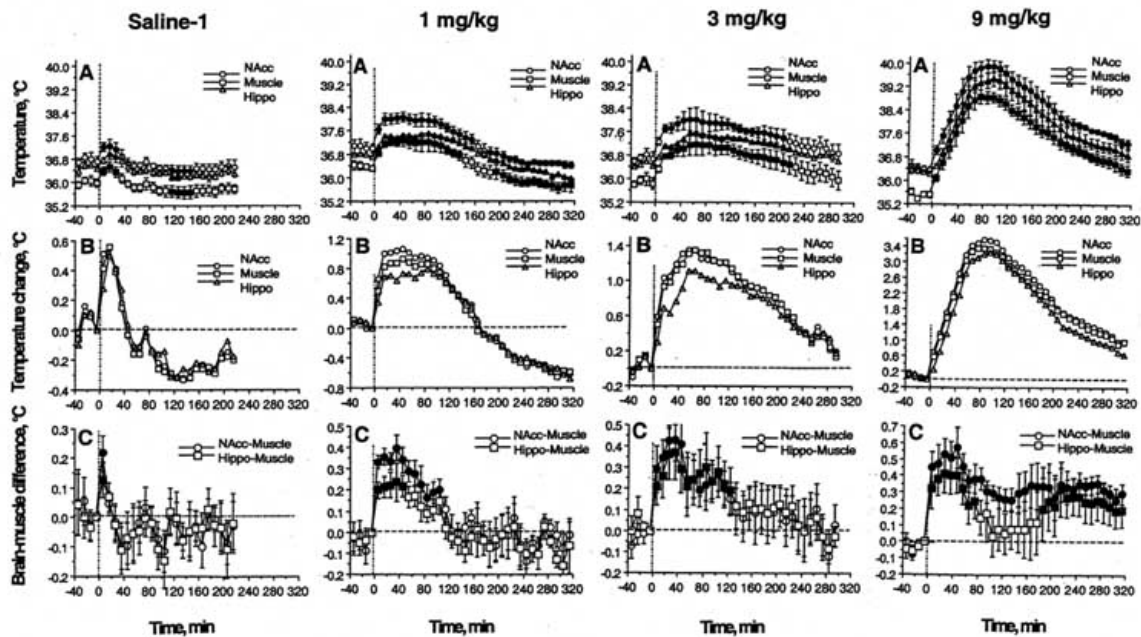
2001). These drugs are also known to cause hyperthermia in both humans (Kalant, 2001) and rodents (Sandoval *et al.*, 2000; Mehan *et al.*, 2001), which appears to contribute to both the acute mortality and neurotoxicity induced by these drugs. Hyperthermia potentiates dopamine and tyrosine-hydroxylase depletion, astrocytosis, and oxidative stress (Omar *et al.*, 1987; Lin *et al.*, 1991), whereas hypothermia protects against these effects (Bowyer *et al.*, 1993, 1994; Miller and O'Callaghan, 1994).

Although the pattern of body hyperthermia after administration of METH is well known (Sandoval *et al.*, 2000), associated changes in brain temperature and their relationships to body hyperthermia have not been thoroughly examined. Since amphetamine-like drugs are typically consumed in social situations (see Kalant *et al.*, 2001 for review), which are accompanied by brain and body hyperthermia, we evaluated the changes in brain and body temperature induced by METH in rats under both quiet resting conditions and during social interaction with another animal (Brown *et al.*, 2003).

Figure (3) shows that METH injected under quiet resting conditions induced dose-dependent brain and body hyperthermia. In contrast to transient temperature increases after exposure to salient environmental stimuli (see Fig. 1), METH-induced elevation was stronger and much more prolonged. At the lowest dose (1 mg/kg), the increase was significant for more than 2 hours, and it exceeded 5 hours at the largest dose (9 mg/kg). While at 1 mg/kg the amplitude of temperature elevation was about 1°C, i.e. within the range occurring under physiological conditions, the increase exceeded 3.5°C (or ~ 40°C) at 9 mg/kg, i.e. well above the physiological range. Similar to physiological brain hyperthermia, the increases in each brain structure were more rapid and stronger than in the muscle, resulting in significant increase in brain-muscle differentials. While this observation suggests that brain metabolic activation is the primary source of observed brain hyperthermia and a force behind more delayed and weaker body hyperthermia, this increase in brain-muscle differentials was much larger (up to 0.5°C) and longer (>5 hours) than that occurring under physiological conditions. Increased body temperature, a most dangerous symptom of METH over-dose intoxication, is, therefore, a consequence of excessive metabolic brain activation induced by the drug. Since this activation exceeds the physiological limits both in amplitude and duration of temperature response, it may be viewed as "pathological."

When the effects of METH were tested in animals during social interaction (presence of female), the hyperthermic effects significantly increased (see Fig. 4A). Similarly, changes in brain-muscle differentials were more profound and long-term than those seen after drug administration during quiet resting conditions (B).

The present data underscore the importance of both the activity state of an individual and the environment in determining the hyperthermic effects of METH. These drug-state and drug-environment interactions are important in mediating both the acute adverse drug's effects and the slow neurotoxic action typical to its chronic use over extended periods of time. Since a wide range of activated conditions is associated with brain hyperthermia and these drugs by



**Fig. (3).** Changes in brain (NAcc, Nucleus accumbens; Hippo, hippocampus) and muscle temperature induced by meth-amphetamine (1, 3, and 9 mg/kg, sc) under quiet resting conditions. A, absolute temperatures, B, relative temperatures; and C, brain muscle differentials.

themselves induce brain hyperthermia, drug use under these conditions will result in stronger effects. As the neurotoxic effects of METH and other amphetamine-like drugs are temperature-dependent (Bowyer *et al.*, 1993, 1994; Alberts and Sonsalla, 1995; Davidson *et al.*, 2001), neurotoxic action should also be stronger when the drug is used under activated conditions.

