Thresholds of thermal damage and thermal dose models

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Image-Guided Non-Invasive Therapeutic Energy

IGNITE for kids

Eruditio et Religio

Objectives

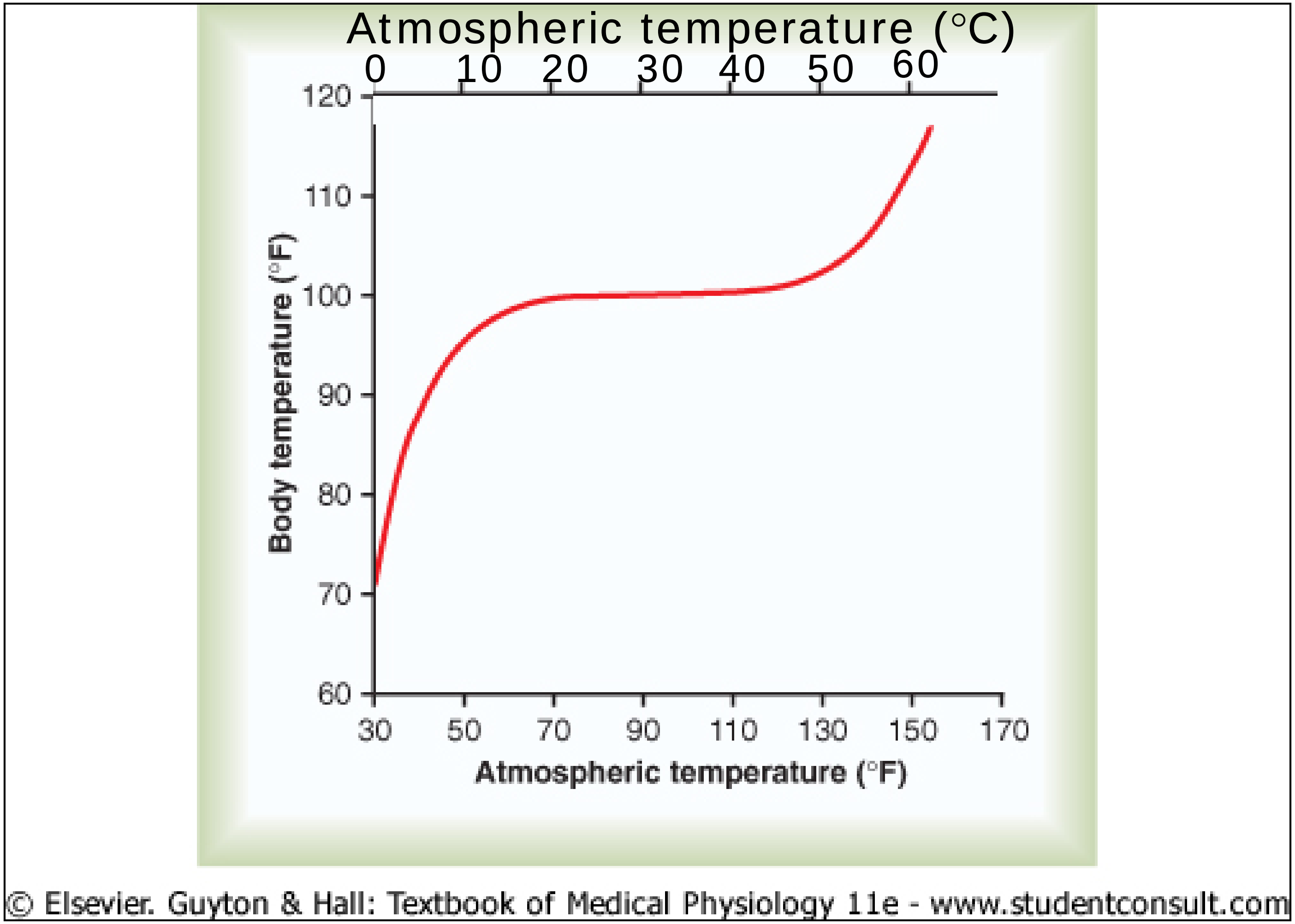
- Biological effects of heat
  - Physiologic effects
  - Adaptive response
  - Damage
- Overview of thermal dosimetry
- Thresholds of thermal damage
  - Interpretability of results
  - Highlights from our recent reviews
    - Brain
    - Testis
    - Other tissues
- Conclusions
  - What effects are significant?
  - Clarity through categorization

Thermoregulation: a unique autonomic system

- Evolved to regulate:
  - a stable core T over wide range of ambient T
  - heat loads from work and exercise, and fever
- Relies on:
  - behavior
  - conscious awareness of the environment

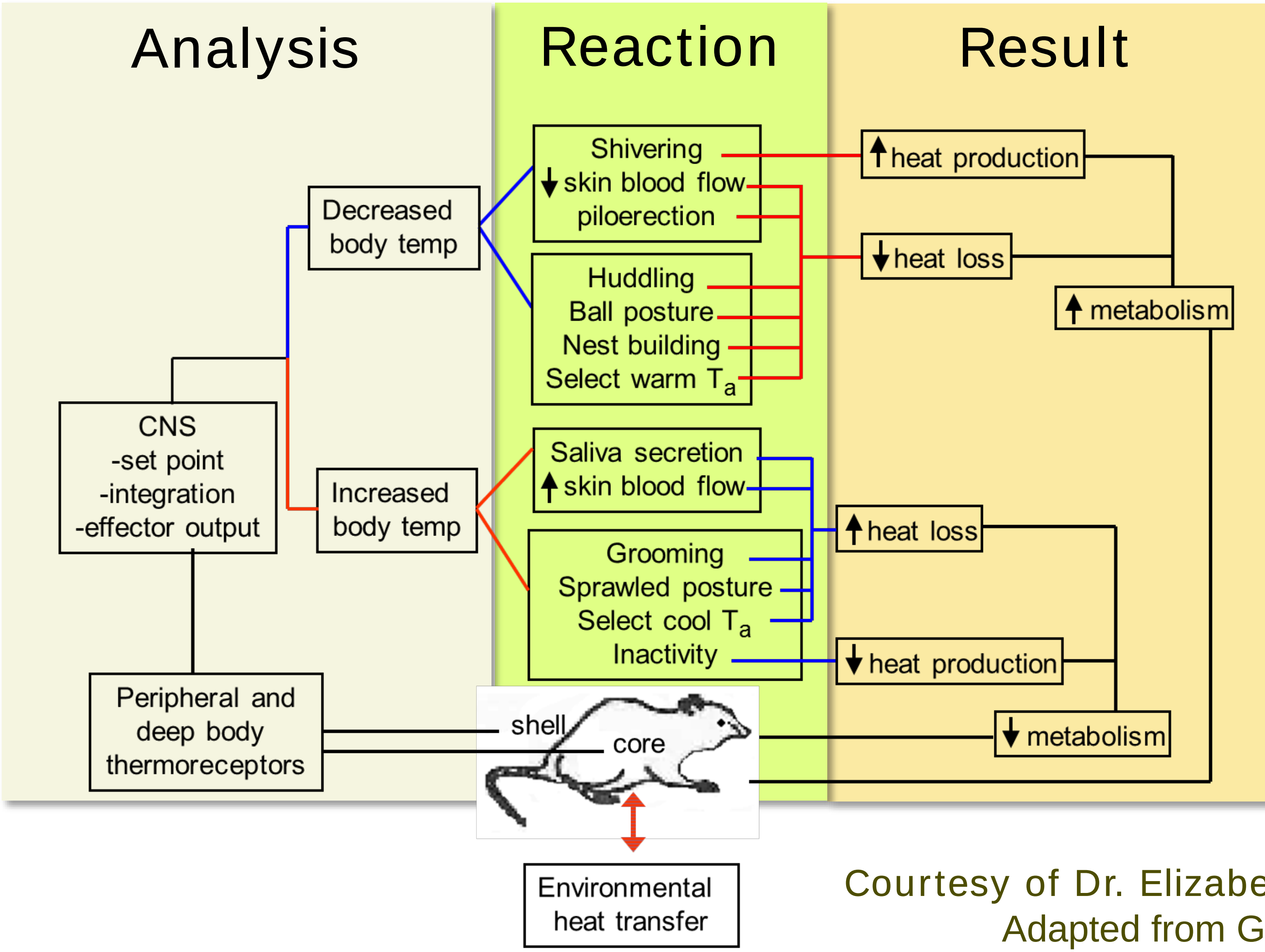
Courtesy of Dr. Elizabeth Repasky

Effectiveness of Human Thermoregulation



Courtesy of Dr. Elizabeth Repasky

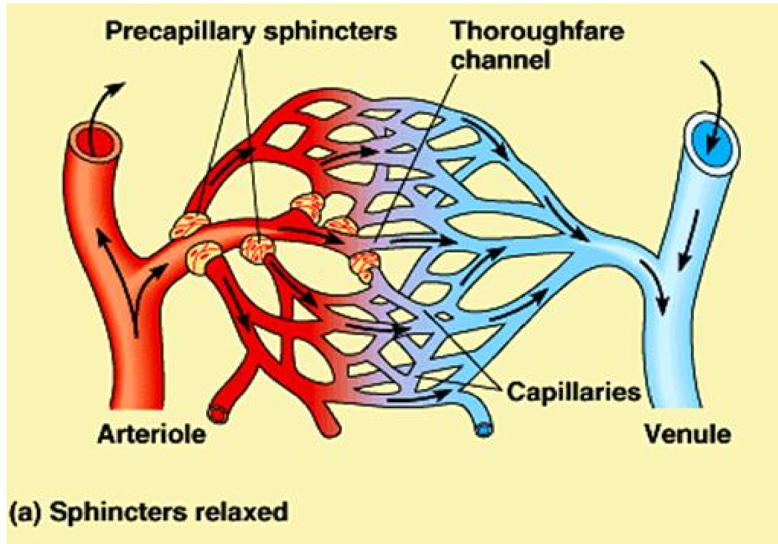
Thermoregulatory Control in a "Typical" Rodent



Courtesy of Dr. Elizabeth Repasky
Adapted from Gordon (1993)

