A SINGLE BOUT OF EXERCISE

AND ENERGY AND FATIGUE STATES: QUANTIFYING THE EFFECT AND TESTING HISTAMINE AS A MECHANISM

by

BRYAN DAVID LOY

(Under the Direction of Patrick J. O'Connor)

ABSTRACT

This dissertation quantified the effect of a single bout of exercise on energy and fatigue mood states, and then tested whether histamine binding to the H_1 receptor is a mechanism that explains the effect. In a systematic review and meta-analysis of 16 studies, it was concluded that acute exercise can increase energy, and the size of the standardized effect was $\Delta = 0.47$ (95% CI = 0.39, 0.56). The effect on energy was homogeneous and moderate, while the effect on fatigue was small and heterogeneous, $\Delta = 0.03$ (95% CI = -0.08, 0.13). Fatigue was only reduced when light or moderate intensity exercise was performed for at least 20 minutes in people with elevated baseline fatigue. The findings highlighted the usefulness of measuring both energy and fatigue changes after exercise, provided evidence that energy and fatigue are separate but related states, and suggested that changes in these states arise through different mechanisms.

A strong inference experiment was conducted next to determine if blocking brain histamine from binding to H_1 receptors would prevent expected exercise-induced increases in energy and reductions in fatigue fatigue. Doxepin hydrochloride (6 mg) or placebo was given to 20 women with elevated fatigue and low energy before they completed 30 minutes of light

intensity cycling exercise. Changes in mental fatigue, but not mental or physical energy, were blocked with doxepin administration. Doxepin also blocked exercise-induced increases in motivation for cognitive work. The findings suggest that exercise-induced histamine binding to brain H_1 receptors has (i) a significant role in reducing mental fatigue and increasing motivation for cognitive work after exercise, and (ii) little effect on mental energy defined as a mood state or inferred from performance on an attention task and related processes requiring visual perceptual processing efficiency and motor speed.

INDEX WORDS: attention, cognition, cycling, doxepin, meta-analysis, motivation, vigor

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DEDICATION

To Mom, Dad, and Sean. Thank you for your love and support.

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CHAPTER 1

INTRODUCTION

Negative effects of pathological mental fatigue have been formally recognized since at least the year 1893 (8). The reported effects of fatigue at that time included i) depression and lowered emotional tone, ii) diminished voluntary control of attention, iii) worry and hypochondria, iv) physical and mental irritability and restlessness, v) reduced sensitivity to stimuli, and vi) mental dullness (8). It has recently been noted that pathological fatigue often cannot be attributed to a single medical condition (1) and the causes of fatigue symptoms among otherwise healthy individuals often are multidimensional. These causes include chronic sleep loss, medications, illness, depression and physical inactivity (21). Fatigue-related impairments negatively impact the safety and productively of society by impairing performance at work (24) and school (2), and increasing accident rates (27).

It has been challenging to precisely identify the prevalence and severity of fatigue due to a lack of standardization in fatigue assessment (17). One study collected data from 1974-1975 and measured fatigue in a large representative sample of over 2,000 people in the United States aged 25-74 years. Fatigue was assessed with a single item in which participants rated the frequency they felt tired or worn out. Responses ranged from (a) “all the time” to (f) “none of the time”. People who answered either “all the time”, “most of the time”, or “quite a bit of the time” were labeled as fatigued. Significantly more women (20.4%) than men (14.3%) suffered from fatigue (6).

Fatigue is a symptom of many physical illnesses (17). Underestimation of the prevalence of fatigue symptoms in medical studies and practice could occur because individuals do not report all symptoms to medical providers (29). In prior epidemiological research, fatigue was positively associated with measures of depression, anxiety, and stress and these findings were independent of sex. For men, fatigue was positively associated with chronic arthritis, asthma, emphysema, and anemia. Arthritis and anemia were positively associated with fatigue in women (6).

Epidemiological studies have consistently found that physical inactivity is positively related to fatigue symptoms (21). For instance, in a community sample of almost 2,400 people, those who reported they were quite physically inactive during a usual day were twice as likely to be categorized as fatigued (6). A weakness of the current epidemiological evidence is that many studies have considered physical activity and fatigue associations in isolation and ignored that correlations among related factors, such as sleep or illness, may exist (17).

Myalgic Encephalomyelitis or Chronic Fatigue Syndrome (ME/CFS) is a disorder that lies at one extreme end of the energy-fatigue continuum (4, 5, 12, 17, 25). ME/CFS is characterized as a new onset of persistent fatigue that lasts for at least 6 months in someone who has no previous history of such symptoms. Other diseases or conditions must also be ruled out as potential causes of fatigue. Minor symptoms must also be met that include low grade fever, swelling of the lymph nodes, sleep disturbance, generalized headache, and muscle weakness or discomfort (15). ME/CFS has also been recently reconceptualized as Systemic Exertion Intolerance Disease to reflect the predominant symptom of post-exertional malaise (7, 28). The prevalence of those meeting the full criteria for ME/CFS is low. Various estimates of prevalence suggest 0.3-1.8% of hospital or clinic visitors may be diagnosed with ME/CFS (30). Others

argue that some of these cases may include individuals who symptoms lie at the extreme of the fatigue continuum, but these cases may not represent the distinct disorder of ME/CFS (17). One study of 13,538 people reported that 23% of the sample had experienced persistent fatigue at some point throughout their lifetime, but only 1 person in the sample met the diagnosis for ME/CFS (20). ME/CFS is distinct from persistent fatigue lasting for 6 or more months. Many people complain of persistent fatigue but do not meet the criteria for CFS (9, 20). In sum, CFS should be distinguished from persistent fatigue and it likely has a separate etiology (15).

The prevalence of low feelings of energy is not well characterized. This may be because researchers and practitioners sometimes view energy and fatigue as existing on opposite ends of a single bipolar construct and not as separate unipolar constructs. Energy and fatigue, however, are at other times measured concurrently as separate constructs (3, 11, 13). There is psychometric evidence supporting the contention that energy and fatigue are separate constructs (18) and treatments for fatigue can result in different sized effects for energy and fatigue when both constructs are measured (19, 22). Future research is needed to better determine the relationship between these two constructs.

Fatigue symptoms are often poorly managed by physicians and health practitioners. Fatigue is such a common complaint that it has limited utility in differential diagnoses of illness. Developing effective countermeasures for fatigue is important so as to avoid problems resulting from individuals diagnosing and treating their own symptoms (26). Sleep is one recognized effective countermeasure to fatigue caused by chronic sleep loss. Busy lifestyles and ubiquitous technology contribute to chronic sleep loss, but the use of naps to combat fatigue remains stigmatized (16). Another potential fatigue countermeasure may be acute exercise. Daytime

exercise is acceptable and recommended to enhance health but its potency as a fatigue countermeasure is uncertain.

Previous research has reported a reduced risk of experiencing fatigue and reduced energy when individuals report being regularly physically active (21). Sedentary people who adopt a chronic physical activity program realize reductions in feelings of fatigue and increases in feelings of energy (23). Experimental studies have examined the effect of completing acute exercise on feelings of energy and fatigue (3, 10, 14). This literature has not been quantitatively summarized and there is a need to know the extent to which acute exercise impacts feelings of energy and fatigue. Research is also needed to establish whether a single bout of exercise has similar effects on symptoms of energy compared to fatigue.

One purpose of this dissertation is to quantify the effect of a single bout of exercise on energy and fatigue and determine moderators of the effect. A second purpose is to explore one potential biological mechanism of this effect.

Chapter 2 of the dissertation presents a succinct review of relevant literature including definitions, measurement techniques used to quantify energy and fatigue, and information about the neurobiology of energy and fatigue. The evidence for a role of the histaminergic system in energy and fatigue is emphasized.

Chapter 3 consists of the first study of the dissertation. A meta-analysis of published experiments was conducted to quantify the effect of a single bout of exercise on symptoms of energy and fatigue and determine the existence of several potential moderators of the effect.

Chapter 4 describes the results of an experiment based on the findings from the narrative review in chapter 2 and meta-analysis in chapter 3. The purpose of the experiment was to determine the role of the histaminergic system in changes in energy and fatigue mood states that

occur in response to a single session of exercise. The study specifically determined if blockade of H_1 receptors by the antagonist drug doxepin blocks the energizing effect of a single session of exercise. The study is novel because the role of histamine in this effect has never been examined, although adequate evidence suggests that exercise-induced increases in central nervous system histamine could influence energy and fatigue states.

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CHAPTER 2

LITERATURE REVIEW

The purpose of this dissertation is to determine the effect of a single session of exercise on energy and fatigue mood states, and to test if histamine binding at the H_1 receptor is a mechanism that impacts the strength of the effect. The purpose of this chapter is to review background literature relevant to the dissertation.

