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Natural Protection Against Cardiac Arrhythmias During Hibernation: Significance of Adenosine

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1. Introduction

Hibernation is a physiological adaptation to periods of seasonal resource limitation (Carey et al., 2003a; Drew et al., 2007). Hibernators undergo several bouts of torpor during a hibernation season. Torpor in hibernation is a period of profound bradycardia, tachycardia, metabolic suppression and decreased core body temperature (Drew et al. 2007). Hibernation is characterized by alternating phases of torpor and euthermia that begins in the fall and continues until the hibernation season ceases in spring (Lyman, 1958; Geiser and Ruf, 1995; Boyer and Barnes, 1999). Based on whole-body metabolic rate and core body temperature each torpor bout consists of an entrance, steady-state, and arousal phases (Boyer and Barnes, 1999; Carey et al., 2003a; Heldmaier et al., 2004; Drew et al., 2007) (Fig.1). Successive torpor bouts are interrupted by a brief period (12-24h) of interbout euthermia.

Cardiac arrhythmia is described as any deviation from the normal sequence of electrical impulses resulting in slow (bradycardia), fast (tachycardia) or erratic heartbeats such as atrial and ventricle fibrillations and conduction disorders (Keating and Sanguinetti, 2001).

Cardiac arrhythmias are observed during hibernation (Chatfield and Lyman, 1950; Eagles et al., 1988; Milsom et al., 1993; Milsom et al., 1999; Toien et al., 2011). In spite of that no untoward effects such as ventricular fibrillation or heart failure are noticed in hibernators and the hearts remain functional even at a body temperature of 0°C (Johansson, 1996). Moreover, hibernators can rewarm to euthermic body temperature of about 36°C in a span of few hours (Lyman, 1958)(Fig1&2) without any cardiac or nervous system complications (Drew et al., 2007). In contrast, similar conditions in non-hibernators including humans lead to fatal cardiac complications and death (Nardone, 1955; Johansson, 1996; Drew et al., 2007). Unresolved intrinsic mechanisms protect the hibernating species against lethal cardiac arrhythmias at reduced body temperatures. Understanding the intrinsic functional mechanisms existing in hibernators can lead to novel therapies in treating several conditions such as cardiac arrest and stroke (Drew et al., 2007).

Patients with cardiac arrest are subjected to hypothermia in a clinical setting (Polderman, 2004; Polderman and Herold, 2009). However, inducing hypothermia beyond a certain level is not without complications. Patients subjected to temperatures colder than 30°C suffer cardiac arrhythmias (Polderman and Herold, 2009). Cooling more slowly should mimic similar drop in body temperature seen during torpor in hibernators and may thus avoid

arrhythmias. The question is how to achieve this state where the temperature can be dropped below 30°C without any cardiac complications.

Difference exists between hibernators and nonhibernators in resisting ventricular fibrillation induced by hypothermia. Several factors are responsible including heart size (Surawicz, 1971). Hibernating animals vary in size (Geiser, 2004). Large hearts tend to develop ventricular fibrillations (Surawicz, 1971). Although bears are regarded as hibernators their body temperature does not fall below 30°C which is above the critical body temperature where ventricular fibrillations are noticed (Johansson, 1984; Eagles et al., 1988; Toien et al., 2011). This chapter discusses about small hibernators in general focusing on the role of nervous system regulation of cardiac function in the light of recent research findings and the importance of adenosine (Miyazawa et al., 2008; Jinka et al., 2011). This chapter gives an overview of hibernation physiology, various mechanisms regulating hibernation, cardiac arrhythmias observed during hibernation, functional difference between hibernator and a non-hibernator, especially in regard to heart function, and finally discusses novel findings and hypothesis that may be translated to treat certain medical conditions such as cardiac arrest and stroke to improve the outcome in such patients.

2. Phases of hibernation and cardiac arrhythmias

2.1 The entrance phase

A decrease in heart rate and metabolism prior to decrease in core body temperature is a characteristic phenomenon observed during entrance into hibernation (Lyman, 1958). Heart rate, metabolism and core body temperature gradually decline during the entrance phase until the core body temperature drops down to the lowest limit where the core body temperature is just above the ambient temperature (Boyer and Barnes, 1999; Tamura et al., 2005). Heart rate declines to 2-7 beats per minute (Dawe and Morrison, 1955), metabolism drops to 2% of resting metabolic rate (Geiser, 1988; Buck and Barnes, 2000) and core body temperature drops to as low as -2.9°C (Barnes, 1989) (Fig. 1&2).

2.1.1 Cardiac arrhythmias during entrance into hibernation

Evidence supports the central nervous system regulation during entrance into hibernation. Administration of adenosine agonist into the brain induces torpor in arctic ground squirrels (Jinka et al., 2011). By lowering the set-point (T_{set}) threshold below the actual hypothalamic temperature (T_{hy}) during entrance into hibernation a smooth entrance is facilitated. An occasional burst of body temperature paralleled by an increase in metabolism is observed when T_{hy} below T_{set} . (Heller et al., 1977; Heldmaier et al., 2004). The changes in heart rate parallel the change in metabolic rate suggesting that entrance into hibernation is a highly regulated, orchestrated event of several physiological processes rather than a consequence of a drop in body temperature (Milsom et al., 1999).

A comparison between heart rate and temperature in hedgehogs during entrance into hibernation indicates a shift towards parasympathetic influence (Dawe and Morrison, 1955). Atropine is a parasympatholytic and increases heart rate by slowing of parasympathetic output. Administration of atropine during entrance into hibernation increased heart rate in hamsters (Lyman and O'Brien, 1963). Cardiac arrhythmias during entrance into hibernation are abolished by administration of atropine in marmots (Lyman, 1982). All these studies suggest that a well coordinated activation of parasympathetic system, preparatory initial changes in the heart rate, skipped beats and asystoles altogether are necessary for decline in heart rate and for a smooth entrance into hibernation (Milsom et al., 1999; Zimmer et al., 2000).

