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Chapter 3

The Anti-Fatigue Effect of Moderate Cooling: The Evidence, Physiological Mechanisms, and Possible Implications for the Prevention or Treatment of CFS

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Abstract

At least eight studies published since 1962 suggest that moderate cooling of the body (in most cases by means of cold water) can reduce fatigue in healthy subjects and in some groups of patients: fibromyalgia, multiple sclerosis, and rheumatoid arthritis. To date, there have been no studies on the effectiveness of this approach in CFS, aside from a pilot study in Australia, which used contrast water therapy in combination with nutritional and exercise interventions. Psychostimulant medications, the anti-fatigue therapy with the strongest level of clinical evidence for a number of disorders, do not appear to be effective in CFS patients.

The possible mechanisms of the anti-fatigue effect of cooling may involve the following: A) A reduction of the total level of serotonin in the brain, as evidenced by direct measurements in laboratory animals and by a drop of the plasma prolactin level in human subjects; this would be consistent with reduced fatigue according to "the serotonin hypothesis of central fatigue." B) Activation of stress-response pathways such as the hypothalamic-pituitary-adrenal axis and sympathetic nervous system. C) Systemic analgesia and reduced muscle pain in particular; this may be mediated by a spike in the plasma level of beta-endorphin, an opioid peptide, as well as by the gate control effects of sensory stimulation by cold water. D) Activation of components of the brainstem arousal system, such as raphe nuclei and locus ceruleus (most likely associated with activation of the sympathetic nervous system). This diffuse modulatory system controls the sleep/wake cycle and minor lesions correlate with severe chronic fatigue. E) Possible activation of

relevant dopaminergic pathways in the brain, such as those projecting to the striatum. F) Activation of the thyroid and increased metabolic rate.

Interestingly, B, D and E resemble physiological effects of psychostimulants. Importantly, A, B, C, and possibly D, seem to be relevant to the pathophysiology of CFS and suggest that repeated moderate cooling may be beneficial for the patients. Successful application of this approach in CFS would require devising a procedure that is acceptable to patients, since regular cold showers and cold-water swimming are highly stressful. If the procedure does not involve psychological distress, inhalation of cold air, and hypothermia, then it would be expected to have little or no adverse effects on health. A lifetime experiment on rats has shown that repeated moderate cooling is most likely safe, at least in healthy subjects.

1. Introduction

Therapeutic use of cold water has a long history, for example, cold water affusions and cold baths were used for the treatment of fever in Europe two centuries ago [1]. Around that time, Scottish physician James Currie noticed that immersion in cold water could act as a central nervous system stimulant [1]. More recently, in the 1960s, two studies investigated specifically the effect of body cooling on mental and physical fatigue [2,3]. The first study (Pratusevich and Shustruiskaia, 1962) showed that exposure to cold air with or without physical exercise can reduce mental fatigue in children [2]. The other study (Roundy and Cooney, 1968) demonstrated that abdominal cold packs and cold showers can reduce physical fatigue in adults [3]. After that, there seems to be a long gap in literature in this field and the effects of systemic cooling on fatigue were revisited only at the beginning of the 21th century by a series of studies that included both healthy subjects and some groups of patients [4-6]. It should be noted that there were also several published studies on the effects of local cooling on muscle fatigue in the 1950s- 70s [7-11].

The recent studies of systemic cooling were prompted in part by the observation that in some groups of patients (e.g. multiple sclerosis), fatigue can increase significantly in a warm environment [12]. This lead to the development of the cooling suit, which is applied to the torso and parts of the head and can reduce the core body temperature of a patient by 0.5-1.0 degrees Celsius by means of a circulating cooled liquid [13]. Two studies that used a small sample of multiple sclerosis patients (8-20 participants) showed that the cooling suit can reduce fatigue both in a warm and in a thermoneutral environment [4,13]. It was concluded that the cooling suit can significantly improve quality of life of multiple sclerosis patients (the majority of whom are heat-sensitive) [4]. Another series of studies investigated physiological effects of winter swimming, a practice that is rather widespread in Scandinavian countries [5,14,15]. After participants in the initial studies reported improved mood and reduced tiredness [14,15], Huttunen et al. (2004) set out to specifically investigate the effects of winter swimming on mood and fatigue [5]. In that study, a mixed group of volunteers (both healthy subjects and some patients with somatic disorders) used winter swimming 4 times per week for 4 months starting in October. The study showed statistically significant reduction of fatigue in the experimental group compared to the control group (no treatment) [5]. The experimental group included patients with rheumatoid arthritis and fibromyalgia, the disorders that are often associated with the symptom of chronic fatigue. These patients

reported reduced fatigue as a result of winter swimming, although these results most likely were not statistically significant because the size of each patient group was too small. The authors concluded that winter swimming can improve general well-being in healthy subjects and in some patients [5]. Although that study did not report adverse effects on health among the participants, winter swimming should be used with caution because it can easily cause hypothermia and the associated negative effects as described in more detail in Section 4 below. One of the more recent studies included 3 healthy participants who used cold affusions and cold showers (15-20°C) on a regular basis, one of them for as long as 19 years at the time of publication [16]. These subjects reported that cold hydrotherapy can reduce fatigue caused by physical exercise or by a febrile illness [16].