Energy and Fatigue States

Feelings of energy are defined as the subjective interpretation of one's capacity to do mental or physical activity (16). People who have high feelings of energy would also be expected to say they feel "vigorous", "active", "lively", and "full of pep" (16, 57). Psychic energy is also required to control attention. In this respect energy is also referred to as a "will, volition, or controlling power". Attention is "inseparably associated with the will, volition, or controlling power" and inhibition of irrelevant stimuli plays a role in focusing attention (20).

Feelings of fatigue are a subjective interpretation that one has a limited capacity to complete physical or mental activities (16). For the purposes of this review, when the word fatigue is used it is not referring to exercise-induced reductions in the ability to produce force. Synonyms of fatigue within the context here include symptoms such as being "exhausted", "sluggish", "weary", or "feeling worn out" (16, 57). Fatigue may exist on a spectrum from normal fatigue, categorized as typical tiredness from daily activities and pathological fatigue defined as "nervous exhaustion" (20). Fatigue could also arise from a condition in which tissue is not allowed to adequately recover, repair, or regenerate (20).

Measurement of Energy and Fatigue States

Energy and fatigue may be measured at a specific time (i.e. right now at this moment; that is, a state measure) or over a prolonged recall period (i.e. usual; that is, a trait measure) or something in between (e.g., past week, including today) (16). The time period to which the measurement instrument refers is important because feeling states can fluctuate from minute-to-minute, hour-to-hour and day-to-day (16). A host of activities, including sleep deprivation (25), completion of cognitive tasks (19), caffeine consumption (2), bright light exposure (4), a nap (48), or completion of a single bout of exercise (9, 28, 38), are expected to influence energy and fatigue states. Changes in feelings of energy or fatigue that are long-lasting are likely to be influenced by multiple factors including chronic changes in sleep (25), diet (11), or exercise training (75) and disease states including stroke (115) and chronic fatigue syndrome (17, 63).

Energy and fatigue states or traits can also refer to the perceived feeling of being able to complete either physical or mental tasks. For this reason, investigators will at times ask specifically about one's perceived capacity to perform physical and mental activities separately (66). This is done in an effort to separate physical aspects of fatigue from mental fatigue.

2.21 Questionnaires

Energy and fatigue feelings are most commonly assessed using questionnaires. At least three questionnaires include unipolar scales for both energy and fatigue. These include the Profile of Mood States (57), the Activation-Deactivation Adjective Check List (97), and the Exercise-Induced Feeling Inventory (30). While there is evidence to support the reliability and validity of all these measures the psychometric evidence is strongest for the Profile of Mood States (65).

One widely used questionnaire, the SF-36 Health Survey (105), measures energy and fatigue feelings during the last month on a single bipolar scale. The subscale, referred to as the "vitality" subscale, places energy and fatigue at opposite ends of one continuum. This may not be advantageous, however, because changes in scores are difficult to interpret. For example, a decreased score would not indicate if energy had decreased, fatigue had increased, or if both had occurred. It has also been hypothesized that separate neural mechanisms may be responsible for feelings of energy or fatigue (16). Failing to measure both feelings of energy and fatigue separately prevents researchers from understanding what specific changes have actually occurred.

Cognitive tasks

Cognitive vigilance (i.e. sustained attention) tasks are also used as a method of assessing mental energy and fatigue. One advantage of using cognitive testing is that an objective measure of energy or fatigue is obtained, whereas questionnaires assessing feelings of energy and fatigue are subjective. Many cognitive vigilance tasks are considered measures of attention (21) but the ability to sustain attention is thought to be especially dependent on the energy and fatigue states of the performer (40).

Most cognitive vigilance tasks require participants to attend for a set period of time and respond as quickly as possible when presented with a set of stimuli. The Bakan Task, for example, requires people to continuously monitor a series of digits presented on a computer screen (6). Each digit is typically presented for 1000 ms and participants are required to press a button every time they see a number 6. Participants must also press a different button each time they see three successive and different odd digits (e.g., 1-5-3). Performance on the Bakan task and other similar vigilance tests is typically assessed by the number of correct responses (i.e.

hits), the number of incorrect responses (i.e. misses), and reaction times to both correct and incorrect responses. The number of times that a participant reacts to the stimulus without presentation of the stimulus (i.e. false alarms) is also often reported. In the case of the Bakan task, these statistics are calculated for both the primary task (i.e. indicating 3 successive odd digits) and the secondary task (i.e. responding to a specific number "6"). Researchers use task performance metrics to infer changes in mental energy or fatigue. Signal detection theory, which compares the ratio of correct responses (hits) to non-responses (false alarm), may also be used to interpret cognitive vigilance data (1). One index based on signal detection theory is [P(Ā)](32), which reflects each participant's probability of hits and misses, where possible values range from 0.5 to 1.0. Signal detection indices may be superior to considering hits and misses alone because hits and misses are influenced by task difficultly and participant strategy. For example, a participant is certain to never commit a false alarm by never responding to the stimulus, but they also would not obtain a hit. (1). If task performance improves from baseline it is assumed that mental energy increased or fatigue is reduced, while worsened task performance suggests an increase in mental fatigue or a reduction in mental energy (67).

Motivation

While energy is defined as the perceived capacity to complete physical and mental tasks, motivation may be defined as the drive or reason for doing these activities. From these definitions it follows that successfully completing a task (especially one requiring vigilance) depends on both levels of energy and motivation. Some view motivation and energetics synonymously, but think that measuring both constructs can be useful in arriving at an accurate interpretation of the data (40). The few studies that have measured both cognitive vigilance and symptoms of fatigue have shown that they are moderately related (13, 31, 64). Yet, it may be

possible to have high feelings of energy but not complete any tasks due to a lack of motivation (i.e. drive). It is also true that someone with high motivation to complete a task may show decrements that can be explained by either low energy or increasing fatigue. For theses reasons it is important to measure motivation to complement cognitive vigilance tasks if they are to be used as measures of energy, and to use motivation as a covariate of performance (54).

There is no single consensus gold standard measure of energy and fatigue states and there are limitations of both cognitive vigilance and self-report data (i.e. feelings and motivation). It is ideal to measure a variety of indicators to estimate different aspects of energy and fatigue states (40).

Neurobiology of Energy and Fatigue States

Changes in energy, fatigue, or motivation are likely caused by central nervous system mechanisms (90). The effects of different neurotransmitters and their interactions have most often been implicated. Low concentrations of serotonin, norepinephrine, dopamine, and histamine are all associated with reduced feelings of energy and increased feelings of fatigue (24, 90). These neurotransmitter systems, and other neuromodulators such as adenosine (26), likely interact to influence self-reported energy and fatigue or behavioral indicators of energy and fatigue. Serotonin and dopamine may interact to cause fatigue during and after prolonged exercise (58). Serotonin dysregulation has also been implicated in chronic fatigue syndrome (23). Noradrenergic drugs may also prolong the onset of fatigue during prolonged exercise performed in the heat (58). Complex combinations of these neurotransmitter and neuromodulation systems may also influence mental fatigue, and alter optimal work productivity or other behaviors such as driving for long time periods (52).

Despite the hypotheses that neurotransmitter systems influence energy and fatigue, the understanding of how this occurs is limited (17). Drugs that result in fatigue symptoms can be used to infer the biological mechanisms of energy and fatigue states when the mechanism of drug action is known.

Drugs that block the H_1 receptor of the histaminergic system, for example, consistently produce fatigue symptoms. A meta-analysis of 18 studies estimated that diphenhydramine, the most commonly used first generation antihistamine, resulted in significant impairments in alertness and psychomotor function compared to placebo ($\Delta = 0.36$; 95% CI, 0.20-0.51). Reaction time, self-reported fatigue, and attention measures yielded the largest effect sizes (10). The diphenhydramine dose might be expected to influence the magnitude of these impairments (79, 108), but this was not analyzed as a moderator variable since diphenhydramine was dosed at 50 mg in 15 of 18 studies. Outcomes were typically assessed 2-4 hours after drug administration in drug naive participants (10). Thus, it is believed that histamine has an important role in influencing alertness and psychomotor function via action in the central nervous system, and that these effects can be moderated through the use of histamine receptor antagonists.

Although it is not precisely known how different neurotransmitter systems interact to produce feelings of energy and fatigue, the brain circuitry that promotes wakefulness is more fully understood. Two major neurological pathways are responsible for activating the forebrain to promote wakefulness. The first pathway originates from the pedunculopontine nucleus and the laterodorsal tegmental nucleus, which project to the thalamus and release acetylcholine. The pedunculopontine and laterodorsal tegmental nuclei release acetylcholine rapidly during wakefulness and show reduced activity during sleep (80).

The second pathway is responsible for activating the cerebral cortex and several groups of monoaminergic neurons are involved in the pathway. These include neurons that release dopamine from the A10 cell group, serotonin releasing neurons from the dorsal and median raphe nuclei, norepinephrine releasing neurons from the locus coeruleus, and histamine releasing neurons from the tuberomammillary nucleus (80). Although histaminergic neurons are located exclusively in the tuberomammillary nucleus, these neurons project throughout the brain (71).