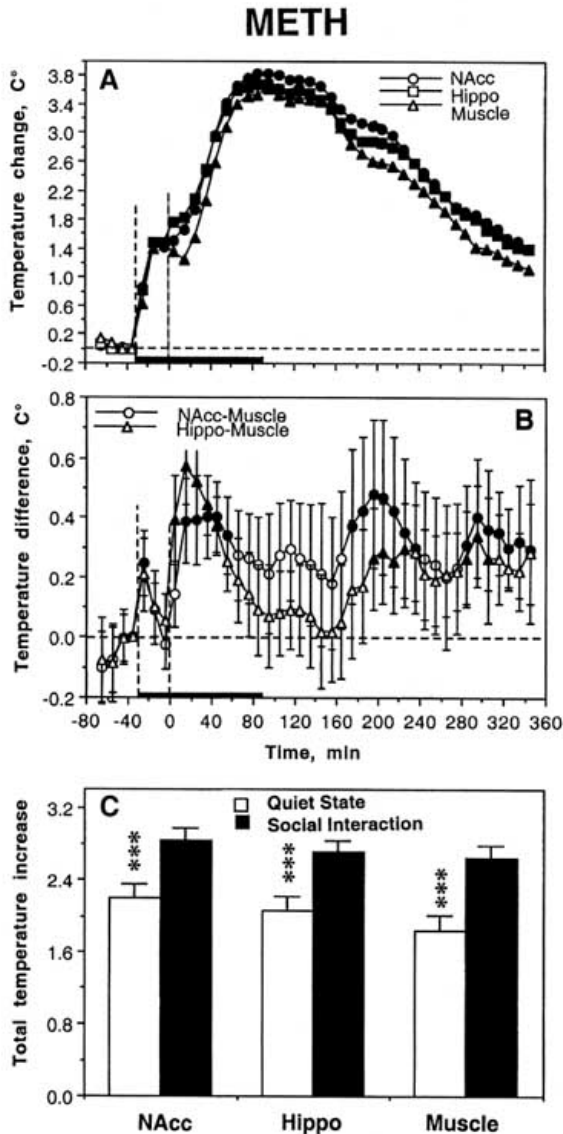
While enhanced intra-brain heat production is an obvious source of brain hyperthermia induced by amphetamine-like substances, diminished heat dissipation because of peripheral vasoconstriction (Pederson and Blessing, 2001) should not be overlooked as a contributor. Vasoconstriction would lead to a decreased ability to dissipate heat from the skin surface to the environment, thus increasing the existing hyperthermia. This hyperthermia will be stronger when the drug is used in association with high physical and emotional activity, and under conditions restricting heat loss from the organism. Under these conditions, body and brain heat production is increased (Nybo *et al.*, 2002), adaptive increases in cerebral blood flow are slowed (Nybo and Nielson, 2001) (because of hyperventilation-induced decrease in arterial CO<sub>2</sub> tension), and peripheral heat loss is strongly impaired. Therefore, it is a combination of specific activity state and environmental conditions coupled with individual drug predisposition that makes amphetamine-like substances especially dangerous. While pathological hyperthermia is a dangerous symptom of acute intoxication induced by amphetamine-like drugs, it is also a factor inducing irreversible damage of mitochondria and cell death (Iwagami, 1996; Lepock, 2003; Willis *et al.*, 2000). Since

hyperthermia strongly potentiates toxicity (Gordon *et al.*, 1991; Lyles and Cadet, 2003; Miller and O'Callaghan, 1995; Seiden and Sabol, 1996), brain hyperthermia is also a significant factor potentiating neurotoxicity—another dangerous complication of chronic use of amphetamine-like substances.

### Brain Hyperthermia and Phasic Temperature Fluctuations During Heroin and Cocaine Self-Administration Behavior

In contrast to METH, whose thermogenic effects increased with drug dose and were strongly potentiated by physiological activation, predisposing individuals to pathological brain hyperthermia and thus, in the long run, to neurotoxicity, other tested addictive drugs induce quite different changes in brain temperature.

Heroin is a representative addictive drug and its recreational use rapidly results in the development of heroin dependence, manifesting in compulsive drug-taking behavior. Recently, we investigated brain and body temperature dynamics during intravenous (iv) heroin self-administration (SA) in rats (Kiyatkin and Wise, 2002). Rats were chronically implanted with thermal probes in several brain structures and temporal muscle and trained to press a lever for iv heroin injection (0.1 mg/kg). Temperatures were recorded with high temporal resolution and changes were analyzed in drug-experienced, trained animals with respect to key events of drug-seeking and drug-taking behavior.



**Fig. (4).** Mean changes in brain and body temperature (A) and brain-muscle differentials (B) induced by methamphetamine injected during social interaction. Filled symbols indicate values significantly different from pre-injection baseline. Duration of social interaction is shown on time lines. (C) shows differences in hyperthermic response induced by METH used under quiet and activated conditions. With respect to each recording point, the total drug-induced temperature increase was significantly larger under activated than quiet conditions.

