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Hypothesis

Possible use of repeated cold stress for reducing fatigue in Chronic Fatigue Syndrome: a hypothesis

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Abstract

Background: Physiological fatigue can be defined as a reduction in the force output and/or energy-generating capacity of skeletal muscle after exertion, which may manifest itself as an inability to continue exercise or usual activities at the same intensity. A typical example of a fatigue-related disorder is chronic fatigue syndrome (CFS), a disabling condition of unknown etiology and with uncertain therapeutic options. Recent advances in elucidating pathophysiology of this disorder revealed hypofunction of the hypothalamic-pituitary-adrenal axis and that fatigue in CFS patients appears to be associated with reduced motor neurotransmission in the central nervous system (CNS) and to a smaller extent with increased fatigability of skeletal muscle. There is also some limited evidence that CFS patients may have excessive serotonergic activity in the brain and low opioid tone.

Presentation of the hypothesis: This work hypothesizes that repeated cold stress may reduce fatigue in CFS because brief exposure to cold may transiently reverse some physiological changes associated with this illness. For example, exposure to cold can activate components of the reticular activating system such as raphe nuclei and locus ceruleus, which can result in activation of behavior and increased capacity of the CNS to recruit motoneurons. Cold stress has also been shown to reduce the level of serotonin in most regions of the brain (except brainstem), which would be consistent with reduced fatigue according to animal models of exercise-related fatigue. Finally, exposure to cold increases metabolic rate and transiently activates the hypothalamic-pituitary-adrenal axis as evidenced by a temporary increase in the plasma levels of adrenocorticotropic hormone, beta-endorphin and a modest increase in cortisol. The increased opioid tone and high metabolic rate could diminish fatigue by reducing muscle pain and accelerating recovery of fatigued muscle, respectively.

Testing the hypothesis: To test the hypothesis, a treatment is proposed that consists of adapted cold showers (20 degrees Celsius, 3 minutes, preceded by a 5-minute gradual adaptation to make the procedure more comfortable) used twice daily.

Implications of the hypothesis: If testing supports the proposed hypothesis, this could advance our understanding of the mechanisms of fatigue in CFS.

Background

There seems to be no universally accepted definition of biological fatigue [1], although it is often defined as a reduction in the force output and/or energy-generating capacity of skeletal muscle after exertion, which may manifest itself as an inability to continue exercise or usual activities at the same intensity [1-4]. Fatigue is thought to be associated with a diminished contractile ability of muscles due to accumulation of lactic acid and depletion of energy stores (glycogen) [5,6] as well as with a reduction in motor neurotransmission delivered to skeletal muscle by the central nervous system (CNS), all of which can result in diminished force output [7,8]. At the level of the CNS, precise mechanisms of fatigue are not well understood, although there is some evidence that it may be associated with diminished activity of a brainstem structure called reticular activating system [9-11] and with increased levels of serotonin in the frontal cortex and hippocampus [12,13].

A typical fatigue-related disorder is chronic fatigue syndrome (CFS), a complex and disabling condition characterized by extended periods of severe fatigue unexplained by known medical causes [14]. Currently, there are no specific diagnostic tests and etiology of CFS remains elusive, although some progress has been made in elucidating its pathophysiology [15,16]. A number of studies have reported insufficient function of the hypothalamic-pituitary-adrenal (HPA) axis (e.g. lowered production of cortisol [16,17]) and a rather frequent occurrence of autonomic nervous system dysfunction in patients with CFS [16,18]. Neither lowered production of cortisol nor dysautonomia appears to be a causative factor in most CFS patients because cortisol injections and various therapeutic approaches to autonomic nervous system abnormalities have so far shown a rather limited effect on CFS symptoms [17,19,20]. Other findings about the pathophysiology of CFS suggest that abnormal fatigability in this disorder is associated with a reduced ability of the CNS to recruit motor neurons [21-23] and with some biochemical abnormalities in skeletal muscle [24-26]. In addition, there is some evidence that CFS patients may have a low opioid tone ([27-30], contrary evidence: [31,32]), as well as an increased level of serotonergic activity in the brain ([33-38], contrary evidence: [39,40]). The latter has been shown to correlate with fatigue in animal models of exercise-related fatigue [13,41-45].

This paper describes a physiological treatment, namely, exposure to moderate cold, which could have a beneficial effect on some of the above-mentioned pathological changes as explained in more detail below.

Presentation of the hypothesis

It is known that small amounts of stressful or harmful agents can be beneficial for animals, a phenomenon known as hormesis [46,47]. In particular, exposure to cold can transiently reverse several physiological changes that are often associated with CFS and therefore, the hypothesis is that repeated cold stress can reduce fatigue in CFS patients. The following is detailed theoretical evidence that appears to support this hypothesis.