All the neuronal groups in this pathway show diurnal firing patterns with the most rapid firing occurring during wakefulness (80). While many neurotransmitter systems remain active during REM sleep (92), this is not true for all neurotransmitter systems. Norepinepherine (5), serotonin (45), and histamine (94) show much higher activity during waking and little or no activity during REM sleep. Drugs that increase the activity of these neurotransmitter systems also can increase feelings of energy (90).

Cells originating in the ventrolateral preoptic nucleus (VLPO) inhibit neurotransmitter release from many of the regions responsible for wakefulness in order to promote sleep. The VLPO releases GABA and projects to the tuberomammillary nucleus, A10 cell group, locus correleus, dorsal raphe nucleus, and median raphe nucleus (35, 80). GABA is not released from the VLPO upon awakening or during states of alertness (35, 36, 80).

The role of the histaminergic system has received relatively little attention by researchers perhaps because histaminergic neurons were only recently discovered compared to dopaminergic, noradrenergic, and serotonergic neurons (35). Histamine in the central nervous system is known to follow a diurnal release pattern and has a role in two neurological pathways that promote wakefulness states (15, 36, 87). The role of the histaminergic system in energy, fatigue, and cognitive processing is the focus of the dissertation.

The Histaminergic System in the Central Nervous System

Histamine is an important neurotransmitter that has a role both in the central nervous system and in the periphery. In the periphery, histamine is released from mast cells and may induce acute allergic reactions (86). H_1 antihistamines, including those that do not readily cross the blood-brain barrier, are effective in treating allergic rhinitis and urticaria (86). It is established that histamine increases in the periphery during exercise and acts as a vasodilator (56). While some data suggests that histamine increases centrally with exercise (104), the research in this area is limited.

Histamine Synthesis and Release

Histamine is synthesized when the amino acid histadine is broken down by the enzyme L-histidine decarboxylase (70, 89). The rate of histamine synthesis is dependent on the bioavailability of the precursor histadine (36). In the central nervous system, histamine is synthesized and released primairly from the tuberomammillary nucleus, which is located within the hypothalamus (8). Histamine neurons from the tuberomamillary nucleus innervate structures throughout the central nervous system. These include the hippocampus, amygdala, posterior pituitary, ventral tegmentum, substantia nigra, medualla, and spinal cord (35). Mast cells may also release and synthesize histamine within the central nervous system, but this accounts for a small amount of total histamine production (70). The blood brain barrier does not allow peripheral histamine to cross into the central nervous system (96).

Histamine Binding

The tuberomammillary nucleus is innervated by several brain regions. Histamine release can be stimulated by neurochemical afferents that release acetylcholine and serotonin (8, 36). ATP release also may result in firing of tuberomammilary neurons (29). Hypocretin neurons also

project to the tuberomammillary nucleus (74) and hypocretin (22, 78) is hypothesized to result in wakefulness in part by acting on the H_1 receptor (43). While hypocretin has a role in arousal, the effect of hypocretin is dependent on histaminergic neurons (43).

Histamine may act on any one of four different receptor types, classified as either H_1, H_2, H_3, or H_4 receptors. Each of these receptors are G-protein coupled metabotropic receptors (86). H_3 receptors are presynaptic autoreceptors located only in the CNS and H_4 receptors are located in blood cells. H_1 and H_2 receptors are found both centrally and peripherally (35, 36, 70, 89). Within the CNS, H_1, H_2, and H_3 receptors are found in nearly all brain structures, and receptor concentration varies (103). Early studies measuring radioactivity of [^{11}C]doxepin, an H_1 antagonist, using positron emission tomography (PET) found the highest density of H_1 receptors in the frontal and temporal cortices and the thalamus. There was no binding in the cerebellum or pons (113). More recently, H_1 receptors were found to be most highly concentrated in the hippocampus, nucleus accumbens, thalamus, and posterior hypothalamus (39).

The overarching role of the histamine system in the central nervous system may be to influence the intensity of motivated behavioral actions or to energize behavior (99, 100). Dysregulation of the histaminergic system may be linked to states of low motivation resulting in limited appetizing food-seeking behavior in rodents (99). Histamine release increases wakefulness and arousal and results in a locomotor response in rodents. Histamine release also inhibits rest responses. A review of literature also provides evidence that H_1 antihistamines can be used to promote learning and reinforcement, and that histamine release may inhibit reinforcement and memory formation (36). This finding, however, has not always been supported (15). These various functions are also receptor-specific (70). This review, however, is

focused on histamine actions on the H_1 receptor because the H_1 receptor has been most closely associated with wakefulness (36, 39, 87).

Histamine and Wakefulness Effects

The primary role of histamine acting on H_1 receptors is to promote wakefulness and attention. It has long been recognized that injury to the posterior hypothalamus results in increased sleep and reduced wakefulness (80). The posterior hypothalamus is the location of the tuberomammillary nucleus which contains the histaminergic neurons within the central nervous system (36, 87).

Histamine binding follows a diurnal rhythm, with very little histamine release during sleep and high levels of histamine release and binding that promote wakefulness during daylight hours (35, 36, 70). Histaminergic cells also have higher firing rates during active waking when compared to quiet waking (47). Higher concentrations of the primary histamine metabolite, tele-methylhistamine, have been observed during waking hours than during the night in children (50). Histamine diurnal variation also did not change in response to sleep deprivation in one study involving cats, suggesting that histamine may not influence the homeostatic drive to sleep (93). Other studies, however, have not sought to replicate this result and supporting evidence is needed to strengthen this assertion. In sum, the finding that histamine follows a pattern of diurnal variation is consistent and has been found and observed across different experiments (96).

Pharmacological agents that either antagonize histamine receptors or influence the enzymes responsible for histamine synthesis and metabolism have also been used to model the effects of histamine on sleep and wake states. Drugs that block histamine synthesis via inhibition of histidine result in reduced wakefulness. Other studies using drugs that prevent histamine metabolism have also shown increases in wakefulness (96). Early studies found that pretreatment

with the antihistamine promethazine resulted in increased non-rapid eye movement (NREM) sleep and reductions in rapid eye movement (REM) sleep in cats (46). However, not all antihistamines are useful for investigating the effect of histamine in sleep due to the poor receptor specificity of some drugs in this class (91).

Further evidence points to histamine binding at the H_1 receptor as the specific reason for increases in wakefulness. H_1 receptors are found throughout structures know to regulate sleep-wake cycles. These include the basal forebrain, locus coeruleus, mesopontine tegmentum, and the thalamus (96). Injection of the H_1 receptor antagonist mepyramine decreases wakefulness and increases slow wave sleep in cats (53). In other studies, only pretreatment with H_1 antihistamines (not H_2) results in increased NREM and reduced REM sleep (49, 96). Conscious rats who receive histamine injections also show increased exploratory behaviors, and H_1, but not H_2, antagonist drugs can block these effects (49). In sum, H_2 agonist or antagonist drugs do not have consistent effects on altering sleep or wake cycles or behaviors indicative of arousal (96). Since the H_3 receptor functions as an autoreceptor, drugs that selectively antagonize this receptor (when administered acutely) also result in wakefulness in a number of studies (96).

An increase in histamine can also induce arousal. Direct histamine injections are shown to increase wakefulness and decrease slow wave sleep in cats. The strength of this effect is dependent on the histamine dose. This effect can also be abolished if cats are pretreated with the H_1 receptor antagonist mepyramine (53).

Arousal may also be operationalized and measured based on attention task performance (67). These tasks have often been used to quantify the effect of H_1 antihistamines. A review concluded that H_1 antihistamines resulted in statistically significant impairment on attention tasks 47% of the time. Studies that measured divided attention found significant differences for

16 of 25 effects (64%) (102). Vigilance tasks that measure sustained attention appear to serve as better objective measures of mental energy than other tasks (67). The impact of H_1 antihistamines on sustained attention have only been measured 30 times, but 43% of the effects were significant (102). This review is limited because only the number of significant results was summed and effect sizes were not calculated, but the findings do suggest that H_1 antihistamines result in significantly worsened performance on divided attention and vigilance tasks. These findings align with previous research, which suggests that histamine influences arousal and wakefulness through binding to the H_1 receptor.

Studies with H_1 receptor knockout (H_1 KO) mice report similar sleep-wake cycles to wild-type mice with a few exceptions. H_1 KO mice show fewer instances of brief awakenings, a faster initiation of NREM sleep, and prolonged NREM episodes (42). These findings suggest the H_1 receptor may specifically have a role in NREM sleep. In response to the evidence that antagonism of the H_1 receptor results in sedation and sleep maintenance, humans routinely use H_1 receptor antagonists to treat insomnia or induce sedation (77, 81, 91).