There seem to be no published studies on the effects of body cooling on patients with chronic fatigue syndrome (CFS). An unpublished observational study was conducted in Australia in the 1990s that included over a hundred CFS patients over a period of several years (Dr. Andriya M. Martinovic, Bidgerdii Community Health Service, Blackwater, QLD, Australia, unpublished data). Cold showers were part of complex protocol that included a visit to a steam room immediately before a cold shower (1-3 hot/cold cycles per session, the contrast water therapy session was repeated daily), and also a program of physical exercise and nutritional changes designed to modify essential fatty acid metabolism [17]. Average duration of enrollment in the study was 4-6 months and some patients reported improvement of physical functioning, although it would be difficult to attribute the clinical change to cold showers specifically.

It should be noted that many of the above-mentioned reports contain a small number participants and the results are not statistically significant. In summary, it can be concluded that the existing empirical data seem promising and further research is needed to confirm the anti-fatigue effect of whole-body cooling.

2. Body Cooling and Athletic Performance

Interestingly, the anecdotal evidence of reduced muscle fatigue as a result of local or systemic cooling has prompted some researchers to investigate whether this approach can improve athletic performance. Various studies have reported the effect of local muscle cooling on total work completed, fatigability, and power output of athletes [7-11,18,19]. Some reports showed reduced or unchanged power output [7,20-22], while others showed an improvement [18,19]. Two reports by Verducci (1999 and 2002) showed that cooling of relevant muscles by local application of ice can reduce fatigability and increase total power output in weight lifters and baseball pitchers [18,19]. Some investigators believe that there is an optimal muscle temperature that results in the greatest total work completed, which is thought to be around 27°C (reviewed in [18]). Studies suggest that both lower and higher temperatures result in smaller amounts of work completed by the muscle [8,10,23,24]. With respect to power output as a function of muscle temperature, there is no consensus among researchers in this field. Some studies suggest that heating of skeletal muscle can increase power output [20,25-27], while others show that heating has no effect on performance whereas cooling can reduce power output [7,22].

As for systemic cooling, two studies showed that precooling of the body before exercise [24,28] or exercising in a moderately cold environment, around 10°C [23], can increase the total work completed and delay the onset of fatigue. A recent paper by Vaile *et al.* has shown that head-out cold-water immersion (15°C for 15 min) repeated daily after bouts of exercise improved performance in twelve cyclists [6]. The authors report that this cooling approach resulted in a statistically significant improvement of both power output and total work completed by the cyclists. The control interventions were hot water immersion and passive recovery. Interestingly, contrast water therapy, i.e. alternating 1-min immersion in hot and cold water (7 cycles) within 14 minutes, has shown a similar performance-enhancing effect compared to cold water immersion [6]. The study design was a multiple-period crossover and each of the four interventions was tested for five consecutive days. The authors conclude that some types of hydrotherapy can improve recovery from exercise-induced fatigue and that their results support the use of cold water immersion and contrast water therapy as performance-enhancing techniques for athletes. It is worth mentioning that these techniques have been used by many athletes for some time now, without firm scientific evidence to support this practice [6].

All of the empirical observations discussed above raise the question of the mechanism behind the anti-fatigue effect of cooling, which is the subject of the next section.

3. Possible Mechanisms of the Anti-Fatigue Effect of Cooling

As described in more detail in the subsections below, possible mechanisms of the reduction of fatigue by body cooling can be the following: A) A reduction of the total level of serotonin in the brain, as evidenced by direct measurements in laboratory animals and by a drop of the plasma prolactin level in human subjects; this would be consistent with reduced fatigue according to “the serotonin hypothesis of central fatigue.” B) Activation of stress-response pathways such as the hypothalamic-pituitary-adrenal axis and sympathetic nervous system. C) Systemic analgesia and reduced muscle pain in particular; this may be mediated by a spike in the plasma level of beta-endorphin, an opioid peptide, as well as by the gate control effects of sensory stimulation by cold water. D) Activation of components of the brainstem arousal system, such as raphe nuclei and locus ceruleus (most likely associated with activation of the sympathetic nervous system). This diffuse modulatory system controls the sleep/wake cycle and minor lesions correlate with severe chronic fatigue. E) Possible activation of relevant dopaminergic pathways in the brain, such as those projecting to the striatum. F) Activation of the thyroid and increased metabolic rate. G) Normalization of elevated body temperature, since hyperthermia (including fever) is usually associated with fatigue.

