THEORETICAL REVIEW

Exercise, sleep and cytokines: Is there a relation?

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Summary
Physical exercise is a modality of non-pharmacological treatment for sleep disorders. Contradicting results are still found in studies of the effect of exercise on sleep. Among the substances that have been described as sleep modulators, cytokines produced during the recovery period after an acute exercise session are very important. Various studies have verified that physical exercise may alter the plasma concentration of the many pro-inflammatory cytokines that may in turn modulate sleep. A number of factors seem to mediate this effect of exercise, including duration, intensity, and form of exercise, in addition to temperature and metabolic alterations. The mechanisms through which exercise promotes alterations in sleep architecture remain to be clarified. Researchers speculate that many hormones and substances produced by metabolism may affect sleep. Therefore, the object of this review is to discuss the effects of exercise and cytokines on sleep, and the relation between these two sleep-regulating components, raising the hypothesis that the alterations in sleep promoted by exercise are mediated by cytokines, which, by increasing the nREM sleep phase, would stimulate the regenerating characteristics of sleep.

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Sleep

Sleep is a functional state that comprises a complex combination of physiological and behavioral processes. It has some characteristic manifestations, such as a cyclic pattern, relative immobility and an increase in the response threshold to external stimuli. Its relevance is evident during sleep deprivation, since deprivation promotes several alterations, including a marked increase in production of stress hormones such as catecholamines and cortisol, a reduction in cognitive capacity and a reduction in the state of alertness, among others.\textsuperscript{1}

Two hypotheses attempt to explain the mechanisms involved in sleep regulation. One addresses circadian markers, while the other is related to the homeostatic effects of sleep.\textsuperscript{2} Sleep can be divided into two phases: the phase in which the electroencephalogram (EEG) records a synchronized tracing known as nonrapid eye movement (nREM) phase, and the phase in which the electroencephalogram records signals similar to those in the wake period, associated with the rapid eye movement, known as rapid eye movement (REM) sleep.\textsuperscript{2}

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Many substances may affect sleep. Among the substances that present convincing evidence of participating in sleep regulation are the cytokines, mainly interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor (TNF).2

The relation between sleep and cytokines was first established based on the observation that sleep deprivation increases the capacity of leukocytes to produce INF-gamma. This marked the beginning of research over the last 20 years on the role of many immunomodulating substances in sleep-wake behavior.

Most studies have focused on cytokines, some chemokines and neurotrophins. In addition, several growth factors have also been investigated with respect to sleep modulation, such as epidermal growth factor, fibroblast growth factor, nerve growth factor, brain derived neurotrophic factor, granulocyte-macrophage colony-stimulating factor, insulin-like growth-factor-1 (IGF-1) and others, but this review focuses on the pro-inflammatory cytokines IL-1, IL-6 and TNF-alpha.

Cytokines

Cytokines are polypeptides released by essentially all cell types. There are five different types of cytokines described in the literature and cloned. These proteins may act in a pleiotropic way or in synergy with other substances, and by modulating the production of other cytokines.3

Cytokines may influence complex neuronal actions and may modulate thermoregulation, food intake, sleep and behavioral patterns.3,4 This influence takes place both under normal and pathological conditions5 and as the result of physical exercise, which may be important in carbohydrate, fat and protein metabolism and inflammatory responses induced by exercise.

The IL-1 family, comprising IL-1alpha and beta and the antagonist receptors (IL-1ra), are produced and stored by many immune cells and other cell types.5 The increase of IL-1 plasma concentration or its exogenous administration may cause fever, sickness behavior, increased heart rate, increased blood flow in many vascular beds and increased sympathetic tone, in addition to changes in intermediate metabolism.3,5 Recent studies suggest that, playing an important role in training, this cytokine may be responsible for some overtraining syndrome signals.5,6 The effects of IL-1 can be reversed by treatment with IL-1Ra, which is an antagonist of IL-1 and whose function is to prevent IL-1 binding to its specific receptors.3

Tumor necrosis factor (TNF-alpha) is produced mainly by phagocytic cells, but other cells such as the lymphocytes, natural killer (NK) cells, endothelial and neural cells may have the capacity to produce it as well.5 In addition, it is a very potent endogenous pyrogen, and may promote changes in physiological temperature set point.7 Moreover, tissues that present marked cachexia show high TNF-alpha activity, as observed in catabolic conditions such as cancer and systemic inflammatory diseases.5

In addition to temperature regulation, IL-6 has several other functions, including the modulation of the metabolism of proteins, carbohydrates and fats. Moreover, it is one of the most powerful mediators of the acute phase response; thus, IL-6 has a significant role in the regulation of the inflammatory response.5 However, due to its capacity to stimulate the hypothalamus–pituitary–adrenal axis to produce cortisol and anti-inflammatory cytokines such as interleukin-4 (IL-4) and interleukin-10 (IL-10), it also has anti-inflammatory properties,5 demonstrating its crucial role in the regulation of the inflammatory response.

