



ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

ARCHIVIO ISTITUZIONALE
DELLA RICERCA

Alma Mater Studiorum Università di Bologna Archivio istituzionale della ricerca

Be cool to be far: Exploiting hibernation for space exploration

This is the final peer-reviewed author's accepted manuscript (postprint) of the following publication:

Published Version:

Cerri M., Hitrec T., Luppi M., Amici R. (2021). Be cool to be far: Exploiting hibernation for space exploration. *NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS*, 128, 218-232 [10.1016/j.neubiorev.2021.03.037].

Availability:

This version is available at: <https://hdl.handle.net/11585/845701> since: 2022-01-15

Published:

DOI: <http://doi.org/10.1016/j.neubiorev.2021.03.037>

Terms of use:

Some rights reserved. The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>).
When citing, please refer to the published version.

(Article begins on next page)

1
2
3
4
5 **BE COOL TO BE FAR: EXPLOITING HIBERNATION FOR SPACE EXPLORATION**
6
7
8

9 **Matteo Cerri,**

10 Affiliation: Department of Biomedical and NeuroMotor Sciences – Alma Mater Studiorum -University of
11 Bologna

12 Address: Piazza di Porta S.Donato, 2 40126 – Bologna - Italy

13 Email: matteo.cerri@unibo.it
14

15
16 **Timna Hitrec,**

17 Affiliation: Department of Biomedical and NeuroMotor Sciences – Alma Mater Studiorum -University of
18 Bologna

19 Address: Piazza di Porta S.Donato, 2 40126 – Bologna - Italy

20 Email: timna.hitrec@gmail.com
21

22
23 **Marco Luppi,**

24 Affiliation: Department of Biomedical and NeuroMotor Sciences – Alma Mater Studiorum -University of
25 Bologna

26 Address: Piazza di Porta S.Donato, 2 40126 – Bologna - Italy

27 Email: marco.luppi@unibo.it
28

29 **Roberto Amici**

30 Affiliation: Department of Biomedical and NeuroMotor Sciences – Alma Mater Studiorum -University of
31 Bologna

32 Address: Piazza di Porta S.Donato, 2 40126 – Bologna - Italy

33 Email: roberto.amici@unibo.it
34

35
36 **Corresponding author:**

37 Matteo Cerri

38 Piazza di Porta S.Donato, 2 40126 – Bologna – Italy

39 Tel: +39 051 209 1731

40 Email: matteo.cerri@unibo.it
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1
2
3
4 **BE COOL TO BE FAR: EXPLOITING HIBERNATION FOR SPACE EXPLORATION**
5

6
7 **Matteo Cerri, Timna Hitrec, Marco Luppi, Roberto Amici**
8

9 Department of Biomedical and NeuroMotor Sciences – Alma Mater Studiorum -University of Bologna
10
11
12
13
14
15

16 **Abstract:** In mammals, torpor/hibernation is a state that is characterized by an active
17 reduction in metabolic rate followed by a progressive decrease in body temperature.
18 Torpor was successfully mimicked in non-hibernators by inhibiting the activity of
19 neurons within the brainstem region of the Raphe Pallidus, or by activating the adenosine
20 A1 receptors in the brain. This state, called synthetic torpor, may be exploited for many
21 medical applications, and for space exploration, providing many benefits for biological
22 adaptation to the space environment, among which an enhanced protection from cosmic
23 rays. As regards the use of synthetic torpor in space, to fully evaluate the degree of
24 physiological advantage provided by this state, it is strongly advisable to move from
25 Earth-based experiments to ‘in the field’ tests, possibly on board the International Space
26 Station.
27
28
29

30
31
32 **Keywords:** Torpor, Hibernation, Synthetic Torpor, Space Exploration, Radioprotection.
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1
2
3
4
5
6
7 **INTRODUCTION**
8
9

10
11 Torpor is a peculiar biological condition that, in mammals such as squirrels, hamsters, mice, bears, bats, and
12 others, is characterized by an active reduction in metabolic rate that causes a progressive decrease in body
13 temperature, proportionally to the thermal gradient between the body and the ambient (Heldmaier et al., 2004). The
14 state of torpor can be considered as the basic building brick of a more complex behavior, such as hibernation. The
15 term torpor usually refers to a single bout of metabolic suppression lasting from a few hours to a few days.
16 Hibernation is a sequence of torpor bouts, often interrupted by brief interbout arousals, lasting around 24 hours
17 (Geiser, 2020, 2013).
18

19
20 The decrease in body temperature in these hypometabolic states can either be extreme, such as in the arctic
21 ground squirrel, one of the mammals able to reach a below-zero temperature (Barnes, 1989; Ruf and Geiser, 2015),
22 or mild, such as in the grizzly bear, the temperature of which rarely drops below 30°C (Nelson and Robbins, 2015).
23 However, even animals living at high ambient temperatures are able to enter torpor (Grimpo et al., 2013; Nowack
24 et al., 2020).
25

26
27 The basic aim of torpor/hibernation is to induce a reduction in metabolic rate that allows hibernators to survive
28 for a long period in adverse environmental conditions, with no access to food or water, but little is known about the
29 mechanism controlling this state. Seasonal hibernators, such as the arctic ground squirrel, have a strong drive to
30 enter hibernation before the arrival of winter. The body of these animals pre-adapts to the hibernation season,
31 reducing, for instance, testicular volume or thyroid activity (Jastroch et al., 2016). These changes suggest that a
32 genetic regulation of this behavior is at work (Schwartz and Andrews, 2013). Other mammals, such as the Siberian
33 hamster, display daily episodes of torpor that are well entrained with their circadian rhythm (Cubuk et al., 2016),
34 whereas other mammals, the so-called facultative heterotherms (such as the mouse), enter torpor only if their energy
35 balance becomes negative (Oelkrug et al., 2011).
36

37
38 Despite the multiple phenotypes and regulations of the appearance of hibernation/torpor, it is reasonable to think
39 that there is a single underlying mechanism that reduces metabolic rate. This could potentially be used by other
40 conditions that induce a reduction in metabolic rate, such as the diving reflex, non-rapid eye movement (NREM)
41 sleep (Silvani et al., 2018), or states in which thermoregulatory control appears to be impaired, such as rapid eye
42 movement (REM) sleep (Capitani et al., 2005; Cerri et al., 2017). The mechanism whereby this occurs is not known
43 at the moment, but some preliminary observations point in the direction of the hypothalamus, and in particular the
44 Dorsomedial Hypothalamus (DMH)(Hitrec et al., 2019) and to a newly discovered set of neurons within the Preoptic
45 area (Hrvatín et al., 2020; Takahashi et al., 2020). A complete understanding of the molecular mechanism triggering
46 torpor would be of great help in the quest to develop a procedure to induce this state in humans (Cerri, 2017a).
47

48
49 At the moment, three procedures have been shown to be effective in mimicking a state that very much resembles
50 torpor in non-hibernators: 1) the inhibition of the neurons located within Raphe Pallidus (RPa), a region located in
51 the brainstem (Cerri et al., 2013); 2) the activation of the adenosine A1 receptor in the brain (Tupone et al., 2013);
52 3) a cocktail of drugs, including xenon, delivered in liposomes (Zakharova et al., 2021, 2019); the activation of the
53 hypothalamic Q neurons (Takahashi et al., 2020) All these methods require more translational research before being
54 used for space exploration, but the objective to be pursued is now clear, and this ambitious goal is no longer out of
55 reach.
56

57
58 It is important to highlight that the degree of resemblance to the most significant torpor features by each of these
59 procedures may vary. Hypothermia by itself differs from torpor, since it requires the overwhelming of the
60 physiological defense by cold: external cooling may even induce an increase in metabolic rate, the opposite of what
61 a technology aimed at mimicking torpor tries to achieve (Nakamura and Morrison, 2008). All of these procedures
62 though don't rely on physical cooling, but, on the contrary, act by inhibiting, in different ways, the central drive for
63
64
65

1
2
3
4 thermogenesis, favoring the induction of a reversible, undefended, centrally-induced hypothermia. The results is
5 that the dynamics of adaptation of many physiological variables to this hypothermic/hypometabolic condition may
6 still differ from what it is described for natural torpor (Geiser et al., 2014; Swoap et al., 2007; Vicent et al., 2017),
7 while many others have been shown to go in the same direction, such as, for instance, the slowing of the rhythms
8 of the electroencephalogram (EEG) (Cerri et al., 2013; Tupone et al., 2013), the after-bout rebound of slow wave
9 sleep (Cerri et al., 2013), the reversible phosphorylation of the Tau protein (TP) (Luppi et al., 2019), the increase in
10 cell radioresistance (Tinganelli et al., 2019).

11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112
113
114
115
116
117
118
119
120
121
122
123
124
125
126
127
128
129
130
131
132
133
134
135
136
137
138
139
140
141
142
143
144
145
146
147
148
149
150
151
152
153
154
155
156
157
158
159
160
161
162
163
164
165
166
167
168
169
170
171
172
173
174
175
176
177
178
179
180
181
182
183
184
185
186
187
188
189
190
191
192
193
194
195
196
197
198
199
200
201
202
203
204
205
206
207
208
209
210
211
212
213
214
215
216
217
218
219
220
221
222
223
224
225
226
227
228
229
230
231
232
233
234
235
236
237
238
239
240
241
242
243
244
245
246
247
248
249
250
251
252
253
254
255
256
257
258
259
260
261
262
263
264
265
266
267
268
269
270
271
272
273
274
275
276
277
278
279
280
281
282
283
284
285
286
287
288
289
290
291
292
293
294
295
296
297
298
299
300
301
302
303
304
305
306
307
308
309
310
311
312
313
314
315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355
356
357
358
359
360
361
362
363
364
365
366
367
368
369
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
385
386
387
388
389
390
391
392
393
394
395
396
397
398
399
400
401
402
403
404
405
406
407
408
409
410
411
412
413
414
415
416
417
418
419
420
421
422
423
424
425
426
427
428
429
430
431
432
433
434
435
436
437
438
439
440
441
442
443
444
445
446
447
448
449
450
451
452
453
454
455
456
457
458
459
460
461
462
463
464
465
466
467
468
469
470
471
472
473
474
475
476
477
478
479
480
481
482
483
484
485
486
487
488
489
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505
506
507
508
509
510
511
512
513
514
515
516
517
518
519
520
521
522
523
524
525
526
527
528
529
530
531
532
533
534
535
536
537
538
539
540
541
542
543
544
545
546
547
548
549
550
551
552
553
554
555
556
557
558
559
560
561
562
563
564
565
566
567
568
569
570
571
572
573
574
575
576
577
578
579
580
581
582
583
584
585
586
587
588
589
590
591
592
593
594
595
596
597
598
599
600
601
602
603
604
605
606
607
608
609
610
611
612
613
614
615
616
617
618
619
620
621
622
623
624
625
626
627
628
629
630
631
632
633
634
635
636
637
638
639
640
641
642
643
644
645
646
647
648
649
650
651
652
653
654
655
656
657
658
659
660
661
662
663
664
665
666
667
668
669
670
671
672
673
674
675
676
677
678
679
680
681
682
683
684
685
686
687
688
689
690
691
692
693
694
695
696
697
698
699
700
701
702
703
704
705
706
707
708
709
710
711
712
713
714
715
716
717
718
719
720
721
722
723
724
725
726
727
728
729
730
731
732
733
734
735
736
737
738
739
740
741
742
743
744
745
746
747
748
749
750
751
752
753
754
755
756
757
758
759
760
761
762
763
764
765
766
767
768
769
770
771
772
773
774
775
776
777
778
779
780
781
782
783
784
785
786
787
788
789
790
791
792
793
794
795
796
797
798
799
800
801
802
803
804
805
806
807
808
809
810
811
812
813
814
815
816
817
818
819
820
821
822
823
824
825
826
827
828
829
830
831
832
833
834
835
836
837
838
839
840
841
842
843
844
845
846
847
848
849
850
851
852
853
854
855
856
857
858
859
860
861
862
863
864
865
866
867
868
869
870
871
872
873
874
875
876
877
878
879
880
881
882
883
884
885
886
887
888
889
890
891
892
893
894
895
896
897
898
899
900
901
902
903
904
905
906
907
908
909
910
911
912
913
914
915
916
917
918
919
920
921
922
923
924
925
926
927
928
929
930
931
932
933
934
935
936
937
938
939
940
941
942
943
944
945
946
947
948
949
950
951
952
953
954
955
956
957
958
959
960
961
962
963
964
965
966
967
968
969
970
971
972
973
974
975
976
977
978
979
980
981
982
983
984
985
986
987
988
989
990
991
992
993
994
995
996
997
998
999
1000

Something more specific needs to be said about two key features of torpor: i) the maintenance of some degree of thermoregulation once a new temperature balance is reached; ii) the ability of the animals to arouse spontaneously from the hypometabolic/hypothermic state. It was shown that thermoregulation can still be activated in hibernators even during the bout of hypothermia (Florant and Heller, 1977; Heller and Colliver, 1974; Ortmann and Heldmaier, 2000), a feature that was so far mimicked only by the activation of Q neurons in mice (Takahashi et al., 2020). Although this important feature shows that torpor is a highly regulated behavior, in a translational view and in an artificial environment, thermal balance during synthetic torpor could be achieved by regulating the ambient temperature. This is especially important in the view that if thermoregulation was somehow still active, it could lead to an increase in energy consumption that may not be optimal for a long permanence in hypometabolism. The maintenance of an optimal energy balance is also critical in view of the periodic arousals that characterize seasonal hibernators, since, during the arousal, energy usage goes way up together with the production or reactive-oxygen species (ROS). The ability to spontaneously arise from hypometabolic states is also crucial since it separates torpor from other “knock out” conditions. So far, a spontaneous arousal was described for all the four procedures for synthetic torpor listed before. A technology that could harvest the advantage of torpor may therefore lead to something different from natural torpor, in a similar fashion to what happened in the field of aeronautics, where aircrafts were developed by obeying to the general physics of flight, and not by strictly trying to replicate the mechanism of wings-flapping typical of birds.

Many of the changes encountered by the body during hibernation could in fact be extremely helpful for humans in a long-term space exploration mission (Choukèr et al., 2019; Nordeen and Martin, 2019). Among the most interesting features we can highlight: the reduced food and water requirement, reduced waste production, reduced awareness, preservation of muscle strength and bone structure, slowed aging, and enhanced radioprotection against radiation damage. The reduced need for supplies, such as food and water, is a direct consequence of the reduced metabolic rate, that is also the cause for the reduced production of biological waste.

Another interesting feature of torpor is radioprotection. Passive shielding and reduction of exposure duration are currently the predominant approaches to protect astronauts, putting substantial constraints on space mission designers. Studies on the resistance of hibernators to very high levels of X- and γ -rays a few decades ago showed that hibernation drastically enhances radioprotection; however, there is still a lack of experimental data as to whether the protective effects measured in X- and γ -rays could be extended to the spectrum of ionizing radiation encountered in space. While extensive experiments have not yet been performed, current technical capabilities would allow for the experimental assessment of torpor and hibernation in counteracting the effects of exposure to ionizing radiation and micro-gravity in space.

Unfortunately, micro-gravity research in animal models offers few analogues. Neither hindlimb suspension protocol nor parabolic flight studies would be appropriate to study the long-term effects of microgravity on hibernators, but the International Space Station would be the ideal place to conduct such studies. We hope that a future research program on torpor/hibernation may use this essential facility, accelerating the development of a very promising technology.

PHYSIOLOGICAL ADAPTATION DURING HIBERNATION

1
2
3
4 **Terminology**
5

6 Hibernation-like state, torpor-like state, hypometabolism, hypothermia, deep hypothermia, suspended
7 animation, stasis, and probably others are some of the terms that are used in the field of translating hibernation to
8 humans. Recently, the expression synthetic torpor was suggested (Cerri, 2017a), and also used by NASA and others
9 (Griko and Regan, 2018; Regan et al., 2020). In this paper, we will use the expression synthetic torpor to refer to a
10 hypometabolic state that is induced by artificial means in either hibernators or non-hibernators, and that resembles,
11 at least partially, the state of natural torpor.
12
13

14
15 **Physiological adaptation in hypometabolic states**
16

17 During both natural hypometabolic states such as torpor/hibernation, and artificial ones, like synthetic torpor,
18 many organs and systems show major changes in response, or in adaptation, to the new body condition. Many of
19 these adaptations may be exploited for health purposes as well as in vision of long-term human space flights.
20
21

22 *The brain*
23

24 The brain is among the organs showing the most drastic changes during torpor. In squirrels, synaptic spines
25 were shown to be largely reabsorbed in many portions of the cerebral cortex, and also of the hypothalamus (Von
26 Der Ohe et al., 2007, 2006). The reduction in the number of synapses may be an adaptive response aimed at reducing
27 the high energy expenditure of the brain. Synapses are in fact among the highest consuming portions of neurons.
28 With such a drastic reduction in synapses, the overall computational capability of the brain is likely to be reduced.
29 It is reasonable that this drop in cortical connectivity will prevent the brain from sustaining complex cognitive tasks,
30 partially or totally, reducing the degree of awareness or consciousness (Cerri, 2017b). Synapses are then reformed
31 very quickly after the return to normothermia (Von Der Ohe et al., 2007, 2006). At the moment, little is known
32 regarding the characteristic of the reformed synapses compared with the re-absorbed ones: are they in the same
33 location? Do they have the same strength? This very peculiar event could be an interesting model with which to
34 study synaptic plasticity (Peretti et al., 2015), but it should also be considered with caution in the case of a long
35 space trip in a hypometabolic state. The time needed for the rewiring of the brain must be taken into account, in the
36 event of emergency arousal, since enough time has to be allowed for the recovery of full cognitive capacity. It is
37 also unclear at the moment whether the neural rewiring could be compromised by other factors, such as drugs or
38 sleep (Zamboni et al., 2004; Baracchi et al., 2008), or the presence of specific genes.
39
40

41
42 Beside the reduction in the number of synapses, during a torpor bout neurons also present changes in some of
43 their key cellular functions. In particular, TP becomes hyperphosphorylated, both in hibernators (Arendt and
44 Bullmann, 2013) and in non-hibernators (Chiocchetti et al., 2021; Hitrec et al., 2021; Luppi et al., 2019). This
45 molecular change resembles the one key change suggested to be at the origin of neurodegeneration in Alzheimer's
46 Disease (Arendt et al., 2015). Data from non-hibernators suggest that the hyperphosphorylation of the TP (P-TP)
47 may be temperature-dependent (Guisle et al., 2020), but other hypotheses are possible. For instance, starvation also
48 promotes P-TP, that could therefore be linked to a reduced metabolism more than to hypothermia (Planel et al.,
49 2001; Yanagisawa et al., 1999). The effect of hypothermia may be only secondary to the metabolic suppression
50 induced by the decrease in temperature, but the specific role of hypothermia vs. hypometabolism in the status of the
51 TP has yet to be elucidated. The purpose of P-TP increase is not known at the moment. Does it serve to protect
52 some structure of neuronal cytoskeleton from damage? Or does it promote a further reduction in energy
53 consumption by lowering the axonal transport (Wang and Mandelkow, 2016)? In terms of mechanism, the
54 accumulation of P-TP is apparently mediated by a relative increase in kinase activity compared to phosphatase
55 activity (Planel et al., 2007, 2004; Su et al., 2008). What is clear is that, shortly after the arousal, P-TP is cleared
56 from the brain. It is certainly suggestive that, in torpor and in synthetic torpor, the brain can be seen as 'diving'
57 into a quickly reversible dementia.
58
59
60
61
62
63
64
65

1
2
3
4 In terms of brain function, an interesting question regards the characterization of torpor and synthetic torpor as
5 reflected in the electroencephalogram (EEG). Is it something akin to sleep? Or to coma? Or to general anesthesia?
6 EEG is strongly affected by temperature, since conduction velocity decreases according to the Q10 factor, leading
7 to a left-shift of the EEG spectrum (Deboer, 1998). However, the reduced number of synapses observed in torpor
8 may also produce effects. EEG recordings during torpor show a signal of low amplitude and low frequencies,
9 differing from all the known sleep stages (Vyazovskiy et al., 2017). EEG recordings in synthetic torpor show a
10 similar pattern, with frequency bands, like the Theta band, shifting to lower frequencies with the lowering of the
11 brain temperature, mirroring something that could be called “slow wakefulness” (Cerri et al., 2013). Apparently,
12 sleep does not appear during torpor, with the possible exception of REM sleep, signs of which were reported to
13 occur in torpid lemurs (Blanco et al., 2016). The absence of sleep, or at least of its EEG signs, during torpor suggests
14 that torpor may be a period of sleep deprivation (Deboer and Tobler, 2003; Royo et al., 2019). Indeed, a long bout
15 of intense sleep rich in slow waves, can be observed in hamsters and in squirrels after the arousal from
16 torpor/hibernation (Deboer and Tobler, 2000; Larkin and Heller, 1999; Strijkstra and Daan, 1998), as well as in
17 lemur (Royo et al., 2019), and in rats after synthetic torpor (Cerri et al., 2013). The nature of this sleep, however, is
18 still controversial. Depriving hamsters of the after-torpor sleep induced a further sleep-rebound, proportional to the
19 length of the torpor bout (Deboer and Tobler, 2003), but the same was not observed in squirrels (Strijkstra and
20 Daan, 1998). More recently, some differences in the nature of the slow wave during recovery sleep as compared to
21 after-torpor sleep have also been reported (Vyazovskiy et al., 2017). Differences in body temperature (much lower
22 in squirrels than in hamsters), or duration of the torpor bout (weeks for squirrels, hours for hamsters) may justify
23 the difference. In mice, no increase in slow waves was reported during sleep soon after torpor, but the short duration
24 of these bouts may be insufficient to induce a sleep debt (Lo Martire et al., 2020). Moreover, the degree of energy
25 expenditure for body rewarming to recover a body temperature of 37°C may also influence sleep intensity after the
26 torpor bout (Cerri et al., 2013). The role of the after-torpor sleep is a factor to be carefully evaluated in the hypothesis
27 of torpor use for space travel. It is possible that the sleep rebound may be an essential part of the “re-synaptization”
28 of the brain, or of the clearance of the P-TP. Are there consequences if such sleep is prevented? Or does it have to
29 be protected and considered as part of the arousal process? All these questions will have to be addressed before
30 considering the use of synthetic torpor for space exploration.