3.a. Cerebral Serotonin and Fatigue

Studies of animal models of exercise-induced fatigue have shown that prolonged exercise (to near-exhaustion) results in an elevated extracellular level of serotonin in certain areas of

the brain, particularly in the hippocampus and frontal cortex, which led to the formulation of "the serotonin hypothesis of central fatigue" [29-35]. Since central serotonin is known to play a role in sleep, lethargy and loss of motivation, it was hypothesized that accumulation of serotonin in certain areas of the brain may cause fatigue [29]. In particular, it is known that one of the most common side effects of drugs that can increase extracellular level of serotonin in the brain is drowsiness (and sometimes also fatigue) [36,37]. These drugs include serotonin-releasing agents such as d-fenfluramine (a now defunct anti-obesity drug) and selective serotonin reuptake inhibitors (SSRIs) such as antidepressants fluoxetine and paroxetine [36,37]. Nonetheless, the studies aimed at establishing a causal connection between brain serotonin and exercise-induced fatigue were inconclusive or contradictory and, at present, it is not clear whether moderately elevated levels of brain serotonin can actually cause fatigue or merely coincide with the onset of exercise-induced fatigue [29,34]. The original serotonin hypothesis of central fatigue has been later modified to account for the role of dopamine in the development of fatigue [38], as discussed in more detail in Section 3.e. The latest version of the theory proposes that central fatigue is associated with an increase of the ratio of extracellular serotonin to dopamine in the brain [29]. It should be mentioned that some researchers take issue with the separation of fatigue into "central" (related to the CNS) and "peripheral" (related to skeletal muscle), since the mechanisms of fatigue that can be arbitrarily labeled as central and peripheral are often interrelated and mutually dependent [29]. The definition of fatigue that seems to be widely accepted in the field of sports medicine is a reduction in the force output of skeletal muscle after exertion, which will result in an inability to continue exercise at the same intensity [39-42]. The reduced force output of skeletal muscle may be caused by reduced electrical drive delivered by motoneurons [43,44] and also by the depletion of energy stores in skeletal [45,46] muscle or from the combination of these two factors.

Precisely how physical exercise can lead to the elevated level of serotonin in the brain is not well understood but the theory that is mostly supported by experimental evidence explains this effect by increased availability of plasma tryptophan for transport through the blood-brain barrier [29,32]. It is thought that increased sympathetic nervous system activity during exercise, in particular the hormone epinephrine, leads to lipolysis and the release of free fatty acids into the circulation from adipose tissue. Free fatty acids are used by skeletal muscle as a source of energy and when the muscle tissue nears depletion of glycogen stores, the uptake of free fatty acids from circulation starts to lag behind their release from adipose tissue and their plasma level rises [29]. Free fatty acids can displace tryptophan from albumin (most tryptophan is normally bound to albumin) in the blood plasma, which leads to an elevated plasma level of "free available tryptophan". This free tryptophan can then cross the blood-brain barrier and is converted into serotonin in the brain (the first reaction is catalyzed by an enzyme called tryptophan hydroxylase) [29,32]. One additional factor that is believed to play a role in this chain of events is branched-chain amino acids (valine, leucine and isoleucine). The branched-chain amino acids in the blood plasma can be depleted during the course of physical exercise and because they share the same transporter-protein in the blood-brain barrier with tryptophan, the low level of plasma branched-chain amino acids can facilitate penetration of free tryptophan through the blood-brain barrier [34]. All these events would be expected to increase the level of serotonin in the brain.

With respect to exposure to cold, studies suggest that it reduces the level of serotonin in most regions of the brain [47,48] except the rostral brainstem [49], which would be consistent with diminished fatigue according to the above-mentioned serotonin hypothesis of central fatigue [29,34]. Two studies showed that the total concentration of serotonin (intracellular plus extracellular) in the brain of laboratory animals declines after exposure to cold [47,48]. Other studies have shown that body cooling results in the drop of plasma concentration of prolactin in human subjects [50-52] (contrary evidence [53]), which would also be consistent with reduced serotonin level or activity in the brain because plasma prolactin is believed to be an indicator of cerebral serotonergic activity [35]. Some investigators have pointed out that the plasma level of prolactin is not a very reliable marker of central serotonin activity because the release of prolactin from the pituitary into the bloodstream is controlled by several other neurotransmitter systems, most notably, by the dopamine system [29,54].

