

Temperature Sensitivity of the Brain

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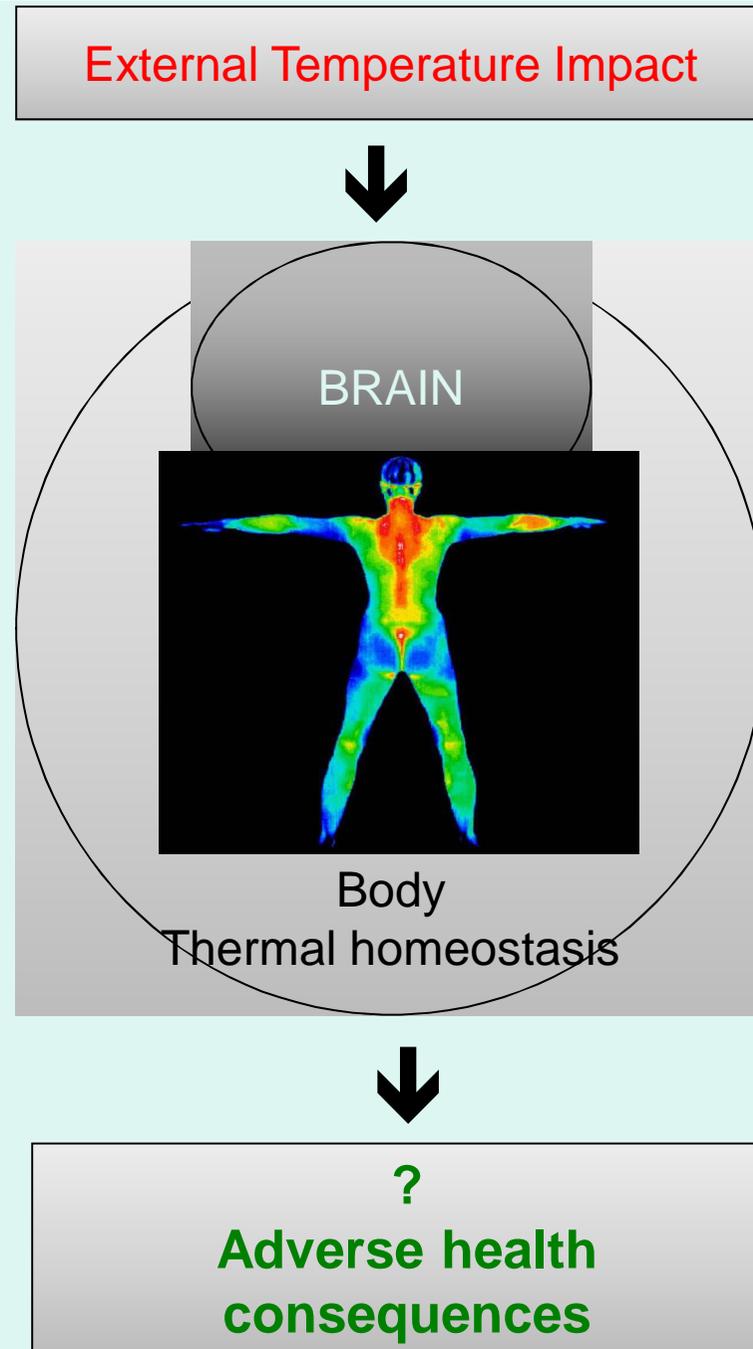
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Humans have sophisticated **thermoregulatory mechanisms** that **maintain stability of internal temperatures** following:

- Robust changes in environmental temperatures
- Enhanced heat production associated with physical activity.

Focus on brain t° and factors that determine its fluctuations



Brain Temperature: Why it is important?

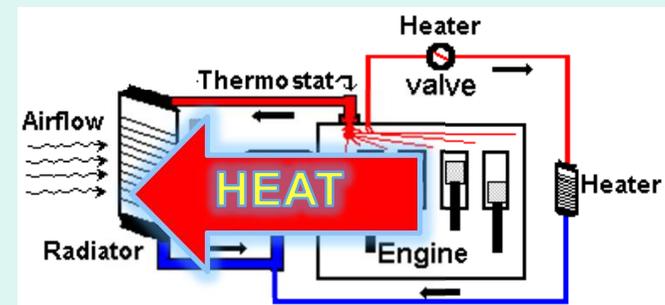
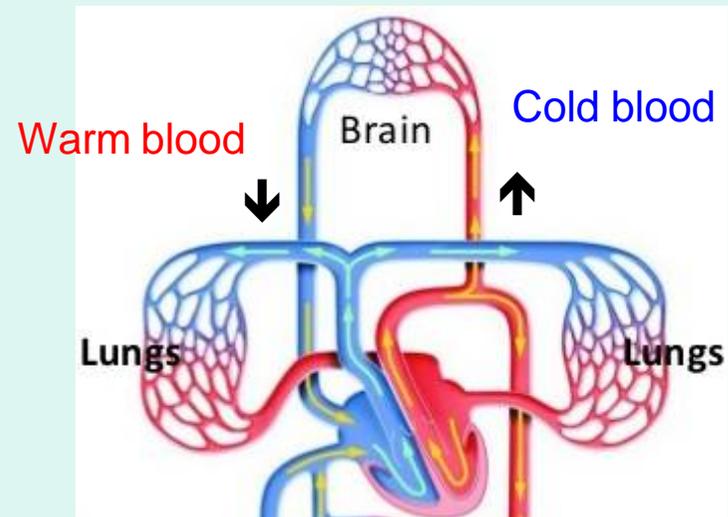
1. The brain is the most important organ for an organism's survival;
2. Brain tissue is exceptionally sensitive to heat
 - structural changes occurring with a 3-4°C increase above normal baseline;
3. The brain accounts for ~20% of the organism's total oxygen consumption at rest and all energy used for brain metabolism is finally transformed into heat.
Therefore, intense heat production appears to be an essential feature of brain metabolic activity
4. In contrast to body temperature, brain temperature measurements are more complicated and usually impossible in humans and our knowledge on brain temperature changes remains very limited;

Brain is a part of the body and its temperature basically depend on and correlates with body T° .