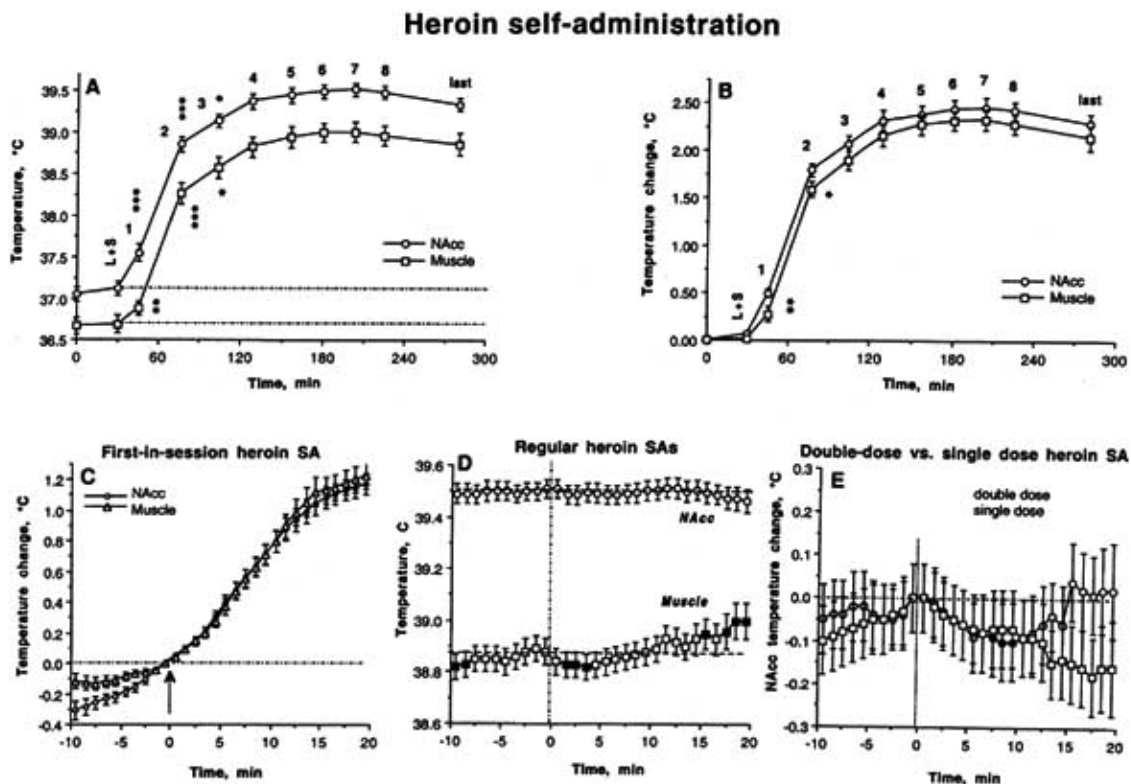
As shown in (Fig. 5), brain and muscle temperature were strongly elevated during heroin SA. The maximal temperature increase, however, occurred after the first-injection SA and after one or two more SAs, temperatures stabilized at elevated and relatively stable plateau ( $\sim 2.3^{\circ}\text{C}$  above baseline or  $39.5^{\circ}\text{C}$ ) for the remainder of the session (A and B). Interestingly, brain temperature also increased preceding the first heroin self-injection (C), obviously

reflecting behavior-related brain activation, similar to that occurring during natural motivated behavior (Kiyatkin and Mitchum, 2003). Similar to physiological neural activation, temperatures in brain sites increased during this period more rapidly and stronger than in the muscle. This rapid and strong ( $\sim 1.25^{\circ}\text{C}$ ) temperature elevation induced by the initial heroin SA occurred at the time, when the rat became transiently hypoactive (freezing) after the injection and continued when the rat became hyperactive again before the second SA. When temperatures reached plateau, they maintained at stable levels despite highly cyclical drug intakes accompanied by biphasic fluctuations in movement activity (freezing followed by hyperactivity). While nucleus accumbens temperatures showed no significant fluctuations in association with regular drug SAs, weak biphasic fluctuations (decrease followed by increase) were seen in the muscle (D). Finally, brain temperature slightly decreased after heroin SA at the double dose ( $0.2\text{ mg/kg}$ ) but returned to the same plateau levels and remained stable at the moment of the next SA (E).

Robust brain hyperthermia seen during heroin SA agrees with the known stimulatory action of opiates on brain metabolism (Lynch *et al.*, 1990; Pavlov and Epstein, 2003), although peripheral vasoconstriction and inhibition of respiration may also be contributing factors. This hyperthermia also reflects behavior-related neural activation, a force that triggers drug-seeking behavior and determines the initial drug intake. While brain and body temperature significantly increased at the start of drug-taking behavior, temperatures remained at enhanced, stable plateau levels during subsequent drug intakes. Therefore, although heroin induced brain hyperthermia, this hyperthermia was tightly "regulated" via behavioral regulation of drug intakes. Such tight behavioral regulation of drug intakes and a known inversion of opiate-induced metabolic activation and body temperatures with dose increase, obviously determine the lack of neurotoxicity induced by these drugs even with long-term intense use (Gradert *et al.*, 2003).

Another pattern of brain temperature fluctuations were found during cocaine SA (Kiyatkin and Brown, 2003). Similar to our heroin experiments, rats were chronically implanted with temperature probes in several brain structures and temporal muscle and trained to press a lever for iv cocaine infusion ( $1\text{ mg/kg}$ ). Temperature data were analyzed in trained animals with respect to major behavioral events. Fig. (6) shows major results of this study (Kiyatkin and Brown, 2003).

While some aspects of temperature changes occurring during cocaine SA were similar to those occurring during heroin SA, other changes were quite different, obviously reflecting a different pharmacological action of cocaine. Similar to heroin SA, trained rats self-administering cocaine showed a gradual and relatively strong temperature increase ( $\sim 0.4^{\circ}\text{C}$ ) before the first drug intake (A and B). Similarly, this elevation was more rapid and stronger in each brain site than in the muscle and was tightly related to pre-press behavioral activation. Therefore, this aspect of brain hyperthermia reflects neural activation associated with drug-seeking behavior, a force that determines drug seeking and results in the initial drug intake. Although temperature



**Fig. (5).** Changes in brain (NAcc, nucleus accumbens) and muscle temperatures during heroin self-administration (SA) in trained rats. (A and B) show changes in absolute and relative temperatures averaged for each consecutive drug SA. L+S, the moment of light+sound presentation, when the lever became accessible and the rat could press a lever. Asterisks show values significantly different from the previous value. (C) shows temperature changes associated with the first-in-session heroin SA (arrow). (D) shows temperature changes associated with regular heroin SAs (filled symbols indicate values significantly different from the last pre-lever-press value (hatched line)). (E) shows differences in temperature changes after a typical single-dose (0.1 mg/kg) and double-dose (0.2 mg/kg) heroin SAs.