1) Insufficient function of the HPA axis has been found to correlate with fatigue [48], for example, a lowered plasma level of stress hormone cortisol (secreted by adrenal glands) is one of the few consistent endocrine changes found in CFS in numerous studies [17], although the level of cortisol in CFS patients is within the normal range and therefore cannot be used as a diagnostic tool [16]. Cold stress is known to transiently activate the HPA axis [49,50] as evidenced by a brief increase in the plasma levels of adrenocorticotropic hormone [51,52] and beta-endorphin (the latter is a secreted by the pituitary gland) [53,54], as well as a modest elevation in the level of cortisol [55,56]. Some studies reported no significant change in cortisol levels following cold stress [57,58], which may be due to gender and diurnal variation of this effect [55,56]. In addition, there is some evidence of another deficiency of the HPA axis in various disorders associated with fatigue: hypofunction of corticotropin-releasing hormone-producing neurons (located in hypothalamus) [48,59,60]. Therefore, "exercising" the HPA system by repeated exposure to cold could potentially restore its normal function in CFS, or at least increase the net HPA activity (without a change in baseline activity [61]) and, possibly, reduce fatigue. For example, repeated cold stress has been shown to enhance HPA axis responsiveness to other stressors [62,63] and to enhance cortisol responses to cold stress [64].

2) Cold hydrotherapy is known to produce a significant analgesic effect [65-67], which could be beneficial in CFS, where pain symptoms are rather common [68,69]. The cold stress-induced analgesia is believed to be mediated by increased production of opioid peptide beta-endorphin, which is an endogenous pain-killer [53,55,70,71].

3) Exposure to cold is known to increase metabolic rate: for instance, head-out immersion in cold water of 20°C almost doubles metabolic rate, while at 14°C it is more than quadrupled [72]. Theoretically, the high metabolic rate may accelerate [73,74] the process of recovery of muscle tissues from fatigue in CFS [24,25,75,76] and some studies indeed show accelerated muscle recovery following immersion in cold water [77,78]. In combination with cold-induced analgesia described above, the increased metabolic rate would be expected to reduce fatigue by

both improving muscle recovery after exertion and by reducing muscle pain [79]. A cold-induced increase in cerebral metabolic rate [80] may also be consistent with reduced fatigue ([7,81] contrary evidence: [82,83]).

4) There is evidence that exposure to cold can activate some components of the brainstem arousal system [84-86] (also known as the reticular activating system [87,88]). In particular, cold stress appears to stimulate activity of serotonergic neurons of raphe nuclei [84,89-91] and noradrenergic neurons of locus ceruleus [84,92], the situation that would be consistent with activation of behavior and enhanced somatomotor function of the brain [9,87,93-96]. This could be beneficial in CFS because abnormally high fatigability of CFS patients appears to be mediated by a reduction in the ability of the CNS to generate motor neurotransmission [21-23]. It is noteworthy that in polio survivors and patients with multiple sclerosis, the presence of minor lesions in the reticular activating system correlates with severe chronic fatigue [10,97]. This kind of lesions can also cause lethargy in laboratory animals [9,88,98]. Reduced electrical activity in the reticular activating system also appears to correlate with fatigue in laboratory animals [99-101]. At present, there is no evidence that CFS patients have lesions in the reticular activating system [9,102], although there is some limited evidence of abnormalities of metabolism, blood flow, and electrical activity in the brainstem [81,103-105], the anatomical site of the reticular activating system [87,88].

5) While the increased level of serotonin in the brainstem [85] is thought to correlate with arousal and increased cortical activity [11,94,106], high levels of serotonin in other areas of the brain, particularly in the hippocampus and frontal cortex, are believed to be associated with fatigue, which is the basis of "the serotonin hypothesis of central fatigue" [12,13,41-45]. Whether high levels of brain serotonin actually cause fatigue or are merely an epiphenomenon is a subject of controversy [12,13]. With respect to cold stress, studies suggest that it reduces the level of serotonin in most regions of the brain [107,108] except the rostral brainstem [85], which would be consistent with diminished fatigue [12,13] and could be beneficial in CFS ([33-38], contrary evidence: [39,40]).

6) Exposure to cold typically causes activation of the sympathetic nervous system (SNS) [49,109], which, theoretically, can be undesirable in CFS because there is evidence of hyperactivity of some components of the SNS in CFS patients [18,110]. It should be noted that physical exercise is also known to transiently activate the SNS [111] and graded exercise appears to be beneficial in CFS [112,113]. Therefore, brief cold stress will not necessarily have adverse effects on CFS patients (more detailed discussion can be found in Additional file 1).

7) As described previously, brief cold hydrotherapy appears to be safe and does not seem to have either short-term or long-term adverse effects on health [109,114-117]. The effect of moderately cold hydrotherapy (16–23°C) on core body temperature is expected to be very small and therefore hypothermia is hardly a concern [118-120].