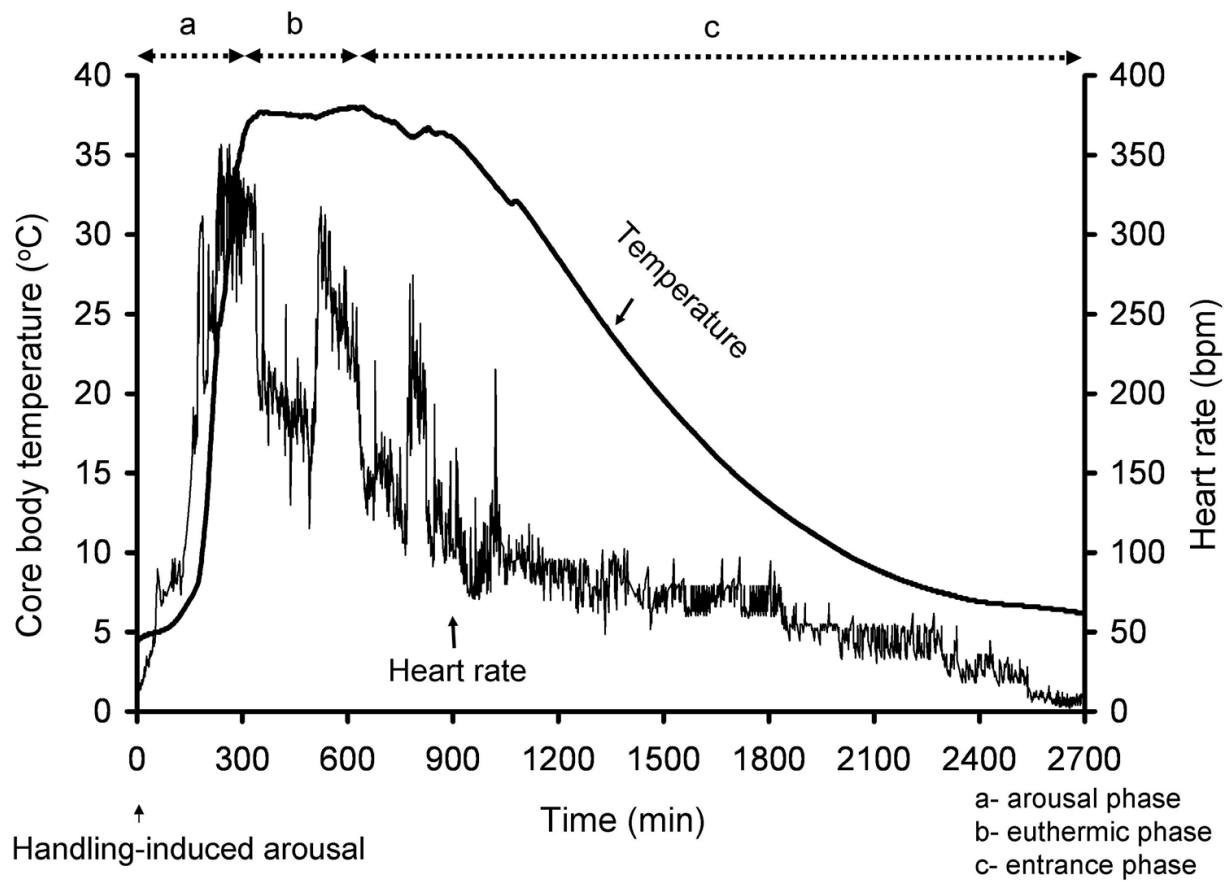


Fig. 1. Core body temperature was measured in an Arctic ground squirrel after arousal from torpor induced by gentle handling and until the animal entered another bout of torpor.

Core body temperature and heart rate were measured with an ip transmitter as described previously (Jinka et al., 2011). Torpor in hibernation is broadly divided into three phases-entrance, steady-state, and arousal (Boyer and Barnes, 1999; Carey et al., 2003a; Heldmaier et al., 2004; Drew et al., 2007). Entrance phase is followed by steady-state phase which lasts for 1-3 weeks before the arousal phase is initiated. Core body temperature in an Arctic ground squirrel can drop to as low as -2.9°C (Barnes, 1989) before it reaches steady-state phase. A fully aroused animal stays at euthermic body temperature of $35-37^{\circ}\text{C}$ for about a day before another torpor bout ensues. Changes in heart rate reflect changes in core body temperature during a hibernation bout.

Several unique behavioral patterns of heart beats are noticed during entrance into hibernation. It is interesting to know how a hibernator can drastically reduce its heart rate during entrance into hibernation without any adverse effects. Heart rate drops prior to any changes in body temperature indicating that a decreased heart rate during entrance into hibernation is independent of body temperature. (Landau and Dawe, 1958; Lyman, 1958; Elvert and Heldmaier, 2005). Appearance of skipped beats is a characteristic feature exhibited by several species of hibernators during entrance into hibernation (Dawe and Morrison, 1955; Lyman, 1958; Twente and Twente, 1978; Lyman, 1982) (Fig.3). A drastic 50% fall in heart rate while a drop in body temperature by 0.6°C observed during initial stages of entrance into hibernation occurs around $33-34^{\circ}\text{C}$ (Strumwasser, 1959).

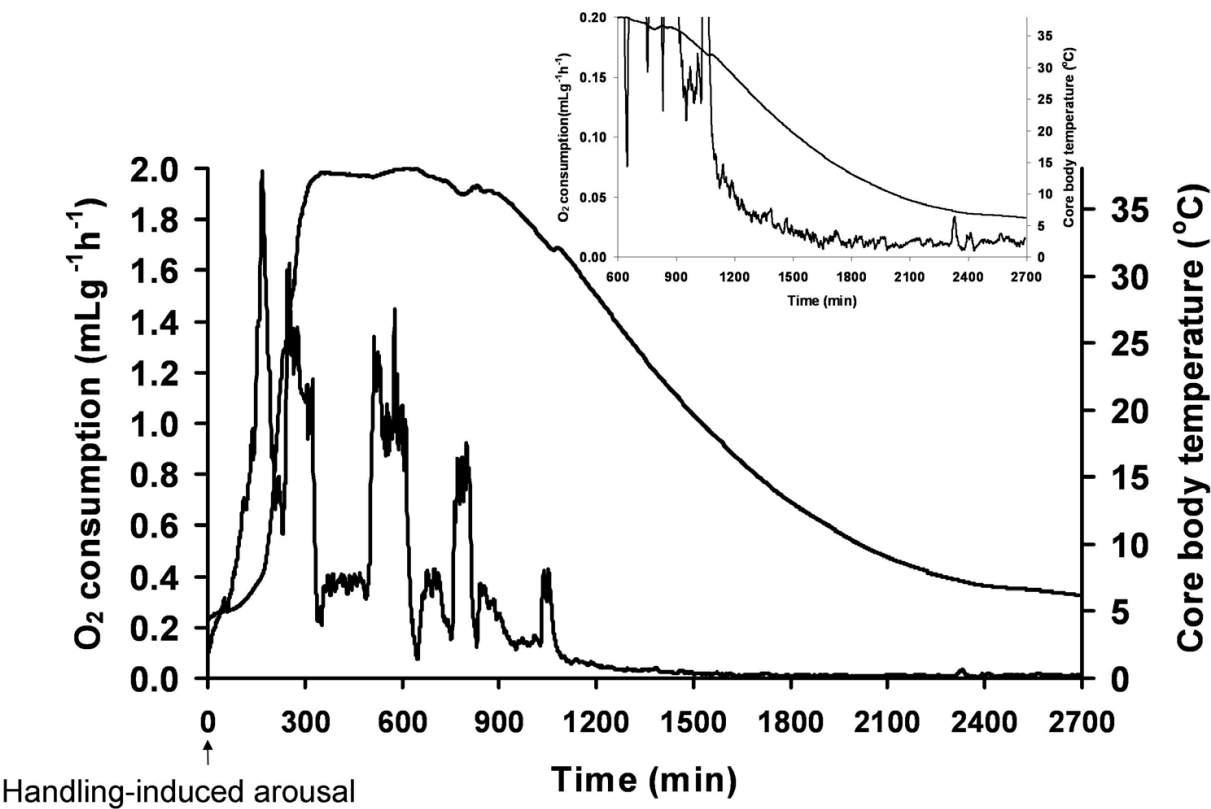


Fig. 2. Changes in core body temperature and whole animal oxygen consumption as measured in an Arctic ground squirrel after arousal from torpor was initiated by gentle handling and until the animal entered another bout of torpor. Core body temperature was measured with an ip transmitter and oxygen consumption was measured using open flow respirometry as described previously (Jinka et al., 2011). The inset illustrates how oxygen consumption precedes a decline in core body temperature during entrance into torpor as shown on a smaller scale. Entrance into hibernation is characterized by a characteristic decline in whole animal oxygen consumption (metabolism) that precedes a decrease in core Tb (Lyman, 1958). [source: (Drew et al., 2009)]

