NIH Blueprint for Neuroscience Research

Sleep Research Society®

Beyond the Symptom: The Biology of Fatigue

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Studying Hibernation Biology to Gain Insights into Fatigue

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Disclaimer and Disclosures

Disclaimer
This certifies that the views expressed in this presentation are those of the author and do not reflect the official policy of the NIH.

Disclosure
I have a financial interest in Be Cool Pharmaceutics.

Hibernation is energy conservation.
"Fatigue" is an *adaptation* to resource limitation.

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Seasonal Cycle of the Arctic Ground Squirrel

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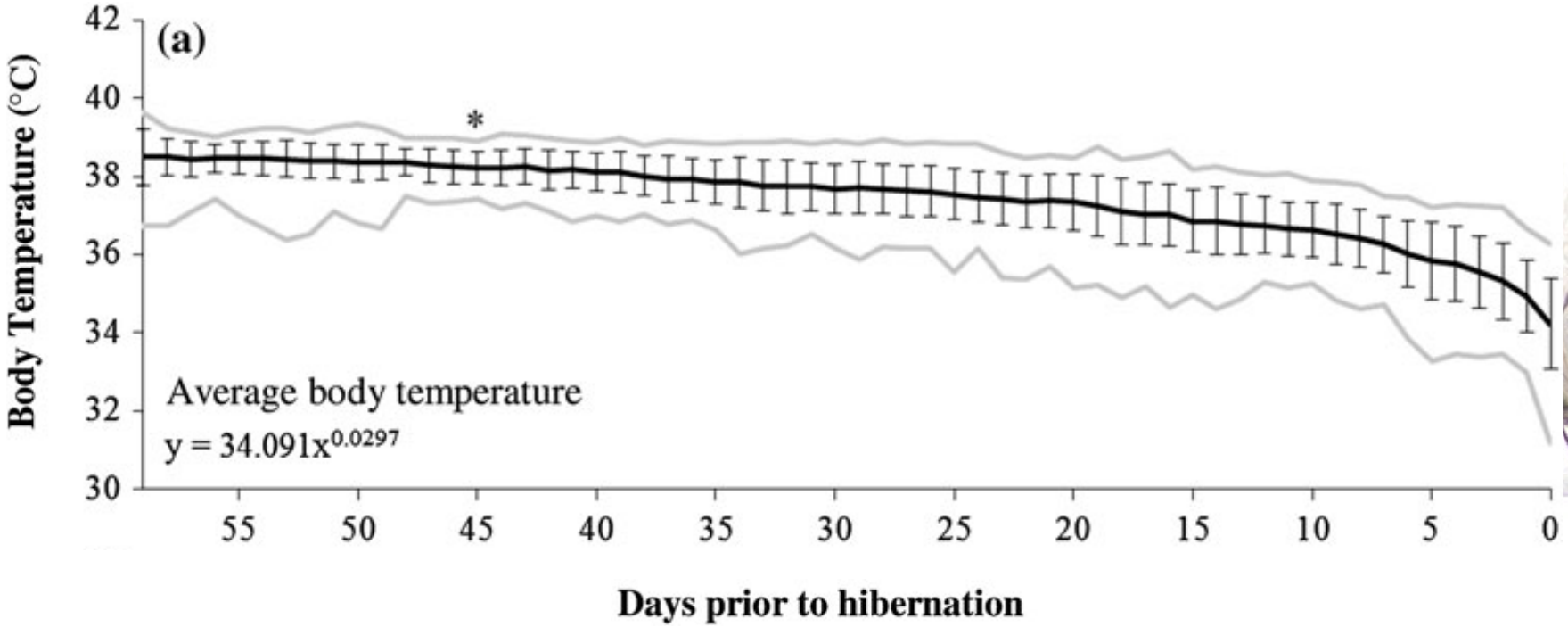
Thermoregulatory changes anticipate hibernation onset by 45 days – Free Ranging AGS



Seasonal decrease in metabolism leads to a decrease in Tb and a decrease in food intake

Sheriff et al., 2012, J Comp Physiol B

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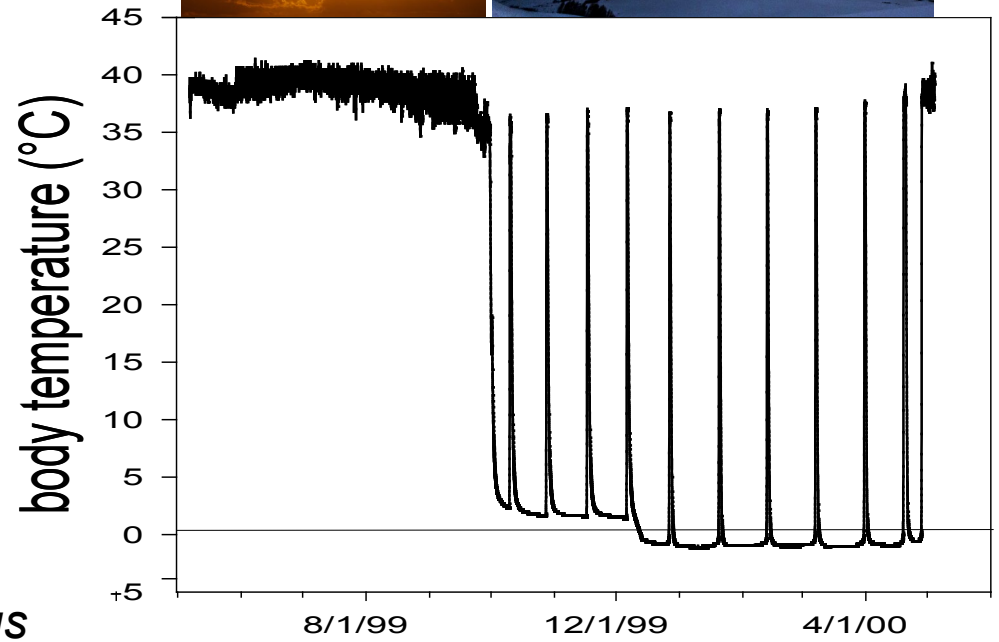
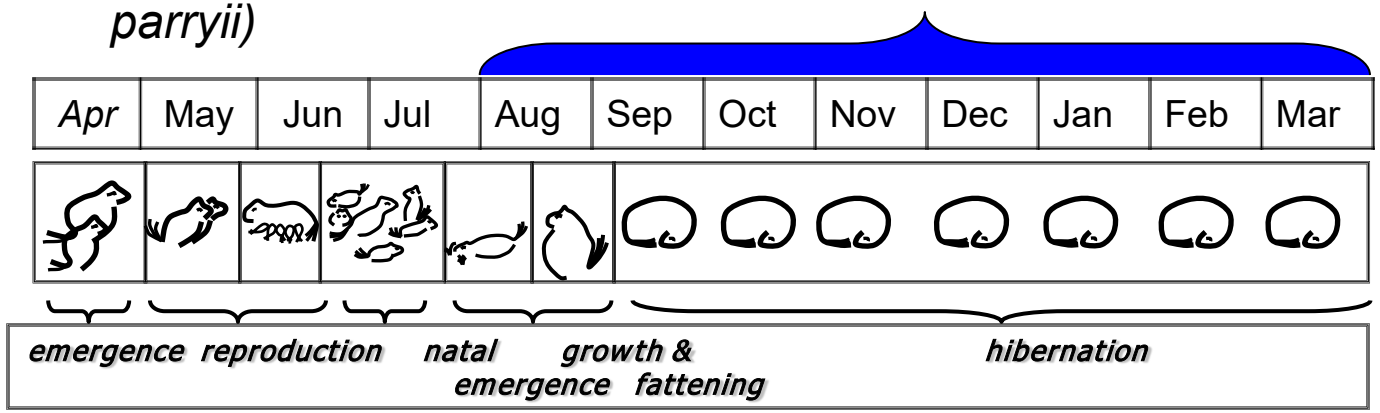
A torpid (hibernating) Arctic ground squirrel.