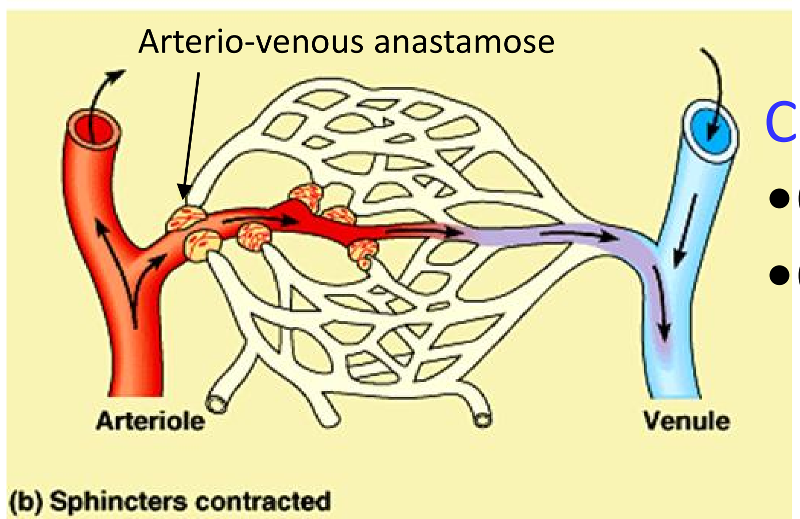
FUNDAMENTALS OF THE MICROCIRCULATION

Perfusion of tissue controlled through neural and local control mechanisms



Dilate sphincters

- Carbon dioxide
- hypoxia
- Heat



Constrict sphincters

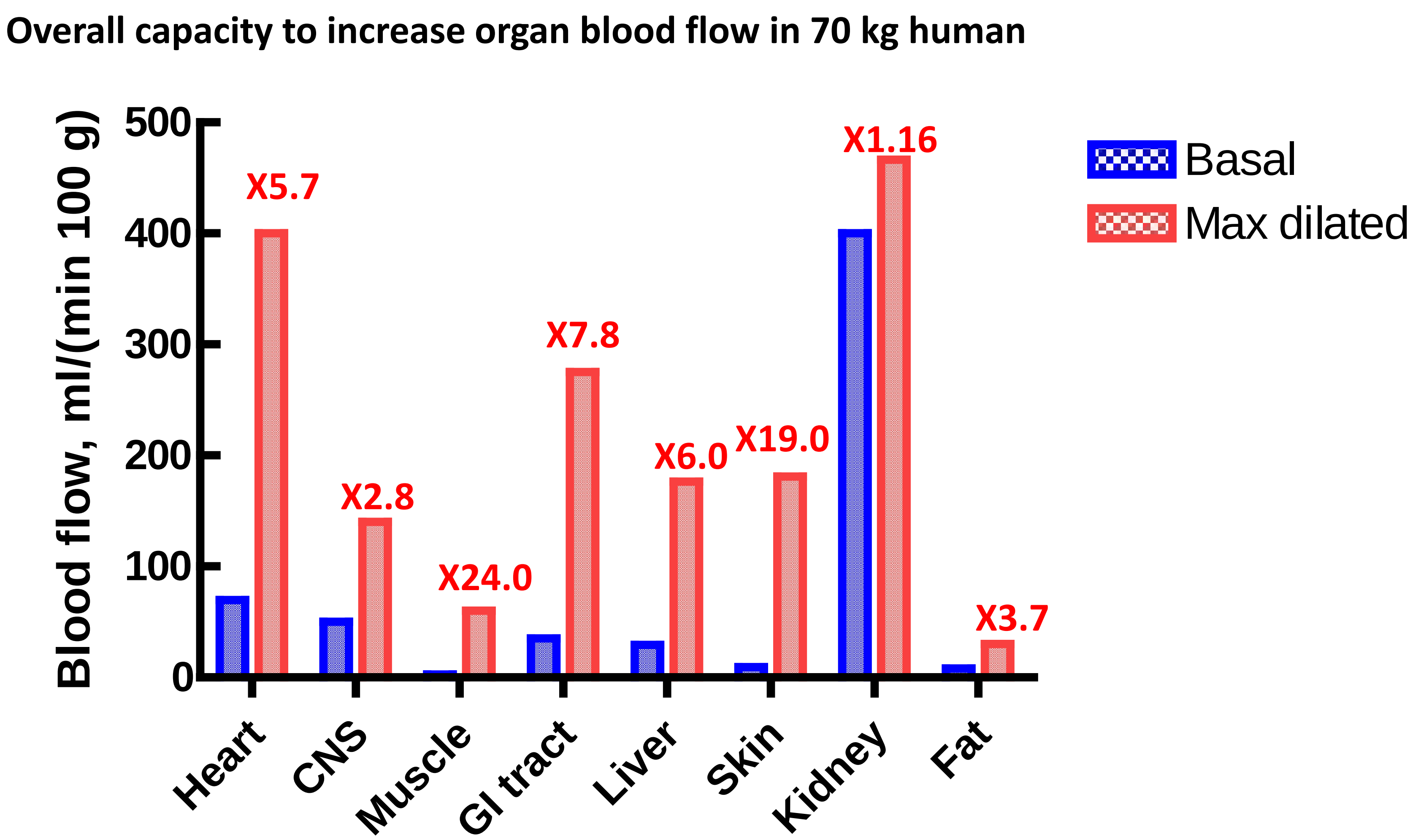
- Oxygen
- Cold

Limitations

- Aging
- Diabetes
- hypertension

Courtesy of Dr. Elizabeth Repasky

CARDIOVASCULAR CAPACITY following Thermal Stimulation



Courtesy of Dr. Elizabeth Repasky

From Mellander & Johansson, 1968

Therapeutic uses of heat

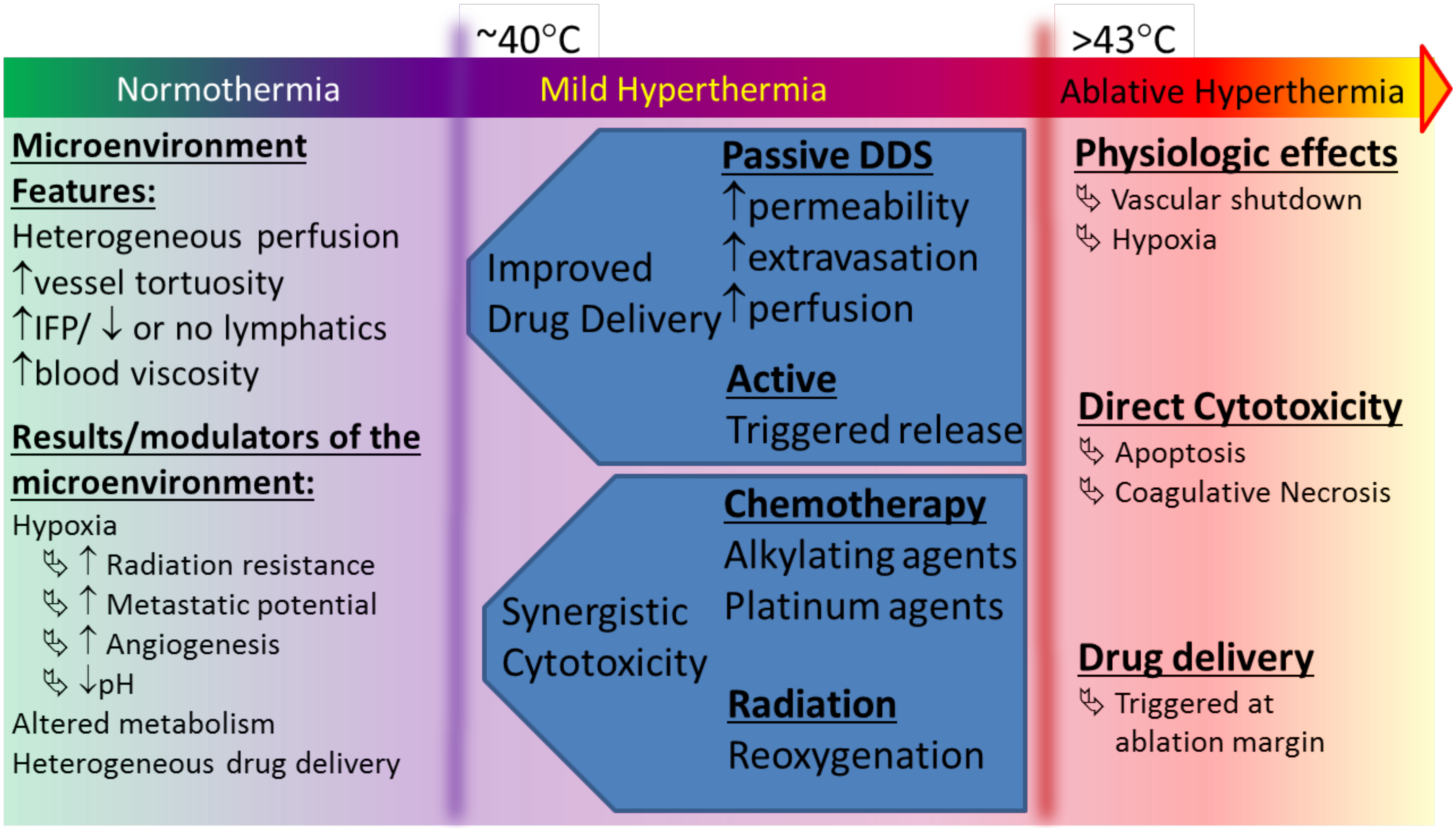
Mild Hyperthermia:

- Local or whole body heating
- Long duration (30 min – 2h)
- Mild T increase: 40-45°C
- Goals:
  - Adjuvant therapy
    - Radiation
    - Chemotherapy

Ablative hyperthermia:

- Local heating (RF, MW, contact)
- Short duration (30s-15min)
- High temperature
- Goals:
  - Direct killing of cells via
    - Coagulative necrosis (↑ exposure)
    - Apoptosis (↓ exposure)
      - Heat-shock proteins+p53