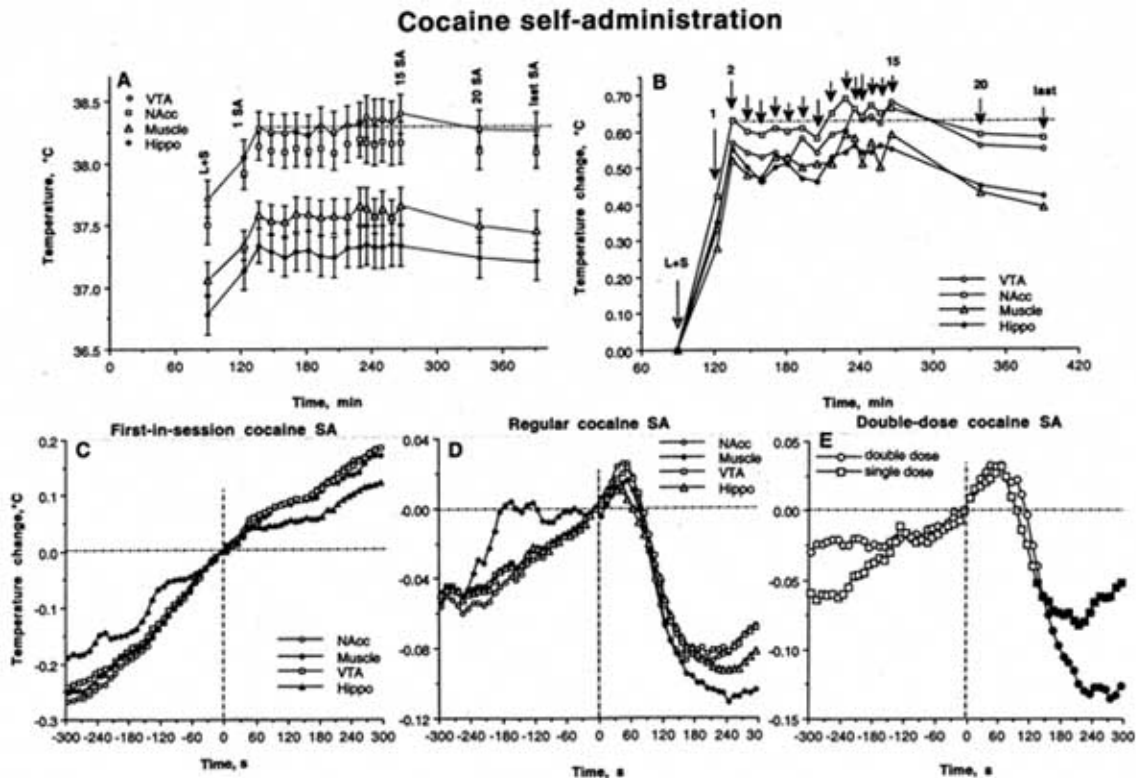
increase continued for some time after the first cocaine injection (C), it was much smaller than that induced by the first heroin injection. Subsequent highly cyclical cocaine SAs were associated with consistent rapid biphasic temperature fluctuations (D) that occurred at the relatively stable tonic plateau levels; this tonic elevation was much smaller than that for heroin and well within the physiological range. Brain temperatures rapidly decreased from ~60 to 210 s after the drug infusion and then gradually increased again, reaching a new peak (but at the same levels) near the moment of the next self-injection. The timing of this temperature fluctuation was around 7-8 min, exactly the modal value of inter-SA intervals. When, instead of a standard 1 mg/kg, the dose of injected drug was doubled (2 mg/kg over 30 s), temperature decreased stronger (E) and for a longer period of time before the rat made the next self-injection.

Although cocaine induces metabolic neural activation, our results suggest that this activation is dramatically modulated by environmental and behavioral variables and depends upon the previous drug effect. With repeated SAs,

cocaine has a biphasic activity pattern, abruptly and transiently inhibiting pre-injection, drug- and behavior-related activation and then inducing activation again. Because of these biphasic fluctuations, which are tightly behaviorally regulated, brain temperature remains very stable during cocaine SA, thus protecting the brain from neurotoxicity. However, cocaine also has a strong vasoconstrictive action, diminishing heat dissipation from the body. Thus, cocaine used during physiological activation in a hot, humid environment, may result in a stronger intra-brain heat accumulation, a higher brain temperature elevation and thus greater adverse effects (Crandall *et al.*, 2002).

## CONCLUSIONS

While the brain plays an essential role in temperature regulation, it is unclear whether the idea of thermoregulation and temperature homeostasis can be applied to the brain itself. The data presented in this review demonstrate that functional neural activation (increase in neural metabolism) in a temperature-neutral and stable environment is accompanied by intra-brain heat production and relatively large



**Fig. (6).** Changes in brain (NAcc, nucleus accumbens; VTA, ventral tegmental area of midbrain, Hippo, hippocampus) and muscle temperatures during cocaine self-administration (SA) in trained rats. (A and B) show changes in absolute and relative temperatures averaged for each consecutive drug SA. L+S, the moment of light+sound presentation, when the lever became accessible and the rat could press a lever. (C) shows temperature changes associated with the first-in-session cocaine SA. (D) shows temperature changes associated with regular cocaine SAs. (E) shows differences in temperature changes after a typical single-dose (1.0 mg/kg) and double-dose (2.0 mg/kg) cocaine SAs.

brain hyperthermia. Hyperthermia therefore is not only a sign of infection or illness but a normal physiological phenomenon that can be enhanced by interaction with common elements of an organism's environment. This hyperthermia is accompanied by an increase in cerebral blood flow, which not only provides oxygen and nutrients for enhanced brain metabolism but also removes potentially dangerous metabolic heat from brain tissue. Because of the temperature-dependence of most physical and chemical processes occurring in the brain, 2-3°C temperature increases occurring under behavioral conditions are sufficient to alter numerous neural functions. Thus, brain temperature increase may have adaptive significance, making neural functions more efficient and serving as more than a "by-product" of neural activity.

While brain hyperthermia associated with physiological and behavioral activation is a transient phenomenon, under several conditions brain temperature increase may exceed physiological limits, producing destructive effects on neural cells and functions of the brain as a whole. First, brain overheating may occur when living beings are exposed to a

hot, humid environment, which restricts heat loss from the organism. While the extreme thermal impact is an obvious cause of this hyperthermia, the organism's activity state and associated physical and behavioral activation are also important contributors. Second, significant intra-brain heat accumulation may occur as a result of excessive physical activity under conditions that diminish heat dissipation to the external environment. This accumulation may be blocked by exercise-induced fatigue, a manifestation of extreme brain tissue overheating and a pathological condition by itself. Third, brain hyperthermia may be induced by various pharmacological drugs, which produce metabolic brain activation and restrict heat loss from the organism. This phenomenon may have important health implications for understanding both acute and chronic adverse effects of addictive drugs that are used uncontrollably, in association with high levels of emotional and physiological activation, and often under conditions restricting heat dissipation from the brain and organism.