Testing the hypothesis

To test the hypothesis, a treatment is proposed that consists of adapted cold showers (20°C, 3 minutes, preceded by 5-minute gradual adaptation) twice a day. The detailed study protocol can be found in Additional file 2. Statistically insignificant preliminary evidence is described in Additional file 3.

Implications of the hypothesis

If statistically significant studies confirm (or refute) the hypothesis, this could further our understanding of the mechanisms of physiological fatigue and possibly contribute to the development of new therapeutic approaches to CFS.

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

The idea and writing are solely N.A.S.'s.

Additional material

Additional file 1

Sympathetic nervous system and chronic fatigue syndrome. *The file name is Additional_File_1.pdf and it contains a brief review of literature on the sympathetic nervous system abnormalities observed in patients with chronic fatigue syndrome. The file contains its own list of references separate from the main text.*

Click here for file
[http://www.biomedcentral.com/content/supplementary/1744-9081-3-55-S1.pdf]

Additional file 2

Proposed study design. *The file name is Additional_File_2.pdf and it contains a detailed protocol of the proposed study including statistical estimates of the sample size. The file contains its own list of references separate from the main text.*

Click here for file
[http://www.biomedcentral.com/content/supplementary/1744-9081-3-55-S2.pdf]

Additional file 3

Limited preliminary evidence. *The file name is Additional_File_3.pdf and it provides a detailed description of preliminary evidence that appears to support the hypothesis. The file contains its own list of references separate from the main text.*