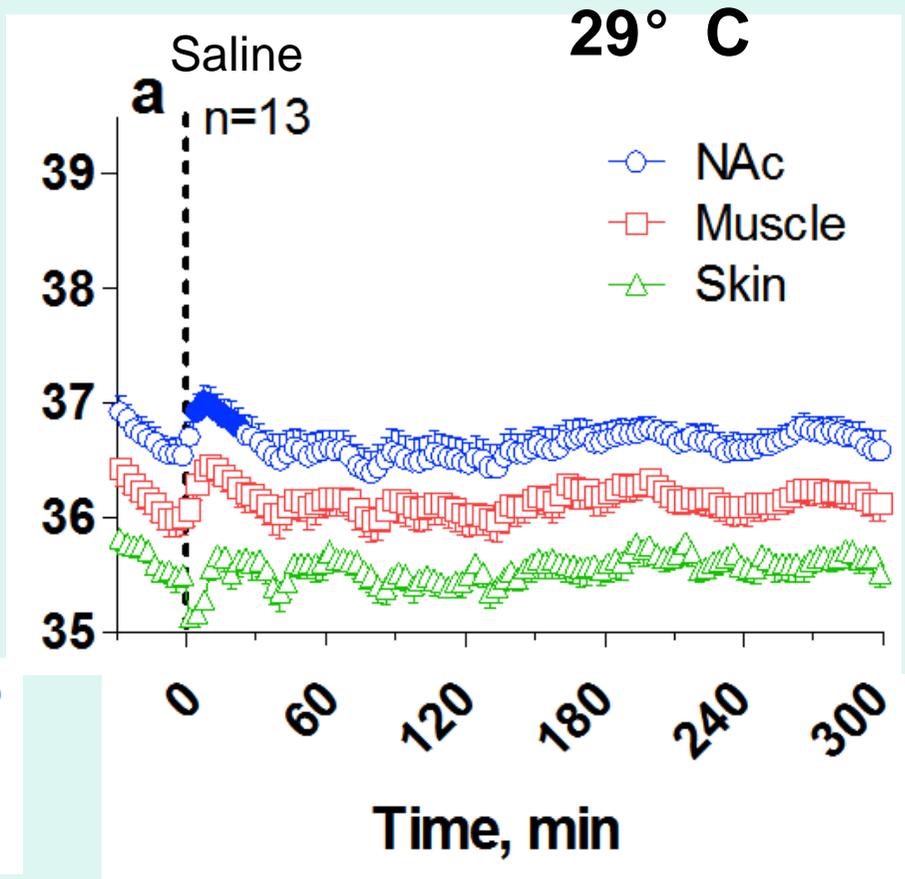
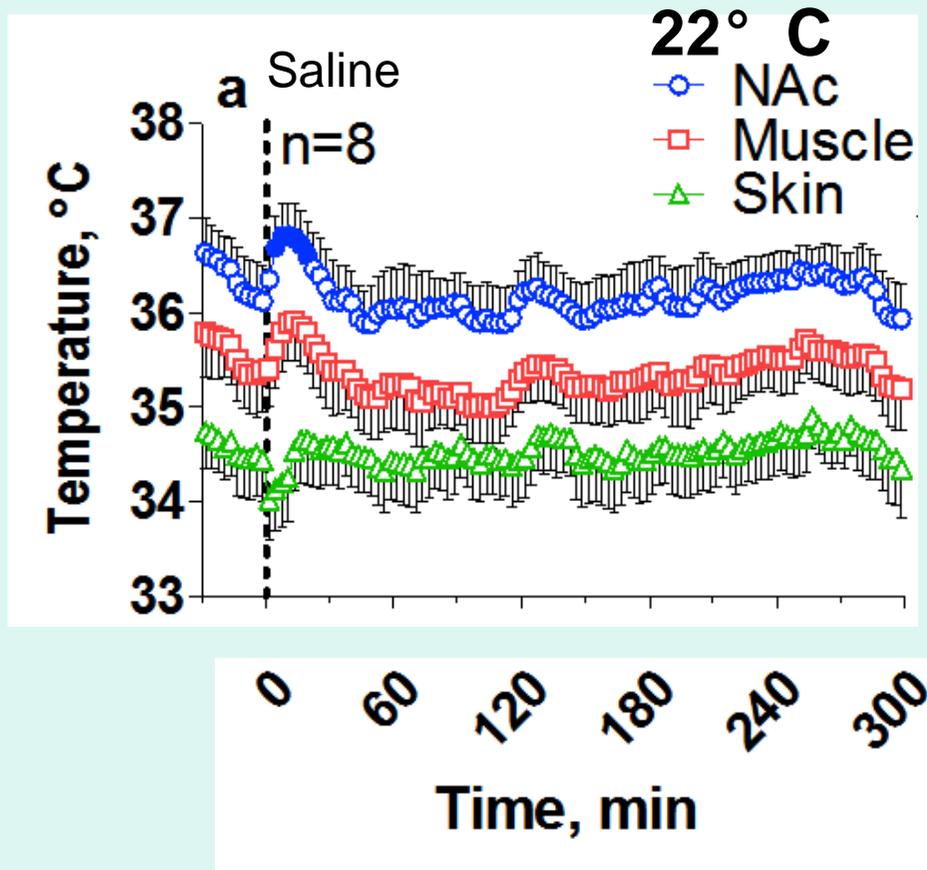
Although **metabolic heat** is intensively produced in brain tissue, it is **effectively removed from the brain via circulation** to the body and then to the external environment, and **brain temperature remains relatively stable.**

The **major cooling mechanism of the brain is inflow of colder arterial blood** that comes from the lungs and outflow of warmer venous blood that travels again to the lungs and skin surfaces for heat dissipation to the external environment

(analogy with internal combustion engine)



Brain t° is very resistant to external temperature impact

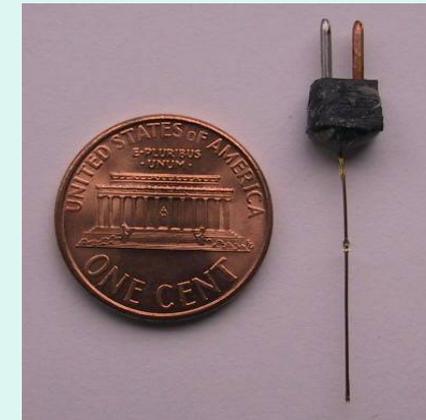
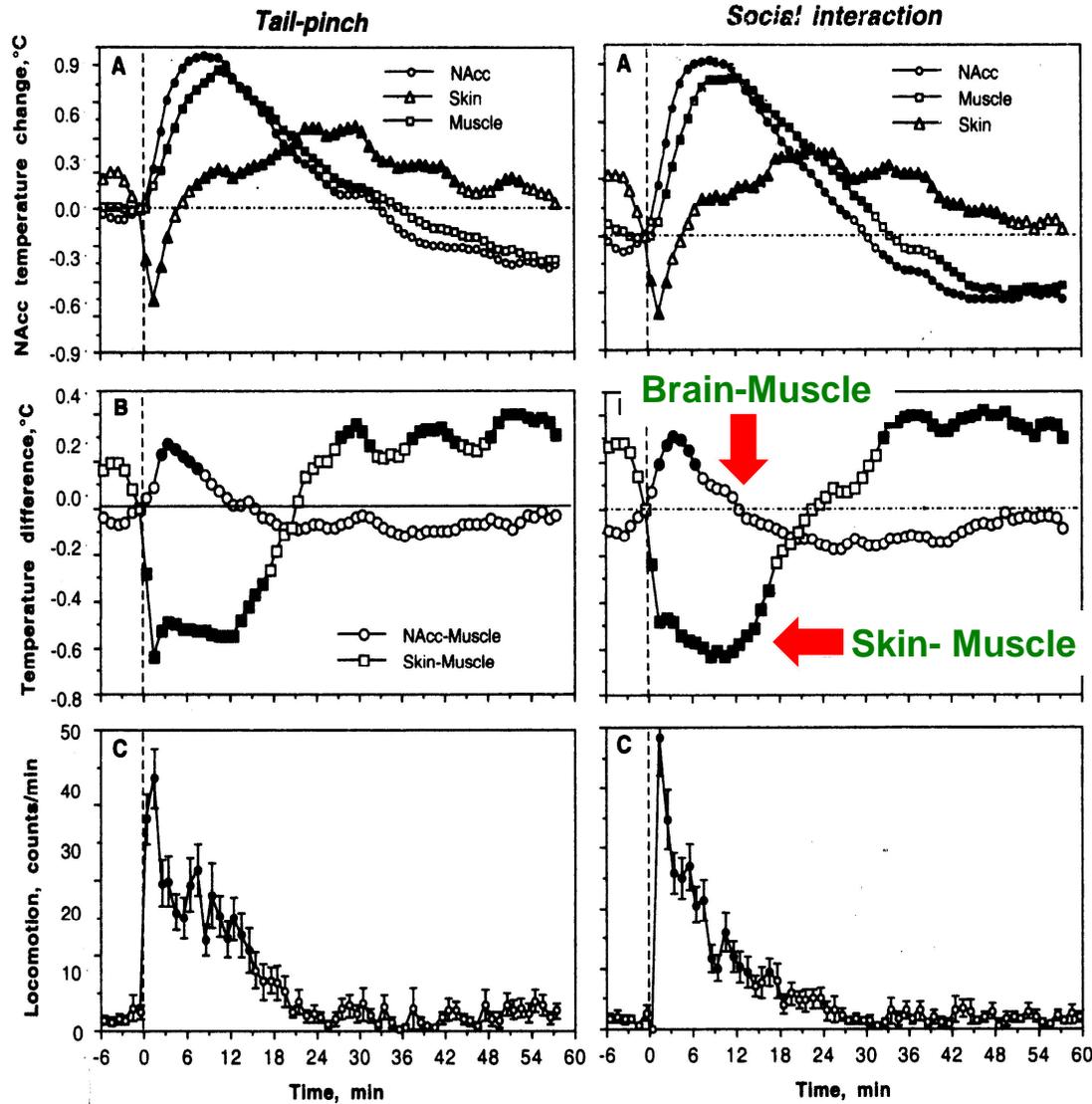


7° C → Δ NAc 0.42° C; Δ Muscle 0.63° C; Δ Skin 1.06° C (slight physiological vasodilation)

However, **under several specific conditions** brain temperature could exceed its normal physiological levels.