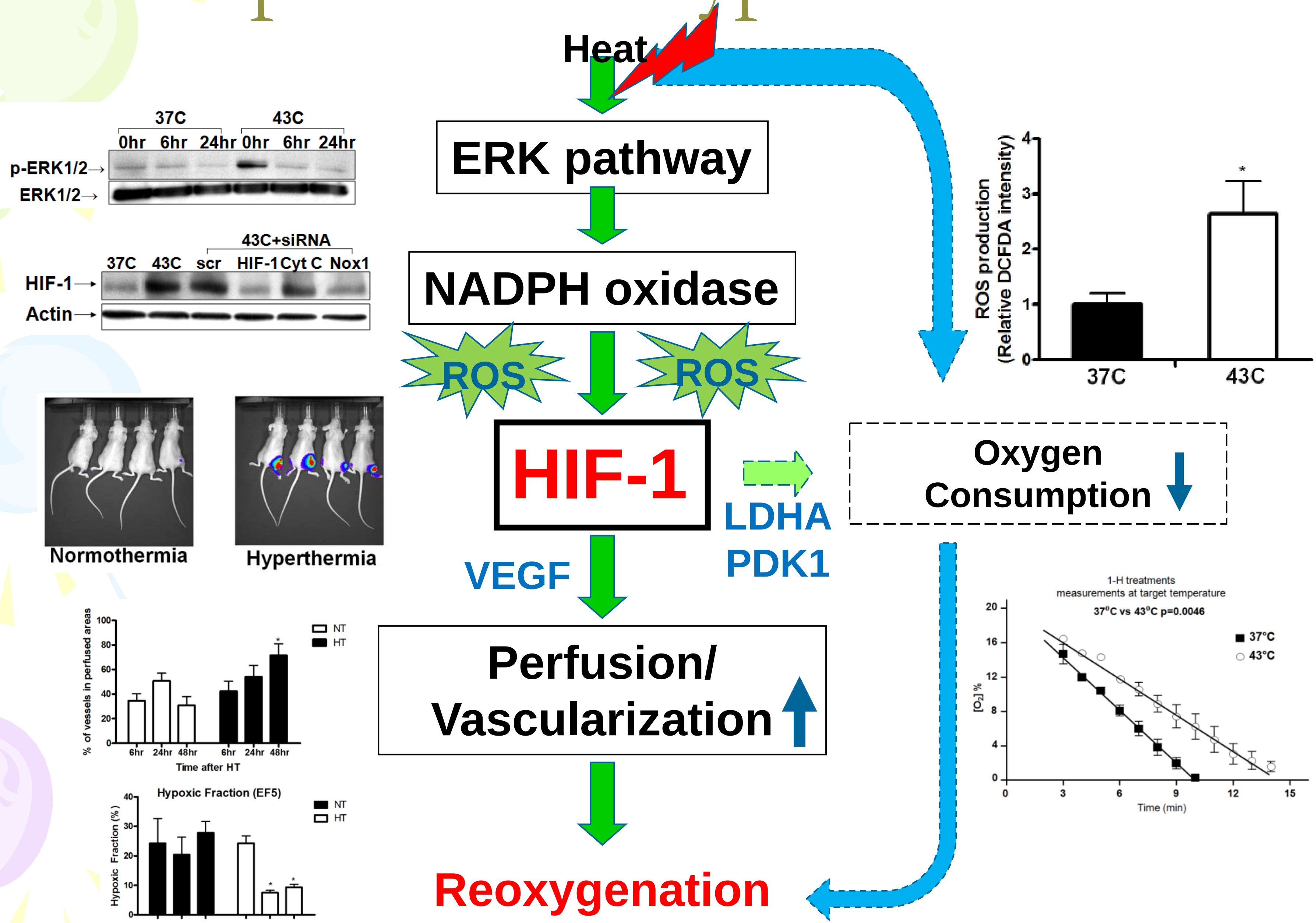
Effects of heat: lessons from oncology



Key mechanisms affected by mild hyperthermia

- Cellular metabolism, stress response, proliferation/survival:
  - Heat-shock protein-mediated responses (many effects)
    - ERK pathway (One of HSP targets)
      - NADPH-mediated ROS production
        - Regulates HIF-1
          - Switch to glycolysis (↓O_2 consumption, ↑ lactic acid)
          - ↑ angiogenesis/related responses
- Vascular perfusion regulation:
  - <>10x ↑ in healthy muscle
  - Variable ↑ in tumors
    - In tumors:
      - ↑O_2 delivery -> Affects HIF-1
      - ↑radiosensitivity

Heat response and hypoxia in tumors

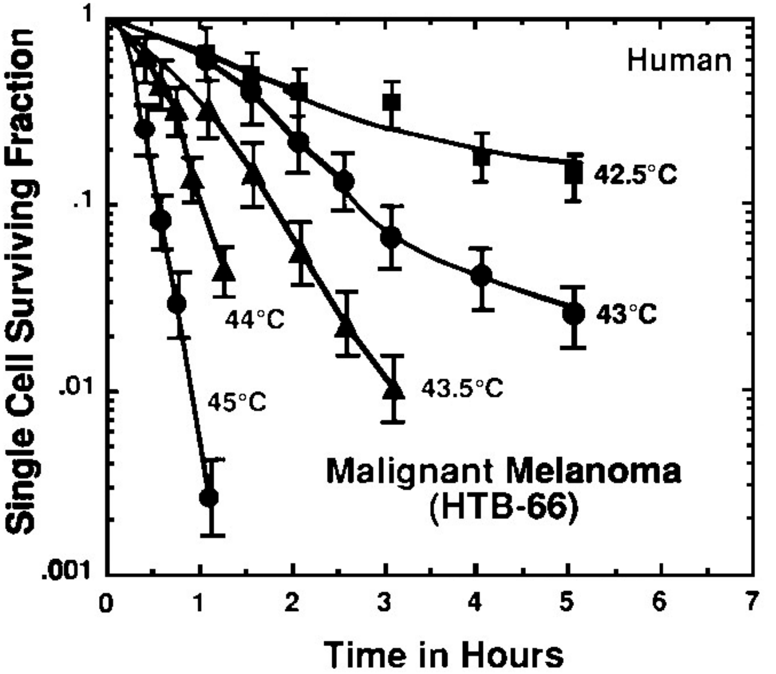


Moon et al. 2010. PNAS

Thermal Dosimetry

- ↑ Variability across:
  - Species
  - Cell/tissue types
  - Organs
- Relate damage to:
  - Exposure type
  - Temperature
  - Duration
- Guide:
  - Therapeutic hyperthermia
  - Diagnostic imaging
  - Exposure safety

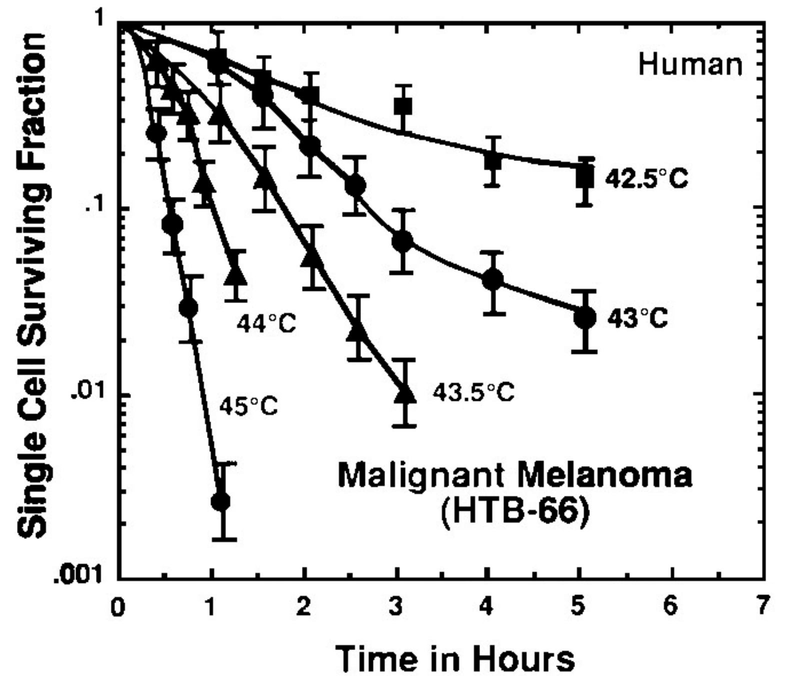
Heat: effect on survival of Human Cells

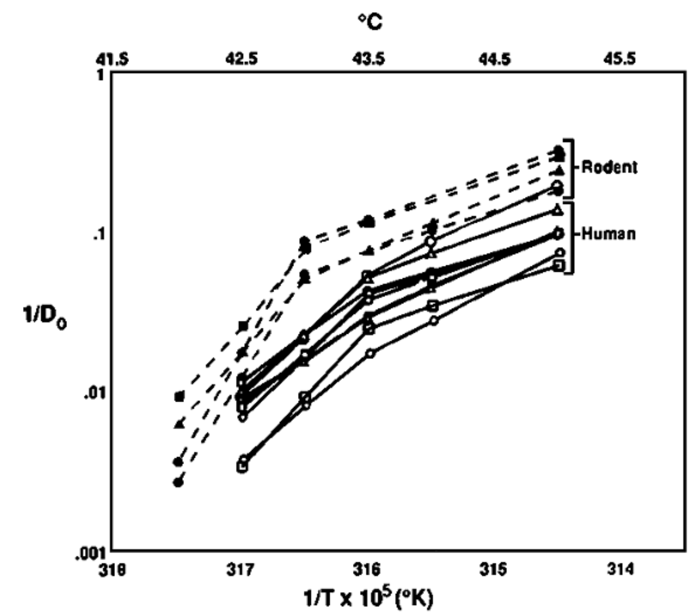


From Roizin-Towle

Thermal dosimetry: An irreversible reaction rate

- Rate of cell kill:
  - Exponential ∝ time
  - Depends on T
- Similar to the Arrhenius relationship:
  - $K = Ae^{(-\frac{E}{RT})}$
    - E=heat of "inactivation" of cells
  - Arrhenius plot:
    - Breakpoint consistent with E for proteins/enzymes
    - No thermotolerance during heating above breakpoint
    - E and breakpoints = different for humans vs rodents





Assessment of thermal damage using Damage Index

Derived from Arrhenius relationship, assumes that damage occurs with 1st order Kinetics

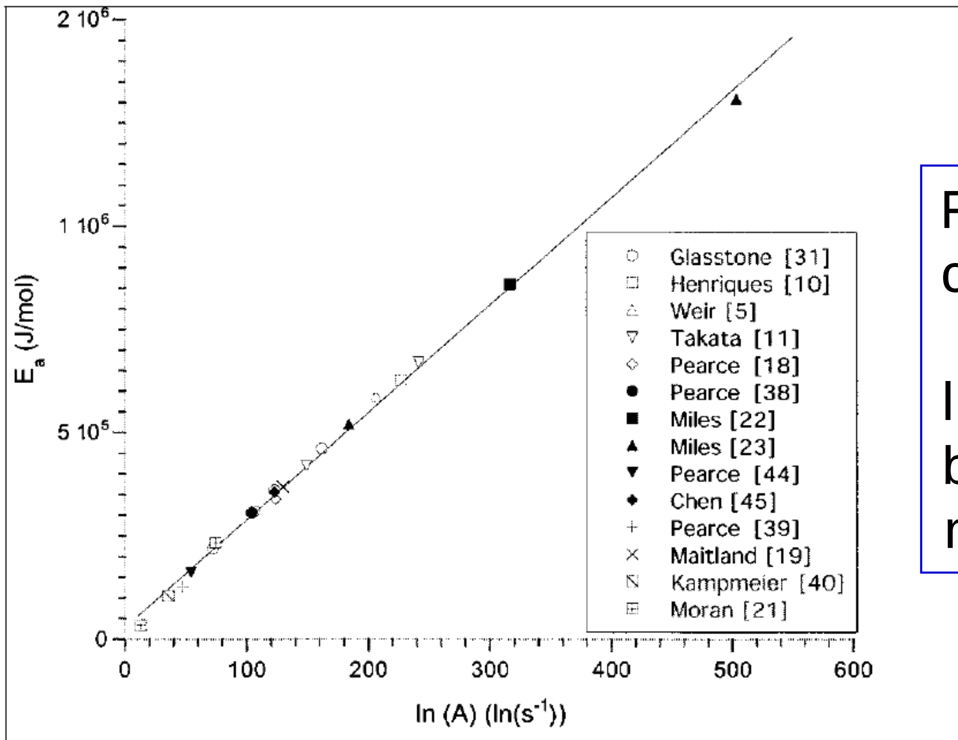
$$Rate\ \ of\ \ damage = {dC(t)}/{dt} = K \cdot C, \quad K = A \cdot \exp\left(\frac{-E_a}{RT(t)}\right)$$

C= % undamaged tissue
K = 1st order reaction constant
t= time
A= frequency factor 1/s
Ea = activation energy (J/mole)
R = universal gas constant
T= time dependent function of temperature, K