2.2 The steady-state phase

Animal enters into a steady-state phase of hibernation after a few hours of initiation of torpor. Steady-state phase represents the nadir of mammalian heart rate, metabolism, and core body temperature (Drew et al., 2007) where the animal maintains its lowest heart rate, metabolism, and core body temperature for about 1-3 weeks (Boyer and Barnes, 1999; Buck and Barnes, 2000; Carey et al., 2003a). An occasional burst of activity paralleled with an increase in heart rate, metabolism and heat production is observed during this phase and is hypothesized as a measure to avoid decreases in body temperature beyond a certain point (Heldmaier et al., 2004).

2.2.1 Cardiac arrhythmias during steady state hibernation

Diastolic arrhythmias are noticed in deep hibernation (Twente and Twente, 1978; Milsom et al., 1999). Different opinions exist on the influence of sympathetic and parasympathetic systems on deep hibernation with no definitive conclusion (Milsom et al., 1999).

2.3 The arousal phase

Periodic arousals from hibernation are noticed in true hibernators (Lyman, 1958; Geiser and Ruf, 1995; Boyer and Barnes, 1999; Karpovich et al., 2009). A characteristic gradual increase in heart rate, metabolism and respiration followed by a gradual increase in core body temperature is observed during arousal from hibernation (Lyman, 1958). It is interesting to note that the rewarming from hibernation without any external source of heat suggests that hibernation is not a state of energy deficiency (Carey et al., 2003a). Animals attain a core body temperature of 35-37°C, then maintain euthermic body temperature for about a day before another hibernation bout starts (Boyer and Barnes, 1999; Carey et al., 2003b).

2.3.1 Cardiac arrhythmias during arousal from hibernation

Cardiac arrhythmias appear throughout arousal (Twente and Twente, 1978). Heart rate gradually increases in frequency as the body temperature increases (Lyman, 1958). The initial rapid increase in heart rate during arousal from hibernation is due to sympathetic activation (Milsom et al., 1993) and as such the increase in endogenous catecholamines are arrhythmogenic (Burn, 1961; Trautwein, 1963). Asystoles are followed by bradycardia during arousal from hibernation. Asystoles appear between 11-18°C during which period the heart rate falls below what it was before the appearance of asystolic episodes, and attains a regular rhythm and a higher rate as soon as the asystoles disappear at about 18°C (Eagles et al., 1988). This waxing and waning appearance of heart rate during arousal may be due to alternating sympathetic and parasympathetic dominance on the way to euthermia (Milsom et al., 1999). A ventricular bigeminy with a repetitive premature ventricular heart beats alternating with supraventricular beats is also demonstrated on ECG (Eagles et al., 1988). During mid to late arousal the heart rate, metabolism and respiratory frequency gradually reach a peak followed by body temperature under the influence of sympathetic tone until the animal reaches euthermia during which period the autonomic balance is restored (Lyman, 1958; Lyman and O'Brien, 1963; Twente and Twente, 1965; Lyman and O'Brien, 1969; Twente and Twente, 1978; Milsom et al., 1993).

3. Cardiac arrhythmias in hibernation vs hypothermia in hibernators

A study on ground squirrels revealed several differences in the ECG during hibernation and hypothermia (Dawe and Morrison, 1955; Nardone, 1955). A slow heart rate in hibernation is facilitated by a 40-70 fold increase in the duration of T-P segment suggesting a slowed SA node during hibernation. A 4-5 fold increase in duration of QRS complex is observed. About a 7 fold increase in the duration of P-R segment of an ECG indicates an increase in conduction time. On the other hand, a gradual decline in heart beats, appearance of right bundle branch block, and a notched QRS complex suggests a possibility of aberration in myocardial conduction. A reduced time span of QRS complex and a faster appearance of T wave soon after QRS complex were also noticed in hypothermia. Forced induction of hypothermia in Syrian hamsters induced J-waves and atrioventricular block while spontaneous hibernation had no adverse effect (Miyazawa et al., 2008). A study in ground squirrel has shown that decreased body temperature during spontaneous hibernation slows ventricular conduction velocity and increases excitation threshold thus avoiding arrhythmias at extreme low body temperatures (Fedorov et al., 2005).