The hypothesis that the administration of several kinds of cytokines could induce alterations in the
nervous system (NS) is based on observations that treatment with some cytokines promotes neuroendocrine alterations, and from studies showing the existence of receptors for these cytokines in many areas of the brain. Additional studies have shown that pro-inflammatory cytokines in high concentrations produce a decrease in the transendothelial electrical resistance, increasing the permeability of the brain barrier.

Cytokines can penetrate the blood–brain-barrier, or they can act indirectly by stimulating the production of chemical messengers (second messengers) that carry the information to the target cell. Finally, we should not disregard the hypothesis that cytokines are produced within the brain itself in response to neuronal activity.

A new hypothesis has recently been proposed to explain the mechanism of action of cytokines on the nervous system. Many studies have shown the existence of an afferent neural pathway by which inflammation in the peritoneal cavity might influence the brain. Subdiaphragmatic transection of the vagus produces reduction of fever, sleep, nocturnal excretion of norepinephrine, as well as the hypothalamic production of IL-1 induced by lipopolysaccharides (LPS) in the peritoneal cavity, validating this hypothesis. These alterations are not due to the reduction in the circulating levels of cytokine or to the attenuation of the inflammatory response induced by LPS, but rather to the impediment of translation of cytokine in the brain.

### Exercise and sleep

The American Sleep Disorders Association considers physical exercise to be a modality of non-pharmacological treatment for sleep disorders. However, conflicting results are still found in studies on the effects of exercise on sleep, since methodological differences such as the time of day at which the exercise is performed, the form, intensity and duration of the exercise and different levels of individual physical fitness do not allow for adequate comparisons.

Moreover, little attention has been given to the interaction between the endocrine, immune and cardiovascular systems in sleep regulation of individuals who perform acute exercise or are training.

Acute physical exercise results in a transient reduction of sleepiness that depends on the intensity and the time of day at which the exercise is performed. This reduced sleepiness might be due to the fact that physical exercise increases total sleep time, delays REM sleep, increases stage 4 and reduces REM sleep time when we compare sedentary and physically active individuals. Moreover, it seems that exercise acts indirectly on the modulation of factors associated with sleep disorders, such as depression, rate of breathing disorders in individuals with sleep apnea and others.

The effect of exercise on trained subjects seems to be less pronounced, but is characterized by an increase in the total sleep time, a longer REM sleep latency, a reduction of REM sleep and an increase of slow wave sleep.

Although a recent study suggests that acute bouts of vigorous exercise do not affect the sleep of trained cyclists, classical studies show that, based on the recommendations regarding sleep hygiene, the time at which the exercise is performed may be crucial in the modulation of sleep, since previous studies point to the fact that exercise performed in the morning can improve sleep, as opposed to exercise performed in the evening.

Even though there is evidence that training promotes changes in the sleep pattern, it is still not clear whether the improvement observed after a period of training is due to the direct influence of exercise on sleep or if it takes place through the improvement of conditions that may negatively influence sleep, such as obesity and depression.

There are at present two main hypotheses that try to explain the effects of physical exercise on the pattern and quality of sleep: the thermoregulatory hypothesis and the metabolic hypothesis. According to the thermoregulatory hypothesis, the onset of sleep is associated with peripheral heat loss through vasodilation and increase of sweat, along with a reduction of the basal metabolic rate and body temperature. However, according to Driver and Taylor, even though this hypothesis has great importance for people considered to be poor sleepers, or people with sleep disorders, it seems to be less effective for those considered to be good sleepers.

On the other hand, the metabolic hypothesis suggests that sleep, through the reduction of metabolic demands, might restore and preserve the energy that would be connected to slow wave sleep and would be proportional to the increase of energetic expenditure during the day.

The mechanisms by which physical exercise promotes changes in sleep architecture are not completely known. It is speculated that many hormones, substances produced by metabolism such as those in response to exogenous drugs,
might affect sleep, although many studies have shown that the number of substances that significantly affect the sleep pattern is small. The cytokines are among the substances that play an effective role in the regulation of sleep.