AGS *(Urocitellus parryii)*



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Laboratory housed animals – 22°C; 12:12 L:D
Winter sleepiness accompanies lower metabolic rate and body temperature (in animals that are *not hibernating*)

Decreased sensitivity to caffeine
Increased sensitivity to adenosine receptor agonists

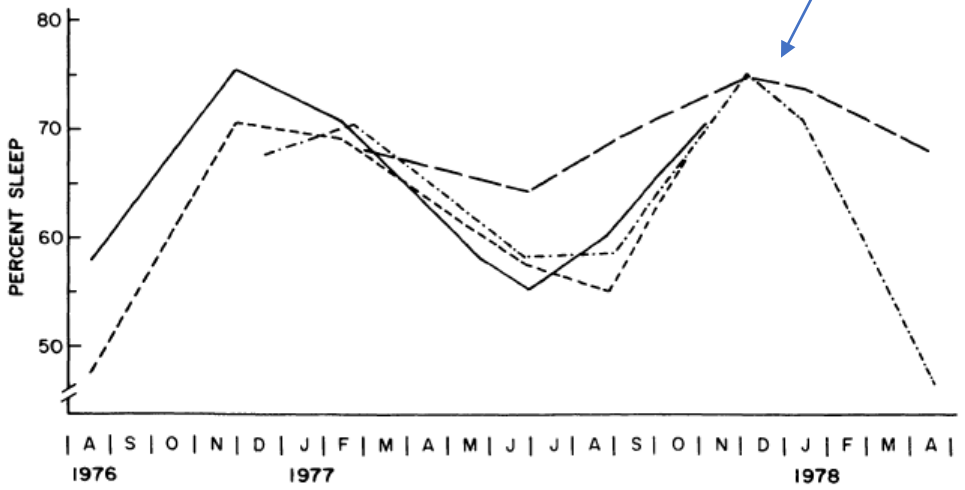

FIG. 1.—Annual changes in percent of a 24-h period spent asleep for each of four golden-mantled ground squirrels maintained at a temperature of 22 C and 12L:12D photoperiod. Animals were euthermic for the duration of all recording periods.

Golden mantel ground squirrel (*Callospermophilus lateralis*)

Walker et al., 1980, Hibernation and Circannual Rhythms of Sleep, Physiological Zoology, Vol. 53(1), pp. 8-11

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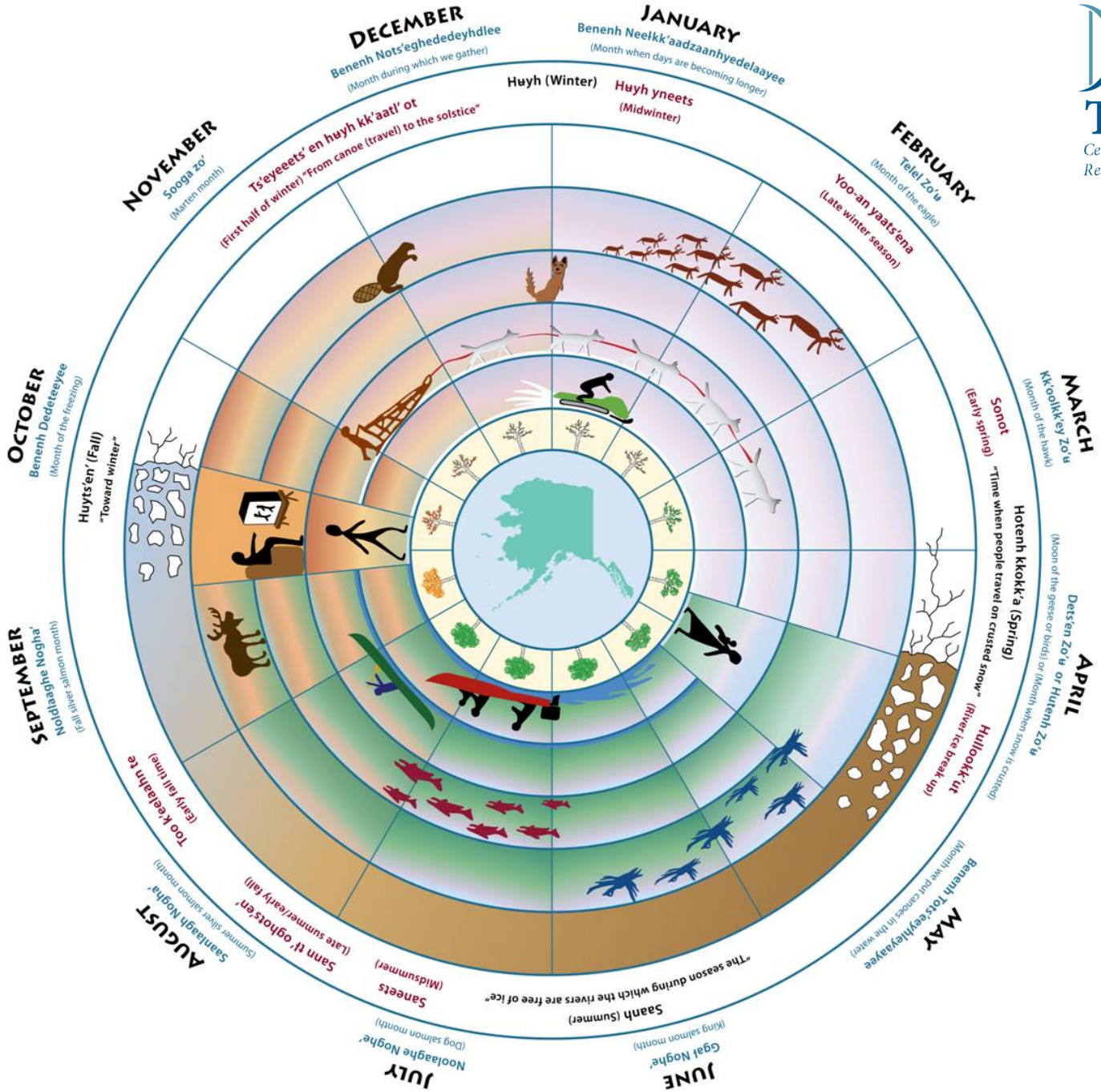
Human circannual rhythms also revolve around resource availability

- A seasonal rhythm modulates thermogenesis and underlies expression of hibernation and seasonal sleepiness.
- Seasonal rhythm is associated with enhanced A_1 adenosine receptor signaling.