Although all addictive drugs induce metabolic neural activation, each has its own dose-dependent effect on brain

and body temperatures. These effects, moreover, are significantly modulated by an individual's activity state and environmental conditions, showing dramatic alterations during the development of drug-taking behavior. While for some drugs, brain metabolism and thermogenic activity invert with increases in dose (i.e., heroin, cocaine, and ketamine), protecting the brain from excessive over-heating, amphetamine-like substances (i.e., METH, MDMA or Ecstasy) have dose-dependent stimulatory effects on brain metabolism, also strongly diminishing heat dissipation because of peripheral vasoconstriction. The thermal effects of these drugs, moreover, are enhanced during activated states, resulting in dangerous brain overheating. Since brain hyperthermia exacerbates drug-induced toxicity and is destructive to neural cells and brain functions, uncontrollable use of these "recreational" drugs under activated conditions that restrict the organism's heat loss may pose a significant health risk, resulting both in acute life-threatening complications and chronic destructive CNS changes.

This review is the first one devoted to brain hyperthermia as a phenomenon that can occur during various physiological and pathological conditions. Although brain temperature is an important homeostatic parameter affecting various neural functions, our knowledge on brain temperature fluctuations is limited and many important questions relating temperature to neuronal activity, brain metabolism and circulation remain unanswered. Also, almost nothing is known about human brain temperature fluctuations under physiological and pathological conditions. Although most neuroscientists overlook brain temperature, data reviewed above suggest that brain thermorecording is an important tool for evaluating neural activity state and functional neural activation. Through brain thermorecording new data may be obtained on the central effects of addictive drugs under conditions that mimic human drug use, the neural mechanisms underlying addictive behavior, and factors determining the acute and chronic adverse effects of these drugs. Finally, brain temperature is important for clinical neuroscientists and clinicians because excessive brain overheating may develop during several pathological conditions and may directly damage neural cells, greatly disturb brain functions, and strongly potentiate the destructive action of various endogenous and exogenous neurotoxic agents. Although brain temperature is usually inaccessible, medical professionals may use the temperature of patients as a guide for their clinical state and treatment, and as a predictor of the efficacy of medical intervention.

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## REFERENCES

Abrams, R, Hammel, HT. (1964) Hypothalamic temperature in unanesthetized albino rats during feeding and sleeping. *Am J Physiol* **206**: 641-646.

- Alberts, DS, Sonsalla, PK. (1995) Methamphetamine-induced hyperthermia and dopaminergic neurotoxicity in mice: Pharmacological profile of protective and nonprotective agents. *J Pharmacol Exp Ther* **275**: 1104-1114.
- Andersen, P, Moser, EI. (1995) Brain temperature and hippocampal function. *Hippocampus* **5**: 491-498.
- Ansah, TA, Wade, LH, Shockley, DC. (1996) Changes in locomotor activity, core temperature, and heart rate in response to repeated cocaine administration. *Physiol Behav* **60**: 1261-1267.
- Blumberg, MS, Mannella, JA, Moltz, H. (1987) Hypothalamic temperature and deep body temperature during copulation in the male rat. *Physiol Behav* **39**: 367-370.
- Bouchama, A, Knochel, JP. (2002) Heat stroke. *N England J Med* **346**: 1978-1988.
- Bowyer, JF, Gough, B, Slikker, W Jr, Lipe, GW, Newport, GD, Holson, RR. (1993) Effects of a cold environment or age on methamphetamine-induced dopamine release in the caudate putamen of female rats. *Pharmacol Biochem Behav* **44**: 87-98.
- Bowyer, JF, Davies, DL, Schmued, L, Broening, HW, Newport, GD, Slikker, W, Holson, RR. (1994) Further studies of the role of hyperthermia in methamphetamine neurotoxicity. *J Pharmacol Exp Ther* **268**: 1571-1580.
- Briese, E. (1995) Emotional hyperthermia and performance in humans. *Physiol Behav* **58**: 615-618.
- Brinnel, H, Nagasaka, K, Cabanac, M. (1987) Enhanced brain protection during passive hyperthermia in humans. *Eur J Appl Physiol Occup Physiol* **56**: 540-545.
- Brown, PL, Wise, RA, Kiyatkin, EA. (2003) Brain hyperthermia is induced by methamphetamine and exacerbated by social interaction. *J Neurosci* **23**: 3924-3929.
- Cabanac, M. (1998) Selective brain cooling and thermoregulatory set-point. *J Basic Clin Physiol Pharmacol* **9**: 3-17.
- Cabanac, M, Germain, M, Blinnel, H. (1987) Tympanic temperatures during hemiface cooling. *Eur J Appl Physiol* **56**: 534-539.
- Cadet, JL, Thiriet, N, Jayanthi, S. (2001) Involvement of free radicals in MDMA-induced neurotoxicity in mice. *Ann Med Intern* **152 Suppl 3**: IS57-59.
- Charkoudian, N. (2003) Skin blood flow in adult human thermoregulation: how it works, when it does not, and why. *Mayo Clin Proc* **78**: 603-612.
- Cheuvront, SN, Haymes, EM. (2001) Thermoregulation and marathon running: biological and environmental influences. *Sports Med* **31**: 743-762.
- Cota, D, Marsicano, G, Tschop M, Glubler, Y. (2002) The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis. *J Clin Invest* **112**: 423-431.
- Crandall, CG, Vongpatanasin, W, Victor, RG. (2002) Mechanism of cocaine-induced hyperthermia in humans. *Ann Intern Med* **136**: 785-791.
- Davidson, C, Gow, AJ, Lee, TH, Ellinwood, EH. (2001) Methamphetamine neurotoxicity: necrotic and apoptotic mechanisms and relevance to human abuse and treatment. *Brain Res Rev* **36**: 1-22.
- DeBow, S, Colbourne, F. (2003) Brain temperature measurements and regulation in awake and freely moving rodents. *Methods* **30**: 167-71.
- Delgado, JMR, Hanai, T. (1966) Intracerebral temperatures in free-moving cats. *Am J Physiol* **211**: 755-769.
- Dewhirst, MW, Viglianti, BL, Lora-Michiels, M, Hanson, M, Hoopes, PJ. (2003) Basic principles of thermal dosimetry and thermal thresholds for tissue damage from hyperthermia. *Int J Hyperthermia* **19**: 267-294.
- Donaldson, GC, Keatinge, WR, Saunders, RD. (2003) Cardiovascular responses to heat stress and their adverse consequences in healthy and vulnerable human populations. *Int J Hyperthermia* **19**: 225-235.
- Endoh, H, Taga, K, Yamakura, T, Sato, K, Watanabe, I, Fukuda, S, Shimoji, K. (1999) Effects of naloxone and morphine on acute hypoxic survival in mice. *Crit Care Med* **27**: 1923-1933.
- Fellows, LK, Boutelle, MG, Fillenz, M. (1993) Physiological stimulation increases nonoxidative glucose metabolism in the brain of the freely moving rat. *J Neurochem* **60**: 1258-1263.
- Fuller, SA, Stein, EA. (1991) Effects of heroin and naloxone on cerebral blood flow in the conscious rat. *Pharmacol Biochem Behav* **40**: 339-334.
- Gordon, CJ, Watkinson, WO, O'Callaghan, JP, Miller, DB. (1991) Effects of 3,4-methylenedioxymethamphetamine on autonomic thermoregulatory responses of the rat. *Pharmacol Biochem Behav* **38**: 339-344.
- Gollub, RL, Breiter, HC, Kantor, H, Kennedy, D, Gastfriend, D, Mathew, RT. (1998) Cocaine decreases cortical cerebellar blood flow but does