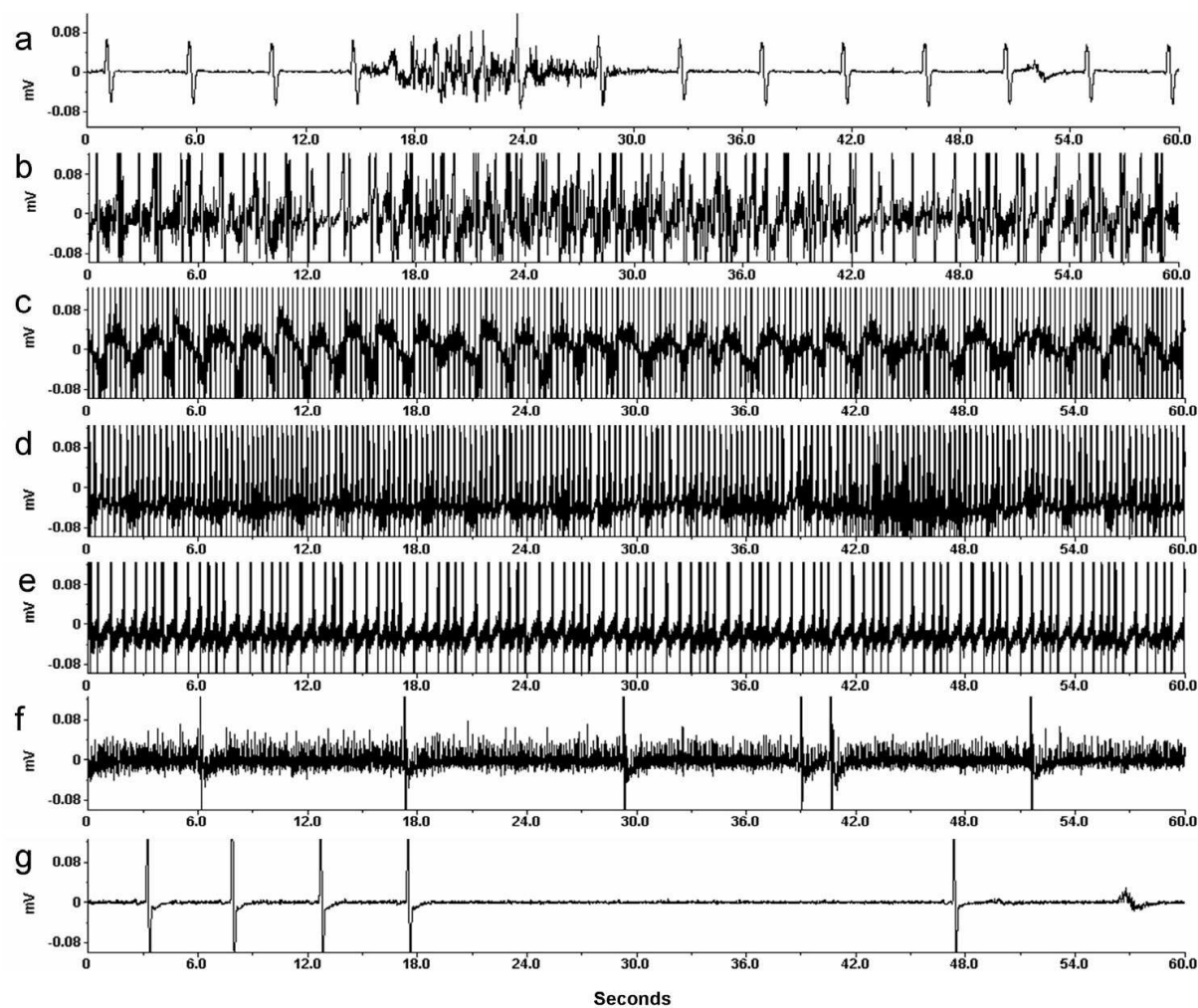


Fig. 3. Electrocardiogram of an arctic ground squirrel at different core body temperatures during different phases of hibernation. Steady-state phase of hibernation is characterized by bradycardia with even beats as shown here at a body temperature of 4°C (a). An increase in heart rate occurs as soon as arousal is initiated as indicated in ECG at a body temperature of 5°C (b). A gradual progressive increase in heart rate is noticed through arousal phase at a body temperature of 20°C (c) until the animal reaches a euthermic body temperature of 37°C (d). Skipped beats and bradycardia follows as the animal prepares to enter into another torpor bout as represented by ECG at a body temperature of 36°C (e) and mid-entrance phase at 15°C (f). A brief pause in heart beats is a characteristic finding during the last stage of entrance phase (g) at a body temperature of 8°C.

4. Anatomical peculiarity of hibernator’s heart

An insight into the anatomy of a hibernator’s heart may provide clues as to how a hibernator can overcome heart failure under extreme hypothermia. The peculiar anatomy of the heart of a hibernator has been described by Walls in a hamster (Walls, 1942). Several interesting features of the conducting tissue have been identified in this study. Purkinje fibers are identified in the sino-atrial node, the pacemaker of the heart, and not in the atria suggesting that Purkinje fibers may have a function other than a simple

conduction of the cardiac contraction impulse. The atrio-ventricular node has a compound nature of fibers which are similar to Purkinje type. Purkinje tissue is absent in the right ventricle and a limited amount of Purkinje tissue is present in the left ventricle whose wall is six times thicker than the right ventricle. In spite of limited Purkinje tissue distribution to the ventricles it is interesting to note that the heart is capable of about 450 beats per minute.

Gap junctions are specialized intercellular connections in the heart and are needed for conduction in the heart. Gap junctions ensure the propagation of action potentials between the myocytes and provide low resistance intercellular channels facilitating coordinated contraction of myocardium (Saitongdee et al., 2000). Connexins are gap junction proteins with four-membrane spanning domains. Among several types of connexins, connexin43 (Cx43) is the major connexin found in the mammalian heart (Beyer et al., 1987). Cx43 and Cx45 are upregulated in the hearts of hibernators (Gros and Jongsma, 1996; Fedorov et al., 2005; Van Der Heyden et al., 2007). Increased density of Cx43 has been identified in ventricular cardiomyocytes of hibernators during hibernation (Saitongdee et al., 2000). Cx43 density returned to normal control levels within 2 hours of arousal from torpor suggesting the importance of Cx43 and Cx45 in overcoming ventricular fibrillation during hibernation. (Saitongdee et al., 2000; Fedorov et al., 2005).

5. Adenosine in hibernation

A growing body of evidence supports the significance of adenosine in hibernation (Drew et al., 2007). Adenosine is a widely distributed inhibitory neuromodulator throughout the central nervous system including the brainstem, the principle cardiovascular control center (Mosqueda-Garcia et al., 1989; Barraco and Phillis, 1991). Adenosine decreases neuronal excitability and modulates the actions of other neurotransmitters (Dunwiddie and Masino, 2001). Adenosine acts through A₁, A_{2a}, A_{2b}, and A₃ receptors (Fredholm et al., 1994; Olah and Stiles, 1995; Dunwiddie and Masino, 2001). Endogenous adenosine is produced from multiple sources in the central nervous system, some sources associated to energy levels and functions as a homeostatic regulator in the CNS (White, 1977; Fredholm et al., 1994; Dunwiddie and Masino, 2001). Dephosphorylation of adenosine triphosphate (ATP) is one of the major sources of endogenous adenosine production where ATP released into synapse is metabolized to adenosine and mediates its effect through adenosine receptors (Fredholm et al., 1994; Dunwiddie and Masino, 2001).

5.1 Adenosine in induction of torpor during hibernation

Central nervous system regulation of hibernation is implicated by several studies (Drew et al., 2007; Jinka et al., 2011). Recent study has shown that administration of the adenosine A₁ receptor agonist N⁶-cyclohexyladenosine (CHA) into the lateral ventricle of arctic ground squirrel induces hibernation. CHA-induced hibernation is similar to natural spontaneous entrance into hibernation. Results indicate that onset of hibernation is regulated within the central nervous system through activation of A₁AR (Jinka et al., 2011). Studies focusing on specific sites in the brain including the hypothalamus and hippocampus indicate a prominent influence of CNS on hibernation (Heller and Colliver, 1974; Popov et al., 1992). Studies on central nervous system also direct towards involvement of adenosine, a neuromodulator in hibernation regulation (Shintani et al., 2005; Tamura et al., 2005; Jinka et al., 2011).

Successful translation of hibernation to non-hibernating species will open possibilities of applying the concept of metabolic suppression and low body temperature to humans in treating conditions such as stroke, hemorrhagic shock, cardiac arrest, cerebral ischemia, and multiorgan failure (Drew et al., 2007).

5.2 Significance of adenosine on dietary restriction induced hypothermia and cardiovascular regulation

Adenosine-induced hypothermia is mediated through A₁AR (Dunwiddie and Masino, 2001; Shintani et al., 2005). Adenosine modulates the cardiovascular system through numerous A₁AR in nucleus tractus solitarius (NTS) (Badman and Flier, 2005; Scislo et al., 2008) located in the brainstem which receives projections from hypothalamus, the thermoregulatory center in the brain (Scislo and O'Leary, 2006). Cardiovascular centers of the medulla are innervated by projections from the hypothalamus which alleviates cardiac arrhythmias by modulating the blood pressure (Willette et al., 1984; Lumb and Lovick, 1993; Kiely and Gordon, 1994; Hirasawa et al., 1996; Krukoff et al., 1997; Yang and Coote, 1998; Hardy, 2001). NTS influences cardiovascular system. Hypotensive responses in the cardiovascular system are mediated through A₁AR in NTS (White et al., 1996). Adenosine microinjections into the NTS result in a slow and regulated decrease in heart rate (Tseng et al., 1995; Phillis et al., 1997; Ho et al., 2008). Thus NTS and A₁AR contribute significantly towards induction of hypothermia and modulation of cardiovascular responses.