9/21/2021

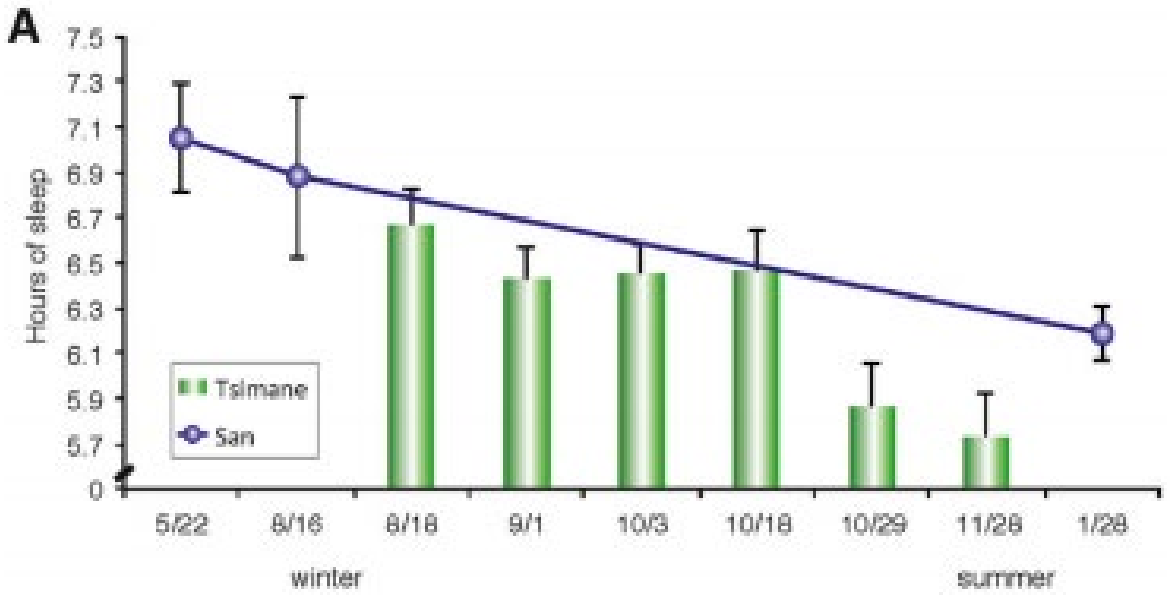
https://www2.ucar.edu/atmosnews/just-published/4279/interior-alaska-subsistence-hunting-warming-world

Current Biology
Volume 25, Issue 21, 2 November 2015, Pages 2862-2868

Report

Natural Sleep and Its Seasonal Variations in Three Pre-industrial Societies

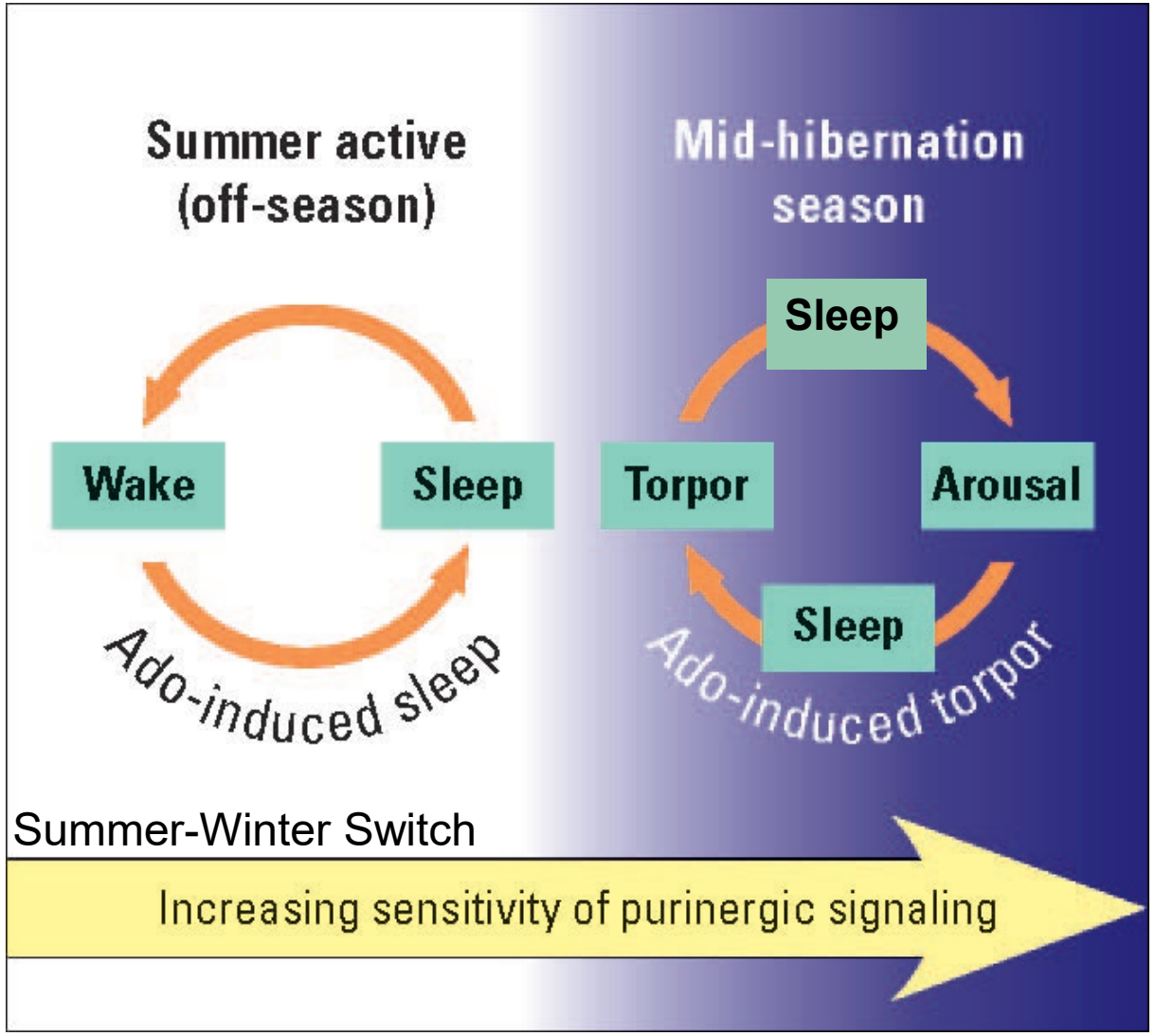
Gandhi Yetish [1], Hillard Kaplan [1], Michael Gurven [2], Brian Wood [3], Herman Pontzer [4], Paul R. Manger [5], Charles Wilson [6], Ronald McGregor [7], Jerome M. Siegel [7, 8, 9]



The Adenosine Model of Hibernation

The Model

The Summer-Winter transition increases sensitivity to A_1 adenosine receptor signaling so that in winter sleep extends into torpor.