What are these conditions?

1. Salient environmental stimulation



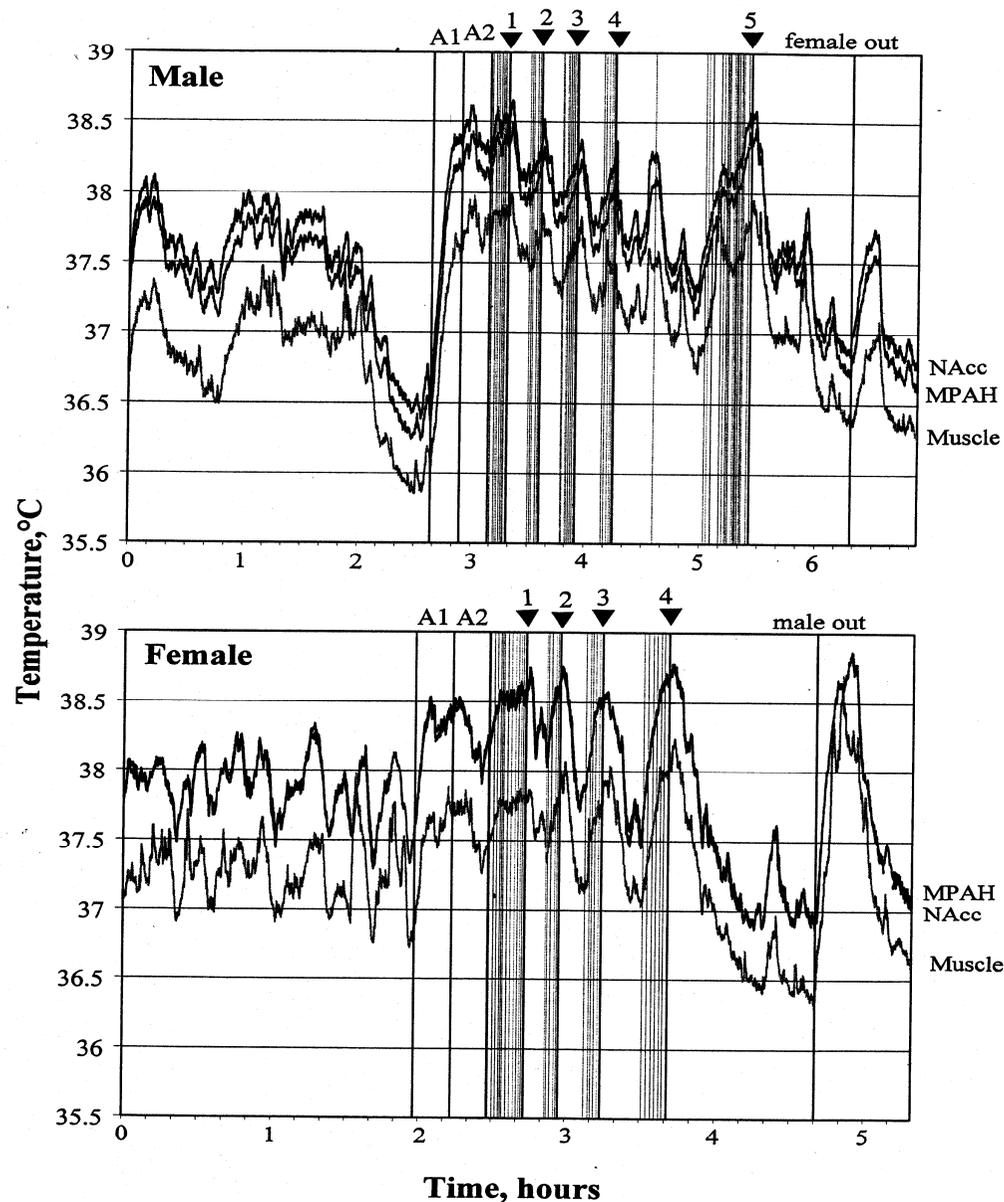
Copper-Constantane
thermocouple sensors
Three-point
thermorecording in rats

↑ Brain and body t°
Brain-Muscle Δ -
metabolic brain activation

↓ Skin t°
Skin-Muscle Δ -
peripheral
vasoconstriction

joint contribution

2. Motivated behaviors



Male and female sexual behavior:

A1-arousing stimulation I (partner is in other cage compartment; impossible to see and interact);

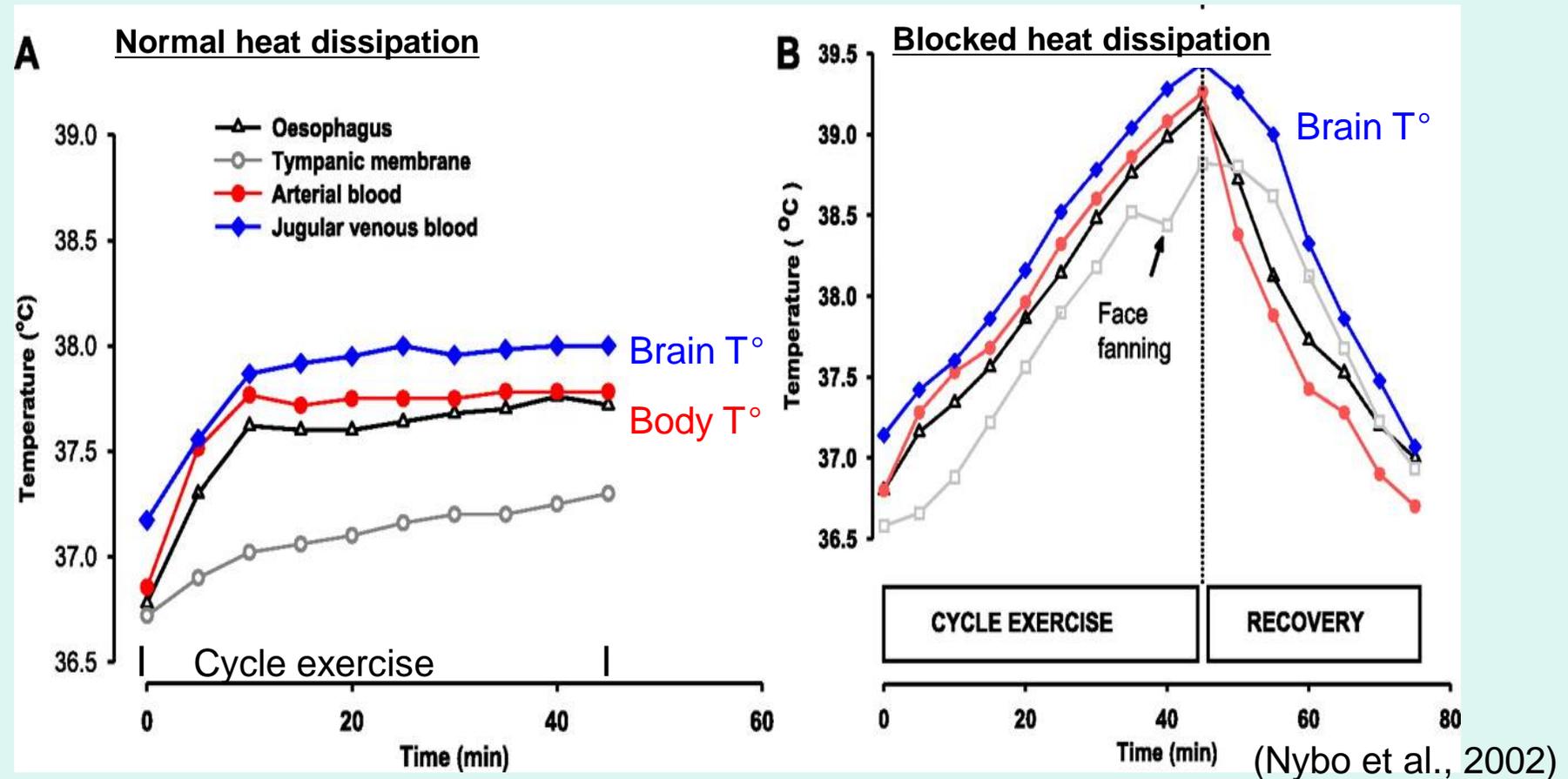
A2-arousing stimulation (partner is seen, but interaction is impossible);