- not obscure regional activation in functional magnetic resonance imaging in human subjects. *J Cereb Blood Flow Metab* **18**: 724-734.
- Graderl, TL, Baze, WB, Satterfield, WC, Hildebrand, KP, Johansen, MJ, Hassenbusch, SJ. (2003) Safety of chronic intrathecal morphine infusion in a sheep model. *Anesthesiology* **99**: 188-98.
- Green, AR, Mehan, AO, Elliott, JM, O'Shea, E, Colado, MI. (2003) The pharmacology and clinical pharmacology of 3,4-Methylenedioxy-methamphetamine (MDMA, "Ecstasy"). *Pharmacol Rev* **55**: 463-508.
- Horvath, TL, Warden, CH, Hajos, M, Lombardi, A, Goglia, F, Diano, S. (1999) Brain uncoupling protein 2: Uncoupled neuronal mitochondria predict thermal synapses in homeostatic centers. *J Neurosci* **19**: 10417-10427.
- Howell, LL, Hoffman, JN, Votaw, JR, Landrum, AM, Wilcox, KM, Lindsey, KP. (2002) Cocaine-induced brain activation determined by positron emission tomography neuroimaging in conscious rhesus monkeys. *Psychopharmacology* **159**: 154-160.
- Ide, K, Secher, NH. (2000) Cerebral blood flow and metabolism during exercise. *Prog Neurobiol* **61**: 397-414.
- Ide, K, Schmalbruch, IK, Quistorff, B, Horn, A, Secher NH. (2000) Lactate, glucose, and oxygen uptake in human brain during recovery from maximal exercise. *J Physiol* **522**: 159-164.
- Iwagami, Y. (1996) Changes in ultrastructure of human cell related to certain biological responses under hyperthermic culture conditions. *Human Cell* **9**: 353-366.
- Jessen, AB, Toubro, S, Astrup, A. (2003) Effect of chewing gum containing nicotine and caffeine on energy expenditure and substrate utilization in men. *Am J Clin Nutr* **77**: 1442-7.
- Kalant, H. (2001) The pharmacology and toxicology of "ecstasy" (MDMA) and related drugs. *Can Med Assoc J* **165**: 917-928.
- King, YT, Lin, CS, Kin, JH, Lee, WC. (2002) Whole body hyperthermia induced thermotolerance is associated with the induction of heat shock protein 70 in mice. *J Exp Biol* **205**: 273-278.
- Kiyatkin, EA, Rebec, GV. (1998) Heterogeneity of ventral tegmental area neurons: Single-unit recording and iontophoresis in awake, unrestrained rats. *Neuroscience* **85**: 1285-1309.
- Kiyatkin, EA, Rebec, GV. (1999) Modulation of striatal neuronal activity by glutamate and GABA: Iontophoresis in awake, unrestrained rats. *Brain Res* **822**: 88-106.
- Kiyatkin, EA, Wise, RA. (2001) Striatal hyperthermia associated with arousal: intracranial thermorecordings in behaving rats. *Brain Res* **918**: 141-152.
- Kiyatkin, EA, Wise, RA. (2002) Brain and body hyperthermia associated with heroin self-administration in rats. *J Neurosci* **22**: 1072-1080.
- Kiyatkin, EA, Brown, PL, Wise, RA. (2002) Brain temperature fluctuation: a reflection of functional neural activation. *Eur J Neurosci* **16**: 164-168.
- Kiyatkin, EA, Brown, PL. (2003) Fluctuations in neural activity during cocaine self-administration: Clues provided by brain thermorecording. *Neuroscience* **116**: 525-538.
- Kiyatkin, EA, Mitchum, R. (2003) Fluctuations in brain temperatures during sexual behavior in male rats: An approach for evaluating neural activity underlying motivated behavior. *Neuroscience* **119**: 1169-1183.
- Kuhn, DM, Geddes, TJ. (2000) Molecular footprints of neurotoxic amphetamine action. *Ann NY Acad Sci* **914**: 92-103.
- Langsjö, JW, Kaisti, KK, Aalto, S, Hinkka, S, Aantaa, R, Oikinen, V, Supila, H, Kurki, T, Silvanto, M, Scheinin, H. (2003) Effects of subanesthetic doses of ketamine on regional cerebral blood flow, oxygen consumption, and blood volume in humans. *Anesthesiology* **99**: 614-623.
- Leker, RR, Gai, N, Mechoulam, R, Ovadia, H. (2003) Drug-induced hypothermia reduces ischemic damage: effects of the cannabinoid HU-210. *Stroke* **34**: 2000-2006.
- Lepock, JR, Cheng, K-H, Al-Qysi, H, Kruuv, J. (1983) Thermotropic lipid and protein transitions in Chinese hamster lung cell membranes: relationship to hyperthermic cell killing. *Can J Biochem Cell Biol* **61**: 421-427.
- Lepock, JR. (2003) Cellular effects of hyperthermia: relevance to the minimum dose for thermal damage. *Int J Hyperthermia* **19**: 252-266.
- Li, SJ, Biswal, B, Li, Z, Risinger, R, Rainey, C, Cho, JK, Salmeron, BJ, Stein, EA. (2000) Cocaine administration decreases functional connectivity in human primary visual and motor cortex as detected by functional fMRI. *Magn Reson Med* **43**: 45-51.