Assessment of thermal damage using damage index

$$Damage\quad Index = \Omega = \ln\left(\frac{C(0)}{C(\tau)}\right) = \int_0^{\tau} A \cdot \exp\left(\frac{-E_a}{RT(t)}\right) dt$$

Ω = Ratio of damage at time 0 vs. time (τ)

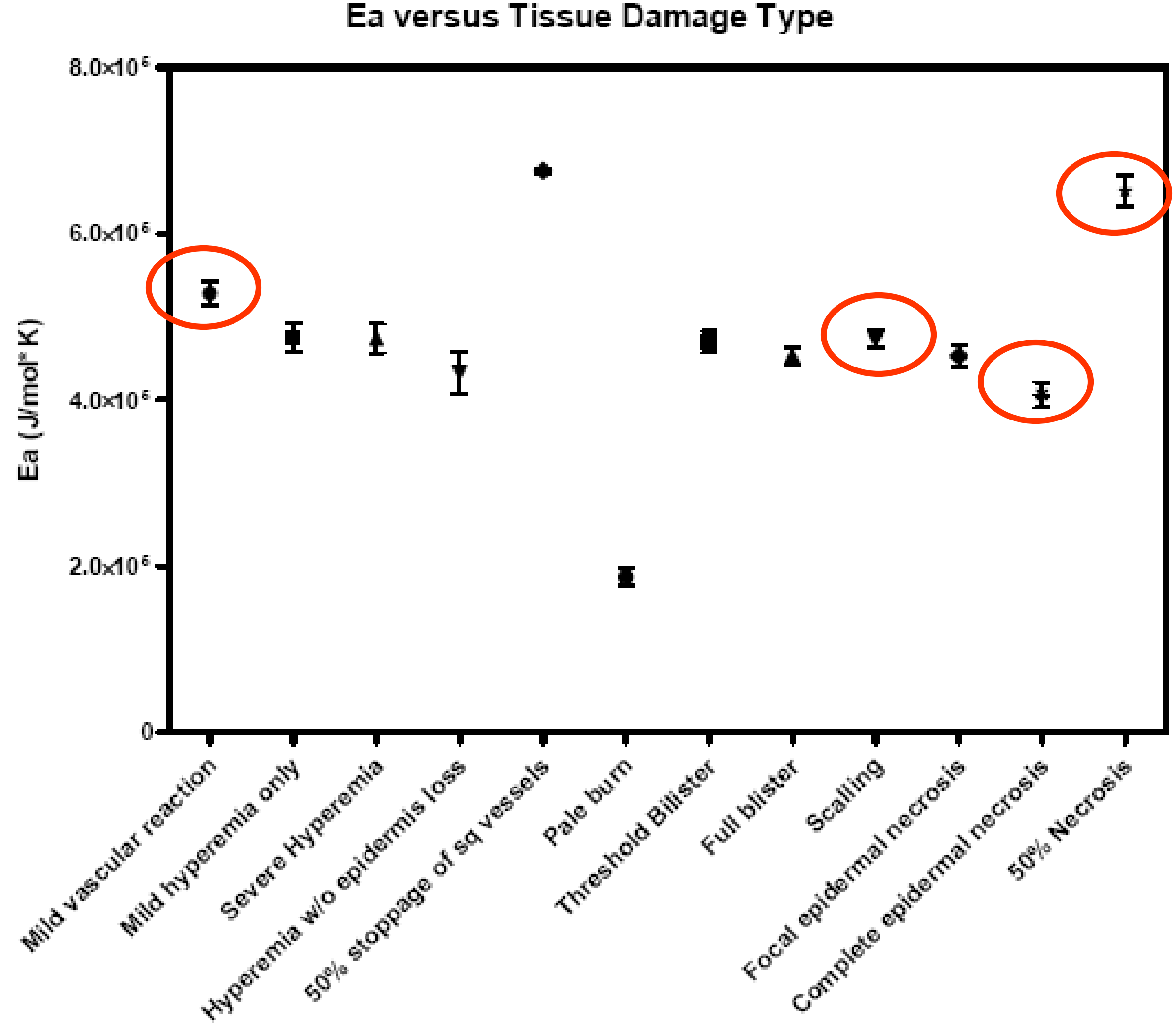


For complete necrosis or collagen denaturation:

log-linear relationship between Ea and ln(A) across many tissues

Wright, N.T., *On a relationship between the Arrhenius parameters from thermal damage studies.* J Biomech Eng, 2003. 125(2): p. 300-4.

Severity of skin damage does not exhibit intuitive relationship with Ea.



Data from Moritz et al.

Requirements to establish damage index as common platform to compare across tissues

- Need to establish a range of time-temperature combinations that yield the same isoeffect
  - Such data are difficult to find
- Need to see a predictable relationship between Ea and severity of damage
- Because there requirements are not yet met:
  - Thermal isoeffect dose = most established method for standardization/estimation of dose

Basis for thermal isoeffect dose

$$CEM43°C = \int_0^t (R^{43-T_{measured}})dt$$

Advantages

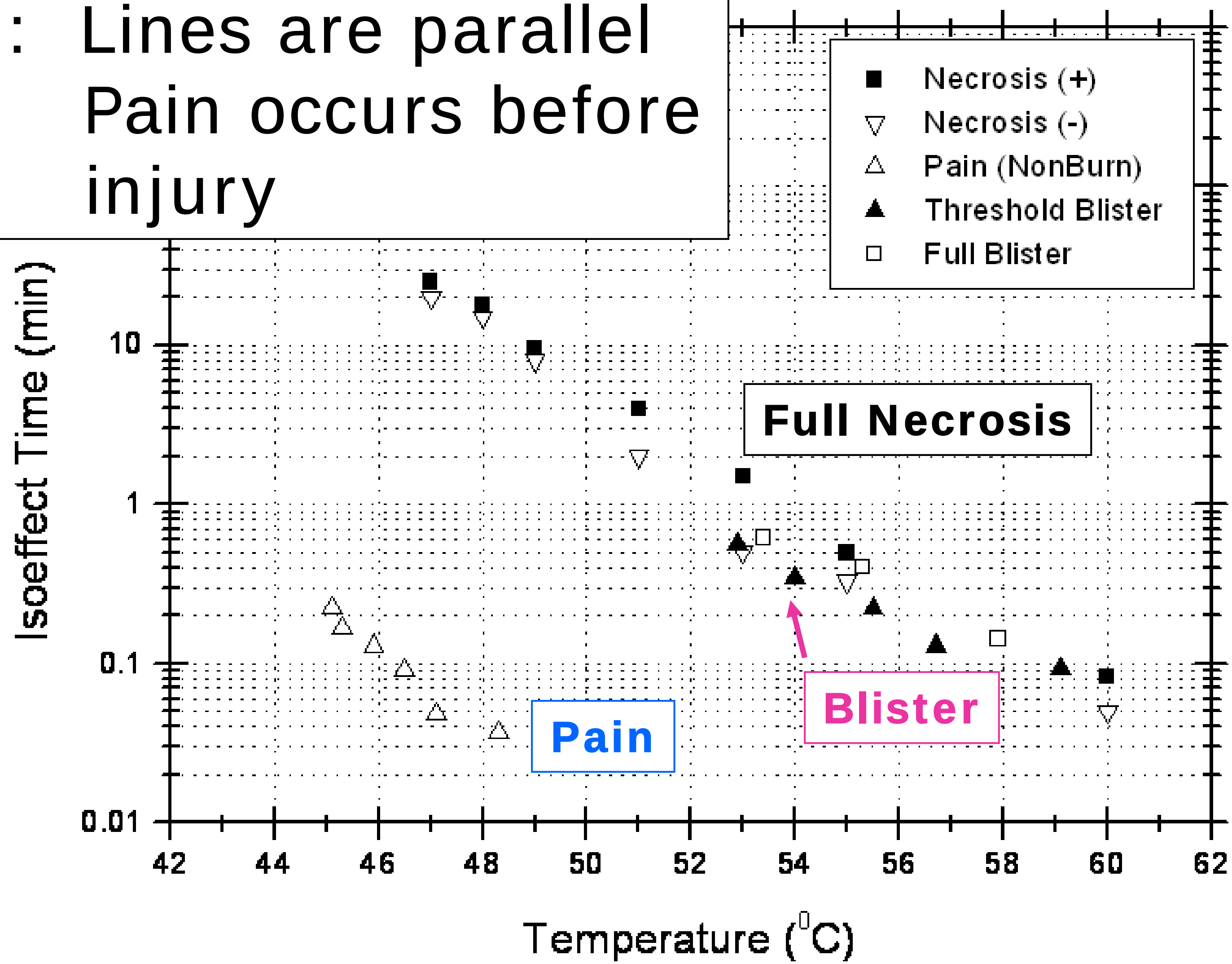
- Convert time-temp combination to standard
- Threshold for thermal damage can be established
- Can establish t-T isoeffect line to avoid thermal damage

Challenges

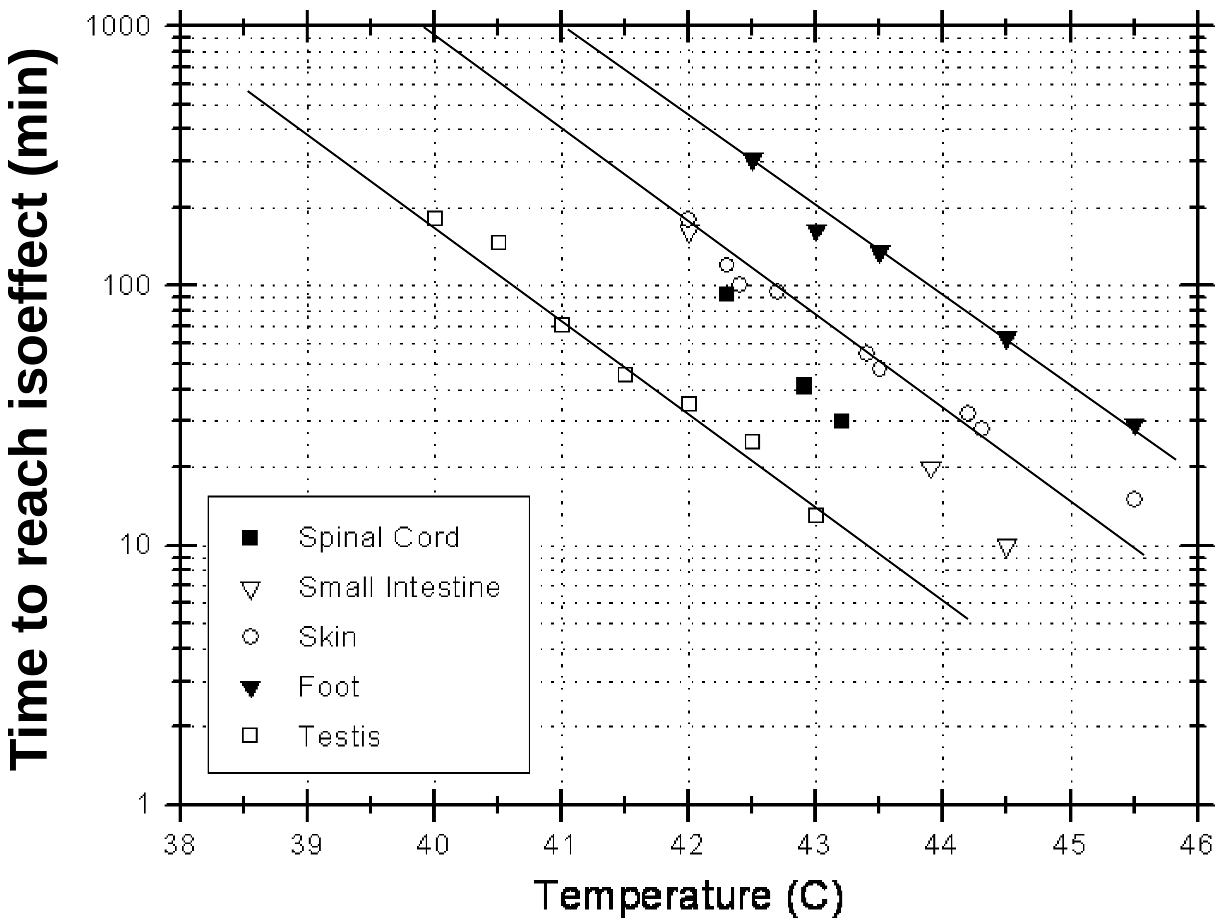
- Arrhenius plot slopes may vary by
  - Tissue
  - Endpoint
  - Species
- Need to have at least 1 time-temp combination for threshold
  - Endpoint dependent