31 32 33 *The gastrointestinal tract*

34
35
36
37
38
39
40 The gastrointestinal tract (GI) is affected by hibernation in a variety of ways. As a matter of fact, the GI tract is
41 a combined organ, merging the actual digestive system and the microbiota living in it. These compartments are
42 affected both by temperature and fasting, the latter being especially prolonged during seasonal hibernation.

43
44 In general, the changes in the physiology of the GI tract during hibernation are in tune with the general melody
45 of metabolic suppression: the cell cycle stops together with all digestive processes. Mucosal size and protein content,
46 as well as villus height, were shown to be reduced during hibernation (Carey, 1990), but a complete atrophy of the
47 mucosa cannot be afforded by the animal, since the GI tract has to be ready to absorb nutrients shortly after arousal.
48 It is probably for this reason that, when the stimulating effect of food presence is lacking, an enhanced area-specific
49 absorption of sodium and glucose takes place on the mucosa. (Carey, 1990; Weitten et al., 2016). Interestingly, the
50 barrier becomes generally leakier, since the number of gap junctions decreases (Carey et al., 2012). Under normal
51 circumstances, this could be a problem, exposing the organism to infection from the residential microbes, but during
52 hibernation an increase in the lymphocytes occurs in the GI tract, possibly preventing microbial invasion (Bouma
53 et al., 2010a; Kurtz and Carey, 2007).

54
55
56 The microbiota is also significantly changed by hibernation, and the lack of nutrients, coupled with the decrease
57 in body temperature, reshapes the bacterial population in the GI tract (Carey and Assadi-Porter, 2017): taxa feeding
58 on host-derived substrates (such as muciniphilia) tend to prevail over taxa requiring diet-related substrates, such as
59 Lachnospiracea (Carey et al., 2013; Dill-McFarland et al., 2014; Stevenson et al., 2014). Changes in microbiota
60
61
62
63
64
65

1
2
3
4 were also shown to induce changes in metabolism when transplanted (Sommer et al., 2016), possibly playing a role
5 in guiding or favoring the metabolic suppression in hibernation.

6
7 Multiple aspects of GI tract adaptation to hibernation could be useful in the medical field (Sisa et al., 2017), but
8 some aspects will require special consideration in vision of a use in space. Atrophy of the GI tract will have to be
9 prevented at all costs, and so far there is no indication as to how the GI tract adapts to long periods of synthetic
10 torpor. It is possible that some strategy will have to be envisioned to maintain GI absorption functionally ready to
11 be activated after the arousal. The composition of the microbiota also has to be kept in consideration, by designing
12 specific probiotics to help the transition from a low-metabolism microbiota to a high-metabolism one.
13
14

15 16 *The immune system* 17

18 The activity of the immune system during torpor/hibernation presents some interesting changes, the main one
19 being the drastic reduction in circulating white cells (Bouma et al., 2010a). Leukopenia has been reported in multiple
20 species (Bouma et al., 2013, 2011, 2010b; Frerichs et al., 1994; Huber et al., 2021; Reitsema et al., 2021; Reznik et
21 al., 1975; Spurrierl and Dawe1, 1973; Suomalainen and Rosokivi, 1973; Tøien et al., 2001; Webb et al., 1982),
22 affecting all types of immune cells (granulocytes, lymphocytes, and monocytes). This drastic drop in the number of
23 white cells poses multiple questions: 1) do the white cells die? Or 2) is the production of white cells halted? And 3)
24 does this immunosuppression make animals more susceptible to infections?
25

26 As far as the first two questions are concerned, at the moment the data suggest that the white cells do not go into
27 apoptosis or die for other reasons, but are mostly segregated in reservoir organs, such as the liver, the spleen, the
28 lymph nodes, or the walls of blood vessels (Bouma et al., 2011; Inkovaara and Suomalainen, 1973; Yasuma et al.,
29 1997), justifying the fast onset of leukopenia as well as the rapid return of white cells to the bloodstream after
30 arousal (Bouma et al., 2011; Suomalainen and Rosokivi, 1973). The segregation of white cells is also coupled with
31 a reduced production rate of new white cells, probably the consequence of the general decrease in the cell cycle
32 (Szilagyi and Senturia, 1972).
33
34

35 The third question opens a more complex scenario. As a matter of fact, hibernators do not die from infectious
36 diseases during hibernations, with the most relevant exception of the recent epidemic of White Nose Syndrome
37 (WSN) in bats. WSN is caused by a fungus that seems to be able to grow comfortably at the temperature usually
38 reached by bats during hibernation, with devastating consequences for the bats (Foley et al., 2011). Interestingly,
39 bats mostly die from depletion of energy reserves because animals must warm up more often to fight against the
40 fungi which causes the diseases, rather than from the infection itself. Interestingly, European bats seem to be able
41 to organize a more effective immune response against the fungus, balancing the increased energy request of the
42 immune system with the opposite metabolic needs. Apart from the WSN, it does not seem that hibernators are more
43 susceptible to other kinds of infective disease during hibernation. A possible explanation is that, in sensitive organs,
44 such as the lungs or the intestine, an increase in the number of white cells was reported (Inkovaara and Suomalainen,
45 1973), suggesting that some sort of immune barrier is attending these sensitive body regions. Interestingly, an
46 activation of neuroinflammation has also been reported for the Syrian hamster (Cogut et al., 2018). Furthermore,
47 the consequences of this transient immunosuppression could also spread to the period immediately after arousal, if
48 the white cell count is not quickly normalized (Havenstein et al., 2016).
49

50 Beside the white cell count, the overall immune response is blunted during hibernation (Bouma et al., 2013;
51 Jaroslow and Serrell, 1972; Prendergast et al., 2002); it is not clear, at the moment, if this is an effect mediated by
52 temperature or if it is something that happens specifically during torpor/hibernation. Hypothermia has been shown
53 to reduce the immune response also in non-hibernators (Ding et al., 2018; Jiang et al., 2013), but no data regarding
54 inflammation during synthetic torpor are currently available.
55

56 In the case of any hibernation-derived technology to be used in long-term space travel, the degree of
57 immunosuppression would have to be carefully assessed for a potential use in space, limiting the crews's
58 susceptibility to developing possible infective diseases.
59
60
61
62
63
64
65

1
2
3
4
5
6 *Locomotor system*

7 The mass of skeletal muscle is the result of the balance between protein synthesis and protein degradation that
8 is physiologically correlated with the mechanical loading on the muscle (Miyazaki and Esser, 2009). Disuse atrophy
9 of the skeletal muscle is the consequence of the reduced protein synthesis and this, in turn, is consequential to the
10 reduced mechanical load in conditions such as prolonged bed rest (Bodine, 2013). Permanence in microgravity is
11 another condition in which the reduced mechanical load on the locomotor system leads to muscle atrophy and bone
12 demineralization (Demontis et al., 2017). At the moment, there are no effective countermeasures that can prevent
13 this condition, and even the daily routine of physical exercise that astronauts are required to follow on board the
14 ISS is not sufficient to preserve the function of the locomotor system (Hargens et al., 2013).

15
16 During hibernation, seasonal hibernators are often subject to extended periods of muscle inactivity and fasting,
17 but do not experience disuse atrophy (Bertile et al., 2021; Cotton, 2016; Giroud et al., 2010; Ivakine and Cohn,
18 2014). Interestingly, the functionality of the skeletal muscle of the locomotor system is preserved both in small
19 hibernators such as the squirrel, that are able to reach a very low body temperature (Andres-Mateos et al., 2012),
20 and in larger hibernators such as the bear, whose body temperature does not drop below 30°C (Harlow et al., 2001).
21 If the hibernator's skeletal muscle were to lose strength, the survival of the animal would be compromised at the
22 moment of arousal.
23
24

25 The mechanism allowing hibernators to preserve the majority of their muscle strength is not fully known (Tessier
26 and Storey, 2016). In the brown bear, an increase in anabolic intracellular signaling may counteract the rest-
27 stimulated catabolism; moreover, the muscle fibers switch to a slow oxidative phenotype and potentiate
28 mitochondrial biogenesis (Miyazaki et al., 2019), changes that are similar to those observed in squirrels (Xu et al.,
29 2013). Although more research is necessary to fully elucidate the degree of preservation of muscle strength and the
30 underlying molecular mechanism, the preservation of the lean mass that have been observed in these may offer a
31 great improvement of the quality of life of astronauts facing a long permanence in space, once the underlying
32 mechanism will be exploitable.
33
34

35 Bones of astronauts are also subject to a demineralization that requires a longer time on Earth to be compensated
36 for (LeBlanc et al., 2007). Demineralization seems to be non-homogenous through the body segments, occurring to
37 a greater degree in the portions that are more subjected to weight load. Similar to skeletal muscle, multiple reports
38 show that bone structure of hibernators is maintained during hibernation (Doherty et al., 2012; McGee-Lawrence et
39 al., 2011; Utz et al., 2009; Wojda et al., 2016, 2012). Larger hibernators seem to achieve this goal through different
40 and more effective mechanisms than smaller hibernators, since the former do not experience any bone loss (McGee-
41 Lawrence et al., 2008). The molecular mechanisms preventing bone loss in hibernators are not fully known, and the
42 role of the central nervous system may be marginal (Cravens et al., 2020) The endocrine system may play a major
43 role, coordinating calcium metabolism and metabolic request (Doherty et al., 2014; McGee-Lawrence et al., 2008),
44 but specific molecular changes in the metabolism of fatty acid and in the endocannabinoid system in bones during
45 hibernation have been reported (Doherty et al., 2016, 2012).
46
47

48 The integrity of the locomotor system is critical for the human exploration of the solar system. Astronauts will
49 have to be able to spend a long time in microgravity and then be able to operate when reaching the surface of other
50 planets. At the moment, the only countermeasures that are considered are compensatory physical exercise and
51 exposure to artificial gravity. A biological countermeasure to the microgravity-induced muscle atrophy and bone
52 demineralization will extend the ability of humans for space exploration and will also have relevant medical
53 applications; hibernation seems to hold the optimal biological counter measurement to this problem.
54
55
56
57

58 *Response to radiation damage*

59 Cosmic radiation represents an important threat to the health of astronauts during long space flights, and, so far,
60 the only strategy to counteract this threat is the use of passive shielding, a solution that does not provide full
61
62
63
64
65

1
2
3
4 protection from the damage, thus limiting the ability of humans to participate in long-term space exploration
5 (Durante and Cucinotta, 2008). A biological strategy aimed at protecting living tissues from radiation damage can
6 therefore produce a relevant improvement, extending humans' possible time of permanence in space (Baird et al.,
7 2011).
8

9 In light of the biological relevance of such a feature, the resistance to radiation damage found in hibernators was
10 intensively studied a few decades ago (Kuskin et al., 1959; Musacchia and Barr, 1968; Prewitt and Musacchia,
11 1975). Briefly, most of the studies investigated the effects of lethal X or Gamma irradiation on hibernators and
12 showed that hibernators increase their probability of survival for each dose tested during the hibernation period,
13 even though later studies pointed out that the radiation damage may remain silent during hibernation, and express
14 itself after awakening (Sazykina and Kryshev, 2011). This last observation, together with the lack of methods to
15 induce hibernation in non-hibernators, and the lack of a biological explanation of the enhanced (or at least transient)
16 radioresistance, seemed to indicate that hibernation was not a valuable way of improving radioprotection for long-
17 term space flights.
18

19
20 Recently, new data and hypotheses have stirred renewed interest in the topic (Petit et al., 2018). Beside the
21 methods shown to induce a torpor-like state in non-hibernators (Cerri et al., 2013; Tupone et al., 2013; Zakharova
22 et al., 2019), new promising molecular substrates that play a valuable role in cell protection have been identified;
23 these include the family of proteins called "Cold Shock Protein" (CSP) (Lleonart, 2010; Peretti et al., 2015) and the
24 Cystathionine β synthase/Hydrogen sulfide pathway, activated by monoamines such as serotonin and dopamine
25 (Dugbartey et al., 2015; Giroud et al., 2021). Moreover, the reduction in oxygen metabolism during hibernation
26 may well provide additional protection against radiation damage. As far as this latter point is concerned, it is
27 important to notice that differences in the dynamics of awakening may affect the overall health status of the animal
28 (Cerri et al., 2013). Moreover, the studies conducted on Earth on radioresistance in hibernators have so far used X-
29 rays or γ -ray irradiation. No study has yet investigated the radioresistance of hibernators to the charged particle
30 component of cosmic rays, which plays a major role in radiation exposure in interplanetary space (Durante, 2014).
31

32
33 Cosmic rays are composed of a mixture of particles of galactic and solar origin, with high-energy charged
34 particles representing the prevalent component in open space. Galactic cosmic rays and particles emitted by the sun
35 during so-called Solar Particle Events (SPEs) present several issues as far as radiation protection is concerned. For
36 instance, it has been estimated that intense SPEs might expose unshielded astronauts to life-threatening doses of
37 radiation (Kim et al., 2009). In fact, due to the high energy of these particles, it is extremely difficult to set up
38 efficient spacecraft shielding with the current technologies, mainly because of the heavy passive materials that are
39 required. Specifically, protons in the energy range 102-105 MeV give the largest contribution in terms of fluence
40 (about 85%). Heavier ions are also present in a much lower percentage (about 15%), but they contribute to an
41 equivalent dose to that of protons, in view of their enhanced quality factor (Durante and Cucinotta, 2011). Moreover,
42 interaction of cosmic rays with the shielding itself leads to further modifications of the radiation spectra to which
43 astronauts are eventually exposed. Concerning long-term interplanetary travel it might thus be useful to quantify
44 the eventual dose-sparing factor that could be associated with induced torpor (Tommasino and Durante, 2015).
45

46
47 Overall, the understanding of the physiology of hibernation could be very useful to make human exploration of
48 the solar system possible (Cerri et al., 2016; Puspitasari et al., 2021), but could also be exploited to improve the
49 treatment or outcome of numerous clinical conditions (Cerri, 2017a) that are treated with radiation.
50
51
52
53

54 *Aging*

55
56 Aging is a very relevant issue for space exploration. Recent data from NASA suggest that the exposure to space
57 radiation may have curious effects on telomere length (Welsh et al., 2019), raising the issue of how space can affect
58 aging. Because of their connection with metabolic rate, telomeres has been well studied in hibernators (Nowack et
59 al., 2019). Telomeres were shown increase their length during torpor bouts (Turbill et al., 2012), suggesting that
60 the aging process may be slowed down. However, in two species of dormice, telomere's length was shown to
61
62
63
64
65

1
2
3
4 decrease during interbout arousal, possible because of the increased oxidative stress resulting from the increase in
5 mitochondrial respiration (Giroud et al., 2014; Hoelzl et al., 2016a; Turbill et al., 2013). The degree of metabolic
6 activity of tissues plays in fact a role in the dynamics of telomere changes in length (Wilbur et al., 2019). However,
7 and quite surprisingly, adult edible dormice can re-elongate their telomeres during the summer season (Hoelzl et
8 al., 2016b; Turbill et al., 2013), even if this could be a feature specific , although interesting, of the species (Hoelzl
9 et al., 2016b).
10

11
12 How the length of telomeres and the speed of the molecular aging process can impact future space travel is still
13 unknown. For instance, the role of arousals from synthetic torpor has to be carefully assessed, since they could
14 dampen the advantages of torpor by increasing the level of oxidative stress. The research on telomeredynamics
15 opens two key questions for the application in humans. The first one is about at what body temperature humans
16 should be maintained in synthetic torpor. Would a bear-like form of synthetic torpor be more effective than a
17 squirrel-like one? The second question is about the arousals: what are they for? And are they indispensable? The
18 degree of oxidative stress the body will be subjected to during the arousal may be a critical variable to be taken into
19 account to design a correct plane of synthetic torpor, that could maximize the advantages of metabolic suppression,
20 minimizing potential tissue damage.
21
22
23
24
25
26
27

28 **TOWARD HUMAN HIBERNATION**

29 **Evolution**

30
31
32 The evolution of hibernation supports the idea that humans could be able to enter such a state. This very peculiar
33 trait is an ancestral trait, probably present in the proto-mammal, and the proto-mammal is proposed by many to be
34 a heterotherm (Lovegrove, 2017). Protomammals appeared about 150-200 million years ago, carrying with them
35 some interesting new traits. The transition from reptiles to mammals forced the organism of the latter to orchestrate
36 a more complex array of physiological regulation to exploit the considerable advantages of the higher metabolic
37 rate that characterizes mammals. Compared to reptiles, the metabolic rate of mammals is about 7- to 10-fold higher;
38 much of this energy usage is devoted to homeothermy, the ability to maintain the temperature of the body
39 independent from the temperature of the environment. Protomammals were nocturnal animals, probably to avoid
40 predation from the smallest dinosaurs, such as the velociraptor, the miniraptor, or the microraptor, and were able to
41 maintain an optimal working temperature for muscles and the brain, thanks to their higher metabolism. Such high
42 energy usage must have required a continuous search for food during the phase of activity but may also have become
43 sustainable thanks to a drastic reduction in metabolic rate aimed at saving energy during the resting phase. After the
44 extinction of most of the dinosaurs, the risk of predation was very much reduced, providing an advantage for these
45 species, that were able to reproduce rapidly and expand in other ecological niches.
46
47
48