Modified from Jinka et al., 2011

Adenosine is a retaliatory metabolite and inhibitory neuromodulator at the heart of energy homeostasis

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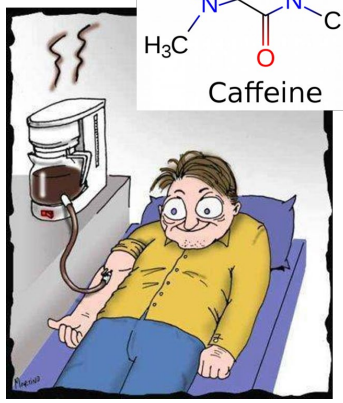
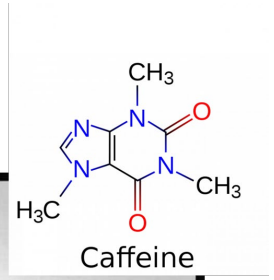




p-AMPK (active)

AMPK (inactive)

AMPKK

↑AMP/ATP

ATP⇆ ADP ⇆**AMP**

NT5E

Ado → S-adenosylhomocysteine

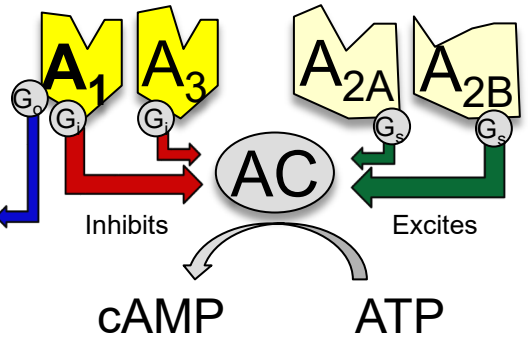
AdK

cAMP

PKA active)

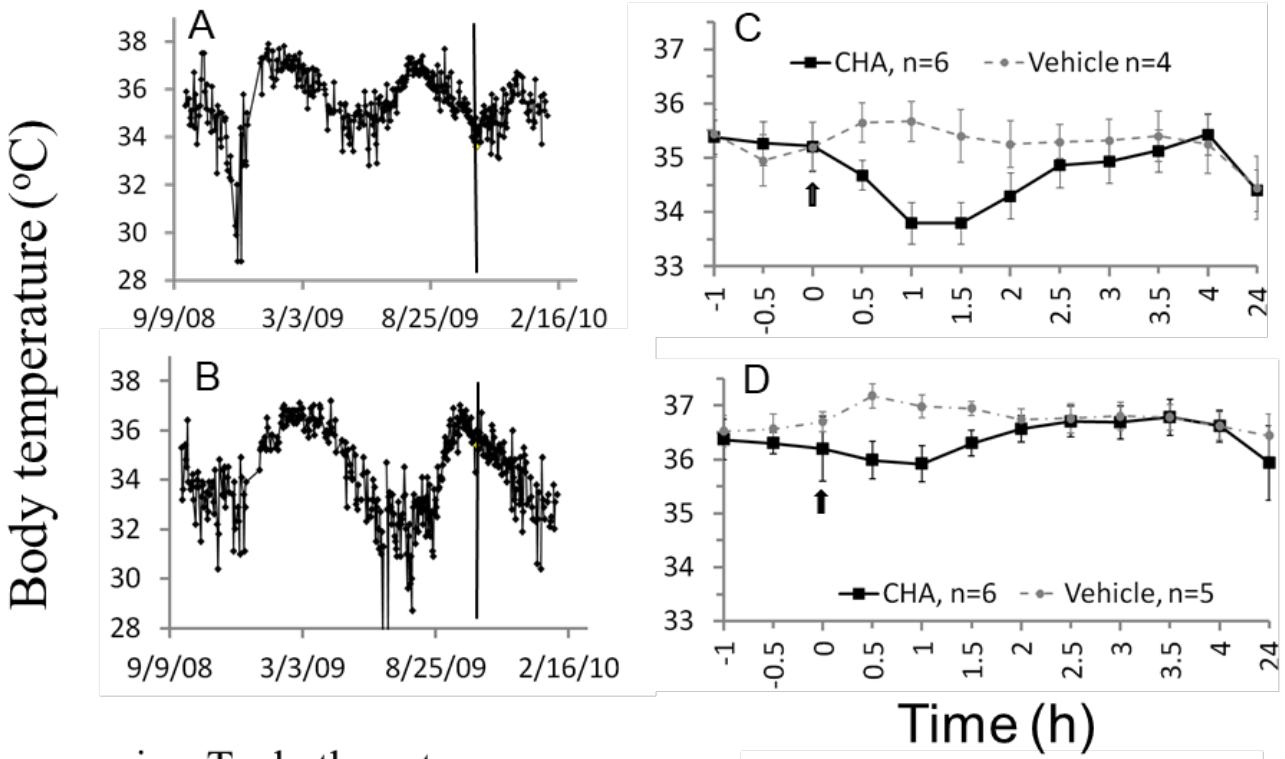
PKA (inactive)

CNS A_1AR increase homeostatic sleep drive



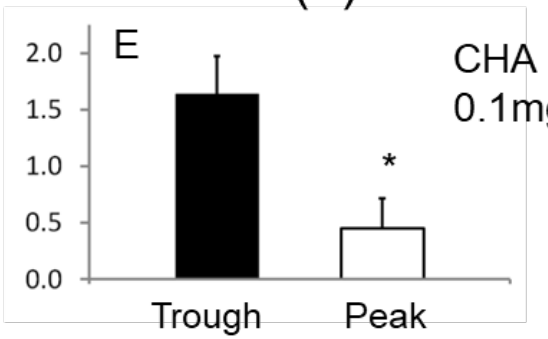
CNS A_1AR turn down the thermostat

Seasonal increase in sensitivity of A_1AR in arctic ground squirrels housed at 20°C and 12:12 L:D



Free running T_b rhythm at rest predicts onset of torpor and sensitivity to CHA

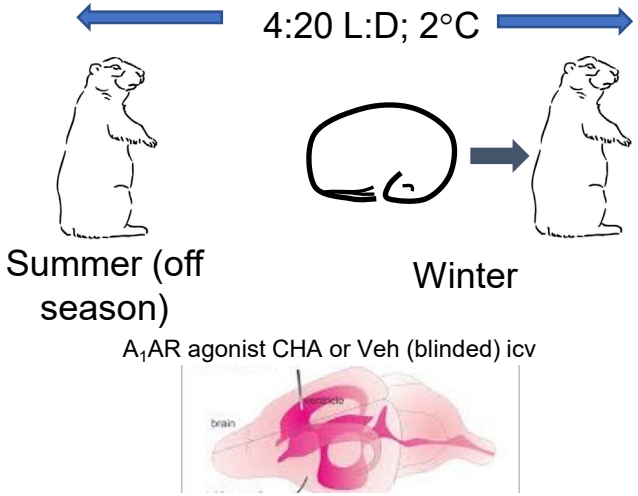
Maximal change in T_b after CHA (°C)