Free interactions: mounts, intromissions and ejaculations (↓);

- highly dynamic and behavior-related
- range in both sexes: 38-39.5° C (↑2.0-3.0° C)
- Medial preoptic anterior Hpt

(Mitchum & Kiyatkin, 2004)

3. Physical activity in adverse environmental conditions (humans)



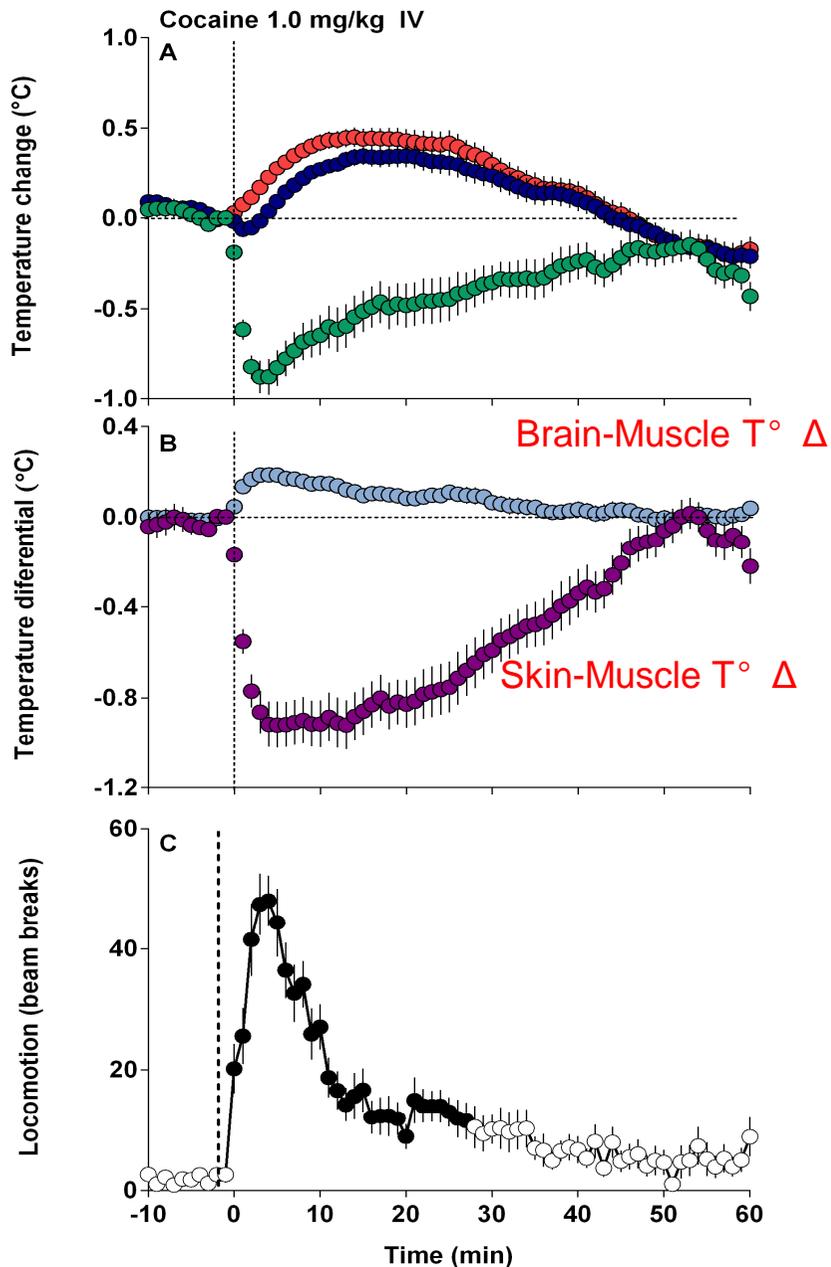
- Physical activity - intense heat production in the body (up to 10x). When heat could dissipate outside, changes in temperature are minor (A).
- When heat dissipation from skin surfaces is blocked, heat is accumulated in the brain and body, and both temperatures going up to high levels (B) mean 39.5° C

4. Drugs of abuse

Psychomotor stimulants (cocaine, METH, MDMA)

Thermogenic activity

IV cocaine at a low dose that is self-administered by rats (1 mg/kg):