49 Indeed, from the presence of metabolic suppression in the phenotype of the proto-mammals, it can be argued
50 that the gene set needed for surviving such a phenotype may be common among modern mammals. The species
51 that are able to activate some kind of metabolic suppression are indeed non-clustered or confined to a specific order
52 (Melvin and Andrews, 2009), as it would be if torpor was a more recent development. This suggests that humans
53 may also possess such a genomic inheritance, a hypothesis strengthened by the discovery of a hibernating primate
54 (Dausmann et al., 2004).
55
56
57

58 **Cases and history**

59 For a long time the induction of human torpor or human hibernation has been considered some sort of science
60 fiction wishful thinking and a target outside our reach, to be confined to movies and novels (Lee, 2008). It would
61 no doubt be considered one of the greatest discoveries of science, but, looking carefully at medical records, it is
62
63
64
65

1
2
3
4 very interesting to see that human torpor may have already happened in the history of our species. In this regard,
5 we can divide the medical records into three categories: i) cases reported to have survived extreme cold; ii) cases in
6 which deep hypothermia was induced in a medical setting; iii), and cases resembling torpor under many aspects. It
7 is important to stretch out the differences between these three categories, since the beneficial effects of hypothermia
8 in terms of survival do not necessarily uses the same mechanisms of cellular protection of torpor. Nevertheless,
9 patients surviving deep accidental hypothermia or induced into deep hypothermia in hospitals may help hibernation
10 research in understanding the role played by hypothermia during torpor.
11
12

13 14 *Cases reported to have survived extreme cold*

15
16 Today, it is not difficult to find records or reports of people surviving for many hours with no heartbeat in
17 circumstances in which they were exposed to severe cold. From the 17th century is the case of Anne Greene: a lady
18 sentenced to death by hanging in London (Breathnach and Moynihan, 2009), to the much more recent case of of
19 Anna Bågenholm , maybe the most famous case of its kind (Gilbert et al., 2000).
20
21
22

23 24 *Cases of deep hypothermia induced in medical settings*

25
26 In the years between 1938 and 1940, Dr. Tample Fay also experimented with deep hypothermia (Fay, 1959). Dr.
27 Fay is known as “the man who broke the cold barrier” (Alzaga et al., 2006), since he was the first to truly venture
28 into the realm of deep hypothermia, as an innovative treatment for cancer As a result, Dr. Fay suggested that if
29 hypothermia had some protective effect toward cancer, it may also have some therapeutic effects (Wang et al.,
30 2006). Patients affected with multi-metastatic cancer were therefore induced into a deep hypothermia, in a later case
31 even down to 9°C (Niazi and Lewis, 1958). Although the treatment did not cure cancer, all the patients recovered
32 from the treatment with no side effects. Even if the treatment did not work, Dr. Fay’s intuition may have been on
33 the right track: later studies showed that cancer seems to halt its progress during hibernation (Lyman and Fawcett,
34 1954).
35
36
37

38 39 *Cases resembling torpor*

40
41 An earlier interesting report comes from the British Medical Journal of 1900 (“Human hibernation,” 2000). In
42 an anonymous short article with the evocative title “human hibernation”, the story of the small Russian town of
43 Pskov is told. Apparently, during winter, the inhabitants’ of this town gathered together in a large construction in
44 the center of the town where they would “go to sleep” in small cells and sleep the winter off, waking up again in
45 spring. As far as we know, there is no other confirmation of this story, but it is worth mentioning. Another
46 possible case of torpor in humans can be found in a short piece from Oliver Sacks:the story of Uncle Toby (Sacks,
47 2019). Uncle Toby was a patient who, apparently, remain for 7 years in a state of stasis, fed and taken care of by
48 his family, as a consequence of a severe form of hypothyroidism.
49
50

51 An immunological cause was suggested as an explanation for a case reported in 2002 in the journal Neurology
52 (Magnifico et al., 2002). This patient complained of excessive fatigue after a self-reported flu or flu-like syndrome.
53 A 5-day recording of his body temperature showed recurring episodes of morning hypothermia at around 6:00 am,
54 that was in no way different from the daily torpor episode that can be observed in animals such as the hamster
55 during the winter season. It is still unclear what caused such episodes since no clear sign of brain or organ
56 dysfunctions was found.
57

58 Another observation that supports the hypothesis that humans could enter torpor/hibernation is found in the
59 measurements of metabolic rate in human fetuses (Singer, 2004, 1999; Singer and Mühlfeld, 2007). The fetus’
60 metabolism, adjusted for body mass, places it on a different body size-metabolism curve compared to other
61
62
63
64
65

1
2
3
4 mammals, with a greater resemblance to hibernating mammals. Fetuses are exposed to the high body temperature
5 of the mother and to a lower oxygen tension than adults, conditions that could both influence metabolic rate.

6
7 In conclusion, although rare, medical reports are supportive of the possibility that humans could enter
8 torpor/hibernation.
9

10 **INDUCING SYNTHETIC TORPOR**

11
12 Synthetic torpor could be induced in multiple ways (Dirkes et al., 2015), and drastically differs from
13 hypothermia-induced lethargic hypothermia (Popovic, 1960). From recent works (Cerri et al., 2013; Tupone et al.,
14 2013), the most promising approach seems to be the inactivation of the central pathways controlling thermogenesis.
15 These pathways and their relationship with thermoregulation have been examined in detail (Morrison and
16 Nakamura, 2019). In theory, every area in the network could be the target for the induction of Synthetic Torpor.
17
18
19

20 **Exploiting the central thermoregulatory pathway**

21
22 To defend their body temperature, mammals monitor ambient temperature and body temperature (see Figure
23 1 for a schematic drawing of the brain network for temperature regulation). The sensing of the external temperature
24 is located mostly in the skin (Filingeri, 2016). Other districts, such as the respiratory mucosae (Cruz and Toghias,
25 2008), or the oral cavity (Lemon, 2017), may be able to detect temperature, but their role has not yet been extensively
26 studied. From the skin, two separate sensorial pathways arise: one for cold sensing (Nakamura and Morrison, 2008),
27 and the other for warm sensing (Nakamura and Morrison, 2010). Most of the receptors involved in temperature
28 sensing are part of the Transient Receptor Potential (TRP) channel family (Wang and Siemens, 2015). TRPM8, for
29 instance, is an important cold receptor, activated by the natural agonist menthol (Babes et al., 2010); TRPV1, on
30 the other hand, is an important warm receptor, activated by the natural agonist capsaicin (Szolcsányi, 2015). Both
31 warm and cold information is relayed in the Parabrachial Nucleus (PBN), located in the brainstem, in two distinct
32 portions of the nucleus itself. Cold afferences are relayed in the External Lateral PBN whereas warm afferences are
33 relayed in the Dorsal Lateral PBN (Madden and Morrison, 2019). Although it seems critical, the role of skin
34 temperature information in modulating the central control of body temperature is still under discussion
35 (Romanovsky, 2014), since is not clear how environmental temperature is computed in the central thermoregulatory
36 areas (Berner and Heller, 1998).
37
38
39
40
41

42 The brain has another temperature sensitive area located in the Preoptic Area (POA) (Conti, 2018). The receptors
43 responsible for such sensing are not fully known (Siemens and Kamm, 2018), but the existence of warm sensitive
44 neurons and cold sensitive neurons have been proven multiple times (Alam et al., 1995; Parmeggiani et al., 1987).
45 The classic view on the dynamics of temperature control was based on the idea of a set point, probably inspired by
46 the early work of Norbert Wiener of Cybernetics (Wiener, 1948). The brain was thought to read its own temperature,
47 compare it with a temperature of reference, and activate the necessary line of defense: heat production or heat
48 dissipation. This view was challenged, and a more recent interpretation of the general mechanism for the
49 preservation of body temperature is based on the idea of open-loop, in which every thermal effector acts
50 independently from the others, based on different thresholds of activation (Romanovsky, 2007). In this latter case,
51 body temperature would not be encoded in the brain, but would be the result of the independent activation of
52 multiple circuits controlling each single effector. Therefore, thermal information is transmitted from the peripheral
53 temperature sensing nerves and reaches the POA, which is considered the master thermoregulatory area. From here,
54 a descending output is thought to reach the DMH and, from here the key relay area of the RPa.
55
56
57
58

59 DMH neurons are involved in multiple aspects of thermoregulation, mediating the preoptic-to-raphé connection
60 controlling cold defense (DiMicco and Zaretsky, 2007), but are probably also involved in the control of torpor
61
62
63
64
65

1
2
3
4 (Hitrec et al., 2019). DMH may also be involved in behavioral thermoregulation and cold-seeking behavior
5 (Almeida et al., 2006).

6
7 The RPa is the final key relay that controls the sympathetic outflow to the thermoregulatory organs. This region
8 is connected to the brown (Cano et al., 2003) and white adipose tissue (Nguyen et al., 2014), to the heart (Standish
9 et al., 1995), to the skeletal muscle (Billig et al., 2001), to the liver (Kalsbeek et al., 2004; Ter Horst et al., 1993),
10 to the thyroid (Kalsbeek et al., 2000), to the adrenergic cells in the adrenal gland (Morrison and Cao, 2000), to the
11 bones (Dénes et al., 2005), to the bone marrow (Dénes et al., 2005), and to the kidney (Huang and Weiss, 1999).
12 Functionally, RPa neurons control brown adipose tissue (Morrison et al., 1999), shivering (Nakamura and Morrison,
13 2011), and cutaneous blood vessels (Cerri et al., 2010; Meyer et al., 2017).

14
15
16 This main circuit, going from the PBN to the RPa is modulated by many other brain regions, that can amplify or
17 reduced the central outflow to the thermal effectors. For instance, an area such as the Suprachiasmatic Nucleus
18 (SCN) receives the retinal information that maintains the circadian oscillation of body temperature, even if non-
19 SCN projecting retinal ganglion cells have recently been reported to play a role (Rupp et al., 2019); the orexinergic
20 neurons in the Lateral Hypothalamus may drive the necessary increase in temperature and metabolic rate that the
21 state of arousal requires (Cerri et al., 2014), and may also be linked to thermogenesis (Tupone et al., 2011), although
22 may be not involved in torpor (Lo Martire et al., 2020); the Nucleus of the Solitary Tract (NTS) may convey
23 information regarding the amount of oxygen available in the bloodstream (Madden et al., 2017). The activity of this
24 central circuit could be modulated in many ways to induce states resembling torpor, since it has been shown that
25 the direction of the changes in body temperature in response to changes in ambient temperature can even be reversed
26 (Tupone et al., 2017).

31 32 **Effective procedures inducing synthetic torpor through the manipulation of the thermoregulatory network**

33 34 *Inhibition of neurons within the RPa*

35 The RPa plays a key role in controlling body temperature. As far as we currently know, there are no pathways
36 from other regions of the brain that bypass the RPa in conveying information to the rest of the body. The RPa is
37 therefore an obligatory relay that reverberates the commands from the higher center to the sympathetic
38 preganglionic neurons within the Lateral Horn of the spinal cords. The activation of neurons within the RPa, by
39 excitation or disinhibition, leads to an increase in thermogenesis (Morrison et al., 1999) and to a reduction in heat
40 dissipation (Cerri et al., 2010). At thermoneutrality, RPa neurons are tonically active, providing a basic drive to the
41 preservation of body temperature (Cerri et al., 2010; Zaretsky et al., 2003). Inhibiting these neurons leads to a
42 transitory reduction in body temperature and an increase in heat dissipation. It is therefore reasonable that, to enter
43 torpor, the activity of RPa neurons must be switched off (Frare et al., 2018; Hitrec et al., 2019).

44
45 Prolonged inhibition of neurons within the RPa was shown to induce a deep hypothermic state resembling natural
46 torpor as regards many features (Cerri et al., 2013). RPa neurons are key in controlling the general metabolic state
47 of the body, and any method of central induction of Synthetic Torpor will, directly or indirectly, affect these neurons.

48
49 RPa inhibition requires a neurosurgical approach. The procedure, by itself, now has the potential to be very
50 straightforward in humans. The use of frameless stereotaxic technology together with virtual neuronavigation would
51 allow a neurosurgeon to carry out the entire procedure in a short time. This would make this technology usable as
52 an “elective procedure” in clinical settings, but its use in emergency conditions would have to be evaluated.

53 54 55 56 57 *Adenosine A1 receptor activation*

58 A1R activation by N6-cyclohexyladenosine (CHA) was shown to induce a deep hypothermic state in rats
59 (Shimaoka et al., 2018; Tupone et al., 2013), and the target region seems to be the NTS. The activation of NTS
60 neurons was shown to inhibit brown adipose tissue thermogenesis (Madden and Morrison, 2005), thus making them
61
62
63
64
65

1
2
3
4 a sensitive target for the induction of hypothermia. The physiology of adenosine-induced synthetic torpor appears
5 slightly different from that observed in regular hibernators (Swoap et al., 2007). Considering that the site of action
6 of CHA was shown to be the NTS, it is possible that CHA activates the diving reflex (Hult et al., 2019; Silvani et
7 al., 2018), a still effective way to reduce oxygen consumption, but with different cardiovascular features. However,
8 adenosine has been shown to be involved in the regulation of hibernation (Drew et al., 2017; Frare et al., 2019);
9 consequently, the actual mechanisms of action are yet to be understood in detail.

10
11 The use of systemic CHA has been coupled with temperature target management (Bailey et al., 2017), and with
12 the use of an adenosine receptor antagonist (Jinka et al., 2015), to counteract the intrasubject difference in CHA
13 response and to reduce the cardiovascular side effects, so far with encouraging results.
14
15
16
17

18 **Further potential approach to synthetic torpor**

19 *Inhibition of skin cold receptors*

20
21 To prevent body temperature from dropping, skin cold receptors activate thermogenesis when the core body
22 temperature is still within a normal range. A pharmacological blockade of their activity may cause the activation of
23 thermogenesis to be prevented, inducing a reduction in body temperature (Feketa and Marrelli, 2015). Among the
24 most relevant cold receptors, TRPM8 seems to play a major role (Babes et al., 2010), and the use of a TRPM8
25 antagonist is effective in inducing a state of moderate hypothermia in rodents (Almeida et al., 2012). Considering
26 that the exposure to a warm temperature also promotes a reduction in metabolic rate and thermogenesis (Grimpo et
27 al., 2013), combining the inhibition of cold sensing with the activation of warm receptors may be a useful synergic
28 combination.
29
30
31
32
33

34 *Exploitation of the skin temperature afference*

35 The PBN receives the thermal information from the skin in two separate regions for cold (Nakamura and
36 Morrison, 2008) and for warmth (Nakamura and Morrison, 2010). Neurons within the lateral PBN have been shown
37 to have intrinsic thermosensitivity (Xu et al., 2019; Xue et al., 2016) and a genetic fingerprint (Geerling et al., 2016),
38 representing a possible new target for the induction of a state of synthetic torpor. Since seasonal hibernators maintain
39 their body temperature well above the temperature of the hibernaculum (Lee et al., 2009), animals in hibernation
40 seem to preserve thermoregulation (Florant and Heller, 1977). Such a response seems to be mainly caused by
41 activation of a central command (Heller and Colliver, 1974; Williams and Heath, 1971), so it is not clear whether
42 the PBN thermosensitive neurons could play a role. Nevertheless, a drug acting selectively on these neurons may
43 be able to induce a safe state of hypothermia.
44
45
46
47

48 *Exploitation of Hypothalamic thermosensitivity*

49 Warm and cold sensitive neurons within the POA of the hypothalamus play the role of the conductor in
50 commanding the orchestra of thermal effectors (Amici et al., 2014; Tabarean, 2018; Tan et al., 2016). Their intrinsic
51 thermal sensitivity can be a target for the modulation of the central thermoregulatory drive. The molecular
52 mechanisms driving intrinsic thermosensitivity are not yet completely known. It has been suggested that changes
53 in ionic current are responsible for thermosensitivity (Boulant, 1998; Griffin et al., 1996), but much is still to be
54 understood (Zhao and Boulant, 2005). Pharmacological activation of different opioid receptors have been shown to
55 modulate the degree of thermal sensitivity in POA neurons in slices (Xin and Blatteis, 1992; Yakimova et al., 1998,
56 1996), and to induce hypothermia in rats (Yakimova and Pierau, 1999). On these bases, it is indeed interesting that
57 naloxone can arouse the hamster from torpor (Margules et al., 1979), since endogenous opioid has been reported to
58
59
60
61
62
63
64
65

1
2
3
4 play a key role in regulating hibernation (Beckman and Lladós-Eckman, 1985; Cui et al., 1993; Oeltgen et al., 1982;
5 Tamura et al., 2012).

6
7 An interesting physiological state characterized by the loss of the intrinsic thermosensitivity of the POA warm
8 and cold sensitive neurons is REM (Parmeggiani, 1986). Cooling of the POA during REM sleep fails to induce the
9 increase in metabolic rate observed when the same stimulation is applied during wakefulness or NREM sleep
10 (Glotzbach and Heller, 1976). Direct recording of POA temperature-sensitive neurons during sleep confirms the
11 loss of thermosensitivity (Alam et al., 1995; Glotzbach and Craig Heller, 1984; Parmeggiani et al., 1987).
12 Interestingly, hypothermia is not observed during REM sleep, a state that is, on the contrary, characterized by an
13 increase in brain temperature (Parmeggiani, 2007); nevertheless, this peculiar lack of central thermosensitivity may
14 be an interesting model for synthetic torpor research, since it also appears to be specific to thermoregulation and
15 not in place for other types of physiological regulation (Luppi et al., 2010). The POA has also been shown to
16 participate in the hypothermic effect of other drugs, such as lithium (Jones et al., 2008).

17
18 NREM sleep also has a reciprocal relationship with thermoregulation (Harding et al., 2019; Szymusiak, 2018).
19 Preoptic neurons, in fact, mediate the heat loss that characterizes NREM sleep (Harding et al., 2018; Kroeger et al.,
20 2018; Zhao et al., 2017). NREM sleep was proposed to be a “small torpor”, since it shares many features with torpor
21 (Silvani et al., 2018).

22
23 Within the hypothalamus, the SCN is the master clock of the organism, dictating the circadian oscillation in
24 body temperature (Saper et al., 2005). SCN neurons were also shown to be intrinsically thermosensitive (Burgoon
25 and Boulant, 2001), making them a possible target for body temperature regulation. The direct input that from the
26 retina hits the SCN neurons could open possibilities for some kind of enhanced light therapy (Rupp et al., 2019).

27
28 Interestingly, a change in central thermal sensitivity may be something that could justify the change in thermal
29 balance experienced even at rest by astronauts, something called “space fever”. An increase in body temperature in
30 astronauts was in fact described during both short (Dijk et al., 2001; Gundel et al., 1997, 1993) and long missions
31 (Stahn et al., 2017). To explain this effect, two hypotheses may be put forward. The first is based on the reduced
32 efficiency of heat loss mechanisms through evaporation and convection (Fortney et al., 1998; Polyakov et al., 2001).
33 This could explain the yet-unexplained systemic vasodilation described in astronauts (Norsk et al., 2015). The
34 second one is based on the idea that the central thresholds for warm defense may be lowered by permanence in
35 space, an effect possibly mediated by inflammatory cytokines (Stahn et al., 2017). This last hypothesis may also
36 explain the fact that body temperature was reported to be elevated even after the return to Earth (Stahn et al., 2017).
37 Sleep deprivation, and fragmentation, often occurring in space (Dijk et al., 2001; Gundel et al., 1997, 1993) may
38 also contribute to the increase in body temperature (Vishwakarma et al., 2020).