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References

1. Weir JP, Beck TW, Cramer JT, Housh TJ: **Is fatigue all in your head? A critical review of the central governor model.** *Br J Sports Med* 2006, **40(7):**573-86; discussion 586.
2. Gandevia SC: **Some central and peripheral factors affecting human motoneuronal output in neuromuscular fatigue.** *Sports Med* 1992, **13(2):**93-98.
3. Guessous I, Favrat B, Cornuz J, Verdon F: **Fatigue: review and systematic approach to potential causes.** *Rev Med Suisse* 2006, **2(89):**2725-2731.
4. Evans WJ, Lambert CP: **Physiological basis of fatigue.** *Am J Phys Med Rehabil* 2007, **86(1 Suppl):**S29-46.
5. Schillings ML, Kalkman JS, Janssen HM, van Engelen BG, Bleijenberg G, Zwarts MJ: **Experienced and physiological fatigue in neuromuscular disorders.** *Clin Neurophysiol* 2007, **118(2):**292-300.
6. Shulman RG, Rothman DL: **The "glycogen shunt" in exercising muscle: A role for glycogen in muscle energetics and fatigue.** *Proc Natl Acad Sci U S A* 2001, **98(2):**457-461.
7. Dalsgaard MK, Secher NH: **The brain at work: A cerebral metabolic manifestation of central fatigue?** *J Neurosci Res* 2007, **85(15):**3334-9.
8. Gandevia SC: **Spinal and supraspinal factors in human muscle fatigue.** *Physiol Rev* 2001, **81(4):**1725-1789.
9. Dickinson CJ: **Chronic fatigue syndrome--aetiological aspects.** *Eur J Clin Invest* 1997, **27(4):**257-267.
10. Staub F, Bogousslavsky J: **Fatigue after stroke: a major but neglected issue.** *Cerebrovasc Dis* 2001, **12(2):**75-81.
11. Sandyk R: **Treatment with weak electromagnetic fields improves fatigue associated with multiple sclerosis.** *Int J Neurosci* 1996, **84(1-4):**177-186.
12. Meeusen R, Watson P, Hasegawa H, Roelands B, Piacentini MF: **Central fatigue: the serotonin hypothesis and beyond.** *Sports Med* 2006, **36(10):**881-909.
13. Blomstrand E: **A role for branched-chain amino acids in reducing central fatigue.** *J Nutr* 2006, **136(2):**544S-547S.
14. **Chronic fatigue syndrome: basic facts** *Centers for Disease Control and Prevention, Atlanta, GA, USA* [http://www.cdc.gov/cfs/cfsbasicfacts.htm].
15. Cho HJ, Skowera A, Cleare A, Wessely S: **Chronic fatigue syndrome: an update focusing on phenomenology and pathophysiology.** *Curr Opin Psychiatry* 2006, **19(1):**67-73.
16. **Chronic fatigue syndrome: possible causes** *Centers for Disease Control and Prevention, Atlanta, GA, USA* [http://www.cdc.gov/cfs/cfscauses.htm].
17. Cleare AJ: **The neuroendocrinology of chronic fatigue syndrome.** *Endocr Rev* 2003, **24(2):**236-252.
18. Freeman R, Komaroff AL: **Does the chronic fatigue syndrome involve the autonomic nervous system?** *Am J Med* 1997, **102(4):**357-364.
19. **Chronic fatigue syndrome: Treatment options** *Centers for Disease Control and Prevention, Atlanta, GA, USA* [http://www.cdc.gov/cfs/cfstreatmentHCP.htm].
20. Peterson PK, Pheley A, Schroeppel J, Schenck C, Marshall P, Kind A, Haugland JM, Lambrecht LJ, Swan S, Goldsmith S: **A preliminary placebo-controlled crossover trial of fludrocortisone for chronic fatigue syndrome.** *Arch Intern Med* 1998, **158(8):**908-914.
21. Schillings ML, Kalkman JS, van der Werf SP, van Engelen BG, Bleijenberg G, Zwarts MJ: **Diminished central activation during maximal voluntary contraction in chronic fatigue syndrome.** *Clin Neurophysiol* 2004, **115(11):**2518-2524.
22. Siemionow V, Fang Y, Calabrese L, Sahgal V, Yue GH: **Altered central nervous system signal during motor performance in chronic fatigue syndrome.** *Clin Neurophysiol* 2004, **115(10):**2372-2381.