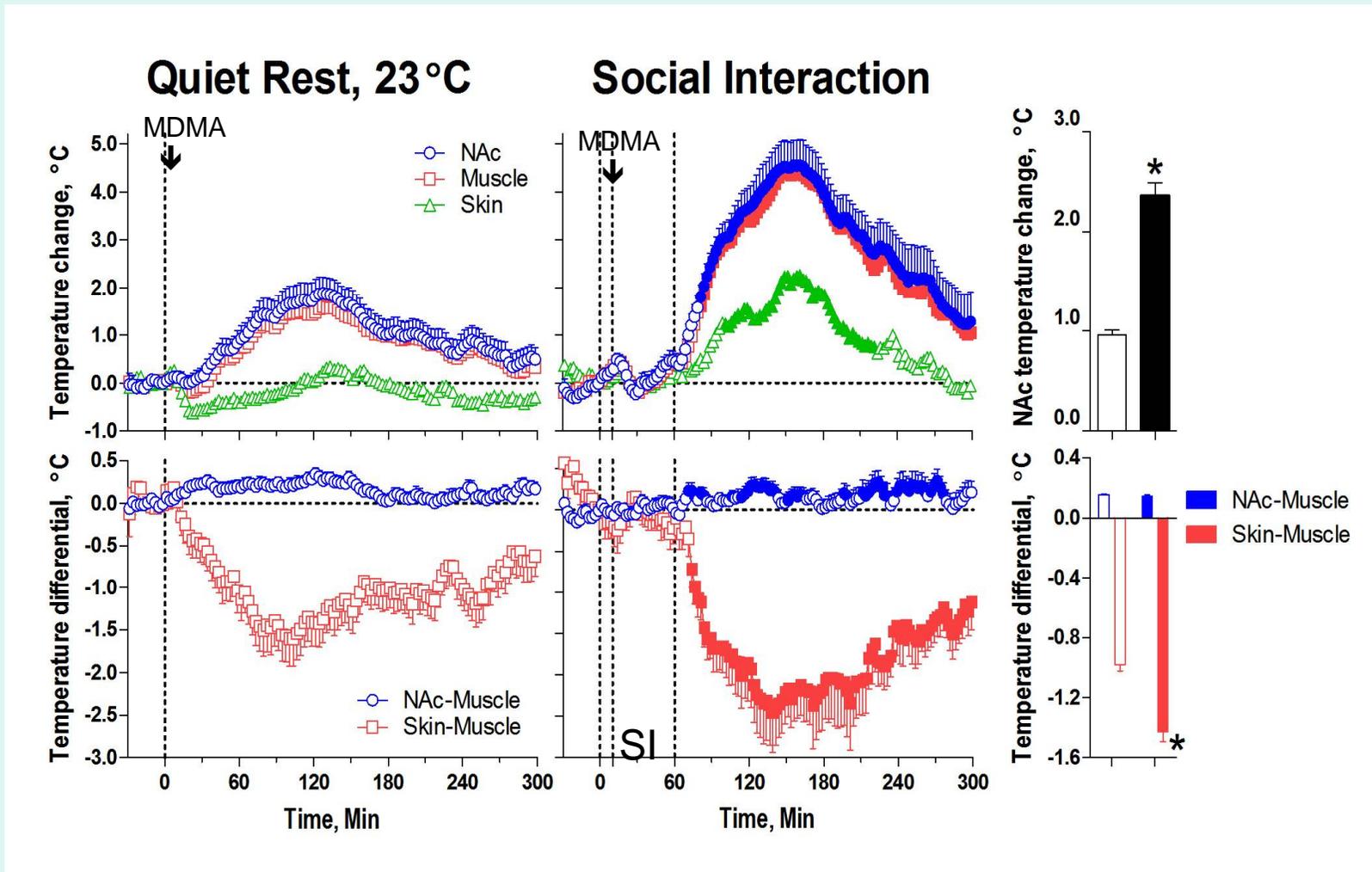


↑ Brain and body t°
– (Brain-Muscle $t^{\circ} \Delta \uparrow$: metabolic activation)

↑ Locomotor activation

↓ Skin t°
– (Skin-Muscle $t^{\circ} \Delta \downarrow$: robust peripheral vasoconstriction)

4-1. MDMA (Ecstasy): potentiation of hyperthermia by activity state



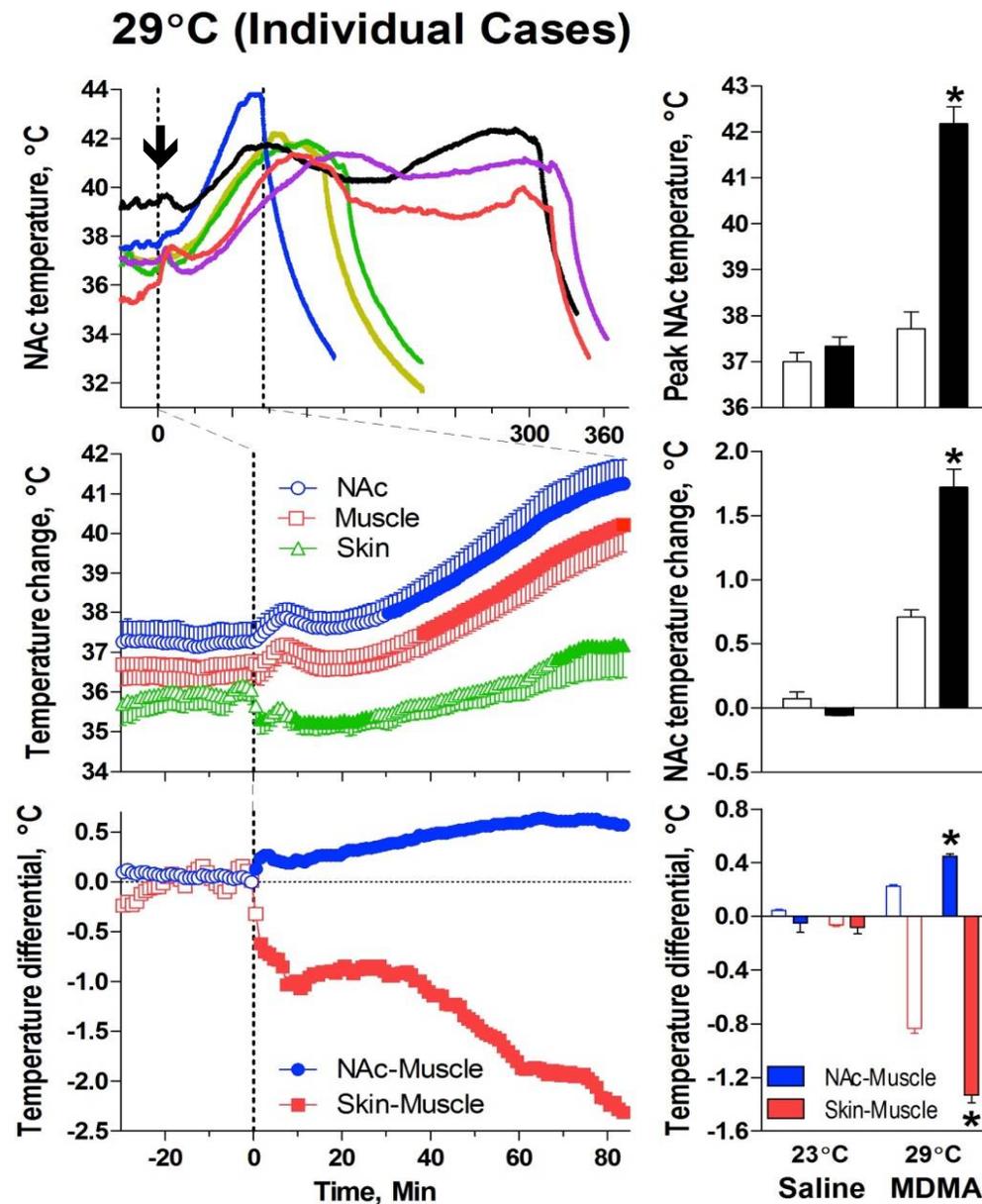
MDMA: 9 mg/kg (~1/5 of LD50, sc) in freely moving rats in two conditions

- Quiet rest versus social interaction (presence of another animal (-30 to 90 min))

(~10% lethality at 40.5-41.0° C)

(Kiyatkin et al., 2014)

4-2. MDMA (Ecstasy): potentiation of hyperthermia by ambient temperatures



- MDMA at the same, moderate, non-toxic dose at 29° C in freely moving rats
- Importantly, in drug-naive animals **brain temperature is minimally affected** (~0.5° C) by these environmental temperatures

Environmental and State Dependency

Club drugs - Raves: intense physical and emotional activity, high temperature and humidity, DRUG



Young adults:
Raves: Drug (MDMA) + Sexual and para-sexual activities (Fatal hyperthermia)