Cytokines and sleep

Physiological, biochemical and cellular data indicate the influence of at least three cytokines upon sleep-wake behavior and regulation of sleep: IL-1, IL-6, and TNF-α. However, cytokine-induced sleep regulation has been suggested to be dose dependent. The pro-inflammatory cytokines, especially IL-1 and TNF-α, may influence sleep by controlling body temperature and through other mechanisms. This influence of cytokines upon sleep may occur direct or indirectly by cytokine actions.

Most experiments have been carried out using intracerebroventricular injections, but studies using intraperitoneal cytokine treatment have obtained similar results. IL-1 and TNF-α have similar mechanisms of action. Treatment with low concentrations of IL-1 and TNF-α increases Ca²⁺ flux, a critical feature of transmitter release in specific sites such as hypothalamic neurons regulating sleep-wake behavior. GABAergic neurons respond to IL-1 in a Ca²⁺-dependent manner to alter GABAergic neurotransmission. TNF-α may help to maintain Ca²⁺ homeostasis; in vitro this cytokine increases cytoplasmatic Ca²⁺ by AMPA and KCl dynamics.

IL-1 cerebrospinal and plasma levels and mRNA expression in brain vary in phase with circadian rhythms. In humans, plasma levels of IL-1 peak at the onset of sleep. IL-1 exogenous administration increases nREM sleep in several mammalian species and is linked to increases in EEG slow-wave amplitudes, supranormal EEG waves reflecting the intensity of nREM sleep. On the other hand, IL-1 inhibition may reduce spontaneous sleep, inhibit sleep rebound after deprivation and attenuate the nREM response induced by microbial products or mild increase in ambient temperature. IL-1 may increase nREM sleep by partial impairment of the activity of wake-related neurons and by activating at least a subset of sleep-related neurons in the preoptic area/basal forebrain.

Another important pro-inflammatory cytokine in sleep regulation is TNF-α. There is a diurnal rhythm of TNF-α in plasma, and the ability of monocytes to produce TNF-α is coupled to sleep-wake behavior and increases during sleep deprivation. Similar to IL-1, TNF-α action in sleep regulation is associated with nREM sleep modulation. Like IL-1, TNF-α exogenous administration increases the duration of nREM. In addition, TNF-α administration in somatosensory cortex has been shown to increase slow waves during nREM sleep, but the fact that this is not followed by altered time spent in wake suggests that the action of TNF-α in cortical neurons is independent from its effect on other cerebral structures such as hypothalamus.

Recent studies suggest that IL-6 may be associated with alterations in sleep during pathological conditions or while IL-6 levels are increased. IL-6 plasma concentration displays a diurnal rhythm, with peak levels during sleep and nadirs during wakefulness. These and other findings suggest a potential role for IL-6 as a modulator of sleep. Although, the first studies to determine the impact of IL-6 on sleep did not confirm such a role. The basis of this discrepancy are not known, but one possible explanation is the fact these studies used recombinant IL-6 from other species, which may be inefficient in human studies due to potential differences in the binding of IL-6 to its receptor complex; recombinant IL-6 from one species displays a lack of effects on sleep-wake behavior when used in non-homologous species. On the other hand, rats treated with recombinant IL-6 from rats at dark onset present fever and altered nREM sleep in a dose-dependent manner. This action upon nREM is biphasic. There is an initial increase in amount of time spent in nREM sleep followed by nREM sleep impairment. REM sleep is not influenced by IL-6.

In addition, IL-6 may have other functions in sleep modulation. In fact, many of the responses initiated by IL-1 and TNF-α are mediated by IL-6, for example, IL-6 is downstream of IL-1 and TNF-α signaling induced by immune and metabolic challenges. IL-6 is important for an effective response to LPS-induced fever, increasing nREM sleep and decreasing REM sleep. Interestingly, the magnitude of this response depends on whether LPS is administered prior to light onset or dark onset. However, IL-6 KO mice stimulated with LPS present a different response, with hypothermia after dark onset administration, attenuated increase in nREM sleep and suppression of REM sleep.