23. Kent-Braun JA, Sharma KR, Weiner MW, Massie B, Miller RG: **Central basis of muscle fatigue in chronic fatigue syndrome.** *Neurology* 1993, **43(1):**125-131.
24. Wong R, Lopaschuk G, Zhu G, Walker D, Catellier D, Burton D, Teo K, Collins-Nakai R, Montague T: **Skeletal muscle metabolism in the chronic fatigue syndrome. In vivo assessment by 31P nuclear magnetic resonance spectroscopy.** *Chest* 1992, **102(6):**1716-1722.
25. Jammes Y, Steinberg JG, Mambrini O, Bregeon F, Delliaux S: **Chronic fatigue syndrome: assessment of increased oxidative stress and altered muscle excitability in response to incremental exercise.** *J Intern Med* 2005, **257(3):**299-310.
26. McCully KK, Smith S, Rajaei S, Leigh JS Jr., Natelson BH: **Blood flow and muscle metabolism in chronic fatigue syndrome.** *Clin Sci (Lond)* 2003, **104(6):**641-647.
27. Scott LV, Burnett F, Medbak S, Dinan TG: **Naloxone-mediated activation of the hypothalamic-pituitary-adrenal axis in chronic fatigue syndrome.** *Psychol Med* 1998, **28(2):**285-293.
28. Conti F, Pittoni V, Sacerdote P, Priori R, Meroni PL, Valesini G: **Decreased immunoreactive beta-endorphin in mononuclear leucocytes from patients with chronic fatigue syndrome.** *Clin Exp Rheumatol* 1998, **16(6):**729-732.
29. Panerai AE, Vecchiet J, Panzeri P, Meroni P, Scarone S, Pizzigallo E, Giamberardino MA, Sacerdote P: **Peripheral blood mononuclear cell beta-endorphin concentration is decreased in chronic fatigue syndrome and fibromyalgia but not in depression: preliminary report.** *Clin J Pain* 2002, **18(4):**270-273.
30. Parker AJ, Wessely S, Cleare AJ: **The neuroendocrinology of chronic fatigue syndrome and fibromyalgia.** *Psychol Med* 2001, **31(8):**1331-1345.
31. Inder WJ, Prickett TC, Mulder RT: **Normal opioid tone and hypothalamic-pituitary-adrenal axis function in chronic fatigue syndrome despite marked functional impairment.** *Clin Endocrinol (Oxf)* 2005, **62(3):**343-348.
32. Prieto J, Subira ML, Castilla A, Serrano M: **Naloxone-reversible monocyte dysfunction in patients with chronic fatigue syndrome.** *Scand J Immunol* 1989, **30(1):**13-20.
33. Cleare AJ, Bearn J, Allain T, McGregor A, Wessely S, Murray RM, O'Keane V: **Contrasting neuroendocrine responses in depression and chronic fatigue syndrome.** *J Affect Disord* 1995, **34(4):**283-289.
34. Bakheit AM, Behan PO, Dinan TG, Gray CE, O'Keane V: **Possible upregulation of hypothalamic 5-hydroxytryptamine receptors in patients with postviral fatigue syndrome.** *BMJ* 1992, **304(6833):**1010-1012.
35. Sharpe M, Hawton K, Clements A, Cowen PJ: **Increased brain serotonin function in men with chronic fatigue syndrome.** *BMJ* 1997, **315(7101):**164-165.
36. Spath M, Welzel D, Farber L: **Treatment of chronic fatigue syndrome with 5-HT3 receptor antagonists--preliminary results.** *Scand J Rheumatol Suppl* 2000, **113:**72-77.
37. Badawy AA, Morgan CJ, Llewelyn MB, Albuquerque SR, Farmer A: **Heterogeneity of serum tryptophan concentration and availability to the brain in patients with the chronic fatigue syndrome.** *J Psychopharmacol* 2005, **19(4):**385-391.
38. Georgiades E, Behan WM, Kilduff LP, Hadjicharalambous M, Mackie EE, Wilson J, Ward SA, Pitsiladis YP: **Chronic fatigue syndrome: new evidence for a central fatigue disorder.** *Clin Sci (Lond)* 2003, **105(2):**213-218.
39. Yatham LN, Morehouse RL, Chisholm BT, Haase DA, MacDonald DD, Marrie TJ: **Neuroendocrine assessment of serotonin (5-HT) function in chronic fatigue syndrome.** *Can J Psychiatry* 1995, **40(2):**93-96.
40. Vassallo CM, Feldman E, Peto T, Castell L, Sharpley AL, Cowen PJ: **Decreased tryptophan availability but normal post-synaptic**