Isoeffect lines for pain vs. thermal damage – human skin

NOTE: Lines are parallel
Pain occurs before injury



Comparison of time-temperature thresholds across tissue types for mouse



NOTE: Lines are parallel
Tissues differ in sensitivity

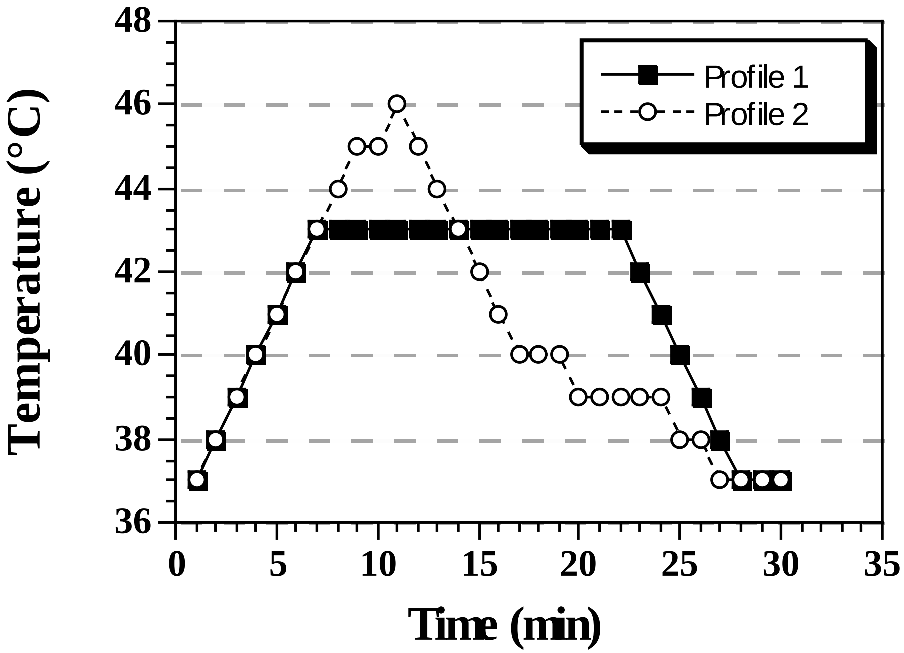
Arrhenius slope characteristics for mouse vs. human cells

$$\text{CEM}43°\text{C} = \int_0^t \left(R^{43-T_{avg}(t)}\right)\text{dt}$$

		R value	
Species	Breakpoint	<Breakpoint	>Breakpoint
Mouse	43.0°C	0.25	0.5
Man	43.5°C	0.13	0.72

NOTE:
Breakpoint for mouse cells provides a more conservative estimate of thresholds for damage

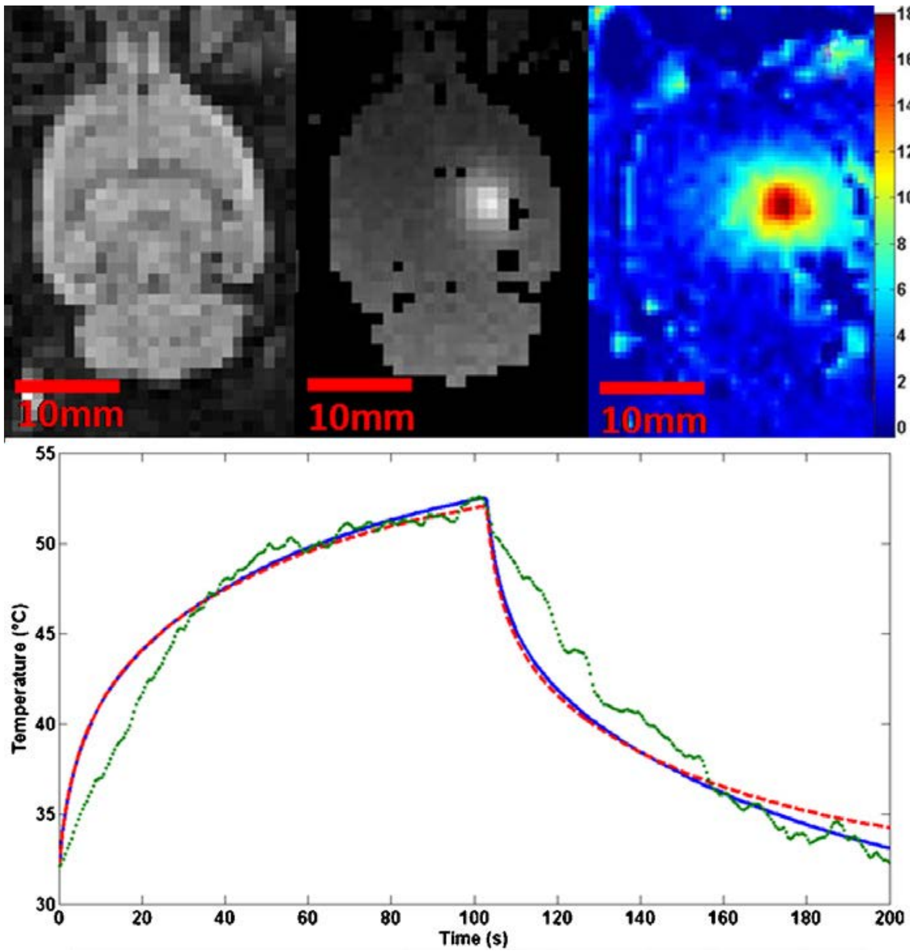
Accurate calculation of CEM 43°C requires full thermal history at location of damage assessment



Which profile has the highest CEM 43°C?

Profile 1 = 17 CEM 43°C
Profile 2 = 27 CEM 43°C

Full thermal data can be obtained from MRI, but are most often not reported



Example-
Rat brain thermal ablation
With HIFU

Beautiful data, but
only temperature data are in the center of the ablation zone –
We need data at the margin and outside the ablation zone to set thresholds

Larrat et. al. Phys Med Biol, 2010

Thermal damage thresholds – a review

Table 1. Keywords used in database searches.		
hyperthermia damage	laser burn	skin
heat damage	heat	tendon
high temperature damage	soft tissue	muscle
heat exposure damage	adipose tissue	epicardium
hyperthermia injury	liver	bone
heat injury	esophagus	spine
high temperature injury	intestine	fat
heat exposure injury	testis/testes	foot
high temperature tissue destruction	prostate	tail
high temperature tissue damage	bladder	spleen
heat tissue destruction	urethra	bone marrow
heat temperature tissue damage	kidney	brain
heat inflammation	eye	spinal cord
heat exposure damage	cornea	blood vessels
heat exposure injury	retina	gonads
CNS/Central Nervous	lens	ovaries/ovary
blood brain barrier	iris	gonads
peripheral nerve system	eyelids	burn injury

463 papers identified since the previous review in 2003

Why are so many papers hard to interpret?

Table 4. Papers included in this review categorized by tissue type and heating method.

Tissue (All Species)	Local Heating	Whole Body Heating
Bladder	1	
Bone	1	
Bone Marrow		1
Brain	3	8
Ear		2
Esophagus	1	
Eye (Cornea, Retina, Eyelids)	4	
Kidney	4	
Liver	6	1
Mammary Gland	1	
Muscle	8	1
Prostate	6	
Skin	4	
Small Intestine		2
Testes	8	3
Thymus		2

117 papers included

Had to exclude:

- Lack of thermal data
  - 131 papers
    - Temperature not measured adequately
    - Temperature not measured at site of damage assessment
- Laser data (doses grossly exceed damage threshold)
- Modeling papers without data
- Reviews
- Done on excised tissues