Some papers suggest that cytokines may be involved in changes of sleep during pathological conditions. IL-6 and TNF plasma concentrations are increased in humans with sleep disorders linked to excessive daytime sleepiness. This increase is important in several pathologies as such sleep apnea, narcolepsy and obesity. In addition, IL-6 exogenous administration in humans in the evening is associated with fatigue and a sleep disturbance.
effect in the first-half of the night; however, this IL-6 effect may be mediated by hypothalamic pituitary adrenal (HPA) activation induced by increase in IL-6 that promotes insomnia, fatigue and poor sleep. The greater HPA activation induced by IL-6 is associated with an increase in body temperature, decreasing the amount of nREM sleep and increasing wakefulness, confirming that insomnia is associated with higher cytokine plasma concentration.

In addition, sleep apnea was associated with increases in IL-6 and TNF-α plasma concentration independent from obesity. In obese humans, visceral fat predisposes them to the development of sleep apnea since apneic obese humans present higher visceral fat stores closely associated with increases in IL-6 and TNF-α elevated plasma concentration and insulin resistance, dyslipidemia, hypertension, diabetes types II and cardio-pathologies—all diseases linked to sleep apnea.

Finally, in a healthy population a modest decrease in sleep time appears to be a characteristic of modern civilization and globalized world economy. In consequence, this decrease in sleep time is associated with an increase in sleepiness, decrease in psychomotor performance and increase mainly in secretions of the pro-inflammatory cytokines IL-6 and TNF-α21 showing again the importance of these cytokines in the development of sleep disorders as well as in the existing strong relation between several physiological systems such as the immune, endocrine, and nervous systems.

Indirectly, cytokines modulate sleep, mediating the output of neurotransmitters such as serotonin. Serotonin regulates several functions such as physiological processes and complex behavior including sleep-wake behavior. The serotonin release during wakefulness promotes wakefulness per se but triggers subsequent sleep via actions on other sleep promoting systems.

There is a strong bi-directional interaction between IL-1 and the serotonin system at various levels, with important consequences on sleep-wake behavior. IL-1 induces serotonin release in several cerebral areas including the hypothalamus while on the other hand it is possible that for total IL-1 action an intact serotonergic system is necessary. In fact, serotonin depletion in brain or blockade of serotonin 5-HT2 receptor promotes partial impairment of IL-1 induced nREM sleep and may inhibit IL-1 mRNA expression in discrete rat brain areas. In addition, many cerebral structures contain IL-1 receptors in addition to serotonin receptors. IL-1 microinjected into the raphe nucleus, which contains serotonergic neurons, increases nREM sleep. This IL-1 effect upon serotonergic neurons from the raphe nucleus is very quick (1–2 min), while the firing rates of these neurons under these conditions are reduced by about 50%; however, these effects are reversible after an IL-1 washout period.

Cytokines and exercise

Plasma concentrations of many cytokines are changed by acute bouts of exercise. The increase in IL-1 plasma concentration may range from a slight increase to an increase of 2.1 times one hour after a marathon race. Physical exercise promotes an increase in the mRNA expression of this cytokine in muscle tissue. There is still controversy regarding the time the plasma concentration of IL-1 takes to return to the basal level after an exercise-related increase, but studies have shown that this period may vary from hours to 5 days. This difference occurs since it has been suggested that the cells which produce IL-1 might store it, not releasing during or immediately after the exercise, so that such late liberation may contribute to an extended elevation of IL-1 plasma concentration.

IL-6 is the most studied cytokine associated with physical exercise. Many studies have investigated the effects of different forms and intensities of exercise on its plasma concentration and tissue expression. The effects of physical exercise seem to be mediated by intensity as well as the duration of effort, the muscle mass involved and the individual physical fitness.

Increases in IL-6 over 100 times above resting values have been found after exhaustive exercise such as marathon races, after moderate exercise intensity (60–65% VO2 max) and resistance exercise, and may last for up to 72 h after the end of the exercise, this increase can be reduced with carbohydrate or vitamin C and E supplementation.

In addition, studies have shown that the regulation of IL-6 release by skeletal muscle might be mediated by autocrine mechanisms, since the infusion of IL-6 increases the mRNA expression of IL-6 in skeletal muscle. Moreover, other regions and cells such as monocytes, fatty tissue, and the brain might contribute, to a small degree, to the increase of IL-6 plasma concentration observed after an exercise session. However, as in the case of IL-1, studies have shown an increase in the intracellular concentration of IL-6, suggesting that cytokine plasma concentration does not necessarily depend on the immediate induction of mRNA expression.

Although some studies show skeletal muscle TNF-α release, unlike IL-6, TNF-α is not released
primarily by the skeletal muscle during exercise. The modulation of TNF-α concentration through exercise might be influenced by the intensity and mainly by the duration of the effort. Most studies have shown an increase in the plasma and urinary concentrations of TNF-α or in the production stimulated by exercise in activities that range from 15 min to about 3.5 h. This increase may occur immediately after the end of exercise or later on, after a recovery period, since studies show that a TNF-α peak might occur up to 72 h after the end of the exercise.