It is not known how body cooling can reduce the level of serotonin in the brain, but one possibility is the reduced level or total plasma tryptophan (both free and albumin-bound) as a result of activation of the liver enzyme tryptophan pyrrolase by exposure to cold [55,56]. Another possible explanation is inhibition of serotonergic pathways in the brain due to activation of noradrenergic neurons of locus ceruleus [57-59], which may be related to activation of the sympathetic nervous system in response to cold exposure [57]. Noradrenergic neurons often have an inhibitory effect on serotonergic neurons in the brain (and vice versa) [60,61] and this kind of inhibition may result in a reduced release of serotonin into the extracellular space, and therefore reduced serotonin turnover and synthesis. Interestingly, several studies have shown that exposure to cold activates some serotonergic neurons in the reticular activating system (in some raphe nuclei) [58,62-64] and also increases the level of serotonin in a small brain region called rostral brainstem [49]. However, the decline of the total brain serotonin level that was shown in experimental animals after exposure to cold [47,48] suggests that activity of the majority of serotonergic neurons in the brain is most likely inhibited by systemic cooling of the body.

Since serotonin is believed to play an important role in the regulation of mood and pharmacological agents that increase extracellular level of cerebral serotonin (SSRIs) are used for the treatment of clinical depression [65], a legitimate question may arise whether exposure to cold can worsen mood or exacerbate symptoms of depression, since cooling can temporarily reduce serotonin content of the brain. The answer appears to be “no” because the role of serotonin in depression is rather complicated [66] and, paradoxically, a pharmacological agent that has the opposite effect to that of SSRIs, the selective serotonin reuptake *enhancer* tianeptine (brand names “Coaxil” and “Stablon”) can also serve as an effective antidepressant [67]. Additionally, several studies have shown that brief cooling of the body tends to improve rather than worsen mood in human subjects [5,14,15,68-73].

The effect of cooling on cerebral serotonin described in this subsection may be relevant to the pathophysiology of CFS because some studies have shown that this disorder is associated with excessive serotonergic activity in the brain [74-79]. Consequently, a temporary reduction of brain serotonin level could potentially be beneficial for CFS patients. It should be mentioned that some studies have failed to support this supposition [80,81], namely they could not establish an elevated cerebral serotonergic activity in CFS patients.

3.b. Stress-Response Pathways

Exposure to cold is known to activate the hypothalamic-pituitary-adrenal (HPA) axis [82,83] and many components of the sympathetic nervous system [82,84], the two stress response pathways that are believed to play a crucial role in the "fight-or-flight" response to external threats [85,86]. The sympathetic nervous system, in particular, is known to be responsible for priming the body for action by increasing the blood flow to skeletal muscle and causing vasoconstriction in most other organs and systems except brain parenchyma and heart [84,86-88]. These changes should theoretically favor improved physical performance compared to the baseline state of the body. Importantly, clinical studies have shown rather frequent occurrence of the sympathetic nervous system dysfunction in patients with CFS [89-91], but it is unclear at this point, whether this dysfunction is a primary factor in CFS or a symptom that is secondary to other factors associated with CFS, such as low physical activity and deconditioning. Therapeutic approaches aimed at correcting the sympathetic nervous system dysfunction have so far had limited success in CFS patients [92-94]. It should also be added that while moderate cooling stimulates many components of the sympathetic nervous system, it inhibits some of them, for example, the heart rate slows down (due to the baroreflex as a result of increased blood pressure) and activity of sweat glands is suppressed [95].

Dysfunction (insufficient function) of the HPA axis has also been found to correlate with fatigue [96], 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 [93]. 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) [96-98]. Nonetheless, the causal relationship between HPA hypofunction and fatigue has been difficult to establish so far [92,93]. For example, cortisol injections have shown a rather limited effect on CFS symptoms [92,93].

As mentioned above, body cooling is known to transiently activate the HPA axis [82,83] as evidenced by a brief increase in the plasma levels of adrenocorticotropic hormone [99,100] and beta-endorphin [101,102], as well as a modest elevation in the level of cortisol [103,104]. Some studies reported no significant change in cortisol levels following cold stress [105,106], which may be due to gender or diurnal variation of this effect [103,104]. Repeated cold stress has been shown to enhance HPA axis responsiveness to other stressors [107,108] and to enhance cortisol responses to combined heat-cold stress [109]. Therefore, repeated exposure to cold could potentially restore normal function of the HPA axis in CFS patients, but whether this improvement will result in reduced fatigue is not known. Similarly, repeated stimulation of the sympathetic nervous system by exposure to cold [82,84] may or may not restore its normal function in CFS patients and it is not clear if this will have any significant effect on fatigue.