- Lin, PS, Quamo, S, Ho, KC, Gladding, J. (1991) Hyperthermia enhances the cytotoxic effects of reactive oxygen species to Chinese hamster cells and bovine endothelial cells *in vitro*. *Radiat Med* **126**: 43-51.
- Lipton, SA, Rosenberg, PA. (1994) Excitatory amino acids as a final common pathway for neurologic disorders. *N Engl J Med* **330**: 613-622.
- Lynch, TJ, Adler, MW, Eisenstein, TK. (1990) Comparison of the mechanisms on interleukin-1 and morphine-induced hyperthermia in the rat. *Ann NY Acad Sci* **594**: 469-471.
- Lyles, J, Cadet, JL. (2003) Methylenedioxy-methamphetamine (MDMA, Ecstasy) neurotoxicity: cellular and molecular mechanisms. *Brain Res Rev* **42**: 155-168.
- Maier, CM, Steinberg, GK. (2003) *Hypothermia and Cerebral Ischemia*. Humana Press: New York, 192 p.
- Marota, JJ, Mendeville, JB, Weisskoff, RM, Moskowitz, MA, Rosen, BR, Kosofsky, BE. (2000) Cocaine activation discriminates dopaminergic projections by temporal response: an fMRI study in rat. *Neuroimage* **11**: 13-23.
- Mariak, Z, Jadeszko, M, Lewko, J, Lebkowski, W, Lyson, T. (1998) No specific brain bropection against thermal stress in fever. *Acta Neurochir (Wien)* **140**: 585-590.
- Mariak, Z, Lebkowski, W, Lyson, T, Lewko, J, Piekarski, P. (1999) Brain temperature during craniotomy in general anesthesia. *Neurol Neurochir Pol* **33**: 1325-1327.
- Mariak, Z, Lyson, T, Peikarski, P, Lewko, J, Jadeszko, M, Szydlak, P. (2000) Brain temperature in patients with central nervous system lesions. *Neurol Neurosurg Pol* **34**: 509-522.
- McElliott, JC, Melzack, R. (1967) Localized thermal changes evoked in the brain by visual and auditory stimulation. *Exp Neurol* **17**: 293-312.
- Mechan, AO, O'Shea, E, Elliott, JM, Colado, MI, Green, AR. (2001) A neurotoxic dose of 3,4-methylenedioxy-methamphetamine (MDMA; ecstasy) to rats results in a long-term deficit in thermoregulation. *Psychopharmacology* **155**: 413-418.
- Miller, DB, O'Callaghan, JP. (1994) Environment-, drug- and stress-induced alterations in body temperature affect the neurotoxicity of substituted amphetamines in the C57BL/6J mouse. *J Pharmacol Exp Ther* **270**: 752-760.
- Mintun, MA, Lundstrom, BN, Snyder, AZ, Vlasenko, AG, Shulman, GL, Raichle, ME. (2001) Blood flow and oxygen delivery to human brain during functional activity: Theoretical modeling and experimental data. *Proc Natl Acad Sci* **98**: 6859-6864.
- Miyazawa, T, Tamara, A, Fukui, S, Hossmann, KA. (2003) Effects of mild hypothermia on focal cerebral ischemia: Review of experimental studies. *Neurol Res* **25**: 457-64.
- Moltz, H. (1993) Fever: causes and consequences. *Neurosci Biobehav Rev* **17**: 237-269.
- Moriyama, E. (1990) Cerebral blood flow changes during localized hyperthermia. *Neurol Med Chir (Tokio)* **30**: 923-929.
- Moser, E, Mathesen, I, Andersen, P. (1993) Association between brain temperature and dentate field potentials in exploring and swimming rats. *Science* **259**: 1324-1326.
- Moser, EI, Mathiesen, J. (1996) Relationships between neuronal activity and brain temperature in rats. *NeuroReport* **7**: 1876-1880.
- Nagata, Y, Katayama, K, Manivel, CJ, Song, CW. (2000) Changes in blood flow in locally heated intestine of rats. *Int J Hyperthermia* **16**: 159-170.
- Nakajima, T, Rhee, JG, Song, CW, Onoyama, Y. (1992) Effect of a second heating on rat liver blood flow. *Int J Hyperthermia* **8**: 679-687.
- Nielson, B, Hyldig, T, Bidstrup, F, Gonzales-Alonso, J, Christoffersen, GRJ. (2001) Brain activity and fatigue during prolonged exercise in the heat. *Eur J Physiol* **442**: 41-48.
- Nybo, L, Nielson, B. (2001) Middle cerebral artery blood velocity is reduced with hyperthermia during prolonged exercise in humans. *J Physiol* **534**: 279-286.
- Nybo, L, Scher, NH, Nielson, B. (2002) Inadequate heat release from the human brain during prolonged exercise with hyperthermia. *J Physiol* **545**: 697-704.
- Ohmori, T, Abekawa, T, Koyama, T. (1996) The role of glutamate in behavioral and neurotoxic effects of methamphetamine. *Neurochem Int* **29**: 301-307.
- Olsen, TS, Weber, UJ, Kammersgaard, LP. (2003) Therapeutic hypothermia for acute stroke. *Lancet Neurol* **2**: 410-416.
- Oobu, K. (1993) Experimental studies on the effect of heating on blood flow in the tongue of golden hamsters. *Fukuoka Igaku Zasshi* **84**: 497-511.
- Omar, RA, Yano, S, Kikkawa, T. (1987) Antioxydant enzymes and survival of normal and simian 40-transformed embryo cells after hyperthermia. *Cancer Res* **47**: 3473-3476.