Although many studies focus on the effects of chronic exercise or training on output and plasma cytokine concentration, much less is known about effects of the training. There are no studies assaying the plasma pro-inflammatory cytokines in healthy people while some studies suggest that the pro-inflammatory cytokine plasma concentration may decrease after physical aerobic training in persons with chronic diseases such as obesity, congestive heart failure and other mainly IL-6 and TNF-α. In contrast, some studies showed that moderate training does not change plasma pro-inflammatory cytokines. Several factors may be responsible for this discrepancy including the duration of the training, gender, age, fitness and nutritional state of the volunteers.

Despite the importance of IL-1 and TNF-α, the majority of studies on the effects of training on pro-inflammatory cytokines are focused on IL-6. Several studies found a negative association between the amount of physical training and basal plasma IL-6 concentration, while other studies showed that basal IL-6 concentration is more closely associated with physical inactivity than other cytokines associated with obesity and chronic diseases. The plasma IL-6 concentration and mRNA from skeletal muscle and adipose tissue is decreased after training in healthy and ill people, however, is controversial since other studies did not observe changes in response to training. On the other hand, it seems the exercise-induced increase of plasma IL-6 is attenuated by training while there is up-regulation of IL-6 receptor mRNA in skeletal muscle. However, it is not known if the enhanced IL-6R expression following training occurs in several tissues or only within the trained skeletal muscle.

Cytokines, sleep and exercise

In the last few years, there has been a great effort to understand the biochemical mechanisms of the sleep, as well as an increased effort to understand the importance of cytokines in the regulation of mechanisms that control sleep. With the large demands imposed by modern society, time spent sleeping has diminished gradually. This condition can be associated with several behavioural and neuroendocrine changes linked to the stress promoted by the diminution of sleep time that, if maintained for a long period of time may be associated with the development of sleep disturbances such as insomnia and apnea in cases of obesity.

Physical exercise, mainly when carried out chronically, may have an important role as an inexpensive and non-pharmacological approach to reducing sleep disturbances. However, controversies still exist in the literature about intensity, duration and schedule of the day in which the exercise should be carried out. Beyond these methodological concerns the basic mechanism by which exercise may beneficially impact sleep is still not clearly understood.

Despite the hypotheses of thermoregulation and of energy expenditure explaining the influence of exercise upon sleep, we propose that modulation may be mediated by other factors such as cytokines, especially pro-inflammatory cytokines that are strongly influenced by physical exercise.

This proposition would justify the dual effect of physical exercise and training upon sleep. In fact, even though studies have described several benefits of exercise on sleep, this is true only for moderate activities. When exercise is performed in a strenuous way, it might bring about harmful effects.

Acute exercise with intensity between 50% and 80% of the maximal oxygen consumption (VO₂ Max) for time over 80 min results in a transitory decrease in sleepiness that is dependent on the exercise load, and more accentuated when the exercise is performed at night. These changes are similar to those observed in the conditions that occur during an increase of IL-1, IL-6 and TNF-α plasma concentration. Pro-inflammatory cytokine concentration, in particular IL-6, increases after exercise. At low concentrations, those cytokines can prompt drowsiness. However at higher concentrations produced by greater exercise loads, IL-6 can be associated with wakefulness.

The changes induced by the physical exercise that we speculate would be mediated by pro-inflammatory cytokines may be the function of the direct action of these cytokines on sleep regulation, or indirectly by the action of these cytokines on HPA activation to increase body temperature, decrease the amount of nREM sleep and increase wakefulness.
In fact, during physical exercise an unquestionable homeostatic break results in release of several hormones, mainly those associated with the stress response. The stress response induced by exercise is mediated by several factors, such as glycemia, increased body temperature and cellular damage in skeletal muscle. Exercise induces an increase in pro-inflammatory cytokine levels and results in corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and cortisol release, whose increase is dependent mainly on the duration of the exercise, as opposed to catecholamines, which increases during exercise and is reverted a few minutes after the end. The hormones from the HPA axis, in particular cortisol, need several hours to days for return to the values at the beginning of the exercise.