44 45 *Exploitation of the mechanism of Motion sickness*

46
47 A peculiar condition that may affect thermoregulation by inducing hypothermia is motion sickness (Nalivaiko,
48 2018). The mechanism behind the kinetosis-induced hypothermia is not yet known. An increase in thermal
49 dissipation was reported as a possible cause (Del Vecchio et al., 2014; Ngampramuan et al., 2014). Since kinetosis
50 is an almost physiological state, it is an interesting model of study that could unlock new interesting pharmacological
51 targets. For instance, endocannabinoids, besides being involved in the modulation of phenotype during hibernation
52 (Mulawa et al., 2018), were shown to play a role in the appearance of motion sickness in people on parabolic flight,
53 where a significant decrease in the blood levels of anandamide characterized subjects with motion sickness
54 compared with subjects who did not experience it (Choukèr et al., 2010; Strewe et al., 2012). Although a reduced
55 activity of the endocannabinoid system may be related with the appearance of motion sickness, hypothermia belongs
56 to the classic tetrad of effects of molecules with cannabinoids property (Lynes et al., 2019; Metna- Laurent et al.,
57 2017). The cannabinoids receptor CB1 seems to be the one involved in the thermal effects of cannabinoids (Metna-
58 Laurent et al., 2017), although recent evidence may also suggest the involvement of other mechanism (Gamage et
59
60
61
62
63
64
65

1
2
3
4 al., 2020). Whether the thermoregulatory effects of cannabinoids are mediated by the central nervous system, by
5 other organs, or by both is still unclear (Boon et al., 2014; Cardinal et al., 2015, 2012; De Azua et al., 2017; Pertwee
6 et al., 1991; Quarta et al., 2010).

7
8 Beside anatomical targets, nutrition may also open the way to facilitating synthetic torpor, since it plays a
9 relevant role in naturally-occurring torpor (Ruf and Arnold, 2008), and also in sleep regulation (Luppi et al. 2014).
10 Hibernators were in fact shown to favor some n-6 polyunsaturated fatty acids (PUFA), and in particular the linoleic
11 acid (Giroud et al., 2013), together with a selective mobilization and utilization of lipid (Giroud et al., 2019).
12 Interestingly, while n-6 PUFA enhance torpor expression, the opposite was shown with n-3 PUFA, (Vuarin et al.,
13 2016). Among the n-6 PUFA, linoleic acid may play a very relevant role. The amount of this fatty acid in the cell
14 membranes can be a relevant factor in determining the degree of the decrease in body temperature during torpor,
15 since it may help maintaining the functionality of the SERCA pump in the heart at low temperature. (Giroud et al.,
16 2018b, 2013). Moreover, since PUFA work as precursors of the eicosanoids, they could affect the inflammatory
17 status during hibernation (Giroud et al., 2018a). All this evidence point to a relevant role of nutritional status in
18 modulating the phenotype of torpor, a role that needs to be evaluated carefully. At present, no study has investigated
19 whether PUFA promote an increase in safety during synthetic torpor, but future studies on this matter are necessary
20 to evaluate the potential use of diet supplements in such condition.
21
22
23
24
25
26
27

28 **TESTING HIBERNATION “IN THE FIELD”: THE ROLE OF THE INTERNATIONAL SPACE** 29 **STATION** 30

31
32
33 The main approaches that could be used to induce synthetic torpor in non-hibernators have been described above,
34 but a comprehensive description of all the possible compounds goes beyond the scope of this article. Research into
35 other mechanisms, and other drugs (Jones et al., 2008), may provide further insights. The multiple methods that
36 are being tested and the growing interest in this topic provide a reasonably optimistic hope that a synthetic torpor
37 technology will be available in the next few decades. This is especially true considering that hibernation research
38 for space applications is at a stage in which it will greatly benefit from the opportunity to run experiments “in the
39 field”. To this aim, we propose hosting a few seasonal hibernators housed in a dedicated cage on board the ISS for
40 several months. The cage will have to be fully automated, in terms of providing the animals with the most
41 comfortable environment to enter hibernation, and in terms of monitoring animals’ physiological parameters (such
42 as oxygen consumption, infrared emissions, motor activity, and more). A similar device was already designed and
43 used in recent years, and could be the base for the construction of un updated model. (Cancedda et al., 2012)The
44 state of the animals after returning to Earth will provide an enormous and critical amount of information that will
45 be precious in developing countermeasures to two of the more severe effects of long-term performance in
46 microgravity: muscle weakness and radiation damage. Besides animal studies, the ISS is also a key location to
47 investigate many physiological correlates of torpor. For instance, the mechanism of space fever is still unknown,
48 and a clear understanding of the impact that microgravity and radiation have on both autonomic and behavioral
49 thermoregulation will be necessary before venturing into synthetic torpor territory. This will also require the
50 development of new and reliable ways to measure body temperature in different districts of the body (Gunga et al.,
51 2008; Opatz et al., 2013).

52
53
54
55
56 The evaluation of the endocrine response should also be another important field of investigation. How the stress
57 of isolation can affect the response of astronauts to microgravity and its interplay with neuroendocrine systems
58 potentially involved in torpor, such as the endocannabinoid system, should be objects of dedicated experiments.
59 Experiments conducted on Earth already shown how relevant this factor is (Feuerecker et al., 2019; Strewé et al.,
60 2018), but little we know on the effect that a prolonged state of hypometabolism may have on the stress response.
61
62
63
64
65

1
2
3
4 The use of the ISS as an experimental station for torpor research may also face some problems. The number of
5 experiments that would need to be planned and organized is high, and many of them would interplay with each
6 other. Many experts in many different fields of science are also necessary to tackle the issue effectively, without
7 wasting precious time and resources in isolated experiments with no long-term vision. We feel that, aside
8 competitive grant, the creation of a governments funded division, or, even better, of a dedicated institute, that could
9 group and coordinate all the excellent scientists who are already working in the field, would be a necessary step
10 towards the ambitious goal of synthetic torpor exploitation. Such an entity could effectively interact with the private
11 sector to develop the necessary technology, gather specialists from other fields when needed, and be a pivot to
12 accelerate the rate of discovery in the field, paving the way to an effective colonization of space.
13
14

15 16 **Acknowledgement**

17
18
19 The authors Ms. Melissa Stott for reviewing the English.
20

21 **Funding**

22
23
24 Funding: This work was supported by the European Space Agency [Research agreement collaboration
25 4000123556].
26
27

28 **References**

- 29
30
31
32 Alam, M.N., McGinty, D., Szymusiak, R., 1995. Neuronal discharge of preoptic/anterior hypothalamic
33 thermosensitive neurons: Relation to NREM sleep. *Am. J. Physiol. - Regul. Integr. Comp. Physiol.* 269.
34 <https://doi.org/10.1152/ajpregu.1995.269.5.r1240>
35 Almeida, C.M., Hew-Butler, T., Soriano, R.N., Rao, S., Wang, W., Wang, J., Tamayo, N., Oliveira, D.L., Nucci,
36 T.B., Aryal, P., Garami, A., Bautista, D., Gavva, N.R., Romanovsky, A.A., 2012. Pharmacological blockade
37 of the cold receptor TRPM8 attenuates autonomic and behavioral cold defenses and decreases deep body
38 temperature. *J. Neurosci.* 32, 2086–2099. <https://doi.org/10.1523/JNEUROSCI.5606-11.2012>
39 Almeida, M.C., Steiner, A.A., Branco, L.G.S., Romanovsky, A.A., 2006. Neural substrate of cold-seeking
40 behavior in endotoxin shock. *PLoS One* 1, e1. <https://doi.org/10.1371/journal.pone.0000001>
41 Alzaga, A.G., Salazar, G.A., Varon, J., 2006. Breaking the thermal barrier: Dr. Temple Fay. *Resuscitation.*
42 <https://doi.org/10.1016/j.resuscitation.2006.02.014>
43 Amici, R., Bastianini, S., Berteotti, C., Cerri, M., Del Vecchio, F., Lo Martire, V., Luppi, M., Perez, E., Silvani,
44 A., Zamboni, G., Zoccoli, G., 2014. Sleep and bodily functions: The physiological interplay between body
45 homeostasis and sleep homeostasis. *Arch. Ital. Biol.* 152, 66–78. <https://doi.org/10.12871/000298292014232>
46 Andres-Mateos, E., Mejias, R., Soleimani, A., Lin, B.M., Burks, T.N., Marx, R., Lin, B., Zellars, R.C., Zhang, Y.,
47 Huso, D.L., Marr, T.G., Leinwand, L.A., Merriman, D.K., Cohn, R.D., 2012. Impaired Skeletal Muscle
48 Regeneration in the Absence of Fibrosis during Hibernation in 13-Lined Ground Squirrels. *PLoS One* 7.
49 <https://doi.org/10.1371/journal.pone.0048884>
50 Arendt, T., Bullmann, T., 2013. Neuronal plasticity in hibernation and the proposed role of the microtubule-
51 associated protein tau as a “master switch” regulating synaptic gain in neuronal networks. *Am. J. Physiol.*
52 *Regul. Integr. Comp. Physiol.* 305, R478-89. <https://doi.org/10.1152/ajpregu.00117.2013>
53 Arendt, T., Stieler, J., Holzer, M., 2015. Brain hypometabolism triggers PHF-like phosphorylation of tau, a major
54 hallmark of Alzheimer’s disease pathology. *J. Neural Transm.* <https://doi.org/10.1007/s00702-014-1342-8>
55 Babes, A., Cristian Ciobanu, A., Neacsu, C., Babes, R.-M., 2010. TRPM8, a Sensor for Mild Cooling in
56 Mammalian Sensory Nerve Endings. *Curr. Pharm. Biotechnol.* 12, 78–88.
57 <https://doi.org/10.2174/138920111793937835>
58 Bailey, I.R., Laughlin, B., Moore, L.A., Bogren, L.K., Barati, Z., Drew, K.L., 2017. Optimization of thermolytic
59
60
61
62
63
64
65

- 1
2
3
4 response to $\alpha 1$ adenosine receptor agonists in rats. *J. Pharmacol. Exp. Ther.* 362, 424–430.
5 <https://doi.org/10.1124/jpet.117.241315>
- 6 Baird, B.J., Dickey, J.S., Nakamura, A.J., Redon, C.E., Parekh, P., Griko, Y. V, Aziz, K., Georgakilas, A.G.,
7 Bonner, W.M., Martin, O.A., 2011. Hypothermia postpones DNA damage repair in irradiated cells and
8 protects against cell killing. *Mutat. Res.* 711, 142–9. <https://doi.org/10.1016/j.mrfmmm.2010.12.006>
- 9 Barnes, B.M., 1989. Freeze avoidance in a mammal: Body temperatures below 0°C in an arctic hibernator.
10 *Science* (80-). 244, 1593–1595. <https://doi.org/10.1126/science.2740905>
- 11 Beckman, A.L., Lladós-Eckman, C., 1985. Antagonism of brain opioid peptide action reduces hibernation bout
12 duration. *Brain Res.* 328, 201–205. [https://doi.org/10.1016/0006-8993\(85\)91030-3](https://doi.org/10.1016/0006-8993(85)91030-3)
- 13 Berner, N.J., Heller, H.C., 1998. Does the preoptic anterior hypothalamus receive thermoafferent information?
14 *Am. J. Physiol. - Regul. Integr. Comp. Physiol.* 274. <https://doi.org/10.1152/ajpregu.1998.274.1.r9>
- 15 Bertile, F., Habold, C., Le Maho, Y., Giroud, S., 2021. Body Protein Sparing in Hibernators: A Source for
16 Biomedical Innovation. *Front. Physiol.* <https://doi.org/10.3389/fphys.2021.634953>
- 17 Billig, I., Hartge, K., Card, J.P., Yates, B.J., 2001. Transneuronal tracing of neural pathways controlling
18 abdominal musculature in the ferret. *Brain Res.* 912, 24–32. [https://doi.org/10.1016/s0006-8993\(01\)02597-5](https://doi.org/10.1016/s0006-8993(01)02597-5)
- 19 Blanco, M.B., Dausmann, K.H., Faherty, S.L., Klopfer, P., Krystal, A.D., Schopler, R., Yoder, A.D., 2016.
20 Hibernation in a primate: Does sleep occur? *R. Soc. Open Sci.* 3. <https://doi.org/10.1098/rsos.160282>
- 21 Bodine, S.C., 2013. Disuse-induced muscle wasting. *Int. J. Biochem. Cell Biol.*
22 <https://doi.org/10.1016/j.biocel.2013.06.011>
- 23 Boon, M.R., Kooijman, S., Van Dam, A.D., Pelgrom, L.R., Berbée, J.F.P., Visseren, C.A.R., Van Aggele, R.C.,
24 Van Den Hoek, A.M., Sips, H.C.M., Lombès, M., Havekes, L.M., Tamsma, J.T., Guigas, B., Meijer, O.C.,
25 Jukema, J.W., Rensen, P.C.N., 2014. Peripheral cannabinoid 1 receptor blockade activates brown adipose
26 tissue and diminishes dyslipidemia and obesity. *FASEB J.* 28, 5361–5375. <https://doi.org/10.1096/fj.13-247643>
- 27 Boulant, J.A., 1998. Hypothalamic neurons: Mechanisms of sensitivity to temperature, in: *Annals of the New*
28 *York Academy of Sciences.* New York Academy of Sciences, pp. 108–115. <https://doi.org/10.1111/j.1749-6632.1998.tb08319.x>
- 29 Bouma, H.R., Carey, H. V., Kroese, F.G.M., 2010a. Hibernation: the immune system at rest? *J. Leukoc. Biol.* 88,
30 619–624. <https://doi.org/10.1189/jlb.0310174>
- 31 Bouma, H.R., Henning, R.H., Kroese, F.G.M., Carey, H. V., 2013. Hibernation is associated with depression of T-
32 cell independent humoral immune responses in the 13-lined ground squirrel. *Dev. Comp. Immunol.* 39, 154–
33 160. <https://doi.org/10.1016/j.dci.2012.11.004>
- 34 Bouma, H.R., Kroese, F.G.M., Kok, J.W., Talaei, F., Boerema, A.S., Herwig, A., Draghiciu, O., Van Buiten, A.,
35 Epema, A.H., Van Dam, A., Strijkstra, A.M., Henning, R.H., 2011. Low body temperature governs the
36 decline of circulating lymphocytes during hibernation through sphingosine-1-phosphate. *Proc. Natl. Acad. Sci. U. S. A.* 108, 2052–2057. <https://doi.org/10.1073/pnas.1008823108>
- 37 Bouma, H.R., Strijkstra, A.M., Boerema, A.S., Deelman, L.E., Epema, A.H., Hut, R.A., Kroese, F.G.M., Henning,
38 R.H., 2010b. Blood cell dynamics during hibernation in the European Ground Squirrel. *Vet. Immunol. Immunopathol.* 136, 319–323. <https://doi.org/10.1016/j.vetimm.2010.03.016>
- 39 Breathnach, C.S., Moynihan, J.B., 2009. Intensive care 1650: The revival of Anne Greene (c. 1628–59). *J. Med. Biogr.* 17, 35–38. <https://doi.org/10.1258/jmb.2007.007041>
- 40 Burgoon, P.W., Boulant, J.A., 2001. Temperature-sensitive properties of rat suprachiasmatic nucleus neurons.
41 *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 281, R706-15.
42 <https://doi.org/10.1152/ajpregu.2001.281.3.R706>
- 43 Cancedda, R., Liu, Y., Ruggiu, A., Tavella, S., Biticchi, R., Santucci, D., Schwartz, S., Ciparelli, P., Falcetti, G.,
44 Tenconi, C., Cotronei, V., Pignataro, S., 2012. The mice drawer system (MDS) experiment and the space
45 endurance record-breaking mice. *PLoS One* 7. <https://doi.org/10.1371/journal.pone.0032243>
- 46 Cano, G., Passerin, A.M., Schiltz, J.C., Card, J.P., Morrison, S.F., Sved, A.F., 2003. Anatomical substrates for the
47 central control of sympathetic outflow to interscapular adipose tissue during cold exposure. *J. Comp. Neurol.*
48 460, 303–26. <https://doi.org/10.1002/cne.10643>
- 49 Capitani, P., Cerri, M., Amici, R., Baracchi, F., Jones, C.A., Luppi, M., Perez, E., Parmeggiani, P.L., Zamboni,
50 G., 2005. Changes in EEG activity and hypothalamic temperature as indices for non-REM sleep to REM
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

- 1
2
3
4 sleep transitions. *Neurosci. Lett.* 383, 182–187. <https://doi.org/10.1016/j.neulet.2005.04.009>
- 5 Cardinal, P., Bellocchio, L., Clark, S., Cannich, A., Klugmann, M., Lutz, B., Marsicano, G., Cota, D., 2012.
6 Hypothalamic CB1 cannabinoid receptors regulate energy balance in mice. *Endocrinology* 153, 4136–4143.
7 <https://doi.org/10.1210/en.2012-1405>
- 8 Cardinal, P., Bellocchio, L., Guzmán-Quevedo, O., André, C., Clark, S., Elie, M., Leste-Lasserre, T., Gonzales,
9 D., Cannich, A., Marsicano, G., Cota, D., 2015. Cannabinoid Type 1 (CB1) Receptors on Sim1-Expressing
10 Neurons Regulate Energy Expenditure in Male Mice. *Endocrinology* 156, 411–418.
11 <https://doi.org/10.1210/en.2014-1437>
- 12 Carey, H. V., Assadi-Porter, F.M., 2017. The Hibernator Microbiome: Host-Bacterial Interactions in an Extreme
13 Nutritional Symbiosis. *Annu. Rev. Nutr.* 37, 477–500. <https://doi.org/10.1146/annurev-nutr-071816-064740>
- 14 Carey, H. V., Pike, A.C., Weber, C.R., Turner, J.R., Visser, A., Beijer-Liefers, S.C., Bouma, H.R., Kroese,
15 F.G.M., 2012. Impact of Hibernation on Gut Microbiota and Intestinal Barrier Function in Ground Squirrels,
16 in: *Living in a Seasonal World*. Springer Berlin Heidelberg, pp. 281–291. https://doi.org/10.1007/978-3-642-28678-0_25
- 17 Carey, H. V., Walters, W.A., Knight, R., 2013. Seasonal restructuring of the ground squirrel gut microbiota over
18 the annual hibernation cycle. *Am. J. Physiol. - Regul. Integr. Comp. Physiol.*
19 <https://doi.org/10.1152/ajpregu.00387.2012>
- 20 Carey, H. V., 1990. Seasonal changes in mucosal structure and function in ground squirrel intestine. *Am. J.*
21 *Physiol. - Regul. Integr. Comp. Physiol.* 259. <https://doi.org/10.1152/ajpregu.1990.259.2.r385>
- 22 Cerri, M., 2017a. The Central Control of Energy Expenditure: Exploiting Torpor for Medical Applications. *Annu.*
23 *Rev. Physiol.* 79, 167–186. <https://doi.org/10.1146/annurev-physiol-022516-034133>
- 24 Cerri, M., 2017b. Consciousness in hibernation and synthetic torpor. *J. Integr. Neurosci.* 16, S19–S26.
25 <https://doi.org/10.3233/JIN-170063>
- 26 Cerri, M., Del Vecchio, F., Mastrotto, M., Luppi, M., Martelli, D., Perez, E., Tupone, D., Zamboni, G., Amici, R.,
27 2014. Enhanced slow-wave EEG activity and thermoregulatory impairment following the inhibition of the
28 lateral hypothalamus in the rat. *PLoS One* 9, e112849. <https://doi.org/10.1371/journal.pone.0112849>
- 29 Cerri, M., Luppi, M., Tupone, D., Zamboni, G., Amici, R., 2017. REM sleep and endothermy: Potential sites and
30 mechanism of a reciprocal interference. *Front. Physiol.* <https://doi.org/10.3389/fphys.2017.00624>
- 31 Cerri, M., Mastrotto, M., Tupone, D., Martelli, D., Luppi, M., Perez, E., Zamboni, G., Amici, R., 2013. The
32 inhibition of neurons in the central nervous pathways for thermoregulatory cold defense induces a suspended
33 animation state in the rat. *J. Neurosci.* 33, 2984–93. <https://doi.org/10.1523/JNEUROSCI.3596-12.2013>
- 34 Cerri, M., Tinganelli, W., Negrini, M., Helm, A., Scifoni, E., Tommasino, F., Sioli, M., Zoccoli, A., Durante, M.,
35 2016. Hibernation for space travel: Impact on radioprotection. *Life Sci. Sp. Res.*
36 <https://doi.org/10.1016/j.lssr.2016.09.001>
- 37 Cerri, M., Zamboni, G., Tupone, D., Dentico, D., Luppi, M., Martelli, D., Perez, E., Amici, R., 2010. Cutaneous
38 vasodilation elicited by disinhibition of the caudal portion of the rostral ventromedial medulla of the free-
39 behaving rat. *Neuroscience* 165, 984–95. <https://doi.org/10.1016/j.neuroscience.2009.10.068>
- 40 Chiocchetti, R., Hitrec, T., Giancola, F., Sadeghinezhad, J., Squarcio, F., Galiazzo, G., Piscitiello, E., De Silva,
41 M., Cerri, M., Amici, R., Luppi, M., 2021. Phosphorylated Tau protein in the myenteric plexus of the ileum
42 and colon of normothermic rats and during synthetic torpor. *Cell Tissue Res.* <https://doi.org/10.1007/s00441-020-03328-0>
- 43 Choukèr, A., Bereiter-Hahn, J., Singer, D., Heldmaier, G., 2019. Hibernating astronauts—science or fiction?
44 *Pflugers Arch. Eur. J. Physiol.* <https://doi.org/10.1007/s00424-018-2244-7>
- 45 Choukèr, A., Kaufmann, I., Kreth, S., Hauer, D., Feurecker, M., Thieme, D., Vogeser, M., Thiel, M., Schelling,
46 G., 2010. Motion sickness, stress and the endocannabinoid system. *PLoS One* 5.
47 <https://doi.org/10.1371/journal.pone.0010752>
- 48 Cogut, V., Bruintjes, J.J., Eggen, B.J.L., van der Zee, E.A., Henning, R.H., 2018. Brain inflammatory cytokines
49 and microglia morphology changes throughout hibernation phases in Syrian hamster. *Brain. Behav. Immun.*
50 68, 17–22. <https://doi.org/10.1016/j.bbi.2017.10.009>
- 51 Conti, B., 2018. Molecular basis of central thermosensation, in: *Handbook of Clinical Neurology*. Elsevier B.V.,
52 pp. 129–133. <https://doi.org/10.1016/B978-0-444-63912-7.00008-4>
- 53 Cotton, C.J., 2016. Skeletal muscle mass and composition during mammalian hibernation. *J. Exp. Biol.* 219, 226–
54
55
56
57
58
59
60
61
62
63
64
65