CHA
0.1mg/kg,ip

Olson et al., 2013

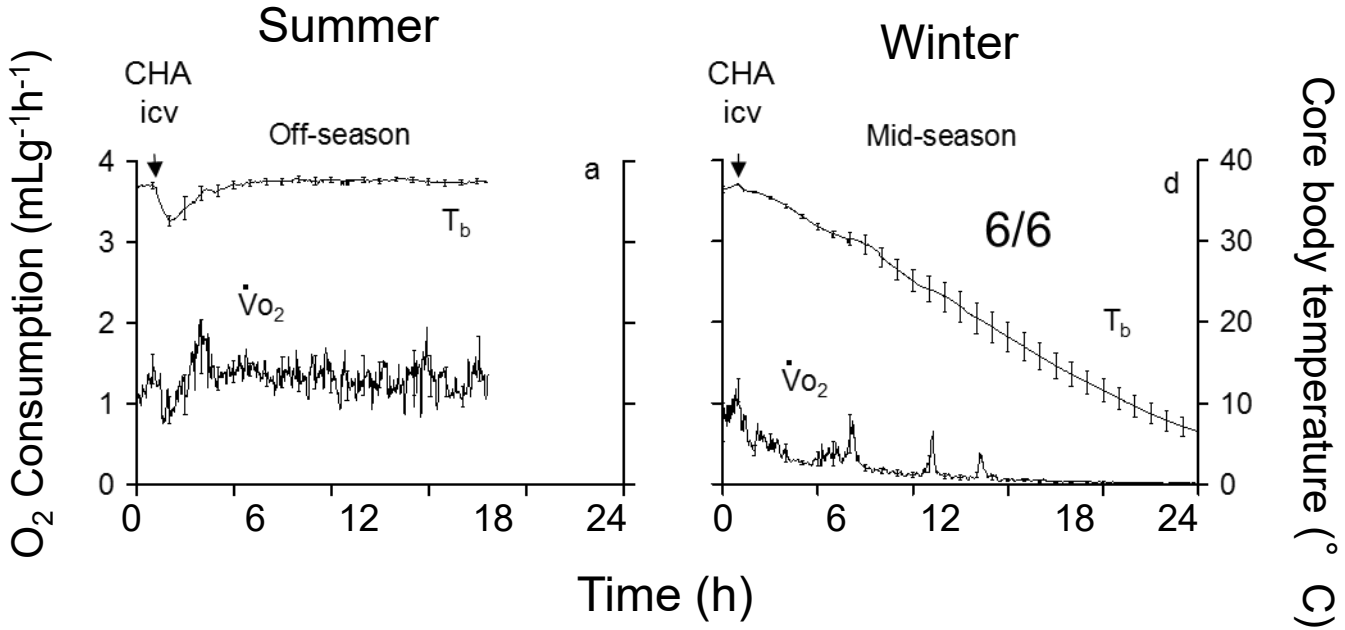
CNS regulation of "fatigue" in the winter season requires A_1 adenosine receptors