Studies show that in healthy individuals CRH administration and high doses of hydrocortisone decrease slow wave sleep; however, the mechanisms of that interaction are still not well understood since they seem to be dependent on the mediators of hormone feedback upon CRH and therefore on the cortisol effect on the nocturnal CRH release, suggesting that other mechanisms are involved after chronic bouts of exercise.

Therefore, it was evident that in order to understand the mechanisms that may modulate the effects of exercise upon sleep, there must be taken into account not only the intensity and duration of the exercise, but also the period of rest that would be sufficient for the re-establishment of rest concentrations of the substances, mainly cytokines, that are likely to regulate the sleep response to acute exercise.

Regarding the effects of training upon sleep, some studies suggest that chronic cytokine increase, mainly of IL-6, is associated with the development of pathologies responsible for sleep disturbances. On the other hand, physical training seems to promote improvement in the quality of the sleep, but only in persons with moderate sleep complaints. Recently, it was suggested that moderate training may revert the chronic inflammation that accompanies some pathologies such as obesity. This hypothesis of a partial reduction of inflammation in chronic illnesses, is justified by two aspects: pro-inflammatory cytokine plasma concentrations decreased simultaneously with an increase in anti-inflammatory cytokine plasma concentrations, in addition to an increase in receptor antagonists. Through this mechanism it is possible to speculate that physical training per se, by decreasing IL-6 and TNF-α plasma concentration, may decrease some disturbances of sleep. However, the effects of training upon sleep are not evident before 8 weeks of training, suggesting that the training effect may be dependent on the overload training and global overload training and more evident in persons with elevated pro-inflammatory cytokine plasma concentrations caused by sleep apnea, insomnia and other pathologies associated with increased IL-6 plasma concentration.

In contrast to the effects of moderate training promoting improvement in the quality of the sleep, athletes submitted to elevated training overload without appropriate rest may suffer from a syndrome named overreaching when overtraining persists for long periods of time. Among the countless alterations related by overtrained athletes are neuroendocrine changes, chronic fatigue and significant sporting performance impairment.

The physiopathological mechanisms responsible for the development of overtraining are not well known but it is speculated to be the consequence of an imbalance in the neuroendocrine axis. In fact, it has been proposed that pro-inflammatory cytokines responsible will promote the signals and symptoms of overtraining, promoting a systemic inflammatory response as a consequence of the insufficient recovery time. Sleep disorders, specifically short sleep time and poor sleep quality are common complaints among athletes suffering from overtraining. Therefore, further investigations are needed regarding the interaction between the immune system, mainly cytokines, and exercise, and between the inflammatory response caused by exercise and sleep regulation.

As discussed in this review, the increase in plasma pro-inflammatory cytokine concentration has been associated with sleep disturbance in pathological conditions, such as severe and chronic sleepiness, apnea and infections as well as in experimental studies with healthy individuals. In these conditions of chronic cytokine increase, the regulation of the mechanism that modulates sleep might act in a specific cerebral zone that regulates sleep or indirectly and dynamically change the profile of several systems that include neurotransmitters, peptides and hormones.

Given all the issues raised in this review, new studies are necessary, which should be designed specifically to evaluate whether the increase of cytokines induced by acute exercise or moderate and exhaustive training can modulate sleep and confirm the hypothesis that sleep disorders, under these circumstances, might be caused, among other mechanisms, by the chronic increase of pro-inflammatory cytokines.
Practice points

1. Cytokines are polypeptides released by almost every cell type. They may influence a complex neuronal network acting on thermoregulation, food intake, sleep and behavioral patterns.

2. Studies demonstrate that at least three cytokines are directly involved in sleep regulation: IL-1, IL-6 and TNF.

3. There are conflicting results in studies on the effects of exercise on sleep, since methodological differences such as the time of day at which the exercise is performed, the form, intensity and duration of the exercise and the level of individual physical fitness do not allow for adequate comparisons.

4. Acute exercise promotes an increase in pro-inflammatory cytokines IL-1, IL-6 and TNF-α concentration and may maintain this elevation several hours after the exercise bout.

Research agenda

1. Studies should be conducted to determine direct actions of pro-inflammatory cytokines on sleep after moderate and exhaustive exercise.

2. The importance of cytokines as mediators of sleep and their association with sleep disturbance during overtraining syndrome needs to be elucidated.

3. The importance of anti-inflammatory cytokines should be investigated as modulators of inflammatory/anti-inflammatory balance during rest.

4. The impact of moderate physical training upon sleep disturbance modulated by cytokines needs to be determined.

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*The most important references are denoted by an asterisk.
Physical exercise, sleep and cytokines