3.c.The Analgesic Effect of Cooling

Cold hydrotherapy is known to produce a significant analgesic effect [110-112], and reduced muscle pain may to some extent be responsible for the reduction of fatigue that is

observed following exposure to cold. There are several possible mechanisms of cold-induced analgesia. Numerous experiments show that laboratory animals subjected to a brief cold water swim experience substantial analgesia for 1-2 hours after the procedure in experiments involving tonic pain and for 5-10 minutes in experiments with phasic pain [110,113-116]. This effect may in part mediated by a many-fold increase in the plasma level of beta-endorphin after exposure to cold [101,102,117] (also reported in humans [103,118,119]), which is an opioid peptide and an endogenous painkiller [101]. The other component of this systemic analgesic effect is non-opioid in nature and appears to be mediated by noradrenergic pathways in the spinal cord and locus ceruleus in the brain [120-122]. While the non-opioid component of analgesia appears to be attenuated with repeated cold swimming [123,124], the opioid component was shown to be augmented [123,125]. An additional possible component of cold swim-induced analgesia is the gate control effect of local sensory stimulation [126]. The gate control theory of pain suggests that pain in the foot, for example, can be relieved by stimulating sensory receptors in the foot through vibration or immersion in cold or hot water, etc [127]. Some regions in the dorsal horn of the spinal cord, called laminae, transmit signals received from both nociceptors and tactile receptors [128]. Stimulation of tactile receptors can suppress transmission of impulses received from pain fibers, in a sense “blocking the gate” for nociception [128]. This gate control effect may explain the analgesic effect of local application of ice or cold water [129-131].

This analgesic effect could be beneficial in CFS, where pain symptoms are rather common [132,133]. In particular, muscle pain is believed to be one of the contributing factors of fatigue in many CFS patients, especially those with comorbid fibromyalgia [134].

3.d. The Reticular Activating System

There is evidence that exposure to cold can activate some components of the reticular activating system [49,58,135] also known as the diffuse modulatory system. It consists of a group of nuclei located mostly in the brainstem and responsible for regulation of the sleep/wake cycle [136,137]. In particular, body cooling appears to stimulate activity of serotonergic neurons of raphe nuclei [58,62-64] and noradrenergic neurons of locus ceruleus [57-59] the changes that can lead to activation of behavior and enhanced somatomotor function of the brain [136,138-142]. In particular, exposure to cold can increase locomotor activity of laboratory animals [143]. Some studies have also reported increased alertness as a result of exposure to cold [4,144,145] in addition to reduction of fatigue [4]. Both of these effects may be related to functionality of the reticular activation system because reduced electrical activity in this system appears to correlate with fatigue in laboratory animals [146-148]. In patients with multiple sclerosis and in polio survivors, the presence of minor lesions in the reticular activating system correlates with severe chronic fatigue [149,150]. This kind of lesions can also cause lethargy in laboratory animals [137,140,151]. Psychostimulant drugs are known to activate components of the reticular activating system, which is believed to be the likely mechanism of their wakefulness-promoting and fatigue-reducing effects [152-156].

Stimulation of the diffuse modulatory system by repeated exposure to cold would be expected to enhance somatomotor function of the brain and could potentially 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 [157-159]. Existing evidence suggests that CFS patients do not have lesions in the reticular activating system [140,160], although there are some data pointing to abnormalities of metabolism, blood flow, and electrical activity in the brainstem [161-164], the anatomical site of the reticular activating system [136,137].

3.e. Dopamine and Fatigue

The strong anti-fatigue and performance-enhancing effects of amphetamine (a psychostimulant drug) have led researchers to examine the role of dopamine in fatigue [165-168]. Amphetamine is a dopamine-norepinephrine reuptake inhibitor and also a dopamine-releasing agent; administration of amphetamine quickly elevates the extracellular level of dopamine in many areas of the brain [169]. Several studies on laboratory animals indeed showed that dopamine may be involved in the development of fatigue; in particular, the extracellular dopamine level in the brain tends to decline during prolonged exercise [38,170]. Additionally, inhibition of dopaminergic activity reduces exercise performance, which can be restored by means of dopamine agonists [171,172]. Administration of amphetamine has been shown to delay the onset of fatigue and to reduce pre-existing fatigue, thus improving exercise performance in both humans and laboratory animals [165-168]. These observations led to the modified version of the serotonin hypothesis of central fatigue, which holds that fatigue may be caused by the increased ratio of cerebral serotonin to dopamine; conversely, a low ratio of central serotonin to dopamine is believed to promote arousal and motivation, resulting in improved endurance performance [29,38].

Interestingly, body cooling can affect cerebral dopamine activity, and one experiment on rats has shown that exposure to cold increases the synthesis of dopamine in the striatum by about 50% [173], which could be one of the possible mechanisms of the anti-fatigue effect of cooling. The increase in the striatal dopamine synthesis is most likely the result of increased firing rate of dopaminergic neurons that project to this brain region from the substantia nigra or from the ventral tegmental area [174]. It can be hypothesized that the activation of dopaminergic neurons of the ventral tegmental area may be responsible for reduction of fatigue because these neurons are thought to control the level of arousal (active wakefulness vs. passive wakefulness) [175].