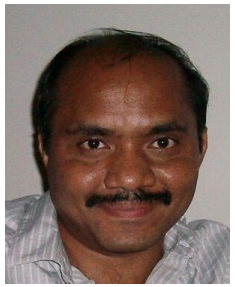
Off-season (summer): May- June

Early hibernation season: Sep-Oct

Mid hibernation season (winter): December



Study Design

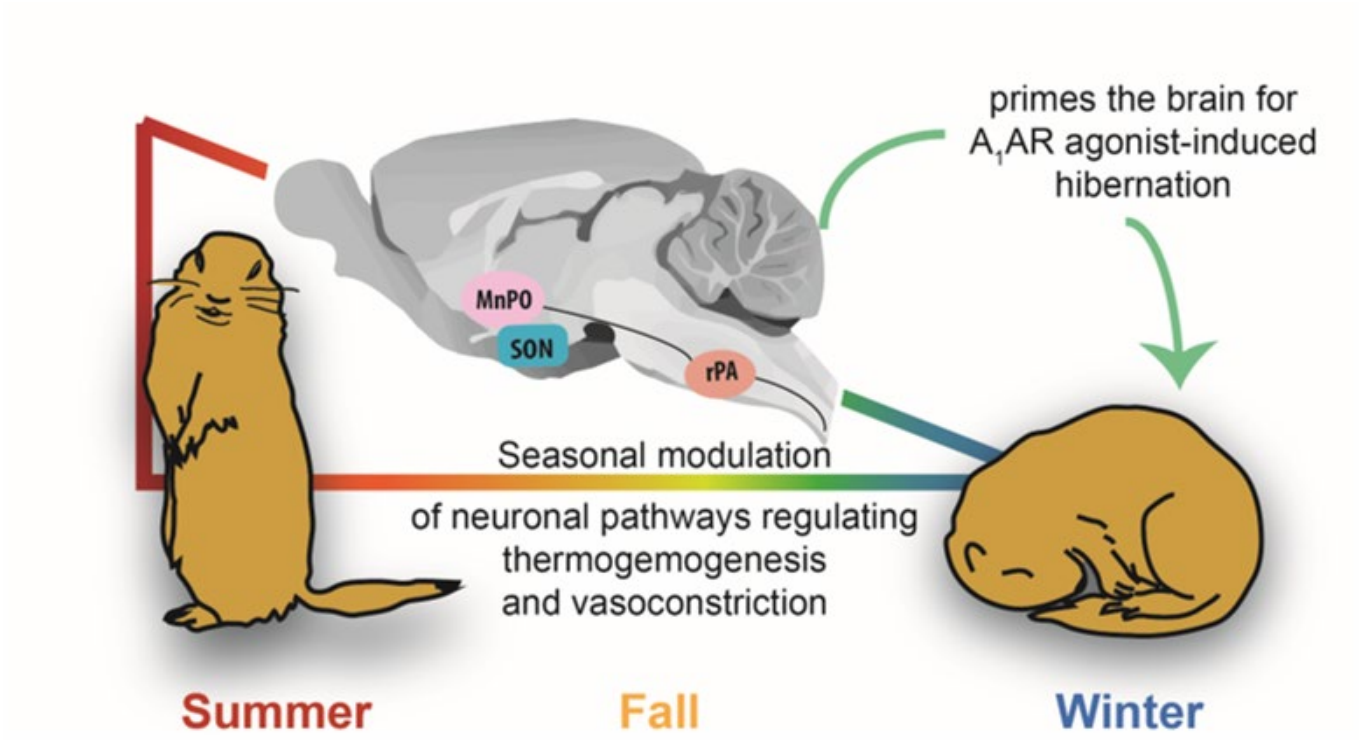


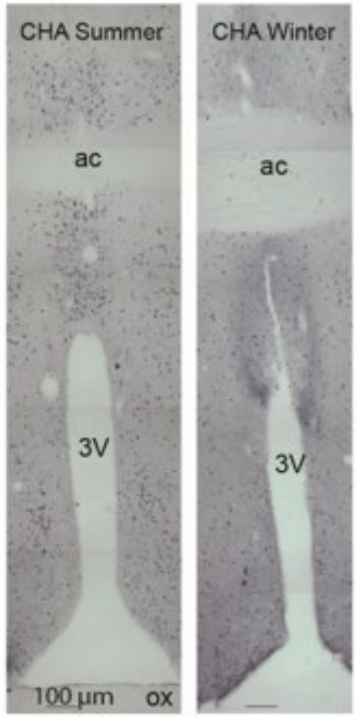
Jinka et al., 2011

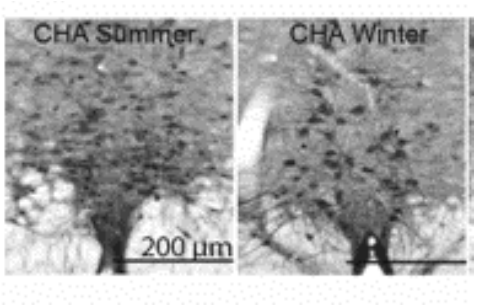
A_1AR stimulation is necessary and sufficient to induce <u>hibernation in arctic ground squirrels</u>

- ✓ Spontaneous hibernation reversed by A_1AR antagonist (CPT), but not A_{2A}AR antagonist (MSX-3)
- ✓ A_3AR agonist (2-CL-IB MECA) did not induce hibernation

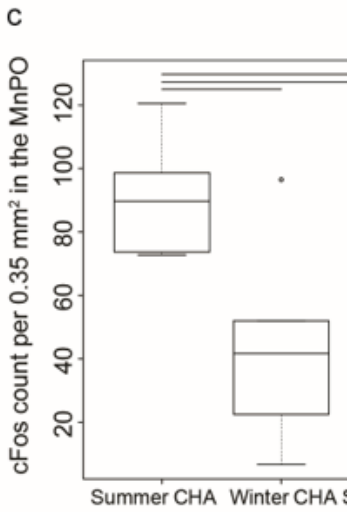
Seasonal modulation of thermoregulatory circuits explain seasonal response to CHA



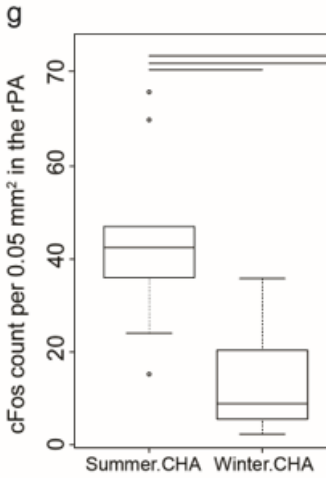




Median Preoptic



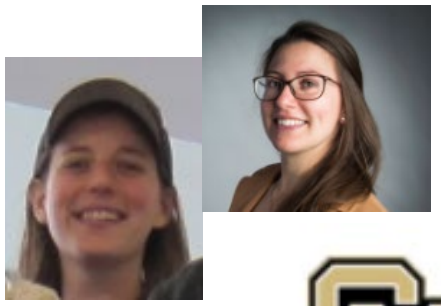
Raphe Pallidus



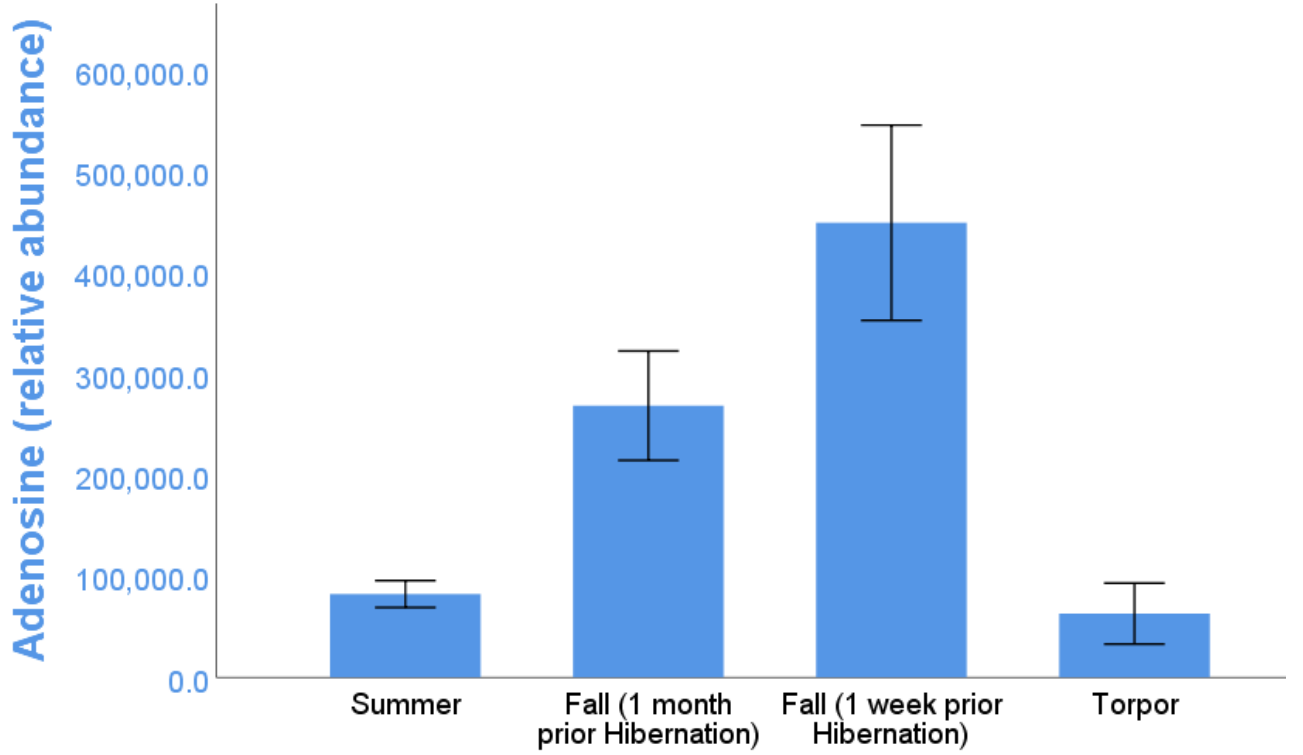
Frare et al.,

J Neurochem. 2019 Nov;151(3):316-335.