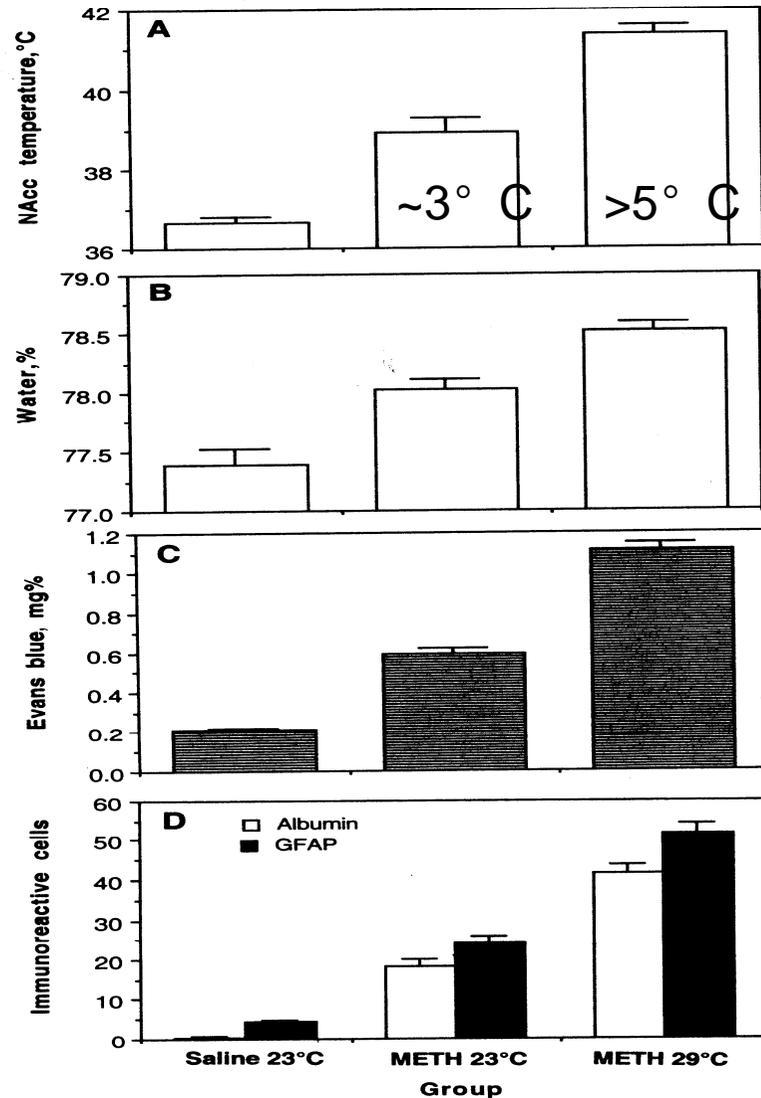
5. Temperature and the toxicity of drugs of abuse

In vitro work:

- brain tissue is exceptionally sensitive to heat;
- temperature exceeding $>40^{\circ}$ C above physiological baseline induce structural changes in brain cells;
- the damage greatly progresses with slight t° increases
- importance of absolute temperature

Sustained brain hyperthermia could induce multiple neurochemical and morphological changes. Whole-body hyperthermia → Leakage of the BBB and multiple histochemical and structural changes in brain cells.

METH-induced functional and morphological brain changes depend upon environmental temperature



Brain hyperthermia
(fatal if experiment continues)



Brain water: edema (!)



Evans blue: BBB leakage

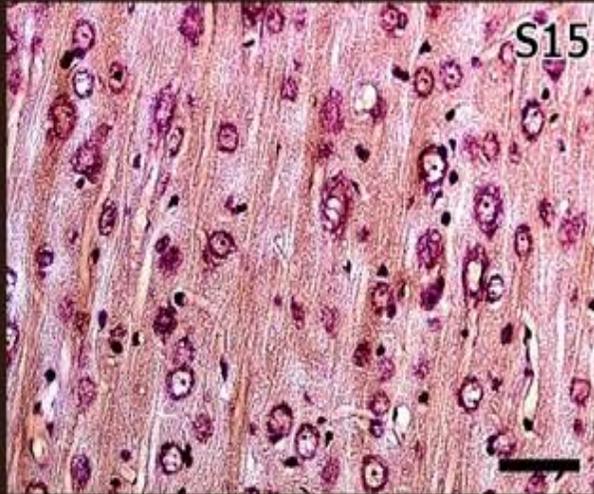


Albumin- and GFAP-positive cells: BBB leakage & acute glial activation

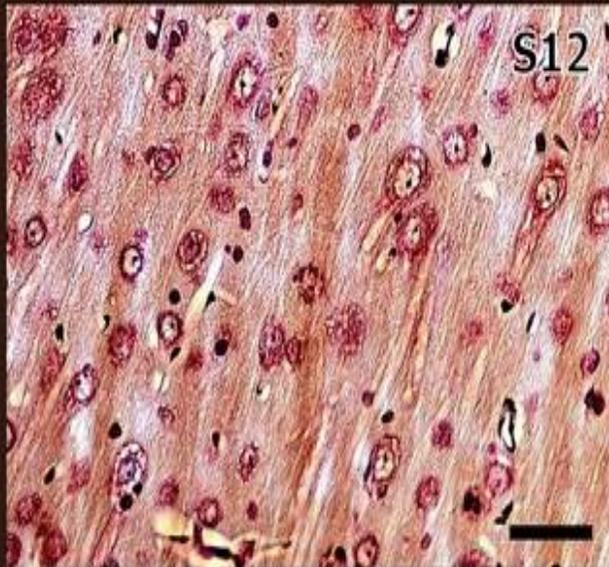
METH at the same dose (9 mg/kg, ~1/5 of LD50) at 22° and 29° C in freely moving rats (brain samples ~90 min post-injection)