Dietary restriction is a dietary regimen defined by a decrease in food intake unassociated with malnutrition which lowers core body temperature, improves longevity, protects heart and attenuates progression of neurodegenerative diseases in animal models (Contestabile, 2009; Katare et al., 2009). These effects have been suggested to be through a reduction in metabolic demand (Ungvari et al., 2008) associated with a decrease in body temperature (T_b) (Conti et al., 2006). Mechanisms involved in induction of hypothermia are under investigation. Results from our studies have shown that DR-induced hypothermia is due to adenosine sensitization (Jinka et al., 2010). Our results have demonstrated that intraperitoneal administration of CHA (0.5mg/kg) in DR-sensitized rats induced a significant cooling undetected in ad libitum (AL) rats. However, it is not clear as to how the heart responds to this induced cooling in DR rats because hypothermia beyond a certain level is not without complications like cardiac arrhythmias (Polderman and Herold, 2009). It was shown that DR has certain beneficial effects on heart (Lee et al., 1999) including protection from arrhythmias (Johnson et al., 2006) although it is yet to be investigated whether these beneficial effects on heart are applicable under hypothermic conditions induced by the A₁AR agonists.

Central administration of A₁AR agonist-induced hypothermia in Syrian hamsters is free of cardiac arrhythmias while forced induction of hypothermia through intraperitoneal pentobarbital sodium causes J-waves and atrioventricular block (Miyazawa et al., 2008). Syrian hamsters undergo periods of food restriction, a process comparatively similar to dietary restriction, which prepares them to hibernate (Stamper et al., 1999). Dietary restriction influences NTS (Badman and Flier, 2005). Thus it can be hypothesized that centrally administered A₁AR agonist-induced hypothermia in dietary restricted rats may avoid cardiac arrhythmias.

5.3 Previous studies and results

In our previous studies we have shown that prolonged DR sensitizes A₁AR agonist-induced cooling. Sprague-Dawley rats were implanted with subcutaneous IPTT-300 transponders for

monitoring body temperature. Rats were fed every other day for 27 days and then administered the A₁AR agonist, N⁶-cyclohexyladenosine (CHA; 0.5mg/kg, ip). Respiratory rate (RR) and subcutaneous body temperature were monitored every day and after drug administration. A lower RR on day 20 and lower body temperature on day 22 were displayed by DR rats when compared to rats fed ad libitum and displayed a larger response to CHA. RR, a metabolic indicator, declined before body temperature in all cases suggesting that a decrease in oxidative metabolism associated with thermogenesis caused animals to cool. This is comparable to torpor because of prior changes in metabolism than body temperature as observed during hibernation (Lyman, 1958). An increased surface expression of A₁AR is demonstrated within the hypothalamus in DR rats. These results suggest that sensitization of thermoregulatory effects of endogenous adenosine through increased surface expression of A₁AR may play a role in enhanced hypothermia associated with DR. These results also suggest that a torpid like effect is seen with CHA-induced hypothermia in DR rats. However, it is not known from these studies as to how the heart responds to this CHA-induced hypothermia in DR rats (Jinka et al., 2010).

5.4 Hypothermia in hibernation vs hypothermia in A₁AR stimulated DR rats

Hypothermia is seen in hibernators during torpor where their core body temperature (T_b) can reach to as low as -2.9°C (Barnes, 1989) without any complications. A sudden drop in metabolism followed by a decrease in core body temperature is the hallmark of hibernation (Lyman, 1958). CHA-induced hypothermia in DR rats resembled torpor in hibernators as there is a sudden decrease in respiration, an indicator of metabolism, followed by a slow decrease in body temperature (Jinka et al., 2010). Central administration of CHA in hibernators results in hypothermia without any untoward effects on heart while cardiac arrhythmias were seen with anesthetic-induced hypothermia (Miyazawa et al., 2008). Atrioventricular blocks and J-waves are observed in nonhibernators during induced hypothermia (Osborn, 1953; Brunson et al., 2005). Appearance of J-waves, also known as Osborne waves, indicates injury, delayed ventricular conduction, tissue anoxia or acidosis (Miyazawa et al., 2008). These studies suggest that an unidentified intrinsic mechanism in the heart of hibernators may be responsible for circumventing heart failure under extreme hypothermia.

5.5 Neuroprotection by induction of hypothermia and circumventing cardiac arrhythmias

Neuronal cell death is one of the major aftermaths of cardiopulmonary arrest and stroke. Under clinical setting, regulated hypothermia induced in the stroke patient in order to mitigate neuronal injury has proven to be helpful. Neuroprotection is evident in hibernators which experience extreme hypothermia. Thus inducing a hibernation-like state would be more beneficial in cardiac arrest patients. DR-induced cooling is well established in various rodents (Conti et al., 2006; Ungvari et al., 2008; Contestabile, 2009). What is novel in the recent research is that adenosine A₁ receptor (A₁AR) agonist; CHA administration induces increased hypothermic response in DR rats (Jinka et al., 2010), although the response of the cardiovascular system is not measured. This CHA-induced hypothermia in DR rats is similar to the torpor seen in hibernation and this is achieved through sensitization of A₁AR in the brain's hypothalamus, the principle thermoregulatory center in the CNS. Recent study in hibernators also has shown that central administration of CHA induces cooling without cardiac arrhythmias (Miyazawa et al., 2008). Hence there is a possibility of circumventing

cardiac arrhythmias in DR rats when hypothermia is achieved through central administration of CHA. Thus it can be hypothesized that A₁AR agonist-induced hypothermia in dietary restricted rats may avoid cardiac arrhythmias.

5.6 Hypothesized model

Sensitized adenosinergic system in DR rats acts through nucleus of the solitary tract (NTS), a primary integrative center for cardiovascular reflex. Adenosine in NTS modulates sympathetic, parasympathetic, and cardiovascular systems which in turn modulate arterial pressure, heart rate and vascular conductance by acting on and tuning the activity of the sympathetic and parasympathetic systems. The effect of adenosine may be one of the mechanisms behind cardioprotective effect (Fig.4) leading to generation of normal cardiac rhythms circumventing cardiac arrhythmias.