The dopamine system also controls prolactin release from the pituitary, namely, dopaminergic neurons cause tonic inhibition of the prolactin release [54]. As was mentioned in Section 3.a, serotonergic neurons have the opposite effect and stimulate the release of prolactin from the pituitary [54]. Serotonergic neurons often have inhibitory projections to dopaminergic neurons in the brain [61]. Both dopamine antagonists (such as neuroleptic drugs) and serotonin agonists (such as SSRIs) can cause hyperprolactinemia, i.e. elevated plasma level of prolactin [176,177]. Importantly, exposure to cold has been shown to reduce the plasma level of prolactin [50-52], which can be the result of reduced serotonergic activity or enhanced dopaminergic activity or both [54]. In any of these cases, the drop of plasma prolactin would be consistent with reduced fatigue according to the latest version of the

serotonin hypothesis of central fatigue [29,38]. Interestingly, psychostimulant drugs, most of which are known to reduce fatigue [156], also reduce the plasma level of prolactin [178-180].

3.f. The Thyroid and Fatigue

Insufficient function of the thyroid gland (hypothyroidism) is typically associated with the symptom of fatigue [181], while chronically hyperactive state of the thyroid (hyperthyroidism) may be associated with higher prevalence of hypomania and mania [182]. Exposure to cold transiently activates the thyroid as evidenced by an increased plasma level of thyroid stimulating hormone, thyroxine and triiodothyronine [183-185]. This could be yet another possible mechanism of cold-induced reduction of fatigue. The thyroid hormones (mainly triiodothyronine) drive metabolism and are involved in thermogenesis (heat production) that is necessary to maintain normal core temperature of the body upon exposure to cold [186]. In particular, body cooling 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 [187]. Theoretically, the high metabolic rate may accelerate [188,189] the process of recovery of muscle tissues from fatigue in CFS [190-193] and some studies indeed show accelerated muscle recovery following immersion in cold water [194,195]. 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 [134]. It should be pointed out that, currently, there is no evidence that CFS is associated with insufficient function of the thyroid or with low cerebral metabolic rate [196-198].

3.g. Fever and Fatigue

Fever as a symptom that can result from a number of medical conditions is almost always associated with fatigue [199,200] while hyperthermia is known to induce fatigue [201-206]. The precise mechanism of hyperthermia-induced fatigue is not clear, however heating of the body can increase the level of serotonin and tryptophan in blood plasma and in the brain [207-209] and is also known to increase the plasma level of prolactin [210], the observations that seem to be consistent with the serotonin hypothesis of central fatigue [29]. These effects of hyperthermia led some investigators to hypothesize that hyperthermia may play a significant role in exercise-induced fatigue, since prolonged exercise usually increases core body temperature [35]. Hyperthermia can also increase permeability of the blood-brain barrier [209] and cause accumulation of various metabolites in the CNS that may have negative effects on its functioning. Therefore, normalizing of elevated body temperature by itself may be expected to diminish fatigue.

One of the first scientific reports of cold water treatments of fever was written by Scottish botanist and military physician William Wright (1735-1819) at the end of the 18th century [211], which was a departure from the then prevailing paradigm according to which fever should be assisted and promoted in order to allow agents of disease to come out of the body

with sweat [1]. This is what he wrote about one of his first experiments during a febrile illness that he caught on a boat near Jamaica in 1777:

"September 9th, having given the necessary directions, about three o'clock in the afternoon I stripped off all my cloaths, and threw a sea cloak loosely about me till I got upon deck, when the cloak also was laid aside: three buckets full of cold salt water were then thrown at once on me; the shock was great, but I felt immediate relief. The head-ach and other pains instantly abated, and a fine glow and diaphoresis succeeded. Towards evening, however, the febrile symptoms threatened a return, and I had recourse again to the same method, as before, with the same good effect. I now took food with an appetite, and, for the first time, had a sound night's rest" [211].

He continued the cold affusions twice a day for two additional days, to prevent a relapse [1,211]. The method was later promoted by another Scottish physician James Currie (1756-1805), who went on to test this approach on scarlet fever, smallpox, measles, influenza, as well as shipboard fevers and tropical fevers (malaria) [1]. Unfortunately, James Currie published most of his findings in his books rather than peer-reviewed journals [212].

Cold water treatments were met with initial enthusiasm, especially in Germany and were used rather widely in Central Europe and in the United States in the late 18th/early 19th century [212]. The interest gradually abated by the 1830s, and cold water treatments of fever were virtually abandoned afterwards [1]. The biographers of James Currie cite several reasons:

1. Cold affusions were too stressful and frightening for patients, and were often vehemently opposed by a patient's family [1]. Patients often preferred the less stressful tepid washings (the equivalent of modern sponging [213]) or tepid baths instead of cold water affusions [1].
2. Reports of success with febrile infections lead to indiscriminate use for other non-febrile conditions and resulted in patient discomfort and disappointing results when used in inappropriate circumstances [1]. This situation was aggravated by the fact that body temperature of patients was rarely measured at the time [1,212].
3. There were other, less stressful treatments of fever, which were often preferred by patients and doctors. Some of these other antipyretic treatments, such as James Currie's favorite bloodletting, could reduce the temperature of limbs but had no actual effect on core body temperature as we know today; these other modalities gradually replaced cold water treatments [1].