- 1
2
3
4 234. <https://doi.org/10.1242/jeb.125401>
- 5 Cravens, E.M., Kirkwood, J.S., Wolfe, L.M., Packer, R.A., Whalen, L.R., Wojda, S.J., Prenni, J.E., Florant, G.L.,
6 Donahue, S.W., 2020. The effects of neurectomy and hibernation on bone properties and the
7 endocannabinoid system in marmots (*Marmota flaviventris*). *Comp. Biochem. Physiol. -Part A Mol. Integr.*
8 *Physiol.* 241. <https://doi.org/10.1016/j.cbpa.2019.110621>
- 9 Cruz, A.A., Togias, A., 2008. Upper airways reactions to cold air. *Curr. Allergy Asthma Rep.*
10 <https://doi.org/10.1007/s11882-008-0020-z>
- 11 Cubuk, C., Bank, J.H.H., Herwig, A., 2016. The chemistry of cold: Mechanisms of torpor regulation in the
12 Siberian hamster. *Physiology*. <https://doi.org/10.1152/physiol.00028.2015>
- 13 Cui, Y., Lee, T.F., Kramarova, L.I., Wang, L.C., 1993. The modulatory effects of mu and kappa opioid agonists
14 on 5-HT release from hippocampal and hypothalamic slices of euthermic and hibernating ground squirrels.
15 *Life Sci.* 53, 1957–65. [https://doi.org/10.1016/0024-3205\(93\)90017-w](https://doi.org/10.1016/0024-3205(93)90017-w)
- 16 Dausmann, K.H., Glos, J., Ganzhorn, J.U., Heldmaier, G., 2004. Hibernation in a tropical primate. *Nature* 429,
17 825–826. <https://doi.org/10.1038/429825a>
- 18 De Azua, I.R., Mancini, G., Srivastava, R.K., Rey, A.A., Cardinal, P., Tedesco, L., Zingaretti, C.M., Sassmann,
19 A., Quarta, C., Schwitter, C., Conrad, A., Wettschureck, N., Vemuri, V.K., Makriyannis, A., Hartwig, J.,
20 Mendez-Lago, M., Bindila, L., Monory, K., Giordano, A., Cinti, S., Marsicano, G., Offermanns, S., Nisoli,
21 E., Pagotto, U., Cota, D., Lutz, B., 2017. Adipocyte cannabinoid receptor CB1 regulates energy homeostasis
22 and alternatively activated macrophages. *J. Clin. Invest.* 127, 4148–4162. <https://doi.org/10.1172/JCI83626>
- 23 Deboer, T., 1998. Brain temperature dependent changes in the electroencephalogram power spectrum of humans
24 and animals. *J. Sleep Res.* 7, 254–262. <https://doi.org/10.1046/j.1365-2869.1998.00125.x>
- 25 Deboer, T., Tobler, I., 2003. Sleep regulation in the Djungarian hamster: comparison of the dynamics leading to
26 the slow-wave activity increase after sleep deprivation and daily torpor. *Sleep* 26, 567–72.
27 <https://doi.org/10.1093/sleep/26.5.567>
- 28 Deboer, T., Tobler, I., 2000. Slow waves in the sleep electroencephalogram after daily torpor are homeostatically
29 regulated. *Neuroreport* 11, 881–5. <https://doi.org/10.1097/00001756-200003200-00044>
- 30 Del Vecchio, F., Nalivaiko, E., Cerri, M., Luppi, M., Amici, R., 2014. Provocative motion causes fall in brain
31 temperature and affects sleep in rats. *Exp. Brain Res.* 232, 2591–2599. <https://doi.org/10.1007/s00221-014-3899-8>
- 32 Demontis, G.C., Germani, M.M., Caiani, E.G., Barravecchia, I., Passino, C., Angeloni, D., 2017. Human
33 pathophysiological adaptations to the space environment. *Front. Physiol.*
34 <https://doi.org/10.3389/fphys.2017.00547>
- 35 Dénes, Á., Boldogkoi, Z., Uherezky, G., Hornyák, Á., Rusvai, M., Palkovits, M., Kovács, K.J., 2005. Central
36 autonomic control of the bone marrow: Multisynaptic tract tracing by recombinant pseudorabies virus.
37 *Neuroscience* 134, 947–963. <https://doi.org/10.1016/j.neuroscience.2005.03.060>
- 38 Dijk, D.J., Neri, D.F., Wyatt, J.K., Ronda, J.M., Riel, E., Cecco, A.R.D., Hughes, R.J., Elliott, A.R., Prisk, G.K.,
39 West, J.B., Czeisler, C.A., 2001. Sleep, performance, circadian rhythms, and light-dark cycles during two
40 space shuttle flights. *Am. J. Physiol. - Regul. Integr. Comp. Physiol.* 281.
41 <https://doi.org/10.1152/ajpregu.2001.281.5.r1647>
- 42 Dill-McFarland, K.A., Neil, K.L., Zeng, A., Sprenger, R.J., Kurtz, C.C., Suen, G., Carey, H. V., 2014.
43 Hibernation alters the diversity and composition of mucosa-associated bacteria while enhancing
44 antimicrobial defence in the gut of 13-lined ground squirrels. *Mol. Ecol.* 23, 4658–4669.
45 <https://doi.org/10.1111/mec.12884>
- 46 DiMicco, J.A., Zaretsky, D. V., 2007. The dorsomedial hypothalamus: A new player in thermoregulation. *Am. J.*
47 *Physiol. - Regul. Integr. Comp. Physiol.* <https://doi.org/10.1152/ajpregu.00498.2006>
- 48 Ding, W., Shen, Y., Li, Q., Jiang, S., Shen, H., 2018. Therapeutic mild hypothermia improves early outcomes in
49 rats subjected to severe sepsis. *Life Sci.* <https://doi.org/10.1016/j.lfs.2018.03.002>
- 50 Dirkes, M.C., van Gulik, T.M., Heger, M., 2015. The physiology of artificial hibernation. *J. Clin. Transl. Res.* 1,
51 78–93.
- 52 Doherty, A.H., Florant, G.L., Donahue, S.W., 2014. Endocrine regulation of bone and energy metabolism in
53 hibernating mammals. *Integr. Comp. Biol.* <https://doi.org/10.1093/icb/ucu001>
- 54 Doherty, A.H., Frampton, J.D., Vinyard, C.J., 2012. Hibernation does not reduce cortical bone density, area or
55
56
57
58
59
60
61
62
63
64
65

- 1
2
3
4 second moments of inertia in woodchucks (*Marmota monax*). *J. Morphol.* 273, 604–617.
5 <https://doi.org/10.1002/jmor.20007>
- 6 Doherty, A.H., Roteliuk, D.M., Gookin, S.E., McGrew, A.K., Broccardo, C.J., Condon, K.W., Prenni, J.E.,
7 Wojda, S.J., Florant, G.L., Donahue, S.W., 2016. Exploring the bone proteome to help explain altered bone
8 remodeling and preservation of bone architecture and strength in hibernating marmots. *Physiol. Biochem.*
9 *Zool.* 89, 364–376. <https://doi.org/10.1086/687413>
- 10 Drew, K.L., Frare, C., Rice, S.A., 2017. Neural Signaling Metabolites May Modulate Energy Use in Hibernation.
11 *Neurochem. Res.* 42, 141–150. <https://doi.org/10.1007/s11064-016-2109-4>
- 12 Dugbartey, G.J., Talaei, F., Houwertjes, M.C., Goris, M., Epema, A.H., Bouma, H.R., Henning, R.H., 2015.
13 Dopamine treatment attenuates acute kidney injury in a rat model of deep hypothermia and rewarming - The
14 role of renal H2S-producing enzymes. *Eur. J. Pharmacol.* 769, 225–233.
15 <https://doi.org/10.1016/j.ejphar.2015.11.022>
- 16 Durante, M., 2014. Space radiation protection: Destination Mars. *Life Sci. Sp. Res.*
17 <https://doi.org/10.1016/j.lssr.2014.01.002>
- 18 Durante, M., Cucinotta, F.A., 2011. Physical basis of radiation protection in space travel. *Rev. Mod. Phys.* 83,
19 1245. <https://doi.org/10.1103/RevModPhys.83.1245>
- 20 Durante, M., Cucinotta, F.A., 2008. Heavy ion carcinogenesis and human space exploration. *Nat. Rev. Cancer.*
21 <https://doi.org/10.1038/nrc2391>
- 22 Fay, T., 1959. Early experiences with local and generalized refrigeration of the human brain. *J. Neurosurg.* 16.
23 <https://doi.org/10.3171/jns.1959.16.3.0239>
- 24 Feketa, V. V., Marrelli, S.P., 2015. Induction of therapeutic hypothermia by pharmacological modulation of
25 temperature-sensitive TRP channels: theoretical framework and practical considerations. *Temp. (Austin,*
26 *Tex.)* 2, 244–57. <https://doi.org/10.1080/23328940.2015.1024383>
- 27 Feuerecker, M., Crucian, B.E., Quintens, R., Buchheim, J.I., Salam, A.P., Rybka, A., Moreels, M., Strewé, C.,
28 Stowe, R., Mehta, S., Schelling, G., Thiel, M., Baatout, S., Sams, C., Choukèr, A., 2019. Immune
29 sensitization during 1 year in the Antarctic high-altitude Concordia Environment. *Allergy Eur. J. Allergy*
30 *Clin. Immunol.* 74, 64–77. <https://doi.org/10.1111/all.13545>
- 31 Filingeri, D., 2016. Neurophysiology of Skin Thermal Sensations. *Compr. Physiol.*
32 <https://doi.org/10.1002/cphy.c150040>
- 33 Florant, G.L., Heller, H.C., 1977. CNS regulation of body temperature in euthermic and hibernating marmots
34 (*Marmota flaviventris*). *Am. J. Physiol.* 232. <https://doi.org/10.1152/ajpregu.1977.232.5.R203>
- 35 Foley, J., Clifford, D., Castle, K., Cryan, P., Ostfeld, R.S., 2011. Investigating and Managing the Rapid
36 Emergence of White-Nose Syndrome, a Novel, Fatal, Infectious Disease of Hibernating Bats. *Conserv. Biol.*
37 <https://doi.org/10.1111/j.1523-1739.2010.01638.x>
- 38 Fortney, S., Mikhaylov, V., Lee, S., Kobzev, Y., Gonzalez, R.R., Greenleaf, J., 1998. Body temperature and
39 thermoregulation during submaximal exercise after 115-day spaceflight. undefined.
- 40 Frare, C., Jenkins, M.E., McClure, K.M., Drew, K.L., 2019. Seasonal decrease in thermogenesis and increase in
41 vasoconstriction explain seasonal response to N6-cyclohexyladenosine-induced hibernation in the Arctic
42 ground squirrel (*Urocitellus parryii*). *J. Neurochem.* 151, 316–335. <https://doi.org/10.1111/jnc.14814>
- 43 Frare, C., Jenkins, M.E., Soldin, S.J., Drew, K.L., 2018. The Raphe Pallidus and the Hypothalamic-Pituitary-
44 Thyroid Axis Gate Seasonal Changes in Thermoregulation in the Hibernating Arctic Ground Squirrel
45 (*Urocitellus parryii*). *Front. Physiol.* 9, 1747. <https://doi.org/10.3389/fphys.2018.01747>
- 46 Frerichs, K.U., Kennedy, C., Sokoloff, L., Hallenbeck, J.M., 1994. Local Cerebral Blood Flow During
47 Hibernation, a Model of Natural Tolerance to “Cerebral Ischemia,” *Journal of Cerebral Blood Flow and*
48 *Metabolism.*
- 49 Gamage, T.F., Barrus, D.G., Kevin, R.C., Finlay, D.B., Lefever, T.W., Patel, P.R., Grabenauer, M.A., Glass, M.,
50 McGregor, I.S., Wiley, J.L., Thomas, B.F., 2020. In vitro and in vivo pharmacological evaluation of the
51 synthetic cannabinoid receptor agonist EG-018. *Pharmacol. Biochem. Behav.* 193.
52 <https://doi.org/10.1016/j.pbb.2020.172918>
- 53 Geerling, J.C., Kim, M., Mahoney, C.E., Abbott, S.B.G., Agostinelli, L.J., Garfield, A.S., Krashes, M.J., Lowell,
54 B.B., Scammell, T.E., 2016. Genetic identity of thermosensory relay neurons in the lateral parabrachial
55 nucleus. *Am. J. Physiol. - Regul. Integr. Comp. Physiol.* 310, R41–R54.
- 56
57
58
59
60
61
62
63
64
65

- 1
2
3
4 <https://doi.org/10.1152/ajpregu.00094.2015>
- 5 Geiser, F., 2020. Seasonal Expression of Avian and Mammalian Daily Torpor and Hibernation: Not a Simple
6 Summer-Winter Affair†. *Front. Physiol.* <https://doi.org/10.3389/fphys.2020.00436>
- 7 Geiser, F., 2013. Hibernation. *Curr. Biol.* <https://doi.org/10.1016/j.cub.2013.01.062>
- 8 Geiser, F., Currie, S.E., O’Shea, K.A., Hiebert, S.M., 2014. Torpor and hypothermia: reversed hysteresis of
9 metabolic rate and body temperature. *Am. J. Physiol. Integr. Comp. Physiol.* 307, R1324–R1329.
10 <https://doi.org/10.1152/ajpregu.00214.2014>
- 11 Gilbert, M., Busund, R., Skagseth, A., Nilsen, P.Å., Solbø, J.P., 2000. Resuscitation from accidental hypothermia
12 of 13-7°C with circulatory arrest. *Lancet* 355, 375–376. [https://doi.org/10.1016/S0140-6736\(00\)01021-7](https://doi.org/10.1016/S0140-6736(00)01021-7)
- 13 Giroud, S., Chery, I., Bertile, F., Bertrand-Michel, J., Tascher, G., Gauquelin-Koch, G., Arnemo, J.M., Swenson,
14 J.E., Singh, N.J., Lefai, E., Evans, A.L., Simon, C., Blanc, S., 2019. Lipidomics Reveals Seasonal Shifts in a
15 Large-Bodied Hibernator, the Brown Bear. *Front. Physiol.* 10, 389.
16 <https://doi.org/10.3389/fphys.2019.00389>
- 17 Giroud, S., Evans, A.L., Chery, I., Bertile, F., Tascher, G., Bertrand-Michel, J., Gauquelin-Koch, G., Arnemo,
18 J.M., Swenson, J.E., Lefai, E., Blanc, S., Simon, C., 2018a. Seasonal changes in eicosanoid metabolism in
19 the brown bear. *Sci. Nat.* 105, 1–10. <https://doi.org/10.1007/s00114-018-1583-8>
- 20 Giroud, S., Frare, C., Strijkstra, A., Boerema, A., Arnold, W., Ruf, T., 2013. Membrane Phospholipid Fatty Acid
21 Composition Regulates Cardiac SERCA Activity in a Hibernator, the Syrian Hamster (*Mesocricetus*
22 *auratus*). *PLoS One* 8, e63111. <https://doi.org/10.1371/journal.pone.0063111>
- 23 Giroud, S., Hibold, C., Nespolo, R.F., Mejías, C., Terrien, J., Logan, S.M., Henning, R.H., Storey, K.B., 2021.
24 The Torpid State: Recent Advances in Metabolic Adaptations and Protective Mechanisms†. *Front. Physiol.*
25 <https://doi.org/10.3389/fphys.2020.623665>
- 26 Giroud, S., Perret, M., Stein, P., Goudable, J., Aujard, F., Gilbert, C., Robin, J.P., Le Maho, Y., Zahariev, A.,
27 Blanc, S., Momken, I., 2010. The Grey Mouse Lemur Uses Season-Dependent Fat or Protein Sparing
28 Strategies to Face Chronic Food Restriction. *PLoS One* 5, e8823.
29 <https://doi.org/10.1371/journal.pone.0008823>
- 30 Giroud, S., Stalder, G., Gerritsmann, H., Kübber-Heiss, A., Kwak, J., Arnold, W., Ruf, T., 2018b. Dietary Lipids
31 Affect the Onset of Hibernation in the Garden Dormouse (*Eliomys quercinus*): Implications for Cardiac
32 Function. *Front. Physiol.* 9, 1235. <https://doi.org/10.3389/fphys.2018.01235>
- 33 Giroud, S., Zahn, S., Criscuolo, F., Chery, I., Blanc, S., Turbill, C., Ruf, T., 2014. Late-born intermittently fasted
34 juvenile garden dormice use torpor to grow and fatten prior to hibernation: Consequences for ageing
35 processes. *Proc. R. Soc. B Biol. Sci.* 281, 1–9. <https://doi.org/10.1098/rspb.2014.1131>
- 36 Glotzbach, S.F., Craig Heller, H., 1984. Changes in the thermal characteristics of hypothalamic neurons during
37 sleep and wakefulness. *Brain Res.* 309, 17–26. [https://doi.org/10.1016/0006-8993\(84\)91006-0](https://doi.org/10.1016/0006-8993(84)91006-0)
- 38 Glotzbach, S.F., Heller, H.C., 1976. Central nervous regulation of body temperature during sleep. *Science* (80-.).
39 194, 537–539. <https://doi.org/10.1126/science.973138>
- 40 Griffin, J.D., Kaple, M.L., Chow, A.R., Boulant, J.A., 1996. Cellular mechanisms for neuronal thermosensitivity
41 in the rat hypothalamus. *J. Physiol.* 492, 231–242. <https://doi.org/10.1113/jphysiol.1996.sp021304>
- 42 Griko, Y., Regan, M.D., 2018. Synthetic torpor: A method for safely and practically transporting experimental
43 animals aboard spaceflight missions to deep space. *Life Sci. Sp. Res.*
44 <https://doi.org/10.1016/j.lssr.2018.01.002>
- 45 Grimpo, K., Legler, K., Heldmaier, G., Exner, C., 2013. That’s hot: Golden spiny mice display torpor even at high
46 ambient temperatures. *J. Comp. Physiol. B Biochem. Syst. Environ. Physiol.* 183, 567–581.
47 <https://doi.org/10.1007/s00360-012-0721-4>
- 48 Guisle, I., Gratuze, M., Petry, S., Morin, F., Keraudren, R., Whittington, R.A., Hébert, S.S., Mongrain, V., Planel,
49 E., 2020. Circadian and sleep/wake-dependent variations in tau phosphorylation are driven by temperature.
50 *Sleep* 43. <https://doi.org/10.1093/sleep/zsz266>
- 51 Gundel, A., Nalishiti, V., Reucher, E., Vejvoda, M., Zulle, J., 1993. Sleep and circadian rhythm during a short
52 space mission. *Clin. Investig.* 71, 718–724. <https://doi.org/10.1007/BF00209726>
- 53 Gundel, A., Polyakov, V. V., Zulle, J., 1997. The alteration of human sleep and circadian rhythms during
54 spaceflight. *J. Sleep Res.* 6, 1–8. <https://doi.org/10.1046/j.1365-2869.1997.00028.x>
- 55 Gunga, H.C., Sandsund, M., Reinertsen, R.E., Sattler, F., Koch, J., 2008. A non-invasive device to continuously
56
57
58
59
60
61
62
63
64
65