Limited research does suggest that H_1 antihistamines only work to alter sleep behavior when the histaminergic system is already active. One study found administering either diphenhydramine, chlorpheniramine or promethazine resulted in decreased wake time when rats were on a grid suspended over water but no changes on wake time were observed when rats were in a normal sawdust environment (98). Histamine is expected to increase in response to danger (15) as could have been caused by the grid and water environment.

While histamine release is related to sleep and wake states, the influence on, and responses to, specific behaviors during waking is unclear. Histamine has a clear role in maintaining overall brain activation, but histamine may interact with other neuromodulators to

influence arousal during specific waking states (3). The role of histamine in specific waking behaviors, particularly in humans, remains to be fully studied.

Histamine and Psychomotor Effects

The histaminergic system influences spontaneous motor activity in rodent models. The effects are varied (69) and may be receptor-dependent. Specifically, histamine injected into the lateral cerebral ventricles increased spontaneous motor activity (i.e. grooming, scratching, locomotion) in rats in one study (49). The injection, however, was conducted during the light cycle when histamine is expected to be lower in rats (36). The increased motor effects were then reversed by injecting the H_1 receptor antagonist diphenhydramine. Injection of the H_2 receptor antagonist cimetidine, however, was ineffective in reducing motor activities (49). Mutant mice lacking the H_1 receptor also have reduced locomotor activity as measured by ambulation distance (44). The motor behaviors of rats with a lesioned tuberomammillary nucleus (containing histaminergic neurons) are also reduced (100). Correlations between peak motor responses and the surviving motor neurons are significant for the dorsal tuberomammillary nucleus but not the ventral tuberomammillary nucleus. These effects, however, were specific for locomotion related to food. There were no differences in total locomotor activity or in diurnal variations of activity between tuberomammillary nucleus lesioned rats and controls (100). These findings collectively suggest that the H_1 receptor has an important role in the locomotor behavior of rats.

Antihistamine drugs that readily cross the blood-brain barrier may also influence motor performance in humans. A review of the cognitive impariments of H_1 antihistamines concluded that driving performance (real and simulated) was significantly impaired in 78% of studies, but this body of literature is not especially large (23 studies) (102). Driving is a motor skill, but also

requires many other cognitive processes. In this case, it is unclear what aspects of the driving process H_1 antihistamines consistently impair.

The review also reported H_1 antihistamines significantly impaired performance on hand-eye coordination tasks in 63% of measurements (73 total), and motor speed impairments in 33% of studies that measured it (18 total). Tracking tasks were frequently used to assess hand-eye coordination and finger tapping was used to quantify impairments in motor speed. Simple reaction time was also significantly slowed by H_1 antihistamines for 53% of effects, but choice reaction time was worse 55% of the time. No difference between the number of significant effects suggests that H_1 antihistamines do not influence the choice of reacting between stimuli, but may strongly influence the speed of any reaction (102). The difference in the number of significant simple reaction time effects (53% of effects), when compared to the number of significant motor speed effects (33% of effects) also suggests that H_1 antihistamines significantly slow the speed of mental reaction to signals to a greater extent than the movement itself. A limitation of this interpretation, however, is that separate studies using different H_1 antihistamines assessed motor speed and simple reaction time. Overall results of this review should therefore be interpreted with caution because statistically significant and insignificant results were tallied. The review ignored study sample size or effect size and the role these factors play in statistical significance. This review also included all drugs that are H_1 receptor antagonists, although different H_1 receptor antagonists may show varying affinities for other neurotransmitter receptors (e.g. serotonin, dopamine) at high doses (91). Both first and second-generation H_1 antihistamines were also reviewed, and second-generation antihistamines are not expected to readily cross the blood-brain barrier and result in psychomotor effects (85).

Limited research has also been done to determine if H_1 antihistamines influence exercise performance in humans. One study examined exercise performance in 12 military personnel two hours after taking either diphenhydramine hydrochloride (50 mg) or terfenadine (60 mg). Each participant completed a graded maximal exercise treadmill test to volitional exhaustion after each treatment. On each additional study day participants also completed a 30 minute treadmill run performed at 55% of VO_2 max on a 5% grade and a test involving alternation of 30 seconds running at 90% of VO_2 max with 30 seconds standing rest until exhaustion. Diphenhydramine had no effect on heart rate, oxygen consumption, or other physiological performance measures (61). Perception of effort or other subjective measures of energy or fatigue, however, were not assessed. The authors also acknowledge that peak drowsiness or impaired mental performance after taking diphenhydramine may follow a different time course than assessed in this study. A narrative review conducted after this study also concluded that antihistamines that act on the H_1 receptor do not either improve or impair exercise performance in humans (62).

Histamine and Cognitive Processing

A review of literature also provides evidence that H_1 antihistamines can be used to promote learning and reinforcement, and that histamine release may inhibit reinforcement and memory formation (12). This finding, however, has not always been supported. The paradigms used to test learning may also be tests of arousal, anxiety, or locomotion (15), and the findings of histamine effects on learning and memory frequently have not been supported in human experiments (102). The learning effects associated with histamine may also be due to binding at the H_3 and not the H_1 receptor as originally hypothesized.

A review of studies in humans that examined the impairment of H_1 antihistamines found that working memory was significantly impaired 36% of the times it was measured. Episodic

memory was altered by H_1 antihistamines only 5% of the time (102). In one study, 20 female participants completed several different tasks (word learning, visual pattern recognition, memory scanning, syntactic reasoning, spatial paired associative learning) after taking either 2 or 4 mg of dexchlorpheniramine, 1 mg scopolamine, or placebo. Dexchlorpheniramine, an H_1 antagonist, only significantly impaired spatial learning and did not have any effect on other tests of learning or memory. Subjective alertness and tests of reaction time and divided attention, however, were significantly impacted by dexchlorpheniramine (101). Initial animal literature suggested that histamine may influence learning and memory (12), but the evidence in human studies for a role in learning and memory is weak.

Other cognitive processes, however, are more consistently influenced by the histaminergic system. Perceptual processing speed, often measured based on Critical Flicker Fusion (CFF) threshold, was significantly worsened by H_1 antihistamines for 45% of the effects reported in a comprehensive review (102). For example, diphenhydramine 75 mg results in a reduction in CFF threshold 2 hours 30 minutes after administration. Modafinil, a drug expected to increase alertness, has no effect on CFF threshold (41). The CFF threshold is also sensitive to drug dose. In one study, doxepin given in doses of 25, 50, or 75 mg resulted in lower CFF threshold at each higher dose (33). H_1 antihistamines that cross the blood-brain barrier (i.e. diphenhydramine) also result in reduced CFF threshold, but second-generation antihistamines (i.e. cetirizine) have no effect on CFF threshold (34). CFF threshold is also significantly correlated with reductions in subjective measures of alertness in response to various H_1 antihistamines that cross the blood-brain barrier (73).

Other experiments have suggested that histamine is important for maintaining vigilance at times of threat. One study found that mice lacking histidine decarboxylase were unable to

remain awake at times their environment was changing (e.g. lights turn off) and vigilance would be required (72). It is currently unknown, however, if histamine also plays a similar role in maintenance of cognitive vigilance in a humans.

Histamine Metabolism

Metabolism of histamine occurs through 1 of 2 major pathways. The common pathway involves N-methyltransferase, which catalyzes histamine to form N-methylhistamine. Secondly, the nonspecific enzyme diamine oxidase may convert histamine to imidazoleacetic acid. Histamine metabolites are not active and are excreted in urine. The metabolite, *N*-methylhistamine, can be measured from the urine to estimate histamine production (89). The half-life of histamine is short at <30 minutes (96).

Antagonism of the H_1 Receptor

Over 45 compounds can act as antihistamines (87). The first-generation antihistamines were developed to counteract the inflammatory response to pathogens or injury. Although generally meant to act peripherally, these drugs readily cross the blood-brain barrier. The first-generation antihistamines reach peak concentrations (measured in the periphery) within 2-3 hours after oral ingestion and effects persist for roughly 6 hours (35, 36, 70). When these compounds cross the blood-brain barrier they result in sedation and cognitive impairments (102). The sedation effects are likely caused by antagonism of the H_1 receptor in the CNS, but the first-generation antihistamines may act on other neurotransmitter systems as well. The sedative effects of the compounds are also proportional to the number of H_1 receptors that are antagonized when measured by positron emission tomography (112). One study determined that cognitive impairment occurs when 60% or more of the H_1 receptors were blocked (68). Drugs that resulted

in less than 20% of H_1 receptor blockade did not result in any cognitive impairment in a separate study (95).

Many compounds exist that antagonize the H_1 receptor while acting on other receptors as well, but few drugs are potent and have high affinity for only the H_1 receptor. The affinities of different compounds for the H_1 receptor vary widely (114). Some compounds originally thought to act as H_1 receptor antagonists actually act as inverse agonists on the H_1 receptor. Inverse agonists bind to a receptor and reduce the activity of the receptor below the basal levels that occur in the absence of any ligand binding. One study found that five antihistamines thought to be antagonists, epinastine, mepyramine, acrivastine, cetirizine, and loratadine, all act as inverse agonists (7). The recognition of inverse agonists, however, is recent (59). It is unclear at this time if other compounds thought to act as H_1 receptor antagonists may also act as inverse agonists.