5-HT2c receptor sensitivity in chronic fatigue syndrome. *Psychol Med* 2001, **31(4):**585-591.
41. Romanowski W, Grabiec S: **The role of serotonin in the mechanism of central fatigue.** *Acta Physiol Pol* 1974, **25(2):**127-134.
42. Soares DD, Coimbra CC, Marubayashi U: **Tryptophan-induced central fatigue in exercising rats is related to serotonin content in preoptic area.** *Neurosci Lett* 2007, **415(3):**274-278.
43. Fernstrom JD, Fernstrom MH: **Exercise, serum free tryptophan, and central fatigue.** *J Nutr* 2006, **136(2):**553S-559S.
44. Davis JM: **Carbohydrates, branched-chain amino acids, and endurance: the central fatigue hypothesis.** *Int J Sport Nutr* 1995, **5 Suppl:**S29-38.
45. Low D, Cable T, Purvis A: **Exercise thermoregulation and hyperprolactinaemia.** *Ergonomics* 2005, **48(11-14):**1547-1557.
46. Arumugam TV, Gleichmann M, Tang SC, Mattson MP: **Hormesis/preconditioning mechanisms, the nervous system and aging.** *Ageing Res Rev* 2006, **5(2):**165-178.
47. Leslie M: **How can we use moderate stresses to fortify humans and slow aging?** *Sci Aging Knowledge Environ* 2005, **2005(26):**nf49.
48. Swain MG: **Fatigue in chronic disease.** *Clin Sci (Lond)* 2000, **99(1):**1-8.
49. Nakamoto M: **Responses of sympathetic nervous system to cold exposure in vibration syndrome subjects and age-matched healthy controls.** *Int Arch Occup Environ Health* 1990, **62(2):**177-181.
50. Nakane T, Audhya T, Kanie N, Hollander CS: **Evidence for a role of endogenous corticotropin-releasing factor in cold, ether, immobilization, and traumatic stress.** *Proc Natl Acad Sci U S A* 1985, **82(4):**1247-1251.
51. Ohno H, Yahata T, Yamashita K, Kuroshima A: **Effect of acute cold exposure on ACTH and zinc concentrations in human plasma.** *Jpn J Physiol* 1987, **37(4):**749-755.
52. Goundasheva D, Andonova M, Ivanov V: **Changes in some parameters of the immune response in rats after cold stress.** *Zentralbl Veterinarmed B* 1994, **41(10):**670-674.
53. Vaswani KK, Richard CW 3rd, Tejwani GA: **Cold swim stress-induced changes in the levels of opioid peptides in the rat CNS and peripheral tissues.** *Pharmacol Biochem Behav* 1988, **29(1):**163-168.
54. Giagnoni G, Santagostino A, Senini R, Fumagalli P, Gori E: **Cold stress in the rat induces parallel changes in plasma and pituitary levels of endorphin and ACTH.** *Pharmacol Res Commun* 1983, **15(1):**15-21.
55. Gerra G, Volpi R, Delsignore R, Maninetti L, Caccavari R, Vourna S, Maestri D, Chiodera P, Ugolotti G, Coiro V: **Sex-related responses of beta-endorphin, ACTH, GH and PRL to cold exposure in humans.** *Acta Endocrinol (Copenh)* 1992, **126(1):**24-28.
56. Smith DJ, Deuster PA, Ryan CJ, Doubt TJ: **Prolonged whole body immersion in cold water: hormonal and metabolic changes.** *Undersea Biomed Res* 1990, **17(2):**139-147.
57. Koska J, Ksinantova L, Sebokova E, Kvetnansky R, Klimes I, Chrousos G, Pacak K: **Endocrine regulation of subcutaneous fat metabolism during cold exposure in humans.** *Ann N Y Acad Sci* 2002, **967:**500-505.
58. Marino F, Sockler JM, Fry JM: **Thermoregulatory, metabolic and sympathoadrenal responses to repeated brief exposure to cold.** *Scand J Clin Lab Invest* 1998, **58(7):**537-545.
59. Gold PW, Licinio J, Wong ML, Chrousos GP: **Corticotropin releasing hormone in the pathophysiology of melancholic and atypical depression and in the mechanism of action of antidepressant drugs.** *Ann N Y Acad Sci* 1995, **771:**716-729.
60. Neeck G, Crofford LJ: **Neuroendocrine perturbations in fibromyalgia and chronic fatigue syndrome.** *Rheum Dis Clin North Am* 2000, **26(4):**989-1002.
61. Dorfman M, Arancibia S, Fiedler JL, Lara HE: **Chronic intermittent cold stress activates ovarian sympathetic nerves and modifies ovarian follicular development in the rat.** *Biol Reprod* 2003, **68(6):**2038-2043.
62. Pardon MC, Ma S, Morilak DA: **Chronic cold stress sensitizes brain noradrenergic reactivity and noradrenergic facilitation of the HPA stress response in Wistar Kyoto rats.** *Brain Res* 2003, **971(1):**55-65.
63. Ma S, Morilak DA: **Chronic intermittent cold stress sensitises the hypothalamic-pituitary-adrenal response to a novel acute stress by enhancing noradrenergic influence in the rat paraventricular nucleus.** *J Neuroendocrinol* 2005, **17(11):**761-769.