- determine heat strain in humans. *J. Therm. Biol.* 33, 297–307. <https://doi.org/10.1016/j.jtherbio.2008.03.004>
- Harding, E.C., Franks, N.P., Wisden, W., 2019. The temperature dependence of sleep. *Front. Neurosci.* <https://doi.org/10.3389/fnins.2019.00336>
- Harding, E.C., Yu, X., Miao, A., Andrews, N., Ma, Y., Ye, Z., Lignos, L., Miracca, G., Ba, W., Yustos, R., Vyssotski, A.L., Wisden, W., Franks, N.P., 2018. A Neuronal Hub Binding Sleep Initiation and Body Cooling in Response to a Warm External Stimulus. *Curr. Biol.* 28, 2263–2273.e4. <https://doi.org/10.1016/j.cub.2018.05.054>
- Hargens, A.R., Bhattacharya, R., Schneider, S.M., 2013. Space physiology VI: Exercise, artificial gravity, and countermeasure development for prolonged space flight. *Eur. J. Appl. Physiol.* <https://doi.org/10.1007/s00421-012-2523-5>
- Harlow, H.J., Lohuis, T., Beck, T.D.I., Iazzo, P.A., 2001. Muscle strength in overwintering bears. *Nature* 409, 997. <https://doi.org/10.1038/35059165>
- Havenstein, N., Langer, F., Stefanski, V., Fietz, J., 2016. It takes two to tango: Phagocyte and lymphocyte numbers in a small mammalian hibernator. *Brain. Behav. Immun.* 52, 71–80. <https://doi.org/10.1016/j.bbi.2015.09.018>
- Heldmaier, G., Ortmann, S., Elvert, R., 2004. Natural hypometabolism during hibernation and daily torpor in mammals, in: *Respiratory Physiology and Neurobiology*. pp. 317–329. <https://doi.org/10.1016/j.resp.2004.03.014>
- Heller, H.C., Colliver, G.W., 1974. CNS regulation of body temperature during hibernation. *Am. J. Physiol.* 227, 583–589. <https://doi.org/10.1152/ajplegacy.1974.227.3.583>
- Hitrec, T., Luppi, M., Bastianini, S., Squarcio, F., Berteotti, C., Lo Martire, V., Martelli, D., Occhinegro, A., Tupone, D., Zoccoli, G., Amici, R., Cerri, M., 2019. Neural control of fasting-induced torpor in mice. *Sci. Rep.* 9, 15462. <https://doi.org/10.1038/s41598-019-51841-2>
- Hitrec, T., Squarcio, F., Cerri, M., Martelli, D., Occhinegro, A., Piscitiello, E., Tupone, D., Amici, R., Luppi, M., 2021. Reversible Tau Phosphorylation Induced by Synthetic Torpor in the Spinal Cord of the Rat. *Front. Neuroanat.* 15. <https://doi.org/10.3389/fnana.2021.592288>
- Hoelzl, F., Cornils, J.S., Smith, S., Moodley, Y., Ruf, T., 2016a. Telomere dynamics in free-living edible dormice (*Glis glis*): The impact of hibernation and food supply. *J. Exp. Biol.* 219, 2469–2474. <https://doi.org/10.1242/jeb.140871>
- Hoelzl, F., Smith, S., Cornils, J.S., Aydinonat, D., Bieber, C., Ruf, T., 2016b. Telomeres are elongated in older individuals in a hibernating rodent, the edible dormouse (*Glis glis*). *Sci. Rep.* 6. <https://doi.org/10.1038/srep36856>
- Hrvatín, S., Sun, S., Wilcox, O.F., Yao, H., Lavin-Peter, A.J., Cicconet, M., Assad, E.G., Palmer, M.E., Aronson, S., Banks, A.S., Griffith, E.C., Greenberg, M.E., 2020. Neurons that regulate mouse torpor. *Nature* 1–7. <https://doi.org/10.1038/s41586-020-2387-5>
- Huang, J., Weiss, M.L., 1999. Characterization of the central cell groups regulating the kidney in the rat. *Brain Res.* 845, 77–91. [https://doi.org/10.1016/S0006-8993\(99\)01937-X](https://doi.org/10.1016/S0006-8993(99)01937-X)
- Huber, N., Vetter, S., Stalder, G., Gerritsmann, H., Giroud, S., 2021. Dynamic Function and Composition Shift in Circulating Innate Immune Cells in Hibernating Garden Dormice. *Front. Physiol.* 12. <https://doi.org/10.3389/fphys.2021.620614>
- Hult, E.M., Bingaman, M.J., Swoap, S.J., 2019. A robust diving response in the laboratory mouse. *J. Comp. Physiol. B Biochem. Syst. Environ. Physiol.* 189, 685–692. <https://doi.org/10.1007/s00360-019-01237-5>
- Human hibernation, 2000. . *BMJ* 320.
- Inkovaara, P., Suomalainen, P., 1973. Studies on the physiology of the hibernating hedgehog. 18. On the leukocyte counts in the hedgehog's intestine and lungs. *Ann. Acad. Sci. Fenn. Biol.* 200, 1–21.
- Ivakine, E.A., Cohn, R.D., 2014. Maintaining skeletal muscle mass: Lessons learned from hibernation. *Exp. Physiol.* 99, 632–637. <https://doi.org/10.1113/expphysiol.2013.074344>
- Jaroslow, B.N., Serrell, B.A., 1972. Differential sensitivity to hibernation of early and late events in development of the immune response. *J. Exp. Zool.* <https://doi.org/10.1002/jez.1401810112>
- Jastroch, M., Giroud, S., Barrett, P., Geiser, F., Heldmaier, G., Herwig, A., 2016. Seasonal Control of Mammalian Energy Balance: Recent Advances in the Understanding of Daily Torpor and Hibernation. *J. Neuroendocrinol.* <https://doi.org/10.1111/jne.12437>

- 1
2
3
4 Jiang, S., He, X., Wang, J., Zhou, G., Zhang, M., Ba, L., Yang, J., Zhao, X., 2013. Therapeutic mild hypothermia
5 improves early outcomes in rabbits subjected to traumatic uncontrolled hemorrhagic shock. *J. Surg. Res.*
6 <https://doi.org/10.1016/j.jss.2012.09.024>
7
8 Jinka, T.R., Combs, V.M., Drew, K.L., 2015. Translating Drug-Induced Hibernation to Therapeutic Hypothermia.
9 *ACS Chem. Neurosci.* 6, 899–904. <https://doi.org/10.1021/acschemneuro.5b00056>
10
11 Jones, C.A., Perez, E., Amici, R., Luppi, M., Baracchi, F., Cerri, M., Dentico, D., Zamboni, G., 2008. Lithium
12 affects REM sleep occurrence, autonomic activity and brain second messengers in the rat. *Behav. Brain Res.*
13 187, 254–61. <https://doi.org/10.1016/j.bbr.2007.09.017>
14
15 Kalsbeek, A., Fliers, E., Franke, A.N., Wortel, J., Buijs, R.M., 2000. Functional connections between the
16 suprachiasmatic nucleus and the thyroid gland as revealed by lesioning and viral tracing techniques in the
17 rat. *Endocrinology* 141, 3832–41. <https://doi.org/10.1210/endo.141.10.7709>
18
19 Kalsbeek, A., La Fleur, S., Van Heijningen, C., Buijs, R.M., 2004. Suprachiasmatic GABAergic inputs to the
20 paraventricular nucleus control plasma glucose concentrations in the rat via sympathetic innervation of the
21 liver. *J. Neurosci.* 24, 7604–7613. <https://doi.org/10.1523/JNEUROSCI.5328-03.2004>
22
23 Kim, M.-H.Y., Hayat, M.J., Feiveson, A.H., Cucinotta, F.A., 2009. Prediction of frequency and exposure level of
24 solar particle events. *Health Phys.* 97, 68–81. <https://doi.org/10.1097/01.HP.0000346799.65001.9c>
25
26 Kroeger, D., Absi, G., Gagliardi, C., Bandaru, S.S., Madara, J.C., Ferrari, L.L., Arrigoni, E., Münzberg, H.,
27 Scammell, T.E., Saper, C.B., Vetrivelan, R., 2018. Galanin neurons in the ventrolateral preoptic area
28 promote sleep and heat loss in mice. *Nat. Commun.* 9, 4129. <https://doi.org/10.1038/s41467-018-06590-7>
29
30 Kurtz, C.C., Carey, H. V., 2007. Seasonal changes in the intestinal immune system of hibernating ground
31 squirrels. *Dev. Comp. Immunol.* 31, 415–428.
32 <https://doi.org/10.1016/j.dci.2006.07.003>
33
34 Kuskin, S.M., Wang, S.C., Rugh, R., 1959. Protective effect of artificially induced hibernation against lethal
35 doses of whole body x-irradiation in CF male mice. *Am. J. Physiol.* 196, 1211–3.
36 <https://doi.org/10.1152/ajplegacy.1959.196.6.1211>
37
38 Larkin, J.E., Heller, H.C., 1999. Sleep after arousal from hibernation is not homeostatically regulated. *Am. J.*
39 *Physiol.* 276, R522-9. <https://doi.org/10.1152/ajpregu.1999.276.2.R522>
40
41 LeBlanc, A.D., Spector, E.R., Evans, H.J., Sibonga, J.D., 2007. Skeletal responses to space flight and the bed rest
42 analog: A review, in: *Journal of Musculoskeletal Neuronal Interactions*. pp. 33–47.
43
44 Lee, C.C., 2008. Is Human Hibernation Possible? *Annu. Rev. Med.* 59, 177–186.
45 <https://doi.org/10.1146/annurev.med.59.061506.110403>
46
47 Lee, T.N., Barnes, B.M., Buck, C.L., 2009. Body temperature patterns during hibernation in a free-living Alaska
48 marmot (*Marmota flaviventris*). *Ethol. Ecol. Evol.* 21, 403–413.
49 <https://doi.org/10.1080/08927014.2009.9522495>
50
51 Lemon, C.H., 2017. Modulation of taste processing by temperature. *Am. J. Physiol. - Regul. Integr. Comp.*
52 *Physiol.* <https://doi.org/10.1152/ajpregu.00089.2017>
53
54 Lleonart, M.E., 2010. A new generation of proto-oncogenes: cold-inducible RNA binding proteins. *Biochim.*
55 *Biophys. Acta* 1805, 43–52. <https://doi.org/10.1016/j.bbcan.2009.11.001>
56
57 Lovegrove, B.G., 2017. A phenology of the evolution of endothermy in birds and mammals. *Biol. Rev.* 92, 1213–
58 1240. <https://doi.org/10.1111/brv.12280>
59
60 Luppi, M., Hitrec, T., Di Cristoforo, A., Squarcio, F., Stanzani, A., Occhinegro, A., Chiavetta, P., Tupone, D.,
61 Zamboni, G., Amici, R., Cerri, M., 2019. Phosphorylation and dephosphorylation of tau protein during
62 synthetic torpor. *Front. Neuroanat.* 13, 57. <https://doi.org/10.3389/fnana.2019.00057>
63
64 Luppi, M., Martelli, D., Amici, R., Baracchi, F., Cerri, M., Dentico, D., Perez, E., Zamboni, G., 2010.
65 Hypothalamic osmoregulation is maintained across the wake-sleep cycle in the rat. *J. Sleep Res.* 19, 394–
399. <https://doi.org/10.1111/j.1365-2869.2009.00810.x>
66
67 Lyman, C.P., Fawcett, D.W., 1954. The Effect of Hibernation on the Growth of Sarcoma in the Hamster. *Cancer*
68 *Res.* 14, 25–28.
69
70 Lynes, M.D., Kodani, S.D., Tseng, Y.H., 2019. Lipokines and Thermogenesis. *Endocrinology.*
71 <https://doi.org/10.1210/en.2019-00337>
72
73 Madden, C.J., Morrison, S.F., 2019. Central nervous system circuits that control body temperature. *Neurosci. Lett.*
74 <https://doi.org/10.1016/j.neulet.2018.11.027>
75

- 1
2
3
4 Madden, C.J., Morrison, S.F., 2005. Hypoxic activation of arterial chemoreceptors inhibits sympathetic outflow to
5 brown adipose tissue in rats. *J. Physiol.* 566, 559–573. <https://doi.org/10.1113/jphysiol.2005.086322>
- 6 Madden, C.J., Santos da Conceicao, E.P., Morrison, S.F., 2017. Vagal afferent activation decreases brown adipose
7 tissue (BAT) sympathetic nerve activity and BAT thermogenesis. *Temperature* 4, 89–96.
8 <https://doi.org/10.1080/23328940.2016.1257407>
- 9 Magnifico, F., Pierangeli, G., Barletta, G., Candela, C., Montagna, P., Bonavina, G., Cortelli, P., 2002.
10 Paroxysmal episodic central thermoregulatory failure. *Neurology* 58, 1300–1302.
11 <https://doi.org/10.1212/WNL.58.8.1300>
- 12 Margules, D.L., Goldman, B., Finck, A., 1979. Hibernation: An opioid-dependent state? *Brain Res. Bull.* 4, 721–
13 724. [https://doi.org/10.1016/0361-9230\(79\)90003-0](https://doi.org/10.1016/0361-9230(79)90003-0)
- 14 McGee-Lawrence, M.E., Carey, H. V., Donahue, S.W., 2008. Mammalian hibernation as a model of disuse
15 osteoporosis: The effects of physical inactivity on bone metabolism, structure, and strength. *Am. J. Physiol.*
16 - Regul. Integr. Comp. Physiol. <https://doi.org/10.1152/ajpregu.90648.2008>
- 17 McGee-Lawrence, M.E., Stoll, D.M., Mantila, E.R., Fahrner, B.K., Carey, H. V., Donahue, S.W., 2011. Thirteen-
18 lined ground squirrels (*Ictidomys tridecemlineatus*) show microstructural bone loss during hibernation but
19 preserve bone macrostructural geometry and strength. *J. Exp. Biol.* 214, 1240–1247.
20 <https://doi.org/10.1242/jeb053520>
- 21 Melvin, R.G., Andrews, M.T., 2009. Torpor induction in mammals: recent discoveries fueling new ideas. *Trends*
22 *Endocrinol. Metab.* 20, 490–8. <https://doi.org/10.1016/j.tem.2009.09.005>
- 23 Metna- Laurent, M., Mondésir, M., Grel, A., Vallée, M., Piazza, P., 2017. Cannabinoid- Induced Tetrad in Mice.
24 *Curr. Protoc. Neurosci.* 80, 9.59.1–9.59.10. <https://doi.org/10.1002/cpns.31>
- 25 Meyer, C.W., Ootsuka, Y., Romanovsky, A.A., 2017. Body Temperature Measurements for Metabolic
26 Phenotyping in Mice. *Front. Physiol.* 8, 520. <https://doi.org/10.3389/fphys.2017.00520>
- 27 Miyazaki, M., Esser, K.A., 2009. Cellular mechanisms regulating protein synthesis and skeletal muscle
28 hypertrophy in animals. *J. Appl. Physiol.* <https://doi.org/10.1152/jappphysiol.91355.2008>
- 29 Miyazaki, M., Shimozuru, M., Tsubota, T., 2019. Skeletal muscles of hibernating black bears show minimal
30 atrophy and phenotype shifting despite prolonged physical inactivity and starvation. *PLoS One* 14.
31 <https://doi.org/10.1371/journal.pone.0215489>
- 32 Morrison, S.F., Cao, W.H., 2000. Different adrenal sympathetic preganglionic neurons regulate epinephrine and
33 norepinephrine secretion. *Am. J. Physiol. - Regul. Integr. Comp. Physiol.* 279.
34 <https://doi.org/10.1152/ajpregu.2000.279.5.r1763>
- 35 Morrison, S.F., Nakamura, K., 2019. Central Mechanisms for Thermoregulation. *Annu. Rev. Physiol.* 81, 285–
36 308. <https://doi.org/10.1146/annurev-physiol-020518-114546>
- 37 Morrison, S.F., Sved, A.F., Passerin, A.M., 1999. GABA-mediated inhibition of raphe pallidus neurons regulates
38 sympathetic outflow to brown adipose tissue. *Am. J. Physiol. - Regul. Integr. Comp. Physiol.* 276.
39 <https://doi.org/10.1152/ajpregu.1999.276.2.r290>
- 40 Mulawa, E.A., Kirkwood, J.S., Wolfe, L.M., Wojda, S.J., Prenni, J.E., Florant, G.L., Donahue, S.W., 2018.
41 Seasonal Changes in Endocannabinoid Concentrations between Active and Hibernating Marmots (*Marmota*
42 *flaviventris*). *J. Biol. Rhythms* 33, 388–401. <https://doi.org/10.1177/0748730418777660>
- 43 Musacchia, X.J., Barr, R.E., 1968. Survival of whole-body-irradiated hibernating and active ground squirrels;
44 *Citellus tridecemlineatus*. *Radiat. Res.* 33, 348–56.
- 45 Nakamura, K., Morrison, S.F., 2011. Central efferent pathways for cold-defensive and febrile shivering. *J.*
46 *Physiol.* 589, 3641–3658. <https://doi.org/10.1113/jphysiol.2011.210047>
- 47 Nakamura, K., Morrison, S.F., 2010. A thermosensory pathway mediating heat-defense responses. *Proc. Natl.*
48 *Acad. Sci. U. S. A.* 107, 8848–8853. <https://doi.org/10.1073/pnas.0913358107>
- 49 Nakamura, K., Morrison, S.F., 2008. A thermosensory pathway that controls body temperature. *Nat. Neurosci.* 11,
50 62–71. <https://doi.org/10.1038/nn2027>
- 51 Nalivaiko, E., 2018. Thermoregulation and nausea, in: *Handbook of Clinical Neurology*. Elsevier B.V., pp. 445–
52 456. <https://doi.org/10.1016/B978-0-444-63912-7.00027-8>
- 53 Nelson, O.L., Robbins, C.T., 2015. Cardiovascular function in large to small hibernators: bears to ground
54 squirrels. *J. Comp. Physiol. B Biochem. Syst. Environ. Physiol.* <https://doi.org/10.1007/s00360-014-0881-5>
- 55 Ngampramuan, S., Cerri, M., Del Vecchio, F., Corrigan, J.J., Kamphee, A., Dragic, A.S., Rudd, J.A.,
56
57
58
59
60
61
62
63
64
65