Side Effects of H_1 Receptor Antagonists

In addition to the previously discussed decrements in alertness and attention that occur with classic H_1 antihistamines, other effects have also been demonstrated (18, 87). The key side effects are changes in sleep architecture, psychomotor retardation, muscarinic and serotonergic effects, and cardiac changes with high doses. These unwanted side effects occurring with therapeutic doses of H_1 antihistamines and the toxicity with large doses has long been recognized (110). While these negative effects do not occur with all classic H_1 antihistamines (84), some recommend that the first-generation H_1 antihistamines should not be available over the counter due to this unfavorable side effect profile of these drugs and the efficacy of second-generation H_1 antihistamines with superior therapeutic indices (18).

Sleep Architecture

Use of H_1 antihistamines at night may increase the initial onset of rapid eye movement (REM) sleep and reduce the overall duration of REM. Residual effects the following morning also have been reported. These include impaired attention and psychomotor performance (14, 18). In one study, nighttime sleep architecture and next day cognitive performance was examined after 18 participants took the first-generation antihistamine chlorpheniramine (6 mg), the second-generation antihistamine fexofenadine (120 mg) and placebo. Chlorpheniramine increased latency to sleep onset compared to placebo and resulted in next day worsened performance on a tracking task used to assess divided attention, a vigilance task, and increased feelings of sleepiness. Chlorpheniramine has a long estimated half-life (17.6 ± 4.4 hours) and this may have contributed to these effects since chlorpheniramine was administered at 22:55. Fexofendadine did not significantly alter measures of sleep architecture (sleep latency, REM sleep latency, duration of REM sleep, duration of NREM sleep) or performance on cognitive or psychomotor tests performed the next day (14). Based on existing evidence, a likely effect of first-generation H_1 antihistamines is a change in REM sleep onset and corresponding effects on next day reaction time tests and feelings of sleepiness. The strength of these effects may be dependent on the dose used and the next-day residual effects could depend on the drug half-life.

Psychomotor Effects

The use of first-generation H_1 antihistamines has been implicated in automobile and airplane accidents (18, 83). An examination of the Civil Aerospace Medical Institutes' Toxicology Database revealed that pilots in 338 of 5,383 fatal airline accidents from 1990-2005 were found to have first-generation H_1 antihistamines in post-partum samples. These findings are only correlational and the interactions of H_1 antihistamines with other drugs or flight conditions

cannot be disentangled (83). However, pilots are typically prohibited from using first generation H_1 antihistamines for 24-48 hours before flight. Second-generation antihistamines have been deemed safe if they do not produce fatigue or cognitive side-effects during personal trials (60).

In a randomized, double-blind study 50 mg diphenhydramine was found to result in impairment levels equal to that of 0.1% blood alcohol concentration in a 1 hour driving simulator. Driving coherence, or the ability to remain a constant driving distance away from a lead car that varied speed randomly, was worse after diphenhydramine compared to alcohol, 60 mg fexofenadine (a second generation antihistamine), or placebo. Lane instability (defined as the root-mean-square deviation from the participant's chosen lane position) and the number of center line crossings were also greater in the alcohol and diphenhydramine conditions compared to fexofenadine (107). In sum, psychomotor impairment for diphenhydramine was equal to or greater than that of alcohol.

Muscarinic Effects

H_1 receptor antihistamines also show affinity for muscarinic receptors and can exhibit antimuscarinic effects (51, 87). The resulting symptoms can include dry mouth, urinary retention, and sinus tachycardia (55, 87). Other side-effects include pupillary dilation, dry eyes, constipation, postural hypotension, and dizziness (86). The first-generation antihistamines are contraindicated for people with glaucoma prostatic hypertrophy (86). These effects, however, are varied across different antihistamines. One study using radioligand binding assays reported the inhibition constants (K_1) of 27 different H_1 receptor antagonists in the bovine cerebral cortex and found that potency for muscarinic receptors varied greatly (K_1 = 5-30,000 nM) across different antihistamines (51).

Serotonergic Effects

First generation antihistamines may also act to block serotonin receptors. This action may increase appetite or lead to weight gain with chronic administration of first-generation antihistamines (87). Associations have been reported between prescription H_1 antihistamine use and obesity in a large population study (76).

Cardiac Effects

The H_1 antihistamines astemizole and terfenadine have been implicated as having serious cardiac effects. These include a prolonged QT interval and one type of ventricular tachycardia, torsades de pointes. Cardiac effects are also thought to occur due to blockade of cardiac potassium channels but are only reported to occur in individuals who have an impairment that limits breakdown of astemizole or terfenadine (109). These drugs, however, are no longer approved for use by most national regulatory agencies. Other first-generation H_1 antihistamines (e.g. promethazine, diphenhydramine, brompheniramine) may also cause a prolonged QT interval and arrhythmias, but only when taken in doses greater than those traditionally recommended (18). Dizziness or postural hypotension may also occur with standard doses of H_1 antihistamines (87).

Overdose Effects

Overdose of diphenhydramine is common and educational and prescription guidelines have been created to address this problem (82). No deaths are reported to have resulted from second generation H_1 receptor antagonists (18), presumably because these compounds only cross the blood-brain barrier to a limited degree.

It is noteworthy that response to the classic H_1 antihistamines is variable and individual differences exist (84). Many of the side effects of first-generation H_1 receptor antagonists

described could occur because these drugs are non-selective antagonists. A highly selective H_1 receptor antagonist, even while readily crossing the blood-brain barrier, may result in less diverse effects (91).

Doxepin

Doxepin hydrocholoride, although developed as a tricyclic antidepressant, is another compound also classified as a classic H_1 receptor antagonist. Doxepin was recognized as having a higher affinity for the H_1 receptor when it was first synthesized and it was thought that doxepin may be a more effective H_1 receptor antagonist than other compounds (27). Since doxepin has high-affinity for the H_1 receptor, it is frequently ^{11}C-labeled and used during positron emission tomography (PET) to image H_1 receptors (113). [^{11}C]-doxepin has also been used as a PET tracer to identify the H_1 receptor occupancy of other antihistamines in human studies (111). Behavioral effects that result from H_1 antihistamines are also related to the amount of the drug bound to H_1 receptors (114).

Since doxepin has a high affinity for the H_1 receptor, a lower dose could be used to achieve desired effects. As a result, doxepin has been given at doses of 1, 3, or 6 mg with fewer resulting side effects than other H_1 antihistamines. The side effects reported are comparable to those that occur with placebo (91). The most common reported side effect of low-dose doxepin in prior trials is headache (88). Greater side-effects are likely to result from using doxepin in higher doses (10 – 225 mg/day), or other first-generation antihistamines, either of which are likely to antagonize receptors in addition to the H_1 receptor (85).

Doxepin given chronically in doses of 10 – 225 mg/day is used as an antidepressant, but at low doses it shows high affinity for selectively antagonizing the H_1 receptor (37). Although the

degree of sedation that results from doxepin occurs in a dose-dependent manner (88), low-dose doxepin has also been used to treat insomnia (106).

Two studies have been conducted to examine the efficacy of low-dose doxepin for the treatment of insomnia. In the first trial, 67 people aged 18-64 with primary insomnia were recruited to take 1, 3, and 6 mg of doxepin or placebo for 2 nights. Each participant took each dose and 2 night trials were separated by 5-12 days. The drug was administered 30 minutes before the participant's mean habitual bedtime. Wake time after sleep was reduced when 6 mg doxepin was taken. Total sleep time was increased and sleep efficiency was also significantly improved by 6 mg doxepin compared to placebo. There were also no next-day residual sedation effects reported (77). These results have also been confirmed in a similarly designed trial of 76 elderly patients with primary insomnia (81). It is evident that low-dose doxepin would help improve sleep at night in an insomniac population, but it is unclear how doxepin would impact non-insomniacs when administered during normal waking hours. It is possible that low-dose doxepin has a potent effect when given at night because release of histamine is expected to be low and H_1 receptor antagonism may assist in preventing remaining histamine from acting. Yet when histamine release is higher during the morning and daytime, higher doses of doxepin may be required to prevent high amounts of histamine from acting on the H_1 receptor (77).

Conclusion

The presented evidence suggests that acute exercise may increase feelings of energy and that single sessions of exercise could be used to combat the problem of low energy and fatigue in the population. The overall effect of acute exercise on energy and fatigue has not been quantitatively summarized. Mechanisms that may explain increased energy after acute exercise are also unknown. The interactions of several neurotransmitters, including serotonin,

norepinephrine, histamine, and dopamine may increase and interact to raise feelings of energy and reduce fatigue. Histamine is specifically involved in wakefulness, and taking H_1-antihistamine drugs results in sleepiness and psychomotor impairment in humans (36). The role of histamine in feelings of energy and fatigue post-exercise has never been examined but the weight of the available evidence suggests that histamine is a strong candidate for playing a role in acute exercise-induced changes in feelings of energy and fatigue as well as vigilance performance.