As described in Section 5, a cold water treatment may be designed such that it is effective, yet minimally stressful, for example, adapted cold showers at 20°C. This author's personal observations suggest that this method is effective in common febrile conditions such as upper respiratory tract infections [70], but, unfortunately, there is no statistically significant evidence that this procedure can serve as an effective antipyretic therapy. It is worth mentioning that physical cooling methods such as ice-water immersion and cold water spraying/evaporation are a quickest and most reliable way of lowering core body temperature known today [206,214]. Some reports show that a cooling speed of up to 0.3°C per minute can be achieved [215,216]. In modern clinical practice, cold baths are not normally used for

reducing fever (antipyretic drugs are usually prescribed [217]), although sponging with tepid water is sometimes used instead of antipyretic drugs [213]. Sponging with tepid water (around 30°C) can reduce fever within 1.5 hours and was found to be less effective than acetaminophen in one study [213]. Cold water treatments on the other hand, are routinely used in the management of heatstroke and severe hyperthermia and can quickly reduce body temperature [206,214]. Despite the cooling effect in the case of elevated body temperature [1,215,216], immersion in 16-23°C water cannot normally cause hypothermia (core body temperature of 35°C or lower) in humans, even if the immersion lasts for several hours [218]. Therefore, it can be hypothesized that cold showers or cold baths at 20°C could be used to achieve rather quick elimination of fever with minimal risk of hypothermia. The procedure may have to be repeated several times per day in order to maintain near-normal temperature [1,211]. Interestingly, there is evidence that exposure to cold can abolish febrile responses to endogenous pyrogens [219], suggesting that the antipyretic effect of exposure to cold is mediated not only by physical cooling but also by neuroendocrine changes. Further studies would be necessary to establish the safety and effectiveness of cold water treatments in febrile conditions. Finally, although CFS patients often report experiencing low-grade fever, there is no evidence that the average body temperature of CFS patients is different from normal [196,220].

4. Potential Adverse Effects of Cold Hydrotherapy

As reported in several studies, moderate (and brief) cold hydrotherapy appears to be safe and does not seem to have either short-term or long-term adverse effects on health [84,221-225]. The effect of moderately cold hydrotherapy (16-23°C) on normal core body temperature is expected to be very small and therefore hypothermia is hardly a concern [218,226,227]. A near-life-time experiment on rats by Holloszy and Smith [222], where the animals had to stand in 23°C water for 4 hours 5 days a week, showed that repeated moderate cooling does not have observable adverse effects on health and actually extended average lifespan of the rats by a statistically insignificant 5% compared to control rats [222]. Two of the biggest studies on healthy human subjects, one lasting 5 weeks (daily 1-hour immersion in 20°C water) [221] and the other 6 weeks (1-hour immersion in 14°C water 3 times a week) [223] also did not report adverse effects on health. Further studies would be necessary to assess the safety of moderate cooling in healthy subjects and in patients.

Review of available literature suggests that the key factors determining safety and comfortable application of cold hydrotherapy are the following: (A) use of moderately cold water (around 20°C), rather than very cold water (12°C and lower [228-230]); (B) gradual adaptation to cold water instead of a stressful sudden whole-body exposure [231,232]; (C) monitoring of body temperature and avoiding cold hydrotherapy in rare cases of hypothermia. Some adverse effects of exposure to cold have been reported in literature and are outlined in detail below.

1. Raynaud’s syndrome, which is characterized by abnormal sensitivity to cold, would be an obvious contraindication for cold hydrotherapy [233].