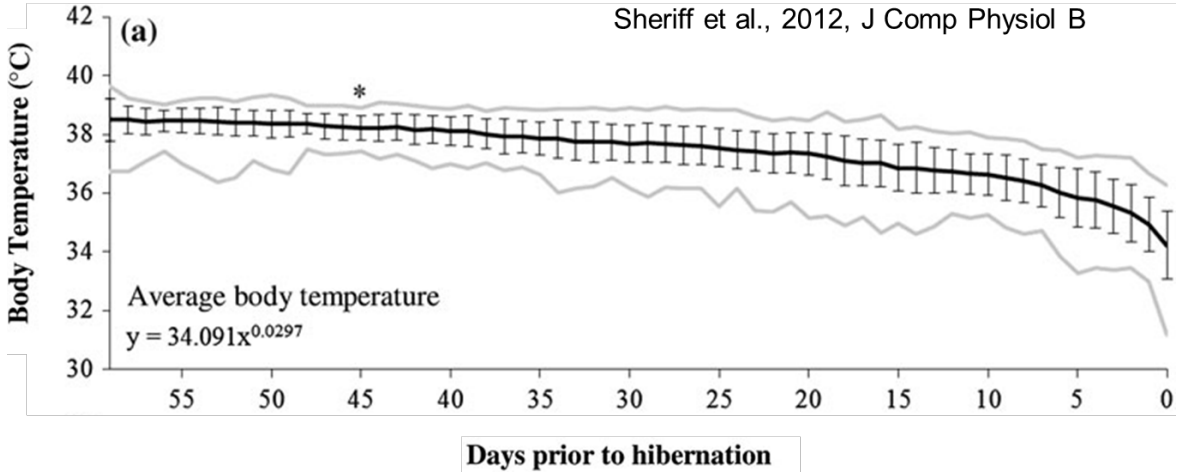
Energy homeostasis may be communicated from the periphery to the brain through retaliatory, signaling metabolites like adenosine



Rice et al., in prep



n=7-10



Sheriff et al., 2012, J Comp Physiol B

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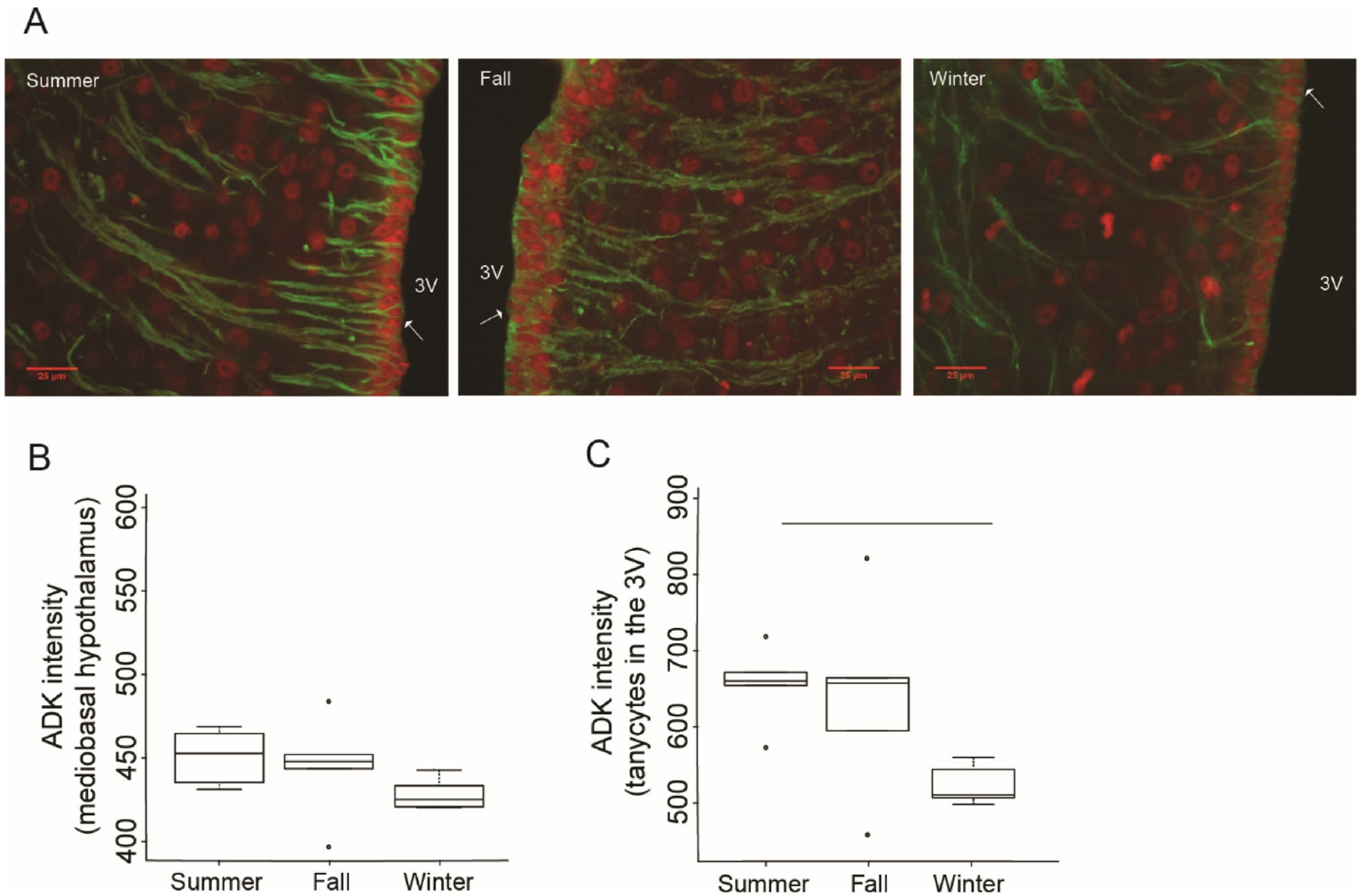
Tanycytes may permit transport of adenosine from blood to brain through seasonal expression of adenosine kinase



Frare and Drew, 2021

J. Neuroanatomy, 113, 101920

Physiol Rev 98: 1591–1625, 2018
Published May 30, 2018; doi:10.1152/physrev.00049.2017

PHARMACOLOGY OF ADENOSINE RECEPTORS: THE STATE OF THE ART

Pier Andrea Borea, Stefania Gessi, Stefania Merighi, Fabrizio Vincenzi, and Katia Varani