The next chapter is a systematic review and meta-analysis of studies that measured both energy and fatigue after a single bout of exercise. The fourth chapter summarizes an experiment that examined the role of histamine H_1 receptors on mental energy, fatigue, and cognition after a single bout of exercise. The fifth chapter is the conclusion of the dissertation.

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CHAPTER 3

THE EFFECT OF A SINGLE BOUT OF EXERCISE ON ENERGY AND FATIGUE STATES: A SYSTEMATIC REVIEW AND META-ANALYSIS[1]

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Abstract

Background: Studies examining acute exercise effects on energy and fatigue levels have not been quantitatively summarized.

Purpose: To estimate the population effects of a single bout of exercise on energy and fatigue states and examine potential moderators.

Methods: Google Scholar and MEDLINE were searched systematically for published studies that measured changes in energy and fatigue after acute exercise. Meta-analytic techniques were used to analyze 58 energy and 58 fatigue effects from the same 16 studies involving 678 participants. Most studies involved 21-40 minutes of moderate intensity aerobic-type exercise.

Result: The homogeneous mean effect for energy was $\Delta = 0.47$ (95% confidence interval [CI] = 0.39, 0.56). The heterogeneous mean effect for fatigue was $\Delta = 0.03$ (95% CI = -0.08, 0.13). The fatigue effect was moderated by a three-way interaction between change in feelings of energy, exercise intensity, and exercise duration.

Conclusion: Acute exercise enhances feelings of energy. Decreases in fatigue occur only when post-exercise increases in energy are at least moderately large after low-to-moderate intensity exercise lasting longer than 20 minutes. Future research should focus on short-duration (< 15 minutes), vigorous-intensity exercise and long-duration (> 40 minutes) exercise in non-student groups.

Keywords: acute exercise, alertness, mood, symptoms, vigor

Introduction

Dozens of experiments have examined the influence of a single bout of daytime exercise on affective states (60, 80). When broad emotional states have been examined (e.g., pleasantness-unpleasantness), increased positive affect is usually reported after exercise (19, 60). For specific negative states, such as anxiety, reductions are typically reported after exercise (56). Less well-documented is the influence of acute exercise on other specific states such as anger (70), depression (8), fatigue, and energy (16). Fatigue and energy could be conceptualized as opposite ends of the same continuum (73), but in acute exercise studies these states have most often been conceptualized and measured as separate constructs (30).

People frequently feel they do not have enough energy, with about 20% of the population reporting fatigue that persists for a month or more (75). Although there is no consensus on how best to measure energy and fatigue, questionnaire scores assessing fatigue or energy have shown associations between high fatigue or low energy and numerous health-related concerns including anxiety (11), depression (7), sub-optimal performance at work (64) and school (6), driving accidents (67), higher risk for mortality among older adults (25), and a range of other medical conditions.

Single bouts of exercise may improve quality of life by temporarily reducing fatigue and enhancing feelings of energy. Improvements in both energy and fatigue have been shown after acute exercise in some studies (16, 57). However, no-exercise control conditions have not always been used (19). In other studies, improvements in energy and fatigue have not been observed (46) or were inconsistent across time (17, 72). Acute exercise may have larger effects on measures of energy than fatigue (16), but biomedical researchers often focus on

fatigue and neglect or de-emphasize energy (1). Changes in energy and fatigue also may be interdependent (74). The effects of acute exercise on both energy and fatigue are poorly understood. In addition, the exercise mode and dose needed to improve feelings of energy and fatigue after exercise are uncertain. Published quantitative reviews have focused on the influence of exercise on anxiety (56) and positive affective states (60), but not on the effects of a single bout of exercise on energy and fatigue.

The primary purpose of this systematic review and meta-analysis was to estimate the population effects of a single bout of exercise on energy and fatigue states. The secondary purpose was to learn whether the energy and fatigue effects were influenced by participant variables, characteristics of the exercise stimulus, or features of the research design hypothesized to be important to energy and fatigue responses to acute exercise.

Methods

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement guided the reporting of this meta-analysis (41).

Data Searches

Similar searches were conducted in Google Scholar and MEDLINE for articles written in English and published between January 1, 1971 and April 1, 2012. In Google Scholar, a single “anywhere in the article” search was conducted for papers containing both the words fatigue and energy AND the exact phrase “single bout” AND at least one of the following words: physical activity, exercise, running, or weight lifting. The reference list of each article included relevant review articles (9, 56, 60, 79, 80) that were also manually searched for other studies that matched the inclusion criteria.

Study inclusion criteria required these elements: (i) a single bout of exercise, (ii) a non-exercise comparison condition or group, (iii) a randomized between-subjects design or a within-subjects design in which the order of exercise and rest conditions were randomized, (iv) participant presence in the testing area for the duration of the study, and (v) measurement of both energy and fatigue states after exercise. Exercise was defined as purposeful physical activity usually performed (i.e. when not part of an experiment) to improve health or physical fitness, and could include yoga or martial arts (21). Non-exercise comparison or control conditions involved participants who either engaged in no physical activity, or conducted limited physical activity to complete activities of daily living rather than to improve health or fitness. The search yielded 204 full-text articles of which 188 were excluded for the following reasons: the absence of a non-exercise control group (n=85), the absence of both energy and fatigue assessments (n=44), a focus on chronic exercise (n=26), the lack of data for effect size calculation (n=19), no random assignment to conditions (n=13) and non-English text (n=1).

Study Characteristics

A total of 16 studies were included in the meta-analysis with 58 energy effects and 58 fatigue effects independently derived by the first and second authors. Any discrepancies in effect size coding (resulting from mathematical or data extraction errors) were resolved so that both authors were in agreement for all effect sizes included in the analysis. The studies had a median sample size of 38 (range = 9-123) and the meta-analysis had a total sample size of 678.

Participants ranged in age from 18-55 years. Nine of 16 studies tested a convenience sample of college students. Four studies included participants with health concerns likely to be associated with lower energy or higher fatigue scores at baseline (8, 16, 24, 29). These health issues included major depressive disorder, persistent fatigue, and bulimia nervosa. The

remaining studies targeted university workers (57), healthy adult men (66) or participants in a qigong class (37). Energy and fatigue were measured with the Profile of Mood States (30), the Activation Deactivation Adjective Check List (68), or the Exercise-Induced Feeling Inventory (22), although our search criteria were not purposefully limited to these measures. Selected features of the studies included in the meta- analysis are presented in Table 3.1.

Effect Size Calculation

Study effect sizes were calculated by first subtracting the mean change of the control group from the mean change of the experimental group. The difference in the experimental and control change scores was divided by the pretest pooled standard deviation (27). The calculations were made so that positive effects sizes were generated when larger increases in energy or larger decreases in fatigue occurred in the exercise condition. Data were obtained from figures for two of the studies (16, 61), rather than contacting the authors for raw data. Effect sizes were adjusted for small sample bias (27).

Selection and Coding of Moderators

Potential effect size moderators for energy and fatigue responses to exercise were selected if adequate data existed and an empirical or logical rationale for moderation could be formulated. The eight moderators selected were categorized as participant variables (i.e., pre-exercise energy T-score, pre-exercise fatigue T-score, physical activity history), characteristics of the exercise stimulus (i.e., intensity, duration, mode), or features of the research design (i.e., measurement time after exercise, control condition, concurrent change in energy or fatigue).

Participant Variables

The participant variables that, *a priori,* were hypothesized to be most likely to influence

energy and fatigue responses to acute exercise were pre-exercise energy and fatigue scores (23). These baseline values were expressed as T-scores derived from data obtained before the exercise condition, using norms or the largest available study. Baseline T-scores were also coded into low (< 40), average (40-60) and high (>60) categories. Because it has been hypothesized that physical activity history can influence mood responses to a single bout of exercise (33), studies also were coded for whether participants met American College of Sports Medicine/American Heart Association physical activity recommendations to promote and maintain health (26). Participants were classified as meeting the recommendations if they reported: (i) moderate intensity aerobic activity for ≥ 30 minutes/day on ≥ 5 days/week; (ii) vigorous intensity aerobic activity for ≥ 20 minutes/day on ≥ 3 days/week; or (iii) muscular strength and endurance activity on ≥ 2 days/week. Studies were coded as including participants who did, or did not meet ACSM/AHA recommendations, unless activity level could not be determined.