2. Prolonged exposure to acute cold can cause severe hypothermia, which has a number of negative effects on health such as hypovolemia, ataxia, atrial dysrhythmias, pulmonary edema, and mental confusion [227,234]. On the other hand, brief immersion (under 1 hour) in moderately cold water (16-23°C) appears to be safe and does not result in hypothermia in healthy human subjects. During this procedure, core body temperature stays almost unchanged during the first hour [218] due to unusual efficiency of the human thermoregulatory system [226]. However, in the elderly or people with certain metabolic disorders, there is a risk of hypothermia even in these moderate conditions, and therefore monitoring of body temperature is necessary and warming techniques such as a warm shower may be needed after cold hydrotherapy [227,234].
3. Water of 14°C and colder can cause pain in the skin [228,235] and may also cause transient slight reddening of the skin [236]. Immersion in water that is 14°C or colder will also cause hypothermia in human subjects [237].
4. As already mentioned above, exposure to acute cold such as swimming in ice-cold water can cause transient pulmonary edema in humans [238], especially after exercise [239,240]. Pulmonary edema in this case is most likely the result of severe hypothermia [227].
5. Sudden acute exposure to cold such as swimming in ice-cold water has been shown to increase permeability of the blood-brain barrier in laboratory animals [229,241]. In particular, this treatment repeated daily was shown to increase mortality of neurovirulent viral infections in mice [231,232], the effect that Ben-Nathan *et al.* attribute to the stressful nature of the sudden plunge into ice-cold water and to dramatic hypothermia induced by the cold swim [241]. Hypothermia is known to increase permeability of the blood brain barrier in normal test subjects (laboratory animals) [242].
6. Some stressful treatments such as isolation have been shown to increase permeability of the blood-brain barrier and increase mortality of neurovirulent viral infections in laboratory animals [231,241]. Therefore, it would be important to design a body cooling procedure that is not stressful, since winter swimming and sudden cold showers are known to be highly stressful [1,16].
7. Studies show that coldest months of the year are associated with higher incidence of stroke and acute heart failure and the difference is most pronounced among the elderly [243-245]. There is also evidence that immersion in cold water can cause transient arrhythmias in some patients with heart problems [246-248]. In the study by Holloszy and Smith [222], where rats were immersed in cold water repeatedly, starting from the age of 6 months to the age of 32 months, prevalence of heart disease as a possible cause of death was increased (while the prevalence of malignancies was diminished and the average lifespan of the cold-exposed rats was slightly increased).
8. There is evidence that influenza epidemics occur predominantly during the winter season, however it is not known if this is due to the exposure to cold environment or to other factors, such as changes in nutrition and lifestyle [249,250]. One possible explanation is that inhalation of cold air can compromise immune defenses of the

respiratory tract mucosa [251], and this may allow influenza virus to proliferate there freely, lysing epithelial cells and causing the corollary illness [252]. For this reason, a body cooling procedure that does not involve inhalation of cold air would not be expected to increase susceptibility to respiratory infections. For example, brief cooling of the body using 20°C water (such as a shower or immersion) in the atmosphere of room temperature air (20-25°C) is not expected to lower the temperature of the respiratory tract because core body temperature in humans will remain above 35°C [218]. Yet, this author's personal experience (unpublished) suggests that if cough is present, cold showers at 20°C may worsen this symptom.

Based on the literature cited above, the practice of winter swimming may carry some risks to health because of the psychological stress and the possibility of hypothermia. Nevertheless, it should be mentioned that the 4-month-long study of winter swimming (performed 4 times a week) did not report adverse effects on health among participants [5].

5. Conclusion

As discussed in the section about possible mechanisms of cold-induced reduction of fatigue, some of these mechanisms may be relevant to the pathophysiology of CFS. These relevant mechanisms include inhibition of cerebral serotonergic activity, activation of the HPA axis, the analgesic effect, and possibly also stimulation of the reticular activating system. The evidence for some of these effects is statistically insignificant and/or comes from animal models only and further studies would be needed for confirmation. Nonetheless, the totality of the currently available mechanistic evidence combined with the evidence of the anti-fatigue effect in healthy subjects and some groups of patients suggests that repeated moderate cooling could have some therapeutic or possibly prophylactic value for CFS patients.

A possible procedure that could test this hypothesis has been proposed by this author in a recent theoretical paper [16] and is briefly outlined below. It was designed to be minimally stressful and to carry little or no risk of hypothermia. The intervention consists of adapted cold showers, 20°C, at a constant flow rate selected from the range 16 to 24 L/min, lasting 3 minutes, and preceded by a 5-minute gradual adaptation phase (expansion of the area of contact with cold water from the feet up, to make the cold shower less shocking), the whole procedure being repeated 2 times per day (morning and afternoon, no later than 7 p.m.). Sample size estimates for the possible clinical study can be found in that same article [16]. At present, it is not known if repeated moderate cooling is beneficial for CFS patients, and this author is not aware of any ongoing studies.

Interestingly, some (but not all) of the physiological effects of body cooling resemble those of psychostimulant agents. In particular, body cooling can enhance dopaminergic activity in the striatum and can reduce the plasma level of prolactin; it stimulates components of the reticular activating system and of the sympathetic nervous system; it can increase locomotor activity of laboratory animals [143,153,253], as described in more detail above. Unfortunately, several studies have shown that psychostimulants are either not effective or

only marginally beneficial for CFS patients [254-257], despite the fact that these medications can be effective at reducing fatigue associated with such medical conditions as major depressive disorder [258-262], idiopathic Parkinson disease [263], primary biliary cirrhosis [264], Charcot-Marie-Tooth disease [265], amyotrophic lateral sclerosis [266], acquired immune deficiency syndrome [267,268], narcolepsy [269], multiple sclerosis [270-273], and occupational sleep deprivation [156,274,275]. Similarly, body cooling may or may not be effective in CFS. Further clinical studies would be needed to determine whether repeated moderate cooling has a significant clinical benefit for CFS patients. Further research would also be needed to assess the safety of this approach in healthy subjects and in patients.

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