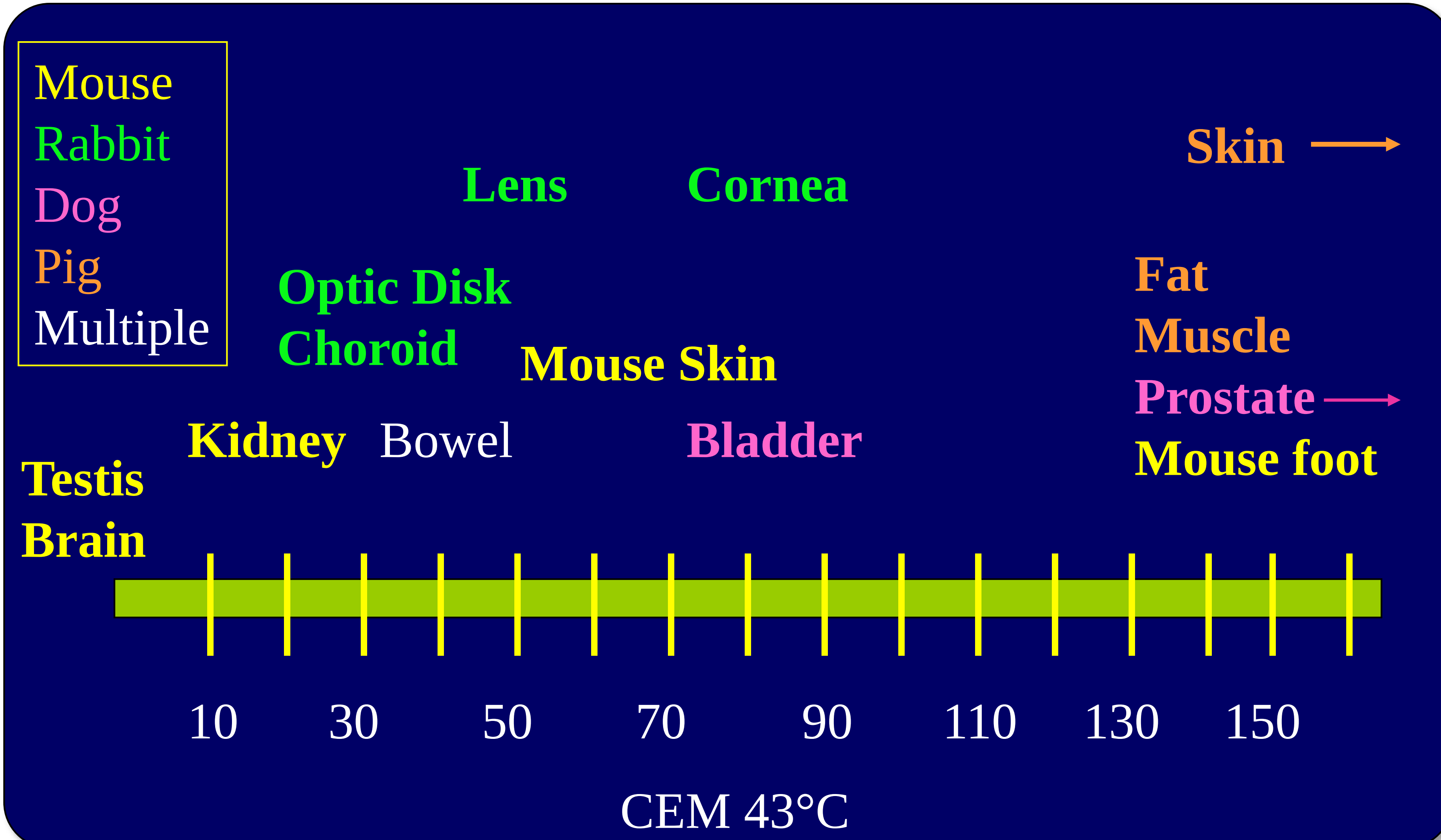
Types of data examined: range of effects, exposure and assessment time

		Type and degree change						
		Acute		Chronic				
CEM_{43} (min)	Tissue type	Minor	Significant	Minor	Significant	Species		Reference
0-20	BBB		H*/F, H/F			Rat/Rabbit	Dog	[4-7]
	Bone				G	Rat		[8]
	Bone Marrow	F/H	H*			Rat	Mouse	[9]
	Brain	H/H	H	H		Rat/Rabbit	Dog/cat	[5, 7, 9-11]
	Cornea		F			Human		[12]
	Esophagus		H			Pig		[13]
	Kidney	H	F			Rabbit	Rabbit	[14]
	Muscle		F*/H			Human/Pig		[15, 16]
	Retina			G/H			Rabbit	
	Testis	F, F/H	H, H/F/G	F, H	F, F	Mouse	Mouse	[17-20]
	Testis		G, H*			Rat		[11, 21]
	Thymus		H*			Rat		[9]
	Small Intestine		F/H			Rat		[22]
	Nerve		F			Rat		[23-25]

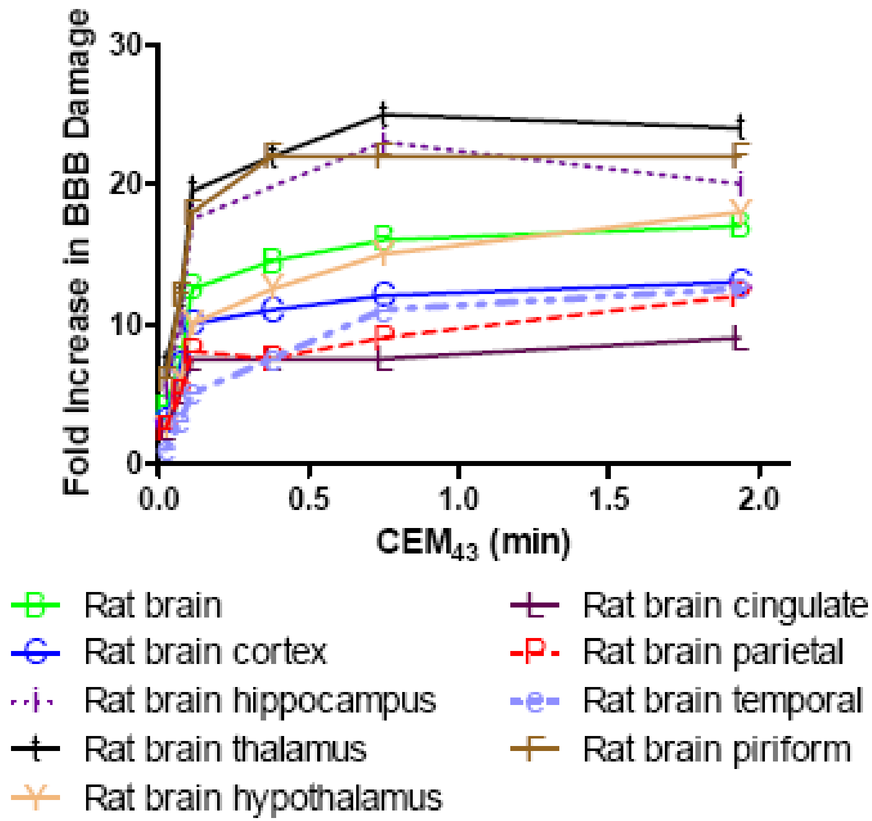
H = histology
F = Function
G = Gross assessment

NOTE: Very few assessments made of chronic consequences of thermal damage

Differences across species and tissues: thermal sensitivity



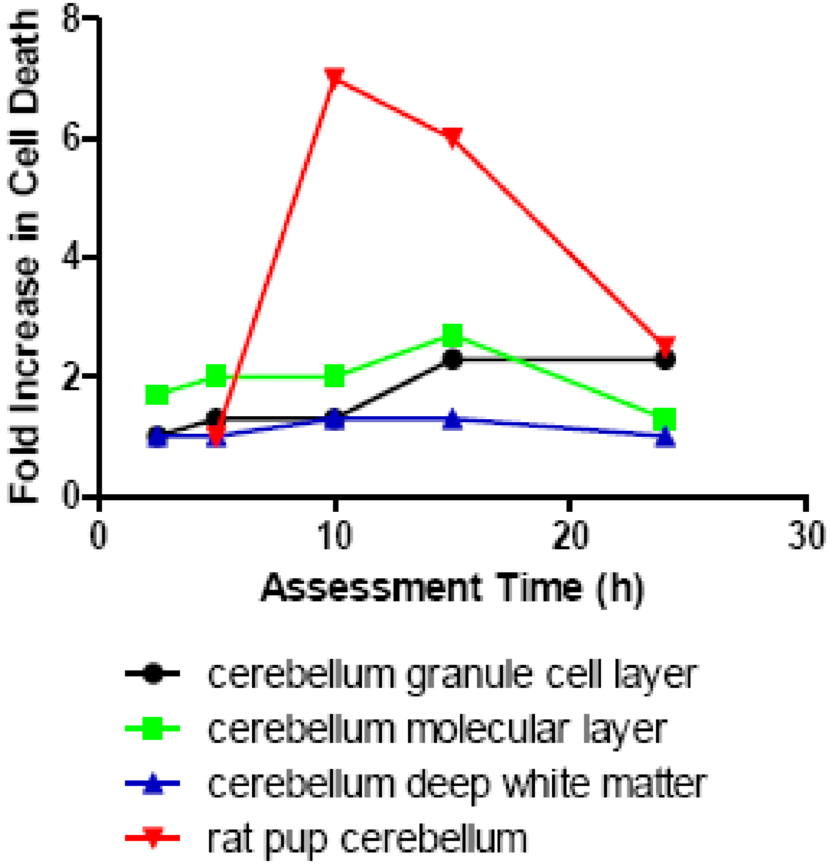
Functional effects detected at low thermal doses



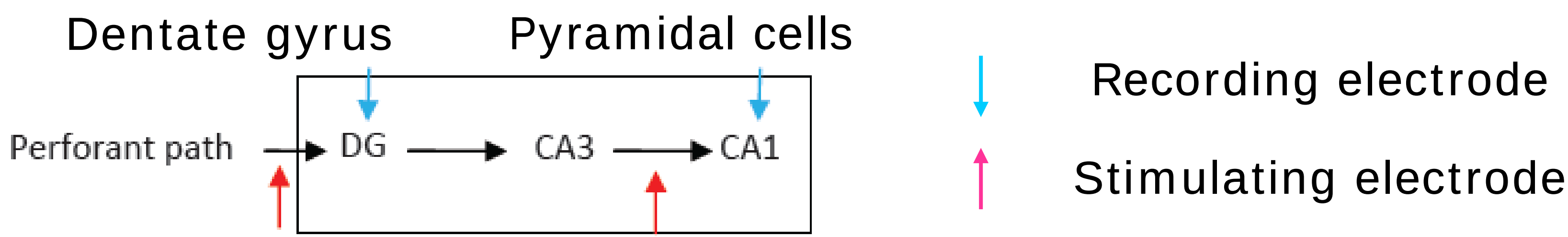
Data from Kiyatkin et al., indicate very low threshold for change in BBB permeability – but threshold is likely to be much higher for local heating- Estimates from J Hoopes in dog = 10-20 CEM 43°C

Sub-regions of brain vary in thermal sensitivity: age and time of assessment

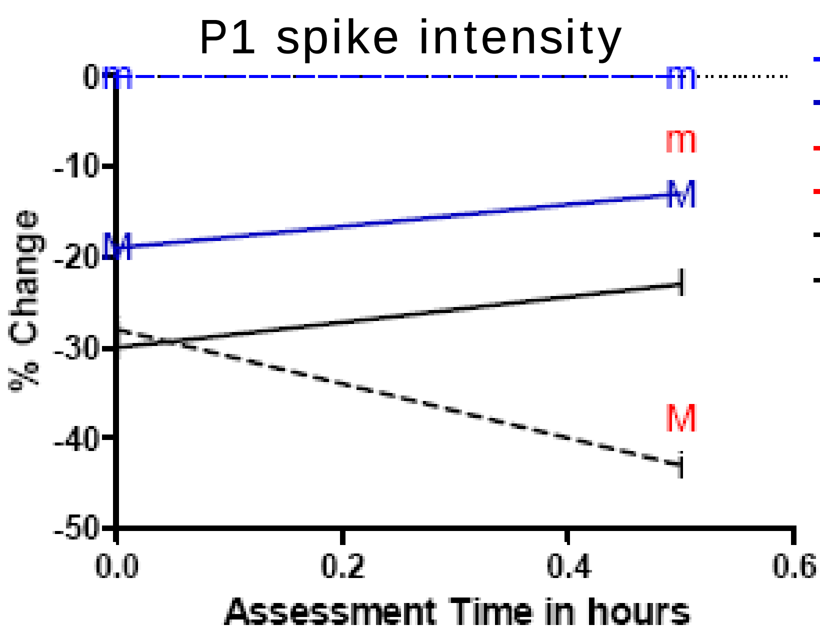
- Assessment of cell death
  - Several brain regions examined
  - Whole body HT
  - Assessed at different times
  - Thermal dose: $5.9CEM_{43}$