Characteristics of the Exercise Stimulus

The exercise stimulus variable that, *a priori,* was most expected to influence energy and fatigue responses to acute exercise was intensity. Exercise intensity has been found (16, 39, 65) with some exceptions (10) to moderate energy and fatigue responses to a single bout of exercise. High-intensity exercise has typically been found to increase fatigue (65), and low-intensity exercise is consistently associated with improvements in positive affect (60). Improvements after exercise of positive-activated affect (including the dimension of energy) are also reported to occur at exercise durations <35 minutes (60). Some reviewers have argued that the exercise modes requiring rhythmic breathing and repetitive movements are most likely to result in changes in affective states (including vigor and fatigue) post-exercise (9), while

others have emphasized that resistance exercise can improve energy and fatigue (53).

Exercise intensity was coded into three categories (very light to light, moderate, or vigorous) based on classifications suggested by the American College of Sports Medicine (21). Exercise duration was coded into two categories of time in minutes: ≤ 20 or > 20 based on ACSM guidelines of exercise durations necessary for health benefits (21) and the distribution of exercise durations in the included studies. Exercise mode was coded as aerobic (e.g., cycling, dancing, jogging, martial arts, swimming, walking) or resistance (weight lifting).

Features of the Research Design

The research design variable that, *a priori,* was expected to most influence energy and fatigue responses to acute exercise was the timing of the post-exercise assessments. Prior research (8, 14) indicates that mood and brain electrocortical responses to acute exercise differ according to the timing of post-exercise assessments. Thus studies were coded into three post-exercise measurement time categories: 0-9, 10-30, or 31-180 minutes. Also coded was the type of control condition according to these categories: attending a lecture/watching a video, performing an activity of daily living (e.g., secretarial work), quiet seated rest/reading, or sitting on the exercise equipment. Finally, it was hypothesized that changes in fatigue could influence the change in energy and vice versa, given previous findings suggesting that changes in energy or fatigue may be interdependent (74). For this reason the individual effect sizes for energy were used in the fatigue moderator analysis.

Statistical Analysis

The mean effect size (D) and the 95% confidence interval (CI) were computed overall for both energy and fatigue using a random effects model (43). Heterogeneity of mean effects was tested using the I^2 statistic, which indicates the percentage of variance between effects

that is not explained by sampling error. I^2 values of 25%, 50%, and 75% conventionally indicate low, moderate, and high heterogeneity between studies (31). In addition, funnel plots were created to examine publication bias (18). The weighted fail-safe sample (N+) was calculated in order to determine how many unretrieved study effect sizes of zero would be needed to reduce the overall effect size to zero (63).

Macros in SPSS (36, 78) were used to calculate the overall mean effect size and to conduct univariate analysis of the eight moderators hypothesized to influence effect size for ratings of fatigue. Moderator analysis was not conducted on effects for ratings of energy because they were homogeneous. Effects were nested within studies (median of 5.5 effects per study), which might systematically differ from each other. Therefore, to adjust for between-study variance and correlated effects within studies, a multi-level mixed model linear regression model with robust maximum likelihood estimation was used according to standard procedures (12, 34) in M*plus* 7.0 (50). Parameters and their errors were estimated with clustering on study using the Huber-White sandwich estimator to calculate standard errors that are robust to heteroskedasticity and correlated effects (20, 76, 77).

First, the effect of each moderator on fatigue effects was tested separately by comparing each conditional model (which included the intercept and the moderator) with the unconditional intercept-only model using a likelihood ratio test and the adjusted Bayesian Information Criterion (BIC) (50). Next, two-way and three-way interactions of characteristics of the exercise stimulus (i.e., intensity, duration, and mode) with change in ratings of energy were tested the same way in a single multiple linear regression model. Significant interactions were decomposed using 95% confidence intervals (12, 58).

Results

Energy

Energy T-scores before and after exercise were 53.3 and 57.9, respectively. The corresponding T-scores for the control conditions were 53.4 and 51.2. The individual study effect size distribution is presented in a forest plot (Fig 3.1). Ninety-one percent (53 of 58) of the energy effect sizes were greater than zero, indicating larger increases in energy after exercise in comparison to control conditions. The mean effect size delta for energy was 0.47 (95% CI = 0.39, 0.56). The effect was homogeneous across studies, I^2 = 0%. None of the weighted observed variance among effects was explained by estimated population variance. A funnel plot (available from the lead author upon request) of the energy effects was symmetrical and did not present visual evidence of publication bias. Egger's test for bias was not significant, $F(1,57)=3.10$, $p > 0.05$. The number of effects needed to reduce the effect to a null result (N+) was 1,648. In the multi-level model (χ^2 (2) = 157.5, BIC = 159.3) the mean delta was 0.48 (95% CI = 0.37, 0.58) with non-significant variance (0.001, SE = .011, z = 0.08, p = .942) between effects.

Fatigue

Fatigue T-scores before and after exercise were 47.7 and 46.4, while T-scores for before and after the control condition were 47.3 and 47.0. The distribution of individual study effect sizes for fatigue is presented in a forest plot (Fig 3.2). Sixty-seven percent (39 of 58) of the fatigue effect sizes were greater than zero, favoring a reduction in fatigue after exercise. The mean effect size delta for fatigue was 0.03 (95% CI = -0.08, 0.13) and was moderately heterogeneous across studies, I^2 = 33% (95% CI = 21%, 43%). The population variance accounted for 33% of the weighted observed variance among effects. A funnel plot (available

from the lead author upon request) of the fatigue effects was symmetrical and did not present evidence of publication bias. Egger's test for bias was not significant, $F(1,57)=3.83$, $p > 0.05$. In the multi-level model (χ^2 (2) = 172.5, BIC = 174.3) the mean delta was 0.047 (95% CI = -0.12, 0.21) with non-significant variance (.080, SE = .056, z = 1.44, p = 0.149) between effects. However, the between-effects variance accounted for 51% of the weighted observed variance. Because statistical power to detect variance that size is low with 16 studies and 58 effects (35), the planned moderator analysis was conducted.

Moderator Analysis for Fatigue

A summary of the univariate fatigue moderator results is presented in Table 3.2. The means for each level of each moderator were homogeneous (95% CI for I^2 included zero), except for the measurement time of 0-9 minutes after exercise, $Q_B(12) = 32.31$, $p < .01$ and I^2 = 63%. Effect size was positively related to change in ratings of energy (beta = .33, SE = .17, z = 1.98, p =.048) and to the fatigue pre-exercise T-score ($p < 0.05$; see Table 3.2). All other univariate fatigue moderators were non-significant ($p > 0.05$).

In the multi-level model, pre-exercise fatigue remained positively related to change in fatigue after exercise (beta = .39, SE = .17, z = 2.23, p = .02) and improved model fit (χ^2 (3) = 166.8, BIC = 169.6) compared to the intercept-only model ($\Delta \chi 2$ (1) = -73.4, p < 0.001). Fatigue after exercise decreased when pre-exercise levels were normal or high (mean delta was 0.11 (95% CI = -0.02, 0.24) and increased when pre-exercise levels were low (mean delta was -0.45 (95% CI = -0.07, 0.96). Compared to the intercept-only model ($\Delta \chi^2$ (1) = 26.1, p < .001), change in fatigue in the multi-level model was no longer related to change in ratings of energy (beta = -0.24, z = 0.098, p = .328) and showed a worsened model fit (χ^2 (3) = 170.1, BIC = 172.9).

However, there was a three-way interaction between change in energy, exercise intensity, and duration of exercise ($z = 2.9$, $p = 0.004$, $\Delta \chi^2 (7) = 71.5$, $p < 0.001$) that improved model fit ($\chi^2 (9) = 146.4$, BIC = 154.3) compared to the intercept-only model ($\Delta \chi^2 (7) = -43.0$, $p < 0.001$). The residual variance was .013 (SE= .018, $z = 0.737$, $p = .461$), indicating that 84% of the variance between effects was explained by the conditional model and 16% was explained by the interaction. When increases in energy were moderately large or larger (≥ 0.50 SD), fatigue was reduced after light-to-moderate intensities lasting more than 20 minutes (mean delta was 0.30 (95% CI = 0.10, 0.50) for 15 effects from 8 studies) but was unchanged after vigorous intensities lasting more than 20 minutes (mean delta was -0.19 (95% CI = -0.67, 0.29) for 9 effects from 4 studies). The interaction remained significant ($z = 3.18$, $p = 0.001$) after including pre-exercise fatigue.

Discussion

Energy

A key finding was that a single bout of exercise consistently increased energy on self-report assessments. The size of the effect ($\Delta = 0.47$) was statistically significant, and the confidence interval encompassed values (95% CI = 0.39, 0.56) that have been suggested as practically meaningful (52). The magnitude of the effect equals the impact of acute exercise on positive-activated affect ($\Delta = 0.47$) (60). While this prior meta-analysis of positive-activated affect included measures of energy, positive affect also incorporates constructs such as positive well-being, positive engagement, arousal, activation, pleasantness, joy, and euphoria (60). Because it is not clear what the nature of the relationship is between acute exercise-induced increases in concurrent positive affect and energy, future research is needed to better understand the link between these important biobehavioral variables.