Parietal cortex

Normothermia



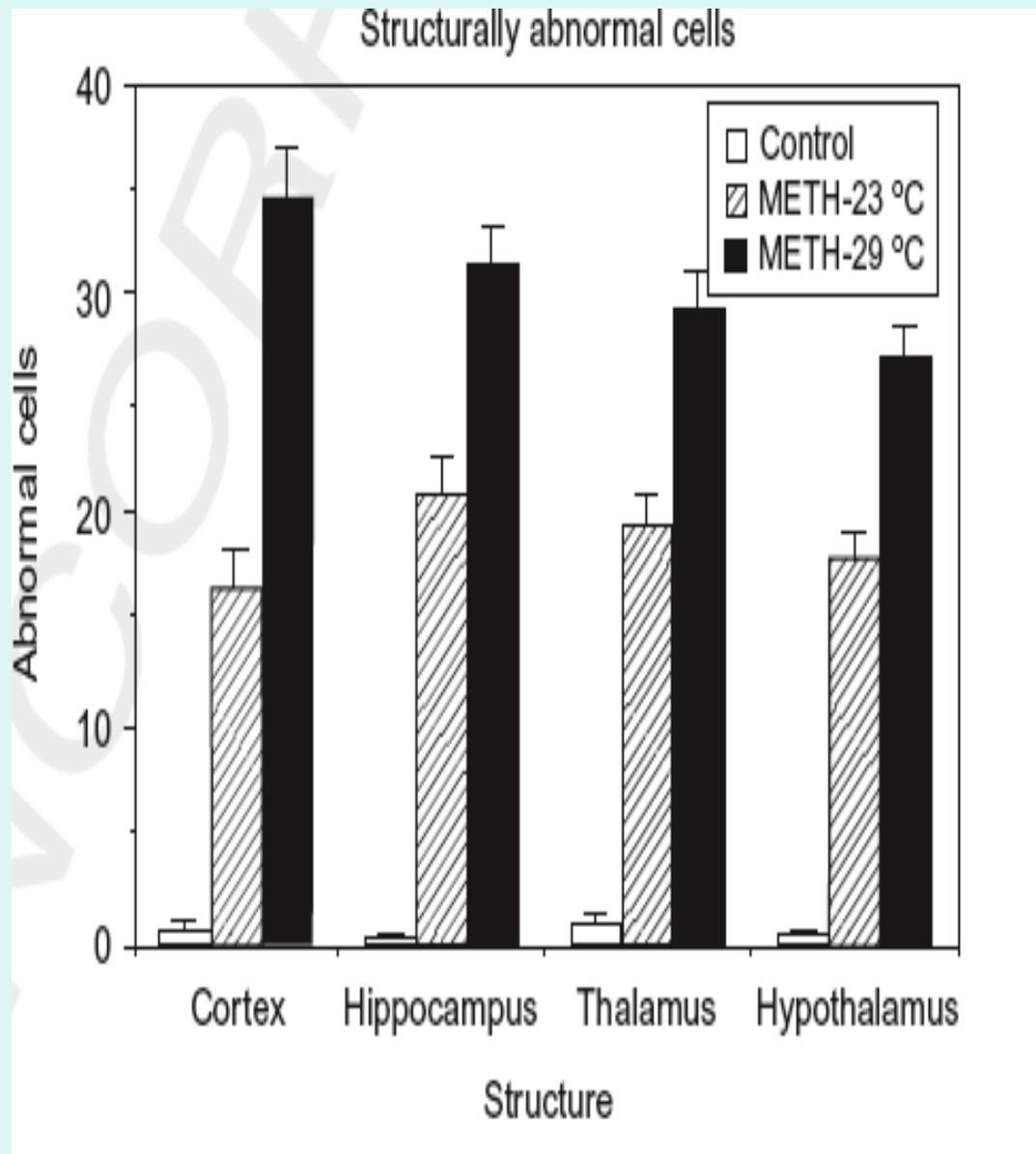
Hyperthermia



Drug- and hyperthermia-induced leakage of the BBB → Brain water accumulation

(cell enlargements, axons)

reversible – irreversible changes
edema (↑2-3% - death)



Drug- and temperature-dependent structural abnormalities of brain cells

different brain structures have different sensitivity to damage

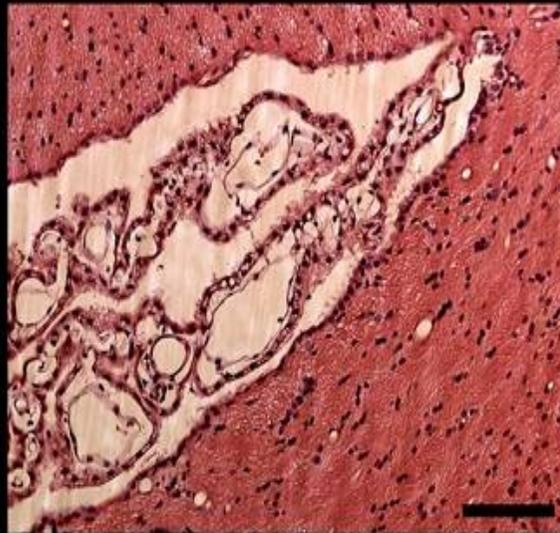
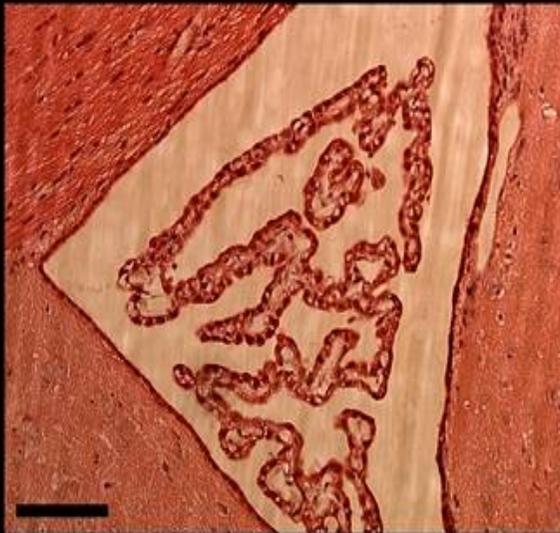
(common and specific changes)

Sharma & Kiyatkin, 2009

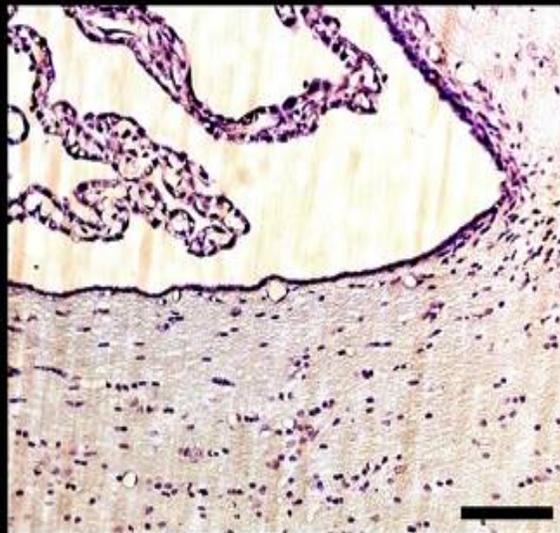
Normothermia

Hyperthermia

H&E



Nissl



choroid plexus

Different types of brain cells have different sensitivity to damage (neurons, glial cell, endothelial cells, epithelial cells)

ability of epithelial cells to regenerate

Conclusions:

1. **Brain temperature is not stable and fluctuates within 2-3° C under physiological conditions, during:**
 - salient environmental stimulation
 - psychophysiological activation
 - intense physical activity

While changes in humans are less pronounced than in rats, human changes became much stronger when natural mechanisms of heat loss are compromised.

However, brain temperature is relatively resistant to changes in environmental temperatures.

2. **Brain temperature could be also affected by different drugs that could induce either robust hyperthermia or hypothermia. The use of drugs under conditions of psychophysiological activation and in hot, humid environments could greatly potentiate drug-induced hyperthermia**

Conclusions:

3. Naturally occurring changes in brain temperature reflect functional neural perturbations - strongly affects neural activity and multiple neural functions.

Both the increases and decreases in brain temperature out of its physiological range ($>39-40^{\circ}$ C and $<33^{\circ}$ C) could induce or contribute to functional and morphological brain abnormalities.

4. Brain hyperthermia is an important contributor to acute and chronic neurotoxic effects of psychomotor stimulant drugs of abuse.

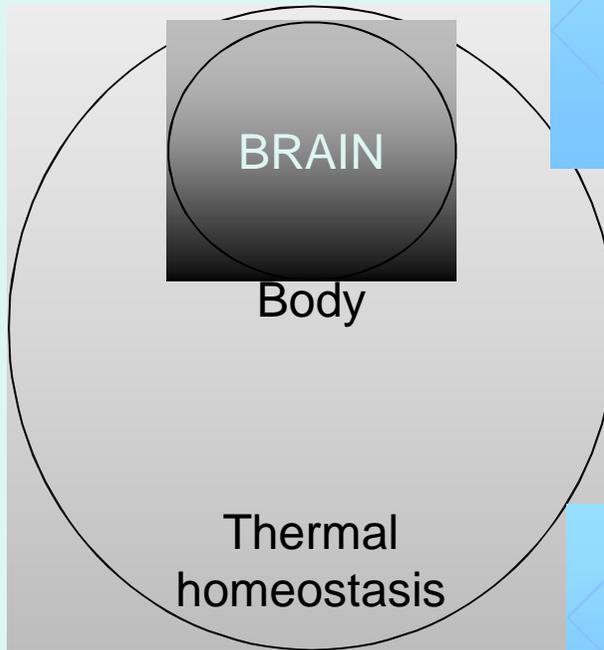
Drug-induced hyperthermia, and therefore drug toxicity, is greatly modulated by the environmental conditions and activity states associated with drug intake.

Summary

In contrast to well-developed ideas on central regulation of body temperature following external thermal impacts, the frameworks of **physiological regulation and homeostasis appear to be inadequate for understanding physiological fluctuations and pathological shifts in brain temperature.**

While different adaptive mechanisms could, within some limits, compensate for an altered heat balance of the brain, **real life often creates the situations when this balance could not be compensated**, resulting in acute and chronic life-threatening health complications.