Effects of HT on hippocampal neuronal excitability – has implications regarding seizure activity

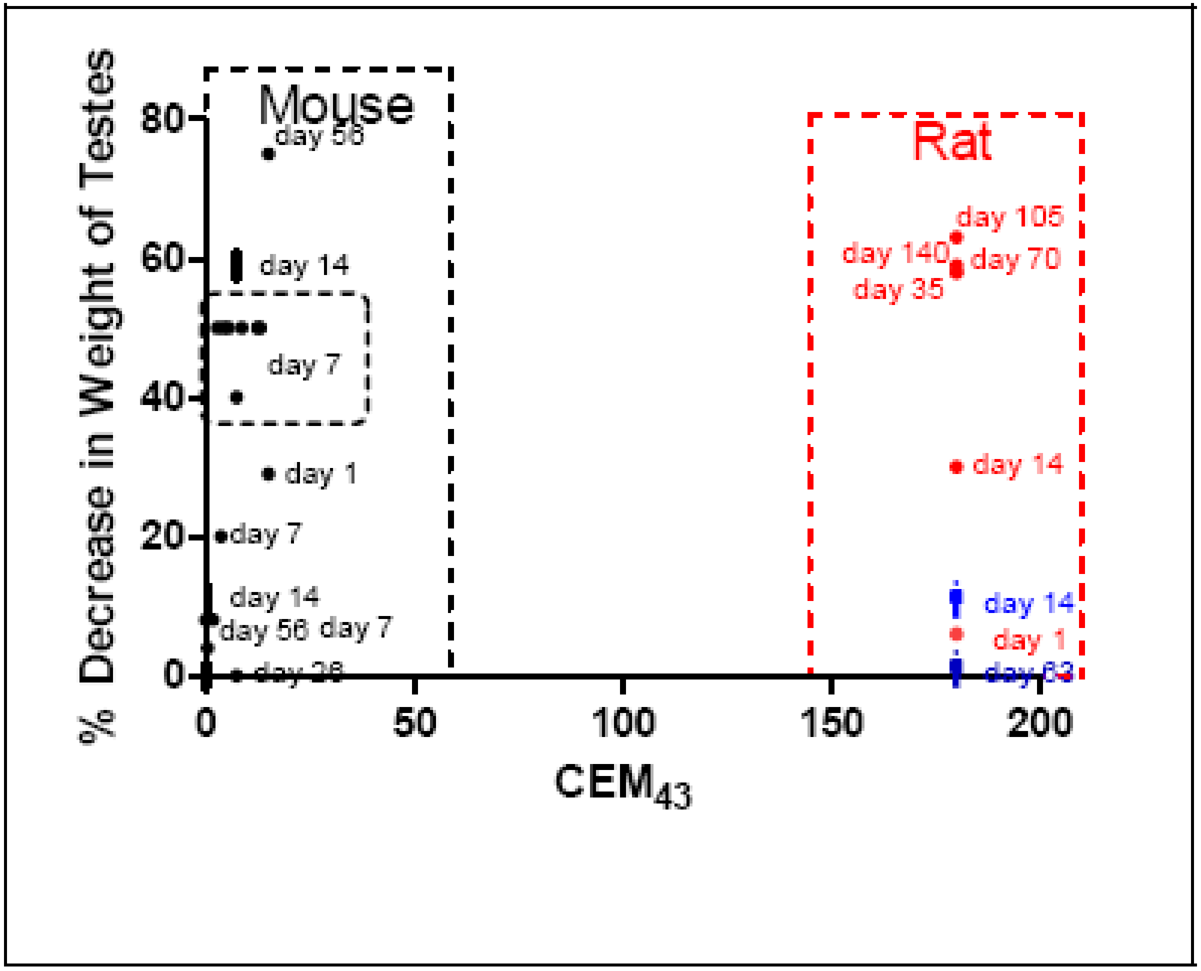


Inhibitory neurons function to dampen excitatory response

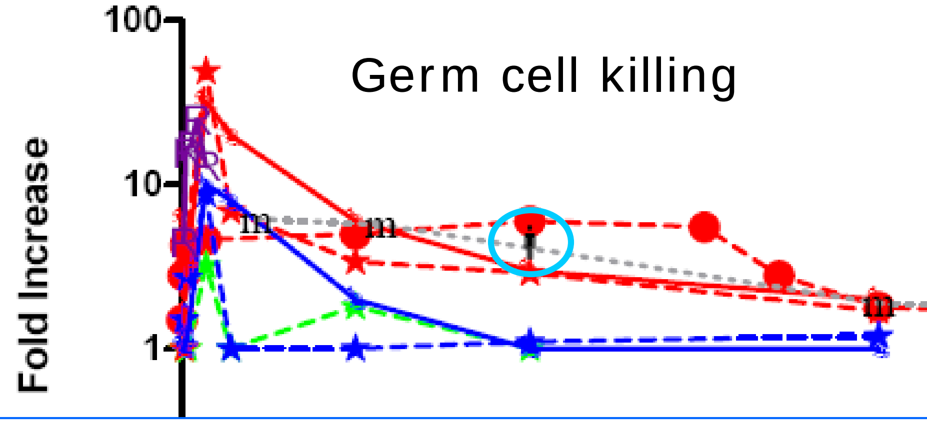


Reduction in neuronal response
Indicates that inhibitory neurons
are sensitive to HT – young >mature
Neurotransmitter, GABA is likely involved

Effects of HT on testis – mouse data may not accurately reflect sensitivity of human



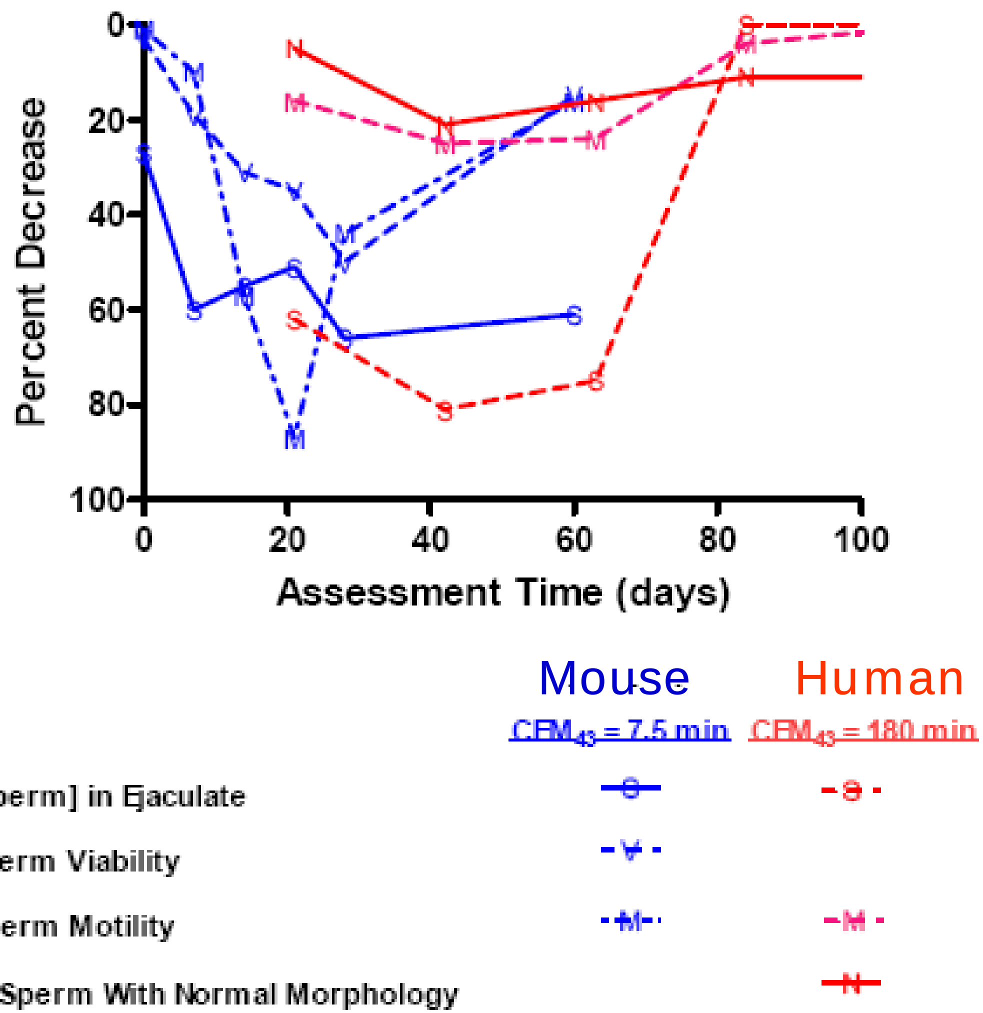
Effect of HT in testis dependent upon time after exposure



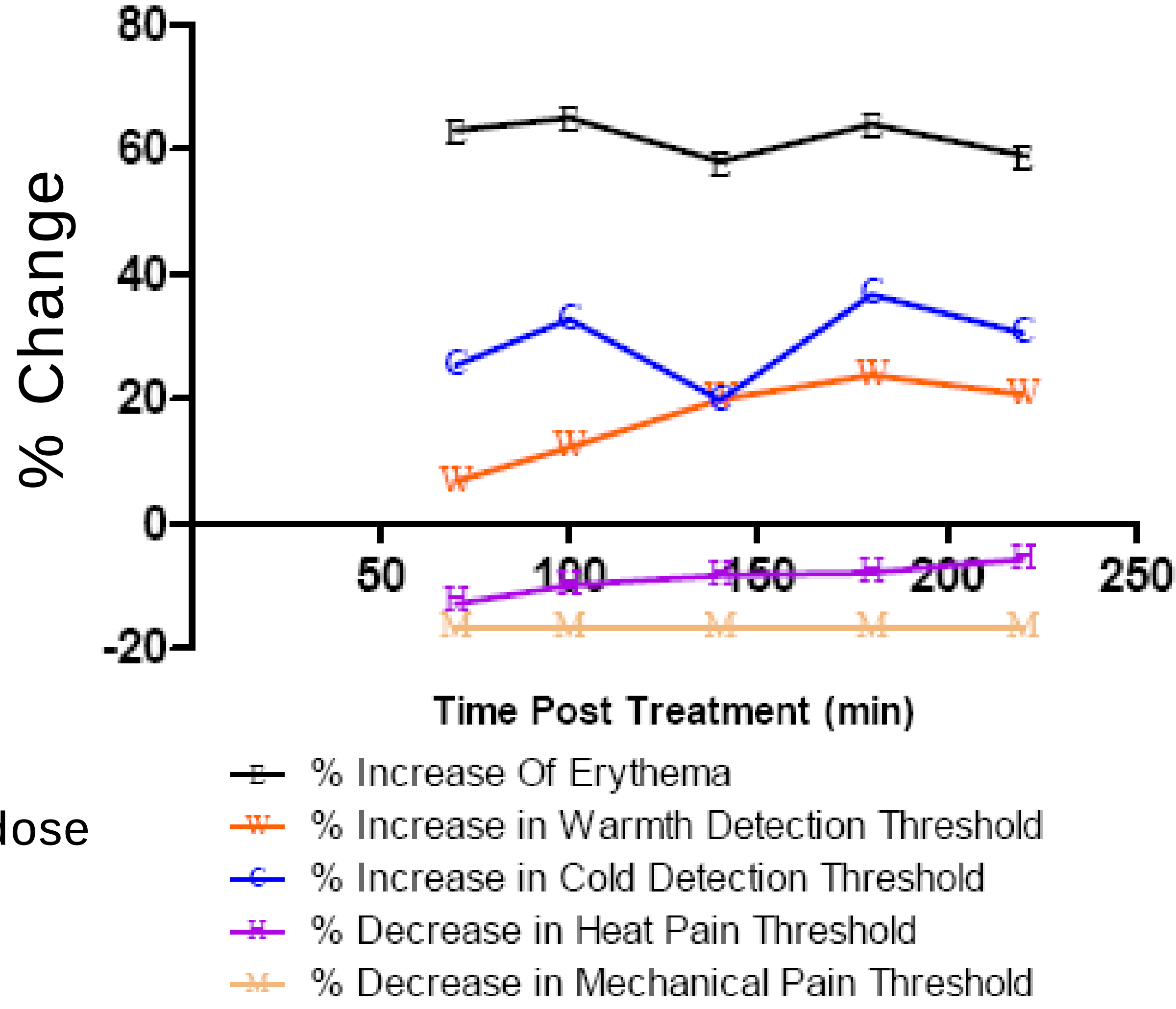
Note:
A threshold for sperm damage is not yet determined particularly for humans. Monkey and human data are similar.