- 1
2
3
4 Romanovsky, A.A., Nalivaiko, E., 2014. Thermoregulatory correlates of nausea in rats and musk shrews.
5 *Oncotarget* 5, 1565–75. <https://doi.org/10.18632/oncotarget.1732>
6
7 Nguyen, N.L.T., Randall, J., Banfield, B.W., Bartness, T.J., 2014. Central sympathetic innervations to visceral
8 and subcutaneous white adipose tissue. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 306, R375–86.
9 <https://doi.org/10.1152/ajpregu.00552.2013>
10
11 Niazi, S.A., Lewis, F.J., 1958. Profound hypothermia in man; report of a case. *Ann. Surg.* 147, 264–266.
12 <https://doi.org/10.1097/00000658-195802000-00019>
13
14 Nordeen, C.A., Martin, S.L., 2019. Engineering human stasis for long-duration spaceflight. *Physiology*.
15 <https://doi.org/10.1152/physiol.00046.2018>
16
17 Norsk, P., Asmar, A., Damgaard, M., Christensen, N.J., 2015. Fluid shifts, vasodilatation and ambulatory blood
18 pressure reduction during long duration spaceflight. *J. Physiol.* 593, 573–584.
19 <https://doi.org/10.1113/jphysiol.2014.284869>
20
21 Nowack, J., Levesque, D.L., Reher, S., Dausmann, K.H., 2020. Variable Climates Lead to Varying Phenotypes:
22 “Weird” Mammalian Torpor and Lessons From Non-Holarctic Species. *Front. Ecol. Evol.*
23 <https://doi.org/10.3389/fevo.2020.00060>
24
25 Nowack, J., Tarmann, I., Hoelzl, F., Smith, S., Giroud, S., Ruf, T., 2019. Always a price to pay: hibernation at
26 low temperatures comes with a trade-off between energy savings and telomere damage. *Biol. Lett.* 15,
27 20190466. <https://doi.org/10.1098/rsbl.2019.0466>
28
29 Oelkrug, R., Heldmaier, G., Meyer, C.W., 2011. Torpor patterns, arousal rates, and temporal organization of
30 torpor entry in wildtype and UCP1-ablated mice. *J. Comp. Physiol. B Biochem. Syst. Environ. Physiol.* 181,
31 137–145. <https://doi.org/10.1007/s00360-010-0503-9>
32
33 Oeltgen, P.R., Walsh, J.W., Hamann, S.R., Randall, D.C., Spurrier, W.A., Myers, R.D., 1982. Hibernation
34 “trigger”: Opioid-like inhibitory action on brain function of the monkey. *Pharmacol. Biochem. Behav.* 17,
35 1271–1274. [https://doi.org/10.1016/0091-3057\(82\)90132-0](https://doi.org/10.1016/0091-3057(82)90132-0)
36
37 Opatz, O., Trippel, T., Lochner, A., Werner, A., Stahn, A., Steinach, M., Lenk, J., Kuppe, H., Gunga, H.C., 2013.
38 Temporal and spatial dispersion of human body temperature during deep hypothermia. *Br. J. Anaesth.* 111,
39 768–775. <https://doi.org/10.1093/bja/aet217>
40
41 Ortman, S., Heldmaier, G., 2000. Regulation of body temperature and energy requirements of hibernating Alpine
42 marmots (*Marmota marmota*). *Am. J. Physiol. - Regul. Integr. Comp. Physiol.* 278.
43 <https://doi.org/10.1152/ajpregu.2000.278.3.r698>
44
45 Parmeggiani, P.L., 2007. Rem sleep related increase in brain temperature: A physiologic problem. *Arch. Ital. Biol.*
46 145, 13–21. <https://doi.org/10.4449/aib.v145i1.863>
47
48 Parmeggiani, P.L., 1986. Interaction Between Sleep and Thermoregulation: An Aspect of the Control of
49 Behavioral States. *Sleep* 10, 426–435. <https://doi.org/10.1093/sleep/10.5.426>
50
51 Parmeggiani, P.L., Cevolani, D., Azzaroni, A., Ferrari, G., 1987. Thermosensitivity of anterior hypothalamic-
52 preoptic neurons during the waking-sleeping cycle: a study in brain functional states. *Brain Res.* 415, 79–89.
53 [https://doi.org/10.1016/0006-8993\(87\)90270-8](https://doi.org/10.1016/0006-8993(87)90270-8)
54
55 Peretti, D., Bastide, A., Radford, H., Verity, N., Molloy, C., Martin, M.G., Moreno, J.A., Steinert, J.R., Smith, T.,
56 Dinsdale, D., Willis, A.E., Mallucci, G.R., 2015. RBM3 mediates structural plasticity and protective effects
57 of cooling in neurodegeneration. *Nature* 518, 236–239. <https://doi.org/10.1038/nature14142>
58
59 Pertwee, R.G., Nash, K., Trayhurn, P., 1991. Evidence that the hypothermic response of mice to Δ^9 -
60 tetrahydrocannabinol is not mediated by changes in thermogenesis in brown adipose tissue. *Can. J. Physiol.*
61 *Pharmacol.* 69, 767–770. <https://doi.org/10.1139/y91-114>
62
63 Petit, G., Koller, D., Summerer, L., Heldmaier, G., Vyazovskiy, V. V., Cerri, M., Henning, R.H., 2018.
64 Hibernation and Torpor: Prospects for Human Spaceflight, in: *Handbook of Life Support Systems for*
65 *Spacecraft and Extraterrestrial Habitats*. https://doi.org/10.1007/978-3-319-09575-2_199-1
66
67 Planel, E., Miyasaka, T., Launey, T., Chui, D.H., Tanemura, K., Sato, S., Murayama, O., Ishiguro, K.,
68 Tatebayashi, Y., Takashima, A., 2004. Alterations in Glucose Metabolism Induce Hypothermia Leading to
69 Tau Hyperphosphorylation through Differential Inhibition of Kinase and Phosphatase Activities:
70 Implications for Alzheimer’s Disease. *J. Neurosci.* 24, 2401–2411.
71 <https://doi.org/10.1523/JNEUROSCI.5561-03.2004>
72
73 Planel, E., Richter, K.E.G., Nolan, C.E., Finley, J.E., Liu, L., Wen, Y., Krishnamurthy, P., Herman, M., Wang, L.,

- 1
2
3
4 Schachter, J.B., Nelson, R.B., Lau, L.F., Duff, K.E., 2007. Anesthesia leads to tau hyperphosphorylation
5 through inhibition of phosphatase activity by hypothermia. *J. Neurosci.* 27, 3090–3097.
6 <https://doi.org/10.1523/JNEUROSCI.4854-06.2007>
7
8 Planel, E., Yasutake, K., Fujita, S.C., Ishiguro, K., 2001. Inhibition of protein phosphatase 2A overrides tau
9 protein kinase I/glycogen synthase kinase 3 beta and cyclin-dependent kinase 5 inhibition and results in tau
10 hyperphosphorylation in the hippocampus of starved mouse. *J. Biol. Chem.* 276, 34298–306.
11 <https://doi.org/10.1074/jbc.M102780200>
12
13 Polyakov, V. V., Lacota, N.G., Gundel, A., 2001. Human thermohomeostasis onboard “Mir” and in simulated
14 microgravity studies, in: *Acta Astronautica*. *Acta Astronaut.* pp. 137–143. [https://doi.org/10.1016/S0094-5765\(01\)00091-1](https://doi.org/10.1016/S0094-5765(01)00091-1)
15
16 Popovic, V., 1960. Physiological characteristics of rats and ground squirrels during prolonged lethargic
17 hypothermia. *Am. J. Physiol.* 199, 467–471. <https://doi.org/10.1152/ajplegacy.1960.199.3.467>
18
19 Prendergast, B.J., Freeman, D.A., Zucker, I., Nelson, R.J., 2002. Periodic arousal from hibernation is necessary
20 for initiation of immune responses in ground squirrels. *Am. J. Physiol. - Regul. Integr. Comp. Physiol.*
21 <https://doi.org/10.1152/ajpregu.00562.2001>
22
23 Prewitt, R.L., Musacchia, X.J., 1975. Radio-protection of arousing ground squirrels (*Citellus tridecemlineatus*) by
24 endogenous catecholamines. *Experientia* 31, 230–232. <https://doi.org/10.1007/BF01990721>
25
26 Puspitasari, A., Cerri, M., Takahashi, A., Yoshida, Y., Hanamura, K., Tinganelli, W., 2021. Hibernation as a tool
27 for radiation protection in space exploration. *Life*. <https://doi.org/10.3390/life11010054>
28
29 Quarta, C., Bellocchio, L., Mancini, G., Mazza, R., Cervino, C., Braulke, L.J., Fekete, C., Latorre, R., Nanni, C.,
30 Bucci, M., Clemens, L.E., Heldmaier, G., Watanabe, M., Leste-Lassere, T., Maitre, M., Tedesco, L., Fanelli,
31 F., Reuss, S., Klaus, S., Srivastava, R.K., Monory, K., Valerio, A., Grandis, A., De Giorgio, R., Pasquali, R.,
32 Nisoli, E., Cota, D., Lutz, B., Marsicano, G., Pagotto, U., 2010. CB1 Signaling in Forebrain and Sympathetic
33 Neurons Is a Key Determinant of Endocannabinoid Actions on Energy Balance. *Cell Metab.* 11, 273–285.
34 <https://doi.org/10.1016/j.cmet.2010.02.015>
35
36 Regan, M.D., Flynn-Evans, E.E., Griko, Y. V., Kilduff, T.S., Rittenberger, J.C., Ruskin, K.J., Buck, C.L., 2020.
37 Shallow metabolic depression and human spaceflight: a feasible first step. *J. Appl. Physiol.* 128, 637–647.
38 <https://doi.org/10.1152/jappphysiol.00725.2019>
39
40 Reitsema, V.A., Oosterhof, M.M., Henning, R.H., Bouma, H.R., 2021. Phase specific suppression of neutrophil
41 function in hibernating Syrian hamster. *Dev. Comp. Immunol.* 119.
42 <https://doi.org/10.1016/j.dci.2021.104024>
43
44 Reznik, G., Reznik Schueller, H., Emminger, A., Mohr, U., 1975. Comparative studies of blood from hibernating
45 and nonhibernating European hamsters (*Cricetus cricetus* L). *Lab. Anim. Sci.* 25, 210–215.
46
47 Romanovsky, A.A., 2014. Skin temperature: Its role in thermoregulation. *Acta Physiol.*
48 <https://doi.org/10.1111/apha.12231>
49
50 Romanovsky, A.A., 2007. Thermoregulation: Some concepts have changed. *Functional architecture of the*
51 *thermoregulatory system*. *Am. J. Physiol. - Regul. Integr. Comp. Physiol.*
52 <https://doi.org/10.1152/ajpregu.00668.2006>
53
54 Royo, J., Aujard, F., Pifferi, F., 2019. Daily Torpor and Sleep in a Non-human Primate, the Gray Mouse Lemur
55 (*Microcebus murinus*). *Front. Neuroanat.* 13, 87. <https://doi.org/10.3389/fnana.2019.00087>
56
57 Ruf, T., Arnold, W., 2008. Effects of polyunsaturated fatty acids on hibernation and torpor: A review and
58 hypothesis. *Am. J. Physiol. - Regul. Integr. Comp. Physiol.* 294, R1044-52.
59 <https://doi.org/10.1152/ajpregu.00688.2007>
60
61 Ruf, T., Geiser, F., 2015. Daily torpor and hibernation in birds and mammals. *Biol. Rev.* 90, 891–926.
62 <https://doi.org/10.1111/brv.12137>
63
64 Rupp, A.C., Ren, M., Altimus, C.M., Fernandez, D.C., Richardson, M., Turek, F., Hattar, S., Schmidt, T.M.,
65 2019. Distinct ipRGC subpopulations mediate light’s acute and circadian effects on body temperature and
sleep. *Elife* 8. <https://doi.org/10.7554/eLife.44358>
Sacks, O., 2019. *Cold Storage*, in: *Everything in Its Place: First Loves and Last Tales*. Knopf, New York (NY)
USA.
Saper, C.B., Lu, J., Chou, T.C., Gooley, J., 2005. The hypothalamic integrator for circadian rhythms. *Trends*
Neurosci. <https://doi.org/10.1016/j.tins.2004.12.009>

- 1
2
3
4 Sazykina, T.G., Kryshev, A.I., 2011. Manifestation of radiation effects in cold environment: data review and
5 modeling. *Radiat. Environ. Biophys.* 50, 105–14. <https://doi.org/10.1007/s00411-010-0336-7>
- 6 Schwartz, C., Andrews, M.T., 2013. Circannual transitions in gene expression: Lessons from seasonal
7 adaptations, in: *Current Topics in Developmental Biology*. Academic Press Inc., pp. 247–273.
8 <https://doi.org/10.1016/B978-0-12-396968-2.00009-9>
- 9 Shimaoka, H., Kawaguchi, T., Morikawa, K., Sano, Y., Naitou, K., Nakamori, H., Shiina, T., Shimizu, Y., 2018.
10 Induction of hibernation-like hypothermia by central activation of the A1 adenosine receptor in a non-
11 hibernator, the rat. *J. Physiol. Sci.* 68, 425–430. <https://doi.org/10.1007/s12576-017-0543-y>
- 12 Siemens, J., Kamm, G.B., 2018. Cellular populations and thermosensing mechanisms of the hypothalamic
13 thermoregulatory center. *Pflugers Arch. Eur. J. Physiol.* <https://doi.org/10.1007/s00424-017-2101-0>
- 14 Silvani, A., Cerri, M., Zoccoli, G., Swoap, S.J., 2018. Is adenosine action common ground for nrem sleep, torpor,
15 and other hypometabolic states? *Physiology*. <https://doi.org/10.1152/physiol.00007.2018>
- 16 Singer, D., 2004. Metabolic adaptation to hypoxia: Cost and benefit of being small, in: *Respiratory Physiology
17 and Neurobiology*. *Respir Physiol Neurobiol*, pp. 215–228. <https://doi.org/10.1016/j.resp.2004.02.009>
- 18 Singer, D., 1999. Neonatal tolerance to hypoxia: A comparative-physiological approach. *Comp. Biochem.
19 Physiol. - A Mol. Integr. Physiol.* [https://doi.org/10.1016/S1095-6433\(99\)00057-4](https://doi.org/10.1016/S1095-6433(99)00057-4)
- 20 Singer, D., Mühlfeld, C., 2007. Perinatal adaptation in mammals: The impact of metabolic rate. *Comp. Biochem.
21 Physiol. - A Mol. Integr. Physiol.* <https://doi.org/10.1016/j.cbpa.2007.05.004>
- 22 Sisa, C., Turroni, S., Amici, R., Brigidi, P., Candela, M., Cerri, M., 2017. Potential role of the gut microbiota in
23 synthetic torpor and therapeutic hypothermia. *World J. Gastroenterol.* <https://doi.org/10.3748/wjg.v23.i3.406>
- 24 Sommer, F., Ståhlman, M., Ilkayeva, O., Arnemo, J.M., Kindberg, J., Josefsson, J., Newgard, C.B., Fröbert, O.,
25 Bäckhed, F., 2016. The Gut Microbiota Modulates Energy Metabolism in the Hibernating Brown Bear *Ursus
26 arctos*. *Cell Rep.* 14, 1655–1661. <https://doi.org/10.1016/j.celrep.2016.01.026>
- 27 Spurrierl, W.A., Dawel, A.R., 1973. SEVERAL BLOOD AND CIRCULATORY CHANGES IN THE
28 HIBERNATION OF THE 13-LINED GROUND SQUIRREL, *CITELLUS TRIDECIMLINEATUS*, *Comp.
29 B&hem. Physiol.* Pergamon Press.
- 30 Stahn, A.C., Werner, A., Opatz, O., Maggioni, M.A., Steinach, M., Von Ahlefeld, V.W., Moore, A., Crucian,
31 B.E., Smith, S.M., Zwart, S.R., Schlabs, T., Mendt, S., Trippel, T., Koralewski, E., Koch, J., Choukèr, A.,
32 Reitz, G., Shang, P., Röcker, L., Kirsch, K.A., Gunga, H.C., 2017. Increased core body temperature in
33 astronauts during long-duration space missions. *Sci. Rep.* 7. <https://doi.org/10.1038/s41598-017-15560-w>
- 34 Standish, A., Enquist, L.W., Escardo, J.A., Schwaber, J.S., 1995. Central neuronal circuit innervating the rat heart
35 defined by transneuronal transport of pseudorabies virus. *J. Neurosci.* 15, 1998–2012.
36 <https://doi.org/10.1523/jneurosci.15-03-01998.1995>
- 37 Stevenson, T.J., Duddleston, K.N., Buck, C.L., 2014. Effects of season and host physiological state on the
38 diversity, density, and activity of the arctic ground squirrel cecal microbiota. *Appl. Environ. Microbiol.*
39 <https://doi.org/10.1128/AEM.01537-14>
- 40 Strewe, C., Feurecker, M., Nichiporuk, I., Kaufmann, I., Hauer, D., Morukov, B., Schelling, G., Choukèr, A.,
41 2012. Effects of parabolic flight and spaceflight on the endocannabinoid system in humans. *Rev. Neurosci.*
42 23, 673–680. <https://doi.org/10.1515/revneuro-2012-0057>
- 43 Strewe, C., Thieme, D., Dangoisse, C., Fiedel, B., Van Den Berg, F., Bauer, H., Salam, A.P., Gössmann-Lang, P.,
44 Campolongo, P., Moser, D., Quintens, R., Moreels, M., Baatout, S., Kohlberg, E., Schelling, G., Choukèr,
45 A., Feurecker, M., 2018. Modulations of neuroendocrine stress responses during confinement in Antarctica
46 and the role of hypobaric hypoxia. *Front. Physiol.* 9. <https://doi.org/10.3389/fphys.2018.01647>
- 47 Strijkstra, A.M., Daan, S., 1998. Dissimilarity of slow-wave activity enhancement by torpor and sleep deprivation
48 in a hibernator. *Am. J. Physiol. - Regul. Integr. Comp. Physiol.* 275.
49 <https://doi.org/10.1152/ajpregu.1998.275.4.r1110>
- 50 Su, B., Wang, X., Drew, K.L., Perry, G., Smith, M.A., Zhu, X., 2008. Physiological regulation of tau
51 phosphorylation during hibernation. *J. Neurochem.* 105, 2098–2108. <https://doi.org/10.1111/j.1471-4159.2008.05294.x>
- 52 Suomalainen, P., Rosokivi, V., 1973. Studies on the physiology of the hibernating hedgehog. 17. The blood cell
53 count of the hedgehog at different times of the year and in different phases of the hibernating cycle. *Ann.
54 Acad. Sci. Fenn. Biol.* 198, 1–8.
- 55
56
57
58
59
60
61
62
63
64
65