64. Dugue B, Leppanen E: **Adaptation related to cytokines in man: effects of regular swimming in ice-cold water.** *Clin Physiol* 2000, **20(2):**114-121.
65. Truesdell LS, Bodnar RJ: **Reduction in cold-water swim analgesia following hypothalamic paraventricular nucleus lesions.** *Physiol Behav* 1987, **39(6):**727-731.
66. Kenunen OG, Prakh'e IV, Kozlovskii BL: **A change in the alarm level entails a change in behavioural strategy of mice in stress and a change in analgesia induced by it.** *Ross Fiziol Zh Im I M Sechenova* 2004, **90(12):**1555-1562.
67. LaFoy J, Geden EA: **Postepisiotomy pain: warm versus cold sitz bath.** *J Obstet Gynecol Neonatal Nurs* 1989, **18(5):**399-403.
68. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A: **The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group.** *Ann Intern Med* 1994, **121(12):**953-959.
69. Meeus M, Nijs J: **Central sensitization: a biopsychosocial explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome.** *Clin Rheumatol* 2007, **26(4):**465-473.
70. Glickman-Weiss EL, Nelson AG, Hearon CM, Goss FL, Robertson RJ: **Are beta-endorphins and thermoregulation during cold-water immersion related?** *Undersea Hyperb Med* 1993, **20(3):**205-213.
71. Pickar D, Davis GC, Schulz SC, Extein I, Wagner R, Naber D, Gold PW, van Kammen DP, Goodwin FK, Wyatt RJ, Li CH, Bunney WE Jr.: **Behavioral and biological effects of acute beta-endorphin injection in schizophrenic and depressed patients.** *Am J Psychiatry* 1981, **138(2):**160-166.
72. Sramek P, Simeckova M, Jansky L, Savlikova J, Vybiral S: **Human physiological responses to immersion into water of different temperatures.** *Eur J Appl Physiol* 2000, **81(5):**436-442.
73. St Rose JE, Murray GW, Howe SA: **Effect of alterations in metabolic rate on the duration of tolerance in neonatally injected animals.** *Int Arch Allergy Appl Immunol* 1976, **52(1-4):**183-187.
74. Vallerand AL, Zamecnik J, Jacobs I: **Plasma glucose turnover during cold stress in humans.** *J Appl Physiol* 1995, **78(4):**1296-1302.
75. McCully KK, Natelson BH: **Impaired oxygen delivery to muscle in chronic fatigue syndrome.** *Clin Sci (Lond)* 1999, **97(5):**603-8; discussion 611-3.
76. Fulle S, Mecocci P, Fano G, Vecchiet I, Vecchini A, Racciotti D, Cherubini A, Pizzigallo E, Vecchiet L, Senin U, Beal MF: **Specific oxidative alterations in vastus lateralis muscle of patients with the diagnosis of chronic fatigue syndrome.** *Free Radic Biol Med* 2000, **29(12):**1252-1259.
77. Nomura T, Kawano F, Kang MS, Lee JH, Han EY, Kim CK, Sato Y, Ohira Y: **Effects of long-term cold exposure on contractile muscles of rats.** *Jpn J Physiol* 2002, **52(1):**85-93.
78. Yanagisawa O, Niitsu M, Yoshioka H, Goto K, Kudo H, Itai Y: **The use of magnetic resonance imaging to evaluate the effects of cooling on skeletal muscle after strenuous exercise.** *Eur J Appl Physiol* 2003, **89(1):**53-62.
79. Cook DB, Nagelkirk PR, Poluri A, Mores J, Natelson BH: **The influence of aerobic fitness and fibromyalgia on cardiorespiratory and perceptual responses to exercise in patients with chronic fatigue syndrome.** *Arthritis Rheum* 2006, **54(10):**3351-3362.
80. Szelenyi Z, Donhoffer Z: **The effect of cold exposure on cerebral blood flow and cerebral available oxygen (aO2) in the rat and rabbit: thermoregulatory heat production by the brain and the possible role of neuroglia.** *Acta Physiol Acad Sci Hung* 1978, **52(4):**391-402.
81. Tirelli U, Chierichetti F, Tavio M, Simonelli C, Bianchin G, Zanco P, Ferlin G: **Brain positron emission tomography (PET) in chronic fatigue syndrome: preliminary data.** *Am J Med* 1998, **105(3A):**54S-58S.
82. Abu-Judeh HH, Levine S, Kumar M, el-Zeftawy H, Naddaf S, Lou JQ, Abdel-Dayem HM: **Comparison of SPET brain perfusion and 18F-FDG brain metabolism in patients with chronic fatigue syndrome.** *Nucl Med Commun* 1998, **19(11):**1065-1071.
83. Siessmeier T, Nix WA, Hardt J, Schreckenberger M, Egle UT, Bartenstein P: **Observer independent analysis of cerebral glucose metabolism in patients with chronic fatigue syndrome.** *J Neurol Neurosurg Psychiatry* 2003, **74(7):**922-928.