- Pavlov, IF, Epstein, OI. (2003) Morphine and antibodies to mu-opiate receptors in ultralow doses: Effect on oxygen consumption. *Bull Exp Biol Med* **1 Suppl**: 137-139.
- Pederson, NP, Blessing, WW. (2001) Cutaneous vasoconstriction contributes to hyperthermia induced by 3,4-methylenedioxymethamphetamine (ecstasy) on conscious rabbits. *J Neurosci* **21**: 8648-8654.
- Perkins, KA, Sexton, JE, DiMarco, A. (1996) Acute thermogenic effects of nicotine and alcohol in healthy male and female smokers. *Physiol Behav* **60**: 305-9.
- Raichle, ME. (2003) Functional brain imaging and human brain functions. *J Neurosci* **23**: 3959-3962.
- Rawson, RA, Anglin, MD, Ling, W. (2002) Will the methamphetamine problem go away? *J Addict Dis* **21**: 5-19.
- Reynolds, LP, Allen, GV (2003) A review of heat shock protein induction following cerebellar injury. *Cerebellum* **2**: 171-7.
- Robinson, R, Iida, H, O'Brien, TP, Pane, MA, Trystman, RJ, Gleason, CA. (2000) Comparison of cerebellar effects of intravenous cocaine injection in fetal, newborn, and adult sheep. *Am J Physiol* **279**: H1-H6.
- Rosen, AD. (1996) Temperature modulation of calcium channel function in GH3 cells. *Am J Physiol* **271**: C863-C868.
- Rosen, AD. (2001) Nonlinear temperature modulation of sodium channel kinetics in GH3 cells. *Biochem Biophys Acta* **1511**: 391-396.
- Rowell, LB. (1983) Cardiovascular aspects of human thermoregulation. *Circ Res* **52**: 367-376.
- Rumana, CS, Gopinath, SP, Uzura, M, Valadka, AB, Robertson, CS. (1998) Brain temperatures exceeds systemic temperatures in head-injured patients. *Clin Care Med* **26**: 562-567.
- Ryan, KL, Taylor, WF, Bishop, VS. (1997) Arterial baroreflex modulation of heat-induced vasodilation in the rabbit ear. *J Appl Physiol* **83**: 2091-2097.
- Sandoval, V, Hanson, GR, Fleckenstein, AE. (2000) Methamphetamine decreases mouse striatal dopamine transporter activity: roles of hyperthermia and dopamine. *Eur J Pharmacol* **409**: 265-271.
- Schlaepfer, TE, Strain, EC, Greenberg, BD, Preston, KL, Lancaster, E, Bigelow, GE, Barta, PE, Pearson, GD. (1998) Site of opiate action in the human brain: mu and kappa agonists' subjective and cerebral blood flow effects. *Am J Psychiatr* **155**: 470-473.
- Schmidt-Nielson, K. (1997) *Animal Physiology. Adaptation and Environment*. 5<sup>th</sup> Ed, Cambridge Univ Press; Cambridge, UK
- Schwab, S, Spranger, M, Aschoff, A, Steiner, T, Hacke, W. (1997) Brain temperature monitoring and modulation in patients with severe MCA infarction. *Neurology* **48**: 762-767.
- Seiden, LS, Sabol, KE. (1996) Methamphetamine and methylenedioxymethamphetamine neurotoxicity: possible mechanisms of cell destruction. *NIDA Res Monogr* **163**: 251-276.
- Selye, H. (1975) *Stress Without Distress*. New American Library: New York.
- Siesjo, B. (1978) *Brain Energy Metabolism*. Wiley: New York.
- Sharma, HS, Alm, P, Westman, J. (1998) Nitric oxide and carbon monoxide in the pathophysiology of brain functions in heat stress. *Prog Brain Res* **115**: 297-333.
- Sharma, HS, Hoopes, PJ. (2003) Hyperthermia-induced pathophysiology of the central nervous system. *Int J Hyperthermia* **19**: 325-354.
- Sokoloff, L. (1999) Energetics of functional activation in neural tissues. *Neurochem Res* **24**: 321-329.
- Spina, MB, Cohen, G. (1989) Dopamine turnover and glutathione oxidation: implications for Parkinson disease. *Proc Natl Acad Sci USA* **86**: 1398-1400.
- Stephens, SE, Yamamoto, BK. (1994) Methamphetamine-induced neurotoxicity: roles for glutamate and dopamine efflux. *Synapse* **17**: 203-209.
- Suehiro, E, Fujisawa, H, Ito H, Ishikawa, T, Maekawa, T. (1999) Brain temperature modifies glutamate neurotoxicity *in vivo*. *J Neurotrauma* **16**: 285-97.
- Uda, M, Tanaka, Y. (1990) Arterial blood flow changes after hyperthermia on normal liver, normal brain, and normal small intestine. *Gan No Rinsho* **36**: 2362-2366.
- Walters, TJ, Rynan, KL, Tate, LM, Mason, PA. (2000) Exercise in the heat is limited by a critical internal temperature. *J Appl Physiol* **89**: 799-806.
- Welsh, WJ. (1992) Mammalian stress response: cell physiology, structure/function of stress proteins, and implications for medicine and disease. *Physiol Rev* **72**: 1063-81.
- Willis, WT, Jackman, MR, Bizeau, ME, Pagliassotti, MJ, Hazel, JR. (2000) Hyperthermia impairs liver mitochondrial functions. *Am J Physiol* **278**: R1240-1246.
- Wise, RA. (2002) Brain reward circuitry: insights from unsensed incentives. *Neuron* **36**: 229-240.
- Wise, R, Bozarth, MA. (1987) Psychomotor stimulant theory of addiction. *Psychol Rev* **96**: 469-492.
- Yablonskiy, DA, Ackerman, JH, Raichle, ME. (2000) Coupling between changes in human brain temperature and oxidative metabolism during prolonged visual stimulation. *Proc Nat Acad Sci* **97**: 7603-7608.
- Xie, T, McGann, UD, Kim, S, Yuan, J, Ricaurte, GA. (2000) Effect of temperature on dopamine transporter function and intracellular accumulation of methamphetamine: Implications for methamphetamine-induced dopaminergic neurotoxicity. *J Neurosci* **20**: 7838-7845.
- Zamani, R, Semnani, S, Fathollahi, Y, Hajizadeh, S. (2000) Systemic naloxone enhances cerebral blood flow in anesthetized morphine-dependent rats. *Eur J Pharmacol* **408**:299-304.