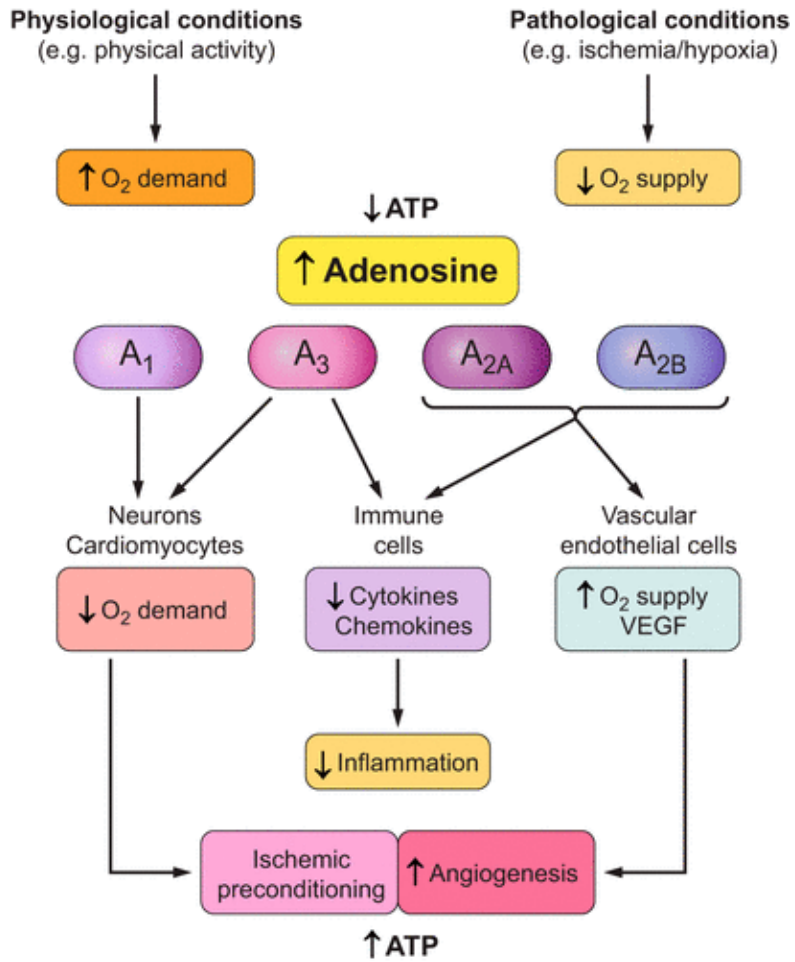


Table 5. *Biological effects of adenosine*

Effects	Receptor Subtype
Central nervous system	
Inhibition of neurotransmitter release	A_1
Neuroprotection	A_1/A_3
Anxiolytic activity	A_1
Anticonvulsant activity	A_1
Reduction of pain	A_1/A_3
Excitatory activity	A_{2A}
Stimulation of glutamate and acetylcholine release	A_{2A}
Reduction of locomotor activity	A_{2A}
Trophic effects	A_{2A}/A_{2B}
Cardiovascular system	
Negative inotropic effect	A_1
Negative chronotropic effect	A_1
Negative dromotropic effect	A_1
Ischemic preconditioning	A_1/A_3
Vasodilation	A_{2A}/A_{2B}
Inhibition of platelet aggregation	A_{2A}
Immune system	
Inhibition of reactive oxygen species	A_{2A}/A_3
Neutrophils	A_1/A_3
Increase of chemotaxis	A_1
Decrease of chemotaxis	A_3
Lymphocytes	
Immunosuppression	$A_{2A}/A_3/A_{2B}$
Monocytes/macrophages	
Inhibition of proinflammatory cytokines release	$A_{2A}/A_3/A_{2B}$
Mast cells	
Stimulation of degranulation	A_3/A_{2B}
Respiratory system	
Bronchoconstriction	$A_1/A_3/A_{2B}$
Renal system	
Vasoconstriction	A_1
Vasodilation	A_{2A}
Reduction of the glomerular filtration rate	A_1
Inhibition of diuresis	A_1
Inhibition of renin secretion	A_1
Gastrointestinal system	
Inhibition of acid secretion	A_1
Stimulation of intestinal chloride secretion	A_{2B}/A_3
Cellular metabolism	
Inhibition of lipolysis	A_1
Inhibition of insulin secretion	A_1
Stimulation of gluconeogenesis	A_{2A}
Production of glucose	A_{2B}

Mechanisms regulating hibernation may underlie mechanisms relevant to fatigue

- In hibernation sleep transitions into torpor (extreme fatigue?)
- Regulated by increased gain in purinergic signaling
- Whole body metabolism communicates with brain
- Tanycytes are positioned to regulate body-brain communication.

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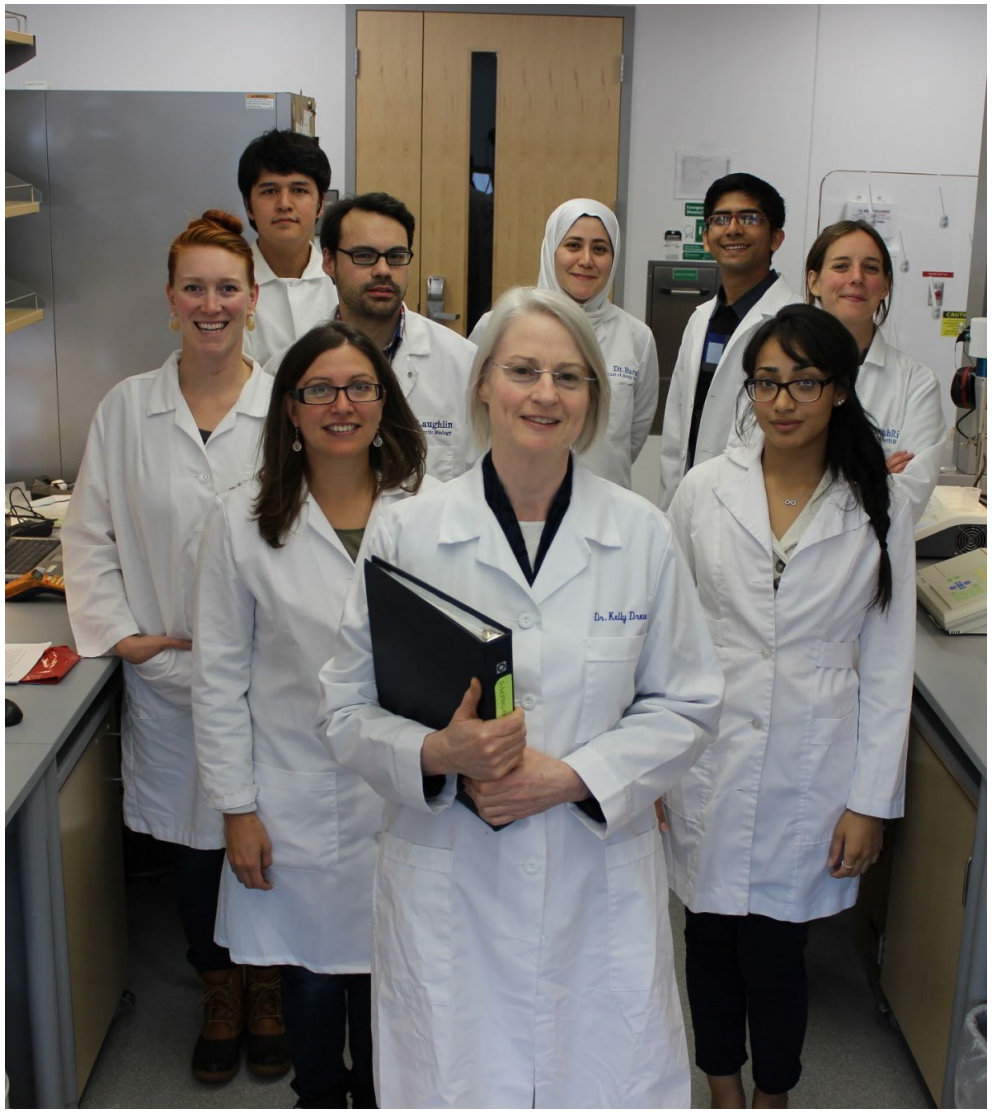

Thank you!

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- Zac Carlson
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- Carla Frare

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