84. Yuan L, Brewer C, Pfaff D: **Immediate-early Fos protein levels in brainstem neurons of male and female gonadectomized mice subjected to cold exposure.** *Stress* 2002, **5(4):**285-294.
85. Passerin AM, Bellush LL, Henley WN: **Activation of bulbospinal serotonergic neurons during cold exposure.** *Can J Physiol Pharmacol* 1999, **77(4):**250-258.
86. Baffi JS, Palkovits M: **Fine topography of brain areas activated by cold stress. A fos immunohistochemical study in rats.** *Neuroendocrinology* 2000, **72(2):**102-113.
87. Kayama Y, Ito S, Koyama Y, Jodo E: **Tonic and phasic components of the ascending reticular activating system.** *Fukushima J Med Sci* 1991, **37(2):**59-74.
88. Siegel J: **Brain mechanisms that control sleep and waking.** *Naturwissenschaften* 2004, **91(8):**355-365.
89. Dickenson AH: **Specific responses of rat raphe neurones to skin temperature.** *J Physiol* 1977, **273(1):**277-293.
90. McAllen RM, Farrell M, Johnson JM, Trevaks D, Cole L, McKinley MJ, Jackson G, Denton DA, Egan GF: **Human medullary responses to cooling and rewarming the skin: a functional MRI study.** *Proc Natl Acad Sci U S A* 2006, **103(3):**809-813.
91. Ootsuka Y, Blessing WW: **Inhibition of medullary raphe/parapyramidal neurons prevents cutaneous vasoconstriction elicited by alerting stimuli and by cold exposure in conscious rabbits.** *Brain Res* 2005, **1051(1-2):**189-193.
92. Jiang XH, Guo SY, Xu S, Yin QZ, Ohshita Y, Naitoh M, Horibe Y, Hisamitsu T: **Sympathetic nervous system mediates cold stress-induced suppression of natural killer cytotoxicity in rats.** *Neurosci Lett* 2004, **358(1):**1-4.
93. Stone EA, Lin Y, Ahsan R, Quartermain D: **Role of locus coeruleus alpha1-adrenoceptors in motor activity in rats.** *Synapse* 2004, **54(3):**164-172.
94. Lovick TA: **The medullary raphe nuclei: a system for integration and gain control in autonomic and somatomotor responsiveness?** *Exp Physiol* 1997, **82(1):**31-41.
95. Kiyashchenko LI, Mileykovskiy BY, Lai YY, Siegel JM: **Increased and decreased muscle tone with orexin (hypocretin) microinjections in the locus coeruleus and pontine inhibitory area.** *J Neurophysiol* 2001, **85(5):**2008-2016.
96. Hornung JP: **The human raphe nuclei and the serotonergic system.** *J Chem Neuroanat* 2003, **26(4):**331-343.
97. Bruno RL, Cohen JM, Galski T, Frick NM: **The neuroanatomy of post-polio fatigue.** *Arch Phys Med Rehabil* 1994, **75(5):**498-504.
98. Szymusiak R, Iriye T, McGinty D: **Sleep-waking discharge of neurons in the posterior lateral hypothalamic area of cats.** *Brain Res Bull* 1989, **23(1-2):**111-120.
99. Derevenco P, Stoica N, Sovrea I, Imreh S: **Central and peripheral effects of 6-hydroxydopamine on exercise performance in rats.** *Psychoneuroendocrinology* 1986, **11(2):**141-153.
100. Boev VM, Krauz VA: **Functional state of the hippocampo-reticular complex during submaximal physical loading and fatigue.** *Zh Vyssh Nerv Deiat Im I P Pavlova* 1981, **31(5):**1029-1037.
101. Fornal CA, Martin-Cora FJ, Jacobs BL: **"Fatigue" of medullary but not mesencephalic raphe serotonergic neurons during locomotion in cats.** *Brain Res* 2006, **1072(1):**55-61.
102. Lewis DH, Mayberg HS, Fischer ME, Goldberg J, Ashton S, Graham MM, Buchwald D: **Monozygotic twins discordant for chronic fatigue syndrome: regional cerebral blood flow SPECT.** *Radiology* 2001, **219(3):**766-773.
103. Neri G, Bianchedi M, Croce A, Moretti A: **"Prolonged" decay test and auditory brainstem responses in the clinical diagnosis of the chronic fatigue syndrome.** *Acta Otorhinolaryngol Ital* 1996, **16(4):**317-323.
104. Bianchedi M, Croce A, Moretti A, Neri G, Barberio A, Iezzi A, Pizzigallo E: **Auditory brain stem evoked potentials in the evaluation of chronic fatigue syndrome.** *Acta Otorhinolaryngol Ital* 1995, **15(6):**403-410.
105. Costa DC, Tannock C, Brostoff J: **Brainstem perfusion is impaired in chronic fatigue syndrome.** *QJM* 1995, **88(11):**767-773.
106. O'Leary OF, Bechtholt AJ, Crowley JJ, Valentino RJ, Lucki I: **The role of noradrenergic tone in the dorsal raphe nucleus of the mouse in the acute behavioral effects of antidepressant drugs.** *Eur Neuropsychopharmacol* 2007, **17(3):**215-226.
107. Aly MS, Mohamed MI, Rahman TA, Moustafa S: **Studies of contents of norepinephrine and 5-hydroxytryptamine in brain--I. Normal and cold exposure.** *Comp Biochem Physiol C* 1985, **82(1):**155-158.
108. Toh CC: **Effects of temperature on the 5-hydroxytryptamine (serotonin) content of tissues.** *J Physiol* 1960, **151:**410-415.
109. Jansky L, Sramek P, Savlikova J, Ulicny B, Janakova H, Horky K: **Change in sympathetic activity, cardiovascular functions and plasma hormone concentrations due to cold water immersion in men.** *Eur J Appl Physiol Occup Physiol* 1996, **74(1-2):**148-152.
110. Wyller VB, Godang K, Morkrid L, Saul JP, Thaulow E, Walloe L: **Abnormal thermoregulatory responses in adolescents with chronic fatigue syndrome: relation to clinical symptoms.** *Pediatrics* 2007, **120(1):**e129-37.
111. Toth MJ, Gardner AW, Arciero PJ, Calles-Escandon J, Poehlman ET: **Gender differences in fat oxidation and sympathetic nervous system activity at rest and during submaximal exercise in older individuals.** *Clin Sci (Lond)* 1998, **95(1):**59-66.
112. Moss-Morris R, Sharon C, Tobin R, Baldi JC: **A randomized controlled graded exercise trial for chronic fatigue syndrome: outcomes and mechanisms of change.** *J Health Psychol* 2005, **10(2):**245-259.
113. Wallman KE, Morton AR, Goodman C, Grove R, Guilfoyle AM: **Randomised controlled trial of graded exercise in chronic fatigue syndrome.** *Med J Aust* 2004, **180(9):**444-448.
114. Holloszy JO, Smith EK: **Longevity of cold-exposed rats: a reevaluation of the "rate-of-living theory".** *J Appl Physiol* 1986, **61(5):**1656-1660.
115. Jansky L, Pospisilova D, Honzova S, Ulicny B, Sramek P, Zeman V, Kaminkova J: **Immune system of cold-exposed and cold-adapted humans.** *Eur J Appl Physiol Occup Physiol* 1996, **72(5-6):**445-450.
116. Castellani JW, IK MB, Rhind SG: **Cold exposure: human immune responses and intracellular cytokine expression.** *Med Sci Sports Exerc* 2002, **34(12):**2013-2020.
117. Banerjee SK, Aviles H, Fox MT, Monroy FP: **Cold stress-induced modulation of cell immunity during acute Toxoplasma gondii infection in mice.** *J Parasitol* 1999, **85(3):**442-447.
118. Doufas AG, Sessler DI: **Physiology and clinical relevance of induced hypothermia.** *Neurocrit Care* 2004, **1(4):**489-498.
119. Tikuisis P: **Heat balance precedes stabilization of body temperatures during cold water immersion.** *J Appl Physiol* 2003, **95(1):**89-96.
120. McCullough L, Arora S: **Diagnosis and treatment of hypothermia.** *Am Fam Physician* 2004, **70(12**2325-2332 [http://www.aafp.org/afp/20041215/2325.html].