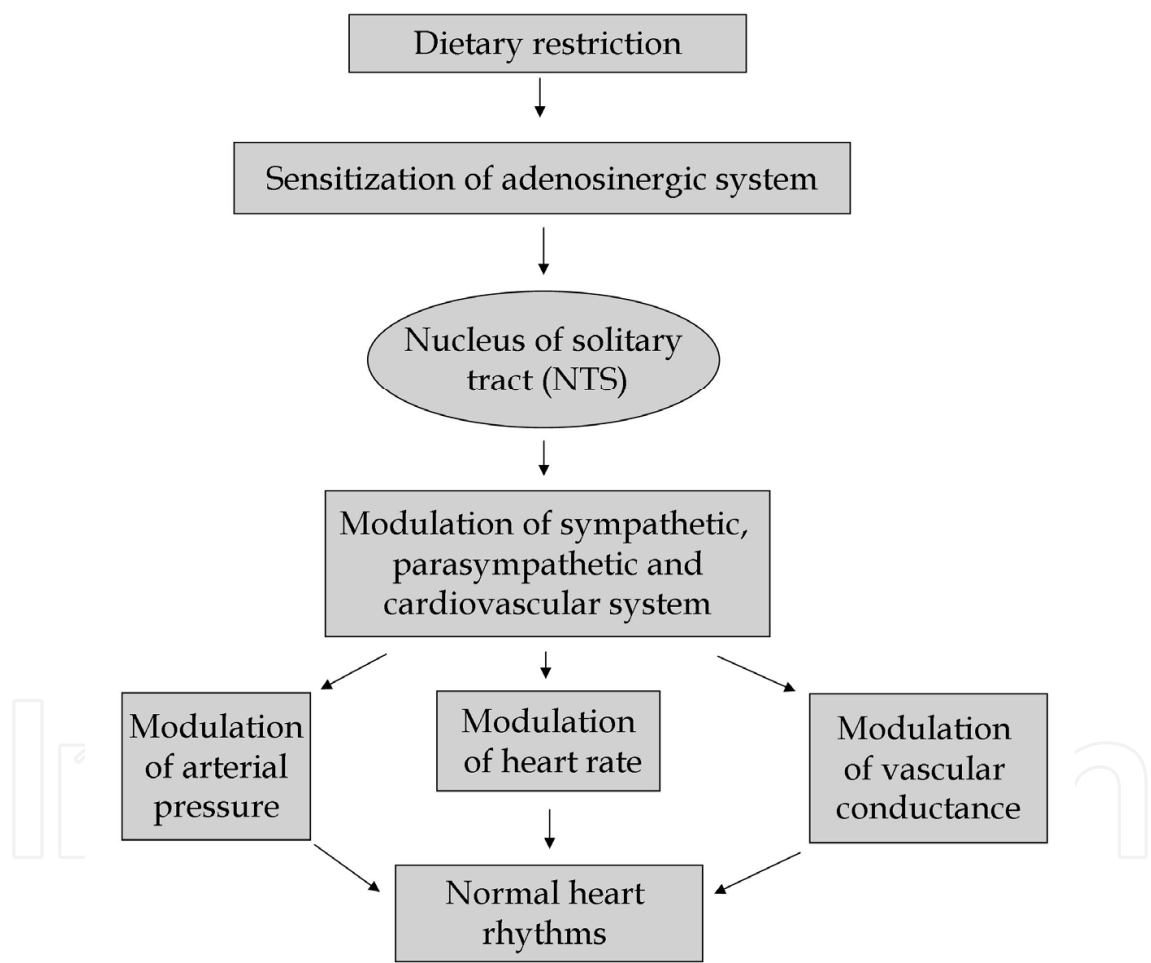


Fig. 4. Hypothesized model of dietary restriction induced cardioprotection.

6. Conclusion

Hibernators undergo a variety of complex morphological, behavioral, and physiological adaptive changes during hibernation period. Profound metabolic suppression, hypothermia, and bradycardia observed at the organismal level during the hibernation period have no

harmful effects (Geiser, 1988; Barnes, 1989; Buck and Barnes, 2000; Drew et al., 2001; Zhou et al., 2001; Carey et al., 2003a; Heldmaier et al., 2004; Tamura et al., 2005; Ross et al., 2006; Drew et al., 2007). The hearts of hibernating mammals remain functional even at 0°C while the hearts of non-hibernating mammals become arrhythmic and stop functioning between 10°C and 15°C (Lyman, 1982; Caprette and Senturia, 1984; Burlington and Darvish, 1988). This implies that an intrinsic difference in functional mechanism may exist between the hearts of a hibernator and a non-hibernator enabling the hibernator to survive despite low body temperatures. Understanding the mechanisms regulating hibernation has the potential to develop therapies for conditions such as cardiac arrhythmias, hemorrhagic shock, stroke, cardiac arrest and cerebral ischemia (Drew et al., 2007).

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8. References

- Badman MK, Flier JS (2005) The gut and energy balance: visceral allies in the obesity wars. *Science* 307:1909-1914.
- Barnes BM (1989) Freeze avoidance in a mammal: body temperatures below 0 degree C in an Arctic hibernator. *Science* 244:1593-1595.
- Barraco RA, Phillis JW (1991) Subtypes of adenosine receptors in the brainstem mediate opposite blood pressure responses. *Neuropharmacology* 30:403-407.
- Beyer EC, Paul DL, Goodenough DA (1987) Connexin43: a protein from rat heart homologous to a gap junction protein from liver. *J Cell Biol* 105:2621-2629.
- Boyer BB, Barnes BM (1999) Molecular and metabolic aspects of hibernation. *Bioscience* 49:713-724.
- Brunson CE, Abbud E, Osman K, Skelton TN, Markov AK (2005) Osborn (J) wave appearance on the electrocardiogram in relation to potassium transfer and myocardial metabolism during hypothermia. *J Investig Med* 53:434-437.
- Buck CL, Barnes BM (2000) Effects of ambient temperature on metabolic rate, respiratory quotient, and torpor in an arctic hibernator. *Am J Physiol Regul Integr Comp Physiol* 279:R255-262.
- Burlington RF, Darvish A (1988) Low-temperature performance of isolated working hearts from a hibernator and a non-hibernator. *Physiol Zool* 1988:387-395.
- Burn JH (1961) The cause of fibrillation. *Can Med Assoc J* 84:625-627.
- Caprette DR, Senturia JB (1984) Isovolumetric performance of isolated ground squirrel and rat hearts at low temperature. *Am J Physiol* 247:722-727.
- Carey HV, Andrews MT, Martin SL (2003a) Mammalian hibernation: cellular and molecular responses to depressed metabolism and low temperature. *Physiol Rev* 83:1153-1181.