- 1
2
3
4 Swoap, S.J., Rathvon, M., Gutilla, M., 2007. AMP does not induce torpor. *Am. J. Physiol. - Regul. Integr. Comp. Physiol.* 293, R468-73. <https://doi.org/10.1152/ajpregu.00888.2006>
- 5
6 Szilagy, J.E., Senturia, J.B., 1972. A comparison of bone marrow leukocytes in hibernating and nonhibernating
7 woodchucks and ground squirrels. *Cryobiology*. [https://doi.org/10.1016/0011-2240\(72\)90044-2](https://doi.org/10.1016/0011-2240(72)90044-2)
- 8
9 Szolcsányi, J., 2015. Effect of capsaicin on thermoregulation: an update with new aspects. *Temperature*.
10 <https://doi.org/10.1080/23328940.2015.1048928>
- 11 Szymusiak, R., 2018. Body temperature and sleep, in: *Handbook of Clinical Neurology*. Elsevier B.V., pp. 341–
12 351. <https://doi.org/10.1016/B978-0-444-63912-7.00020-5>
- 13 Tabarean, I., 2018. Central thermoreceptors, in: *Handbook of Clinical Neurology*. Elsevier B.V., pp. 121–127.
14 <https://doi.org/10.1016/B978-0-444-63912-7.00007-2>
- 15 Takahashi, T.M., Sunagawa, G.A., Soya, S., Abe, M., Sakurai, K., Ishikawa, K., Yanagisawa, M., Hama, H.,
16 Hasegawa, E., Miyawaki, A., Sakimura, K., Takahashi, M., Sakurai, T., 2020. A discrete neuronal circuit
17 induces a hibernation-like state in rodents. *Nature* 583, 109–114. <https://doi.org/10.1038/s41586-020-2163-6>
- 18 Tamura, Y., Shintani, M., Inoue, H., Monden, M., Shiomi, H., 2012. Regulatory mechanism of body temperature
19 in the central nervous system during the maintenance phase of hibernation in Syrian hamsters: Involvement
20 of β -endorphin. *Brain Res.* 1448, 63–70. <https://doi.org/10.1016/j.brainres.2012.02.004>
- 21 Tan, C.L., Cooke, E.K., Leib, D.E., Lin, Y.C., Daly, G.E., Zimmerman, C.A., Knight, Z.A., 2016. Warm-
22 Sensitive Neurons that Control Body Temperature. *Cell* 167, 47-59.e15.
23 <https://doi.org/10.1016/j.cell.2016.08.028>
- 24 Ter Horst, G.J., Van den Brink, A., Homminga, S.A., Hautvast, R.W., Rakhorst, G., Mettenleiter, T.C., De
25 Jongste, M.J., Lie, K.I., Korf, J., 1993. Transneuronal viral labelling of rat heart left ventricle controlling
26 pathways. *Neuroreport* 4, 1307–10. <https://doi.org/10.1097/00001756-199309150-00005>
- 27 Tessier, S.N., Storey, K.B., 2016. Lessons from mammalian hibernators: Molecular insights into striated muscle
28 plasticity and remodeling. *Biomol. Concepts* 7, 69–92. <https://doi.org/10.1515/bmc-2015-0031>
- 29 Tinganelli, W., Hitrec, T., Romani, F., Simoniello, P., Squarcio, F., Stanzani, A., Piscitiello, E., Marchesano, V.,
30 Luppi, M., Sioli, M., Helm, A., Compagnone, G., Morganti, A.G., Amici, R., Negrini, M., Zoccoli, A.,
31 Durante, M., Cerri, M., 2019. Hibernation and radioprotection: Gene expression in the liver and testicle of
32 rats irradiated under synthetic torpor. *Int. J. Mol. Sci.* 20. <https://doi.org/10.3390/ijms20020352>
- 33 Tøien, Drew, K.L., Chao, M.L., Rice, M.E., 2001. Ascorbate dynamics and oxygen consumption during arousal
34 from hibernation in arctic ground squirrels. *Am. J. Physiol. - Regul. Integr. Comp. Physiol.* 281.
35 <https://doi.org/10.1152/ajpregu.2001.281.2.r572>
- 36 Tommasino, F., Durante, M., 2015. Proton radiobiology. *Cancers (Basel)*. <https://doi.org/10.3390/cancers7010353>
- 37 Tupone, D., Cano, G., Morrison, S.F., 2017. Thermoregulatory inversion: A novel thermoregulatory paradigm.
38 *Am. J. Physiol. - Regul. Integr. Comp. Physiol.* 312, R779–R786.
39 <https://doi.org/10.1152/ajpregu.00022.2017>
- 40 Tupone, D., Madden, C.J., Cano, G., Morrison, S.F., 2011. An orexinergic projection from perifornical
41 hypothalamus to raphe pallidus increases rat brown adipose tissue thermogenesis. *J. Neurosci.* 31, 15944–
42 15955. <https://doi.org/10.1523/JNEUROSCI.3909-11.2011>
- 43 Tupone, D., Madden, C.J., Morrison, S.F., 2013. Central activation of the A1 adenosine receptor (A1AR) induces
44 a hypothermic, torpor-like state in the rat. *J. Neurosci.* 33, 14512–14525.
45 <https://doi.org/10.1523/JNEUROSCI.1980-13.2013>
- 46 Turbill, C., Ruf, T., Smith, S., Bieber, C., 2013. Seasonal variation in telomere length of a hibernating rodent.
47 *Biol. Lett.* 9. <https://doi.org/10.1098/rsbl.2012.1095>
- 48 Turbill, C., Smith, S., Deimel, C., Ruf, T., 2012. Daily torpor is associated with telomere length change over
49 winter in Djungarian hamsters. *Biol. Lett.* 8, 304–307. <https://doi.org/10.1098/rsbl.2011.0758>
- 50 Utz, J.C., Nelson, S., O’Toole, B.J., Van Breukelen, F., 2009. Bone strength is maintained after 8 months of
51 inactivity in hibernating goldenmantled ground squirrels, *spermophilus lateralis*. *J. Exp. Biol.* 212, 2746–
52 2752. <https://doi.org/10.1242/jeb.032854>
- 53 Vicent, M.A., Borre, E.D., Swoap, S.J., 2017. Central activation of the A1 adenosine receptor in fed mice
54 recapitulates only some of the attributes of daily torpor. *J. Comp. Physiol. B Biochem. Syst. Environ.*
55 *Physiol.* 187, 835–845. <https://doi.org/10.1007/s00360-017-1084-7>
- 56 Vishwakarma, L.C., Sharma, B., Singh, V., Jaryal, A.K., Mallick, H.N., 2020. Acute sleep deprivation elevates
57
58
59
60
61
62
63
64
65

- 1
2
3
4 brain and body temperature in rats. *J. Sleep Res.* <https://doi.org/10.1111/jsr.13030>
- 5 Von Der Ohe, C.G., Darian-Smith, C., Garner, C.C., Heller, H.C., 2006. Ubiquitous and temperature-dependent
6 neural plasticity in hibernators. *J. Neurosci.* 26, 10590–10598. [https://doi.org/10.1523/JNEUROSCI.2874-](https://doi.org/10.1523/JNEUROSCI.2874-06.2006)
7 06.2006
- 8 Von Der Ohe, C.G., Garner, C.C., Darian-Smith, C., Heller, H.C., 2007. Synaptic protein dynamics in
9 hibernation. *J. Neurosci.* 27, 84–92. <https://doi.org/10.1523/JNEUROSCI.4385-06.2007>
- 10 Vuarin, P., Henry, P.Y., Perret, M., Pifferi, F., 2016. Dietary supplementation with n-3 polyunsaturated fatty acids
11 reduces torpor use in a tropical daily heterotherm. *Physiol. Biochem. Zool.* 89, 536–545.
12 <https://doi.org/10.1086/688659>
- 13 Vyazovskiy, V. V., Palchykova, S., Achermann, P., Tobler, I., Deboer, T., 2017. Different Effects of Sleep
14 Deprivation and Torpor on EEG Slow-Wave Characteristics in Djungarian Hamsters. *Cereb. Cortex* 27,
15 950–961. <https://doi.org/10.1093/cercor/bhx020>
- 16 Wang, H., Olivero, W., Wang, D., Lanzino, G., 2006. Cold as a therapeutic agent. *Acta Neurochir. (Wien)*. 148,
17 565–70; discussion 569-70. <https://doi.org/10.1007/s00701-006-0747-z>
- 18 Wang, H., Siemens, J., 2015. TRP ion channels in thermosensation, thermoregulation and metabolism.
19 Temperature. <https://doi.org/10.1080/23328940.2015.1040604>
- 20 Wang, Y., Mandelkow, E., 2016. Tau in physiology and pathology. *Nat. Rev. Neurosci.*
21 <https://doi.org/10.1038/nrn.2015.1>
- 22 Webb, G.P., Jagot, S.A., Jakobson, M.E., 1982. Fasting-induced torpor in *Mus musculus* and its implications in
23 the use of murine models for human obesity studies. *Comp. Biochem. Physiol. -- Part A Physiol.* 72, 211–
24 219. [https://doi.org/10.1016/0300-9629\(82\)90035-4](https://doi.org/10.1016/0300-9629(82)90035-4)
- 25 Weitten, M., Oudart, H., Habold, C., 2016. Maintenance of a fully functional digestive system during hibernation
26 in the European hamster, a food-storing hibernator. *Comp. Biochem. Physiol. -Part A Mol. Integr. Physiol.*
27 193, 45–51. <https://doi.org/10.1016/j.cbpa.2016.01.006>
- 28 Welsh, J., Bevelacqua, J.J., Keshavarz, M., Mortazavi, S.A.R., Mortazavi, S.M.J., 2019. Is Telomere Length a
29 Biomarker of Adaptive Response? Controversial Findings of NASA and Residents of High Background
30 Radiation Areas. *J. Biomed. Phys. Eng.* 9, 381. <https://doi.org/10.31661/jbpe.v9i3jun.1151>
- 31 Wiener, N., 1948. *Cybernetics: Or Control and Communication in the Animal and the Machine*, second ed. ed.
32 Hermann & Cie; The MIT Press, Paris; Cambridge (MA).
- 33 Wilbur, S.M., Barnes, B.M., Kitaysky, A.S., Williams, C.T., 2019. Tissue-specific telomere dynamics in
34 hibernating arctic ground squirrels (*Urocitellus parryii*). *J. Exp. Biol.* 222.
35 <https://doi.org/10.1242/jeb.204925>
- 36 Williams, B.A., Heath, J.E., 1971. Thermoregulatory responses of a hibernator to preoptic and environmental
37 temperatures. *Am. J. Physiol.* 221, 1134–1138. <https://doi.org/10.1152/ajplegacy.1971.221.4.1134>
- 38 Wojda, S.J., Gridley, R.A., McGee-Lawrence, M.E., Drummer, T.D., Hess, A., Kohl, F., Barnes, B.M., Donahue,
39 S.W., 2016. Arctic ground squirrels limit bone loss during the prolonged physical inactivity associated with
40 hibernation. *Physiol. Biochem. Zool.* 89, 72–80. <https://doi.org/10.1086/684619>
- 41 Wojda, S.J., McGee-Lawrence, M.E., Gridley, R.A., Auger, J., Black, H.L., Donahue, S.W., 2012. Yellow-bellied
42 Marmots (*Marmota flaviventris*) preserve bone strength and microstructure during hibernation. *Bone* 50,
43 182–188. <https://doi.org/10.1016/j.bone.2011.10.013>
- 44 Xin, L., Blatteis, C.M., 1992. Hypothalamic neuronal responses to interleukin-6 in tissue slices: Effects of
45 indomethacin and naloxone. *Brain Res. Bull.* 29, 27–35. [https://doi.org/10.1016/0361-9230\(92\)90005-I](https://doi.org/10.1016/0361-9230(92)90005-I)
- 46 Xu, J., Tang, Y., Qi, H., Yu, X., Liu, M., Wang, N., Lin, Y., Zhang, J., 2019. Electrophysiological properties of
47 thermosensitive neurons in slices of rat lateral parabrachial nucleus. *J. Therm. Biol.* 83, 87–94.
48 <https://doi.org/10.1016/j.jtherbio.2019.05.020>
- 49 Xu, R., Andres-Mateos, E., Mejias, R., MacDonald, E.M., Leinwand, L.A., Merriman, D.K., Fink, R.H.A., Cohn,
50 R.D., 2013. Hibernating squirrel muscle activates the endurance exercise pathway despite prolonged
51 immobilization. *Exp. Neurol.* 247, 392–401. <https://doi.org/10.1016/j.expneurol.2013.01.005>
- 52 Xue, Y., Yang, Y., Tang, Y., Ye, M., Xu, J., Zeng, Y., Zhang, J., 2016. In vitro thermosensitivity of rat lateral
53 parabrachial neurons. *Neurosci. Lett.* 619, 15–20. <https://doi.org/10.1016/j.neulet.2016.02.058>
- 54 Yakimova, K.S., Pierau, F.K., 1999. Nociceptin/orphanin FQ: Effects on thermoregulation in rats. *Methods Find.*
55 *Exp. Clin. Pharmacol.* 21, 345–352. <https://doi.org/10.1358/mf.1999.21.5.541912>
- 56
57
58
59
60
61
62
63
64
65

- 1
2
3
4 Yakimova, K.S., Sann, H., Pierau, F.K., 1998. Effects of kappa and delta opioid agonists on activity and
5 thermosensitivity of rat hypothalamic neurons. *Brain Res.* 786, 133–42. [https://doi.org/10.1016/s0006-](https://doi.org/10.1016/s0006-8993(97)01456-x)
6 8993(97)01456-x
7 Yakimova, K.S., Sann, H., Pierau, F.K., 1996. Neuronal basis for the hyperthermic effect of mu-opioid agonists in
8 rats: decrease in temperature sensitivity of warm-sensitive hypothalamic neurons. *Neurosci. Lett.* 218, 115–
9 8. [https://doi.org/10.1016/s0304-3940\(96\)13133-5](https://doi.org/10.1016/s0304-3940(96)13133-5)
10 Yanagisawa, M., Planel, E., Ishiguro, K., Fujita, S.C., 1999. Starvation induces tau hyperphosphorylation in
11 mouse brain: implications for Alzheimer’s disease. *FEBS Lett.* 461, 329–33. [https://doi.org/10.1016/s0014-](https://doi.org/10.1016/s0014-5793(99)01480-5)
12 5793(99)01480-5
13 Yasuma, Y., McCarron, R.M., Spatz, M., Hallenbeck, J.M., 1997. Effects of plasma from hibernating ground
14 squirrels on monocyte- endothelial cell adhesive interactions. *Am. J. Physiol. - Regul. Integr. Comp.*
15 *Physiol.* <https://doi.org/10.1152/ajpregu.1997.273.6.r1861>
16 Zakharova, N.M., Tarahovsky, Y.S., Fadeeva, I.S., Komelina, N.P., Khrenov, M.O., Glushkova, O. V.,
17 Prokhorov, D.A., Kutysenko, V.P., Kovtun, A.L., 2019. A pharmacological composition for induction of a
18 reversible torpor-like state and hypothermia in rats. *Life Sci.* 219, 190–198.
19 <https://doi.org/10.1016/j.lfs.2019.01.023>
20 Zakharova, N.M., Tarahovsky, Y.S., Komelina, N.P., Fadeeva, I.S., Kovtun, A.L., 2021. Long-term
21 pharmacological torpor of rats with feedback-controlled drug administration. *Life Sci. Sp. Res.* 28, 18–21.
22 <https://doi.org/10.1016/j.lssr.2020.11.002>
23 Zaretsky, D. V., Zaretskaia, M. V., DiMicco, J.A., 2003. Stimulation and blockade of GABAA receptors in the
24 raphe pallidus: Effects on body temperature, heart rate, and blood pressure in conscious rats. *Am. J. Physiol.*
25 *- Regul. Integr. Comp. Physiol.* 285, R110-6. <https://doi.org/10.1152/ajpregu.00016.2003>
26 Zhao, Y., Boulant, J.A., 2005. Temperature effects on neuronal membrane potentials and inward currents in rat
27 hypothalamic tissue slices. *J. Physiol.* 564, 245–257. <https://doi.org/10.1113/jphysiol.2004.075473>
28 Zhao, Z.D., Yang, W.Z., Gao, C., Fu, X., Zhang, W., Zhou, Q., Chen, W., Ni, X., Lin, J.K., Yang, J., Xu, X.H.,
29 Shen, W.L., 2017. A hypothalamic circuit that controls body temperature. *Proc. Natl. Acad. Sci. U. S. A.*
30 114, 2042–2047. <https://doi.org/10.1073/pnas.1616255114>
31
32
33
34
35
36

37 **Legends**

38
39 Figure 1 shows an illustrative drawing of the central thermoregulatory network. Blue lines =
40 Cold sensing pathways; Red lines = Warm sensing pathways; Yellow lines = Modulatory pathways
41
42

43 **Figures**

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

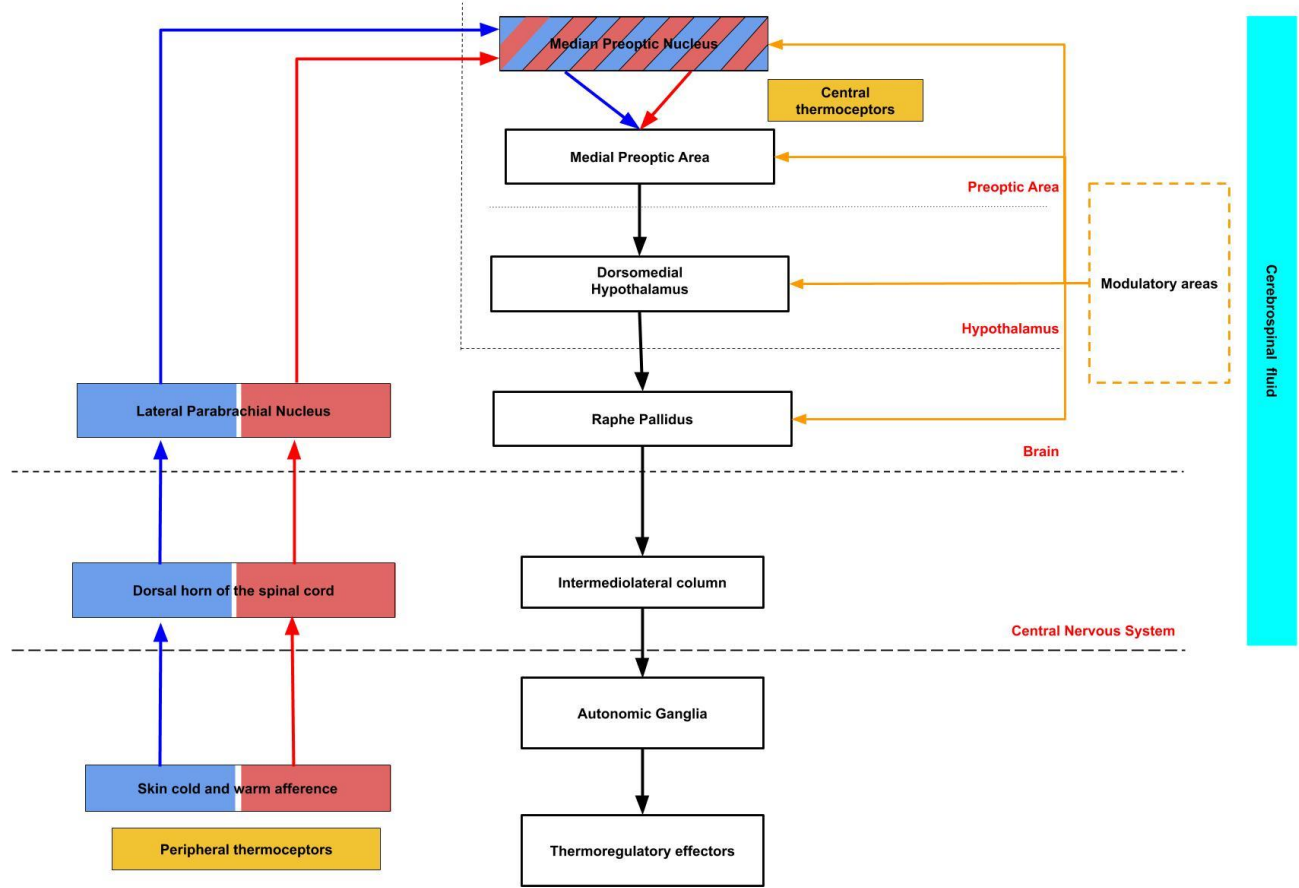


Figure 1

Figure 1