External Temperature Impact



Activity state/Environmental stimulation

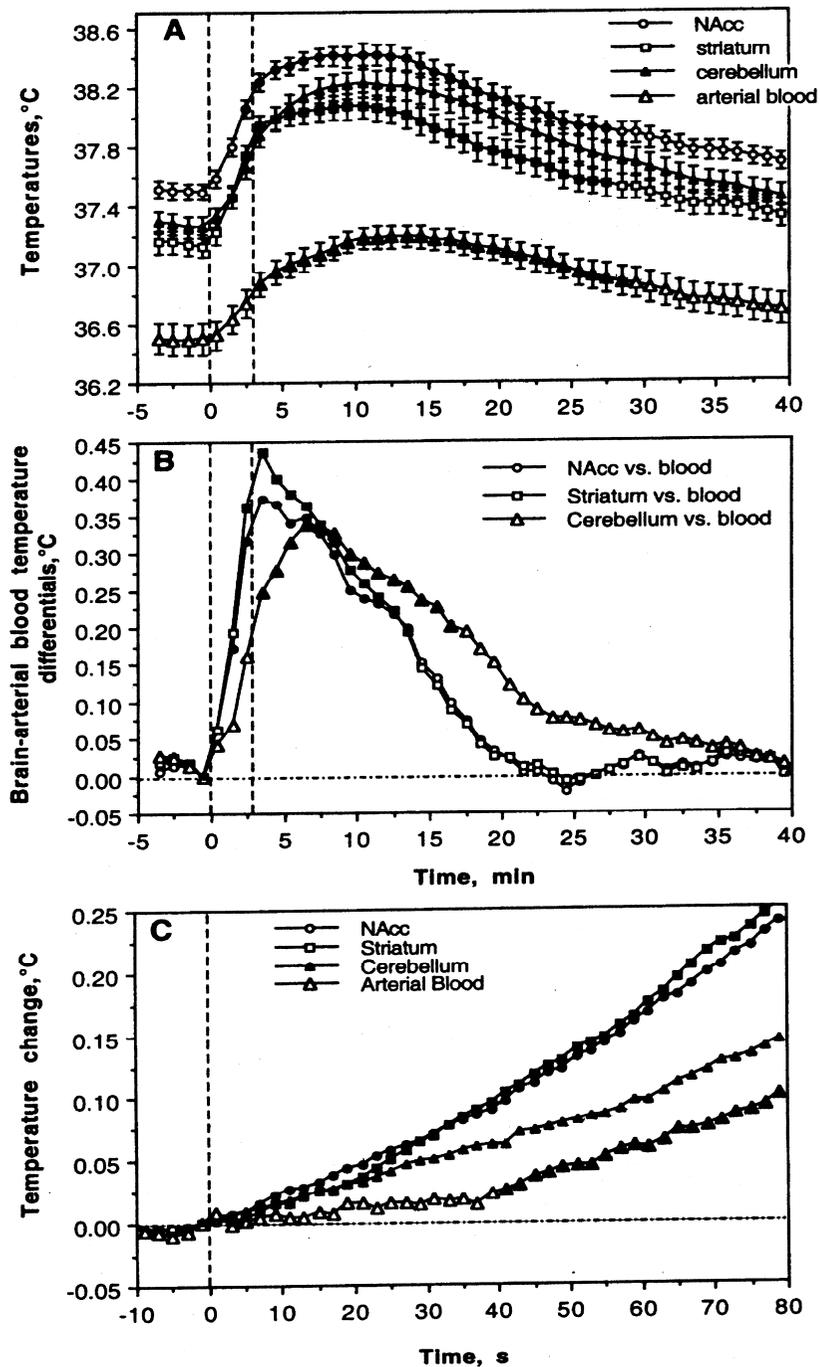
Drugs that increase metabolism and decrease heat dissipation

Ability to escape, Abilities to dissipate metabolic heat

Adverse health consequences

Contributors and collaborators:

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Roy A. Wise,
Jeremy Tang
Suelynn Ren*



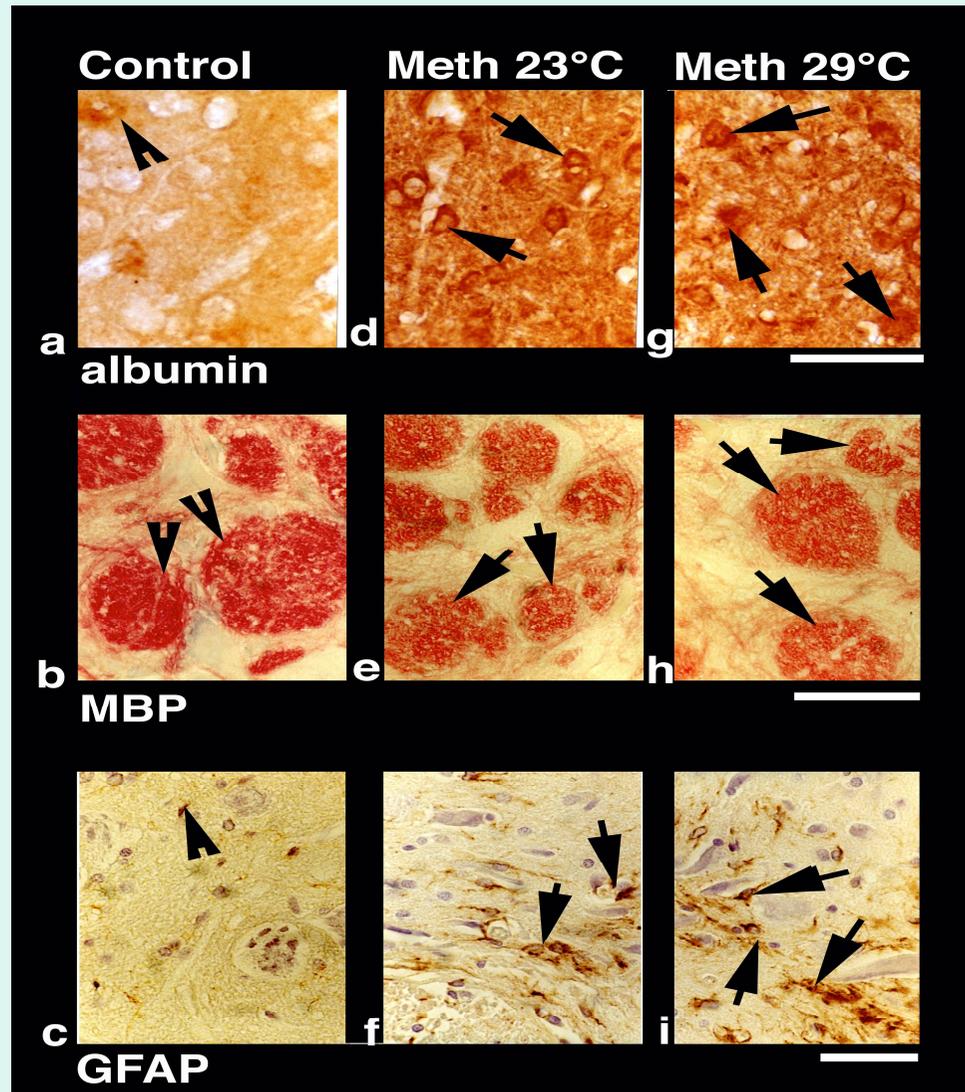
While changes in circulation is an important factor determining brain temperature fluctuations, **neural activation and intra-brain heat production appears to be the primary cause of brain temperature increases**

thermocouple sensors in the brain location and in abdominal aorta:

- t° in arterial blood is always < than in the brain and body sites;
- t° in brain sites always increases more quickly and stronger than in arterial blood;
- brain temperature increase is very rapid (8-10 s), differing in different structures and preceding more delayed increases in arterial blood temperature

(Kiyatkin et al., 2002)

METH-induced functional and morphological brain changes depend upon environmental temperature



METH **at the same dose** (9 mg/kg) at 23° and 29° C in freely moving rats (brain samples ~90 min post-injection)