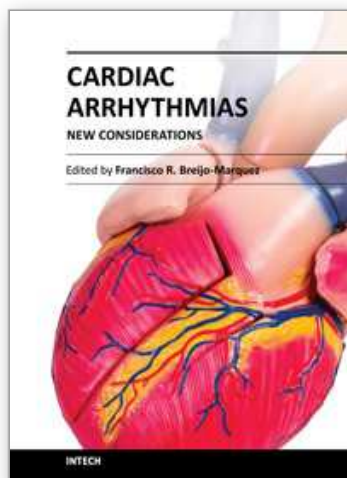
- Carey HV, Rhoads CA, Aw TY (2003b) Hibernation induces glutathione redox imbalance in ground squirrel intestine. *J Comp Physiol [B]* 173:269-276.
- Chatfield PO, Lyman CP (1950) Circulatory changes during process of arousal in the hibernating hamster. *Am J Physiol* 163:566-574.
- Contestabile A (2009) Benefits of caloric restriction on brain aging and related pathological States: understanding mechanisms to devise novel therapies. *Curr Med Chem* 16:350-361.
- Conti B, Sanchez-Alavez M, Winsky-Sommerer R, Morale MC, Lucero J, Brownell S, Fabre V, Huitron-Resendiz S, Henriksen S, Zorrilla EP, de Lecea L, Bartfai T (2006) Transgenic mice with a reduced core body temperature have an increased life span. *Science* 314:825-828.
- Dawe AR, Morrison PR (1955) Characteristics of the hibernating heart. *Am Heart J* 49:367-384.
- Drew KL, Rice ME, Kuhn TB, Smith MA (2001) Neuroprotective adaptations in hibernation: therapeutic implications for ischemia-reperfusion, traumatic brain injury and neurodegenerative diseases. *Free Radic Biol Med* 31:563-573.
- Drew KL, Christian LS, Jinka TR, Hollen L, Dehn J (2009) "Natural" tolerance in hibernators: Can we learn from physiological and preconditioning against ischemic or hypoxic brain injury? In: *Ischemic Tolerance of the Brain* (Schaller BJ, ed), pp 1-44. Trivandrum: Research Signpost.
- Drew KL, Buck CL, Barnes BM, Christian SL, Rasley BT, Harris MB (2007) Central nervous system regulation of mammalian hibernation: implications for metabolic suppression and ischemia tolerance. *J Neurochem* 102:1713-1726.
- Dunwiddie TV, Masino SA (2001) The role and regulation of adenosine in the central nervous system. *Annu Rev Neurosci* 24:31-55.
- Eagles DA, Jacques LB, Taboada J, Wagner CW, Diakun TA (1988) Cardiac arrhythmias during arousal from hibernation in three species of rodents. *Am J Physiol* 254:R102-108.
- Elvert R, Heldmaier G (2005) Cardiorespiratory and metabolic reactions during entrance into torpor in dormice, *Glis glis*. *J Exp Biol* 208:1373-1383.
- Fedorov VV, Li L, Glukhov A, Shishkina I, Aliev RR, Mikheeva T, Nikolski VP, Rosenshtaukh LV, Efimov IR (2005) Hibernator *Citellus undulatus* maintains safe cardiac conduction and is protected against tachyarrhythmias during extreme hypothermia: possible role of Cx43 and Cx45 up-regulation. *Heart Rhythm* 2:966-975.
- Fredholm BB, Abbracchio MP, Burnstock G, Daly JW, Harden TK, Jacobson KA, Leff P, Williams M (1994) Nomenclature and classification of purinoceptors. *Pharmacol Rev* 46:143-156.
- Geiser F (1988) Reduction of metabolism during hibernation and daily torpor in mammals and birds: Temperature effect or physiological inhibition? *J Comp Physiol B* 158:25-37.
- Geiser F (2004) Metabolic rate and body temperature reduction during hibernation and daily torpor. *Annu Rev Physiol* 66:239-274.
- Geiser F, Ruf T (1995) Hibernation versus daily torpor in mammals and birds : physiological variables and classification of torpor patterns *Physiol Zool* 68:935-966.

- Gros DB, Jongsma HJ (1996) Connexins in mammalian heart function. *Bioessays* 18:719-730.
- Hardy SG (2001) Hypothalamic projections to cardiovascular centers of the medulla. *Brain Res* 894:233-240.
- Heldmaier G, Ortmann S, Elvert R (2004) Natural hypometabolism during hibernation and daily torpor in mammals. *Respir Physiol Neurobiol* 141:317-329.
- Heller HC, Colliver GW (1974) CNS regulation of body temperature during hibernation. *Am J Physiol* 227:583-589.
- Heller HC, Colliver GW, Beard J (1977) Thermoregulation during entrance into hibernation. *Pflügers Arch* 369:55-59.
- Hirasawa M, Nishihara M, Takahashi M (1996) The rostral ventrolateral medulla mediates suppression of the circulatory system by the ventromedial nucleus of the hypothalamus. *Brain Res* 724:186-190.
- Ho WY, Lu PJ, Hsiao M, Hwang HR, Tseng YC, Yen MH, Tseng CJ (2008) Adenosine modulates cardiovascular functions through activation of extracellular signal-regulated kinases 1 and 2 and endothelial nitric oxide synthase in the nucleus tractus solitarii of rats. *Circulation* 117:773-780.
- Jinka TR, Toien O, Drew KL (2011) Season primes the brain in an arctic hibernator to facilitate entrance into torpor mediated by adenosine A1 receptors. *J Neurosci* 31:10752-10758.
- Jinka TR, Carlson ZA, Moore JT, Drew KL (2010) Altered thermoregulation via sensitization of A1 adenosine receptors in dietary-restricted rats. *Psychopharmacology (Berl)* 209:217-224.
- Johansson BW (1984) Cardiac responses in relation to heart size. *Cryobiology* 21:627-636.
- Johansson BW (1996) The hibernator heart--nature's model of resistance to ventricular fibrillation. *Cardiovasc Res* 31:826-832.
- Johnson JB, Laub DR, John S (2006) The effect on health of alternate day calorie restriction: eating less and more than needed on alternate days prolongs life. *Med Hypotheses* 67:209-211.
- Karpovich SA, Toien O, Buck CL, Barnes BM (2009) Energetics of arousal episodes in hibernating arctic ground squirrels. *J Comp Physiol [B]*.
- Katare RG, Kakinuma Y, Arikawa M, Yamasaki F, Sato T (2009) Chronic intermittent fasting improves the survival following large myocardial ischemia by activation of BDNF/VEGF/PI3K signaling pathway. *J Mol Cell Cardiol* 46:405-412.
- Keating MT, Sanguinetti MC (2001) Molecular and cellular mechanisms of cardiac arrhythmias. *Cell* 104:569-580.
- Kiely JM, Gordon FJ (1994) Role of rostral ventrolateral medulla in centrally mediated pressor responses. *Am J Physiol* 267:H1549-1556.
- Krukoff TL, Mactavish D, Jhamandas JH (1997) Activation by hypotension of neurons in the hypothalamic paraventricular nucleus that project to the brainstem. *J Comp Neurol* 385:285-296.
- Landau BR, Dawe AR (1958) Respiration in the hibernation of the 13-lined ground squirrel. *Am J Physiol* 194:75-82.
- Lee J, Yu BP, Herlihy JT (1999) Modulation of cardiac mitochondrial membrane fluidity by age and calorie intake. *Free Radic Biol Med* 26:260-265.