		CEM$_{43}$ (min)					
		0.03	0.05	5.9	7.5	60	180
Mouse	Testes germ cell death [17]				---●---		
	Testes germ cell death [19]	--★--	--★--		--★--		
	Overall cell death In testes [18]		--*--		--*--		
Rat	Cell death In seminiferous tubules [11]			R			
Monkey	Testes germ cell death [31]					··m··	
Human	Testes Germ Cell Death [36]						i

HT effects on sperm function show recovery over time

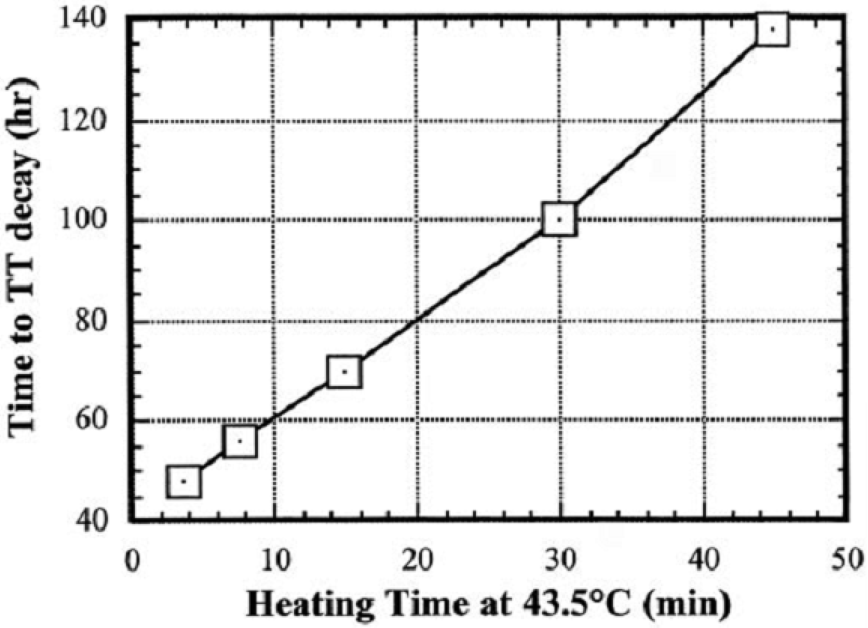


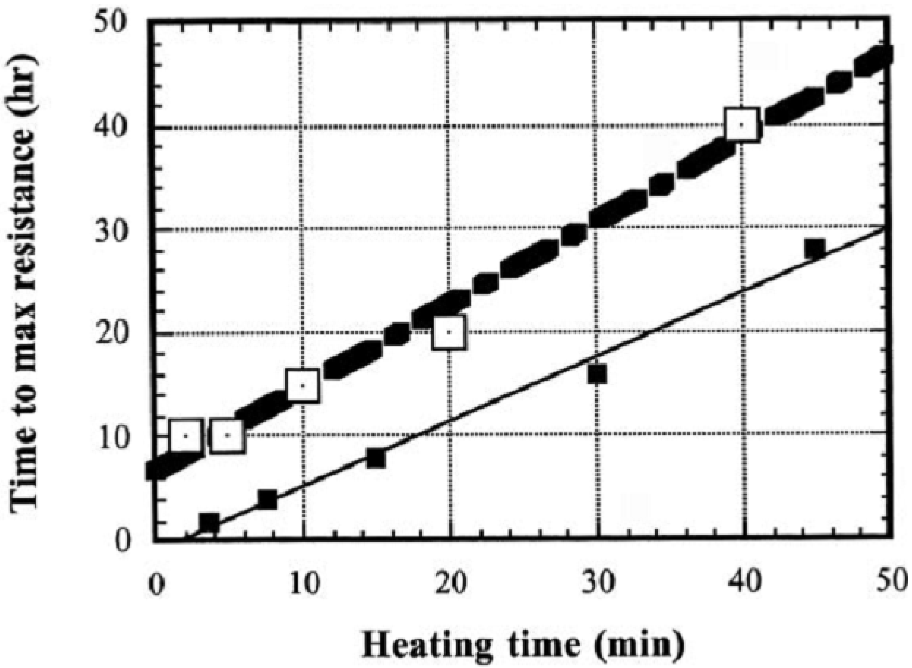
Skin- Thresholds for pain are dependent on prior thermal exposure



Initial thermal dose
112 CEM43°C

Thermotolerance: dependence on heating exposure





Rate of thermotolerance decay depends on severity of initial exposure

Time to max thermotolerance dependent severity of initial exposure

Data from: Nielson, 1982 & Law, 1979

Conclusions: effects of heat

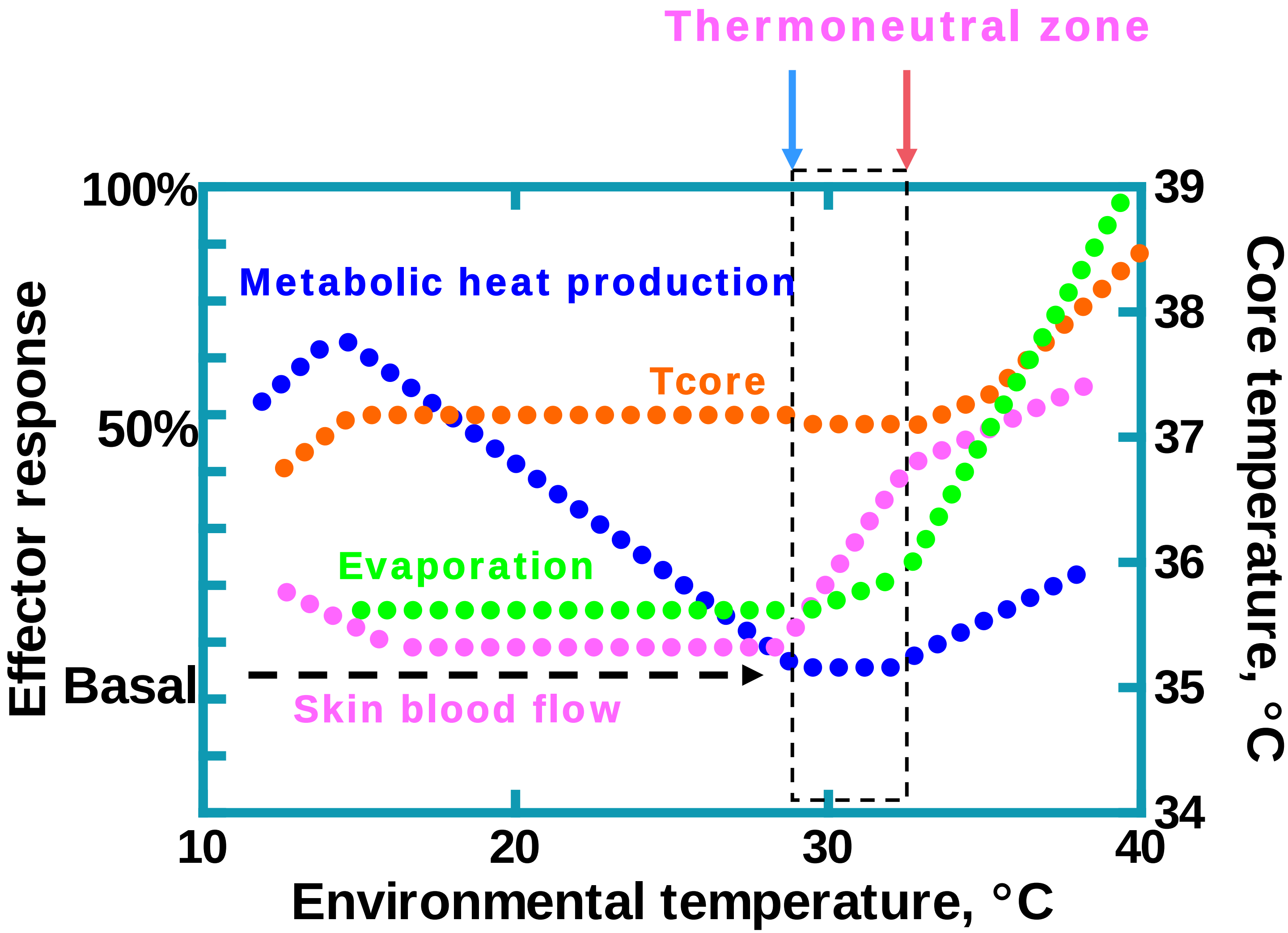
- Effects of heat vary depending on species, tissue type and exposure
- Heat stimulates a myriad of physiological responses, some of which are controlled by stress-related pathways and others are more associated with thermoregulation
- There is a clear link between biological response to heat and regulation of angiogenesis and oxygen homeostasis

Conclusions: thresholds of thermal damage

- Important to assess T at sites above and below threshold for damage
- Important to utilize standardized isoeffects
  - Identify various levels of severity of effect
- Insufficient data between 40-300 CEM43°C for many organs and tissues
- Assessment time after exposure is critical
  - Few data on chronic effects
- Virtually no data on repeated exposures

Thank you!

Mammal thermoneutral profile



Slide and data from Dr. Christopher Gordon