- Lumb BM, Lovick TA (1993) The rostral hypothalamus: an area for the integration of autonomic and sensory responsiveness. *J Neurophysiol* 70:1570-1577.
- Lyman CP (1958) Oxygen consumption, body temperature and heart rate of woodchucks entering hibernation. *Am J Physiol* 194:83-91.
- Lyman CP, ed (1982) The hibernating state, Recent theories of hibernation. . New York: Academic Press.
- Lyman CP, O'Brien RC (1963) Autonomic Control of Circulation during the Hibernating Cycle in Ground Squirrels. *J Physiol* 168:477-499.
- Lyman CP, O'Brien RC (1969) Hyperresponsiveness in hibernation. *Symp Soc Exp Biol* 23:489-509.
- Milsom WK, Burlington RF, Burleson ML (1993) Vagal Influence On Heart-Rate In Hibernating Ground-Squirrels. *Journal Of Experimental Biology* 185:25-32.
- Milsom WK, Zimmer MB, Harris MB (1999) Regulation of cardiac rhythm in hibernating mammals. *Comp Biochem Physiol A Mol Integr Physiol* 124:383-391.
- Miyazawa S, Shimizu Y, Shiina T, Hirayama H, Morita H, Takewaki T (2008) Central A1-receptor activation associated with onset of torpor protects the heart against low temperature in the Syrian hamster. *Am J Physiol Regul Integr Comp Physiol* 295:R991-996.
- Mosqueda-Garcia R, Tseng CJ, Appalsamy M, Robertson D (1989) Modulatory effects of adenosine on baroreflex activation in the brainstem of normotensive rats. *Eur J Pharmacol* 174:119-122.
- Nardone RM (1955) Electrocardiogram of the arctic ground squirrel during hibernation and hypothermia. *Am J Physiol* 182:364-368.
- Olah ME, Stiles GL (1995) Adenosine receptor subtypes: characterization and therapeutic regulation. *Annu Rev Pharmacol Toxicol* 35:581-606.
- Osborn JJ (1953) Experimental hypothermia; respiratory and blood pH changes in relation to cardiac function. *Am J Physiol* 175:389-398.
- Phillis JW, Scislo TJ, O'Leary DS (1997) Purines and the nucleus tractus solitarius: effects on cardiovascular and respiratory function. *Clin Exp Pharmacol Physiol* 24:738-742.
- Polderman KH (2004) Application of therapeutic hypothermia in the intensive care unit. Opportunities and pitfalls of a promising treatment modality--Part 2: Practical aspects and side effects. *Intensive Care Med* 30:757-769.
- Polderman KH, Herold I (2009) Therapeutic hypothermia and controlled normothermia in the intensive care unit: practical considerations, side effects, and cooling methods. *Crit Care Med* 37:1101-1120.
- Popov VI, Bocharova LS, Bragin AG (1992) Repeated changes of dendritic morphology in the hippocampus of ground squirrels in the course of hibernation. *Neuroscience* 48:45-51.
- Ross AP, Christian SL, Zhao HW, Drew KL (2006) Persistent tolerance to oxygen and nutrient deprivation and N-methyl-D-aspartate in cultured hippocampal slices from hibernating Arctic ground squirrel. *J Cereb Blood Flow Metab* 26:1148-1156.
- Saitongdee P, Milner P, Becker DL, Knight GE, Burnstock G (2000) Increased connexin43 gap junction protein in hamster cardiomyocytes during cold acclimatization and hibernation. *Cardiovasc Res* 47:108-115.

- Scislo TJ, O'Leary DS (2006) Adenosine receptors located in the NTS contribute to renal sympathoinhibition during hypotensive phase of severe hemorrhage in anesthetized rats. *Am J Physiol Heart Circ Physiol* 291:H2453-2461.
- Scislo TJ, Ichinose TK, O'Leary DS (2008) Stimulation of NTS A1 adenosine receptors differentially resets baroreflex control of regional sympathetic outputs. *Am J Physiol Heart Circ Physiol* 294:H172-182.
- Shintani M, Tamura Y, Monden M, Shiomi H (2005) Characterization of N(6)-cyclohexyladenosine-induced hypothermia in Syrian hamsters. *J Pharmacol Sci* 97:451-454.
- Stamper JL, Dark J, Zucker I (1999) Photoperiod modulates torpor and food intake in Siberian hamsters challenged with metabolic inhibitors. *Physiol Behav* 66:113-118.
- Strumwasser F (1959) Thermoregulatory, brain and behavioral mechanisms during entrance into hibernation in the squirrel, *Citellus beecheyi*. *Am J Physiol* 196:15-22.
- Surawicz B (1971) Ventricular fibrillation. *Am J Cardiol* 28:268-287.
- Tamura Y, Shintani M, Nakamura A, Monden M, Shiomi H (2005) Phase-specific central regulatory systems of hibernation in Syrian hamsters. *Brain Res* 1045:88-96.
- Toien O, Blake J, Edgar DM, Grahn DA, Heller HC, Barnes BM (2011) Hibernation in black bears: independence of metabolic suppression from body temperature. *Science* 331:906-909.
- Trautwein W (1963) Generation and conduction of impulses in the heart as affected by drugs. *Pharmacol Rev* 15:277-332.
- Tseng CJ, Ger LP, Lin HC, Tung CS (1995) Attenuated cardiovascular response to adenosine in the brain stem nuclei of spontaneously hypertensive rats. *Hypertension* 25:278-282.
- Twente JW, Twente JA (1965) Effects of core temperature upon duration of hibernation *Citellus lateralis*. *J Appl Physiol* 20:411-416.
- Twente JW, Twente J, eds (1978) *Autonomic regulation of hibernation by Citellus and Eptesicus*. New York: Academic Press.
- Ungvari Z, Parrado-Fernandez C, Csiszar A, de Cabo R (2008) Mechanisms underlying caloric restriction and lifespan regulation: implications for vascular aging. *Circ Res* 102:519-528.
- Van Der Heyden MA, Kok B, Kouwenhoven EN, Toien O, Barnes BM, Fedorov VG, Efimov IR, Opthof T (2007) Cloning, sequence analysis and phylogeny of connexin43 isolated from American black bear heart. *DNA Seq* 18:380-384.
- Walls EW (1942) Specialized conducting tissue in the heart of the golden hamster (*Cricetus auratus*). *J Anat* 76:359-368 352.
- White PJ, Rose-Meyer RB, Hope W (1996) Functional characterization of adenosine receptors in the nucleus tractus solitarius mediating hypotensive responses in the rat. *Br J Pharmacol* 117:305-308.
- White TD (1977) Direct detection of depolarisation-induced release of ATP from a synaptosomal preparation. *Nature* 267:67-68.
- Willette RN, Gatti PA, Sapru HN (1984) GABAergic mechanisms in the ventrolateral medulla alter vasopressor responses from the anterior hypothalamus. *J Cardiovasc Pharmacol* 6:476-482.

- Yang Z, Coote JH (1998) Influence of the hypothalamic paraventricular nucleus on cardiovascular neurones in the rostral ventrolateral medulla of the rat. *J Physiol* 513 (Pt 2):521-530.
- Zhou F, Zhu X, Castellani RJ, Stimmelmayer R, Perry G, Smith MA, Drew KL (2001) Hibernation, a model of neuroprotection. *Am J Pathol* 158:2145-2151.
- Zimmer MB, Harris MB, Milsom WK (2000) Control of cardiac and ventilation frequencies during hibernation in ground squirrels. In: *In Life in the Cold: Proceedings of the 11th International Hibernation Symposium* (Klingenspor GHaM, ed), pp 159-167. Berlin, Heidelberg, New York: Springer-Verlag.



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The most intimate mechanisms of cardiac arrhythmias are still quite unknown to scientists. Genetic studies on ionic alterations, the electrocardiographic features of cardiac rhythm and an arsenal of diagnostic tests have done more in the last five years than in all the history of cardiology. Similarly, therapy to prevent or cure such diseases is growing rapidly day by day. In this book the reader will be able to see with brighter light some of these intimate mechanisms of production, as well as cutting-edge therapies to date. Genetic studies, electrophysiological and electrocardiographic features, ion channel alterations, heart diseases still unknown, and even the relationship between the psychic sphere and the heart have been exposed in this book. It deserves to be read!

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