The population effect sizes for other interventions with acute energizing consequences such as naps (15), caffeine (55), and modafinil (45) are unknown. The mean effect of a single bout of exercise on feelings of energy found here approximates that observed after consuming 64 milligrams of caffeine, an amount of caffeine less than the amount in a typical 8-oz cup of coffee but more than in most 12-oz cola drinks (2). No study appears to have compared the energizing effects of caffeine in any dose to an acute dose of exercise. The effects of a single bout of exercise on energy states have rarely been compared to other energy-enhancing techniques in a single investigation. One study did find that a 10-minute afternoon walk outdoors improved feelings of energy to a greater extent than did eating a candy bar of unspecified size or composition (69). One quasi-experimental study found that a drug-induced (10 mg zolpidem [Ambien]) nap is superior to periodic 10-minute bouts of treadmill exercise in reducing decrements in energy associated with sleep deprivation (40).

Fatigue

One key finding was that a single bout of exercise did not consistently decrease fatigue. Although high intensity exercise certainly can increase fatigue (59), most individuals across populations infrequently engage in high intensity exercise bouts compared to low or moderate intensity activities such as gardening and walking (4). The majority of the studies analyzed here involved very light, light, or moderate intensity (~55% of the effects) aerobic exercise lasting from 25 to 40 minutes (~81% of the effects). The fact that this common type of exercise stimulus does not increase fatigue runs counter to what some authors contend is a "…general perception that acute exercise will induce fatigue and physical exhaustion…" (67).

The absence of a significant mean reduction in fatigue does not appear to have been caused by a floor effect. The three studies that used the fatigue scale of the 30-item Profile of

Mood States (Score range of 5 fatigue items: 0-20) reported a pre-exercise mean of 7.13 and studies using the 65-item Profile of Mood States had a pre-exercise mean fatigue score of 6.42 (seven fatigue items). These fatigue scores, although relatively low, could still have been reduced in the post-exercise assessment. Furthermore, the absence of fatigue reduction did not result from a significant increase in fatigue in the control conditions in these studies because the mean T-scores before and after the control tasks were nearly identical for fatigue (47.4 and 47.0, respectively). However, only four studies examined samples of participants expected to report high fatigue (8, 16, 24, 29).

There are several possible explanations as to why a single bout of exercise influences energy levels to a greater extent than fatigue. The present finding could be the result of recruitment bias that selected for people who may selectively focus on an increase in energy in response to a single bout of exercise rather than a reduction in the intensity of an (unpleasant) fatigue state. Bias may also be influenced by expectations supported by media reports that exercise can increase energy levels (54). Alternatively, shifts in attention away from unpleasant emotional stimuli and toward more pleasant stimuli during moderate intensity exercise may contribute to a bias toward improved energy (71). A third possibility is that the energy measures were more sensitive to change in response to a single bout of exercise than the fatigue measures. The sensitivity of various energy and fatigue measures to assess change with acute exercise has not been directly explored.

The larger energy effect size documented here is consistent with findings from exercise investigations that have addressed related research questions. Larger effects for energy in comparison to fatigue have been reported after increased physical activity in

naturalistic environments (23) and following short-term exercise deprivation among habitual exercisers (47). Finally, responses to some items (e.g. worn out, exhausted) on existing fatigue questionnaires, when administered after more intense exercise, may be confounded by participants' residual perceptions of physical exertion that are unique to muscular effort at higher intensities. Responses indicating increased fatigue on these items may mask the experience of reduced mental fatigue that might otherwise be reported after low exercise intensities (49). Future researchers should explore changes in various scale (both unipolar and bipolar scales) and item scores (both energy and fatigue items) in response to acute exercise to clarify how participant responses are related to individual differences in sensitivity to detect change.

Fatigue Moderators

Despite low statistical power to detect moderator effects (28), a significant three-way interaction was detected for changes in fatigue scores after exercise that depended upon increases in energy and the intensity and duration of exercise. When increases in energy were at least moderately large, fatigue was reduced after light to moderate intensity exercise, but not after vigorous exercise lasting longer than 20 minutes. An interaction involving changes in energy and changes in fatigue is consistent with bipolar conceptualizations of energy and fatigue (44) and could be the result of a common rating style, as those willing to endorse a moderate or larger improvement in energy may also be willing to endorse a reduction in fatigue (51).

A recent study (16) illustrates the interaction of energy and fatigue changes in adults with persistent fatigue who were randomly assigned to complete a no-exercise control condition or 20 minutes of low or moderate intensity cycling thrice weekly for six weeks.

Energy and fatigue responses to acute exercise were assessed during weeks 1, 3 and 6. Fatigue was reduced after low-intensity exercise during weeks 3 and 6 of the training program but unchanged after moderate-intensity exercise. Energy symptoms were increased after low-intensity exercise during weeks 3 and 6 of the training program. However, since none of the studies included in this review simultaneously manipulated intensity and duration of exercise, the causal influences implied by this analysis require experimental investigation. Studies should be conducted in which energy and fatigue are concurrently measured in response to random assignment of participants to light-to-moderate or vigorous intensities of varying durations. Findings from these studies would assist in determining the appropriate dose (intensity x duration) that elicits a change in both energy and fatigue states.

Although our analysis did include one study of patients with major depressive disorder (8), one study of patients with bulimia (24), and two studies of non-patients with persistent fatigue (16, 29) the analysis primarily involved college students. Consequently, it is uncertain whether the moderators identified here will generalize to medical patients or other groups with elevated fatigue. One uncontrolled study of chronic fatigue syndrome patients reported small reductions in fatigue five minutes after ten 3-minute bouts of treadmill walking at a self-selected comfortable speed rated "somewhat hard" on average (13). However, a study that included a control group found that patients with chronic fatigue syndrome reported increased mental and physical fatigue after 25 minutes of combined arm and leg exercise which was described as "moderately intense " (42).

Limitations and Future Research Recommendations

The ability to understand the influence of a single bout of exercise on energy and fatigue is limited in part because there were inadequate data across the full range of

possible exercise stimuli. Some of the studies documented the influence of vigorous intensity exercise (20 effects), but none examined the effect of exercise intensity classified as near-maximal to maximal (21). The analysis did not include any effects on exercise of very long duration (no effects involved durations over 40 minutes), despite the fact that recreational and professional athletes engage in this type of exercise regularly. Only 11 of the effects involved short duration exercise bouts (< 21 minutes), which could be of sufficient length to enhance public health (26). Clearly, there is a need for more studies that focus on short duration exercise in order to learn the minimum dose of activity needed to enhance energy levels. Clearly, short duration exercise can be time-efficient.

High-intensity interval training, consisting of a handful of short duration (30 seconds to 4 minutes), high intensity ($\geq$ 90% VO_2 peak) exercise bouts separated by several minutes of rest, has been shown to have beneficial health-related physiological adaptations (5). It would be useful to learn if this type of exercise produces severe post-exercise fatigue, and if such tiredness influences whether individuals are willing to adopt or maintain this type of activity independent of the physiological adaptations and physical health benefits. To date, the impact of a single bout of this type of exercise on energy or fatigue has not been examined.

Another limitation in the literature analyzed is the focus on self-reported energy and fatigue, rather than objective measures. Objective cognitive outcomes thought to reflect energy and fatigue processes, such as measures of sustained attention, represent assessments that could complement the dominant use of questionnaires (32). This area of research could be advanced by including selected cognitive measures concurrently with fatigue and energy state measures (48).

A final concern is that several potential moderators could not be considered, including biological sex (62), variations in exposure to bright light resulting from indoor versus outdoor exercise (3), and variations in sleepiness resulting from the prior night's sleep or daytime naps (38). Understanding the effect of acute exercise on energy and fatigue is also limited in part because of inadequate reporting of physical activity history as well as the dimensions of the acute exercise stimulus (intensity, duration, mode). Without these data, it is difficult to determine what aspect of the exercise is responsible for changes in energy or fatigue.

Since the majority of studies in this analysis involved college students who performed very light to moderate intensity exercise for 21 - 40 minutes, these findings should not be generalized to the entire population for all types of exercise. Before the present results can be most effectively applied to an entire population with practical recommendations, researchers need to conduct additional studies with a variety of groups performing a wider range of exercise intensities and durations. Research designs should include comparisons to well-described control groups or conditions including other energy-provoking stimuli such as naps and caffeine.

Summary

In summary, the primary findings of this systematic review and meta-analysis are: (i) a

single bout of exercise consistently enhances energy but does not consistently change fatigue and (ii) decreases in fatigue after a single bout of exercise occur only after low-to-moderate intensity exercise of more than 20 minutes duration that results in moderately large post-exercise increases in energy levels. Thus, practitioners have stronger evidence for advising clients that a single bout of exercise can boost energy. Also, professionals in evidence-based practice should avoid assuming that acute exercise uniformly reduces fatigue.

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Table 3.1
Selected characteristics of the individual studies.

Authors	# of Effects	Sample	Measure	Exercise Mode	Control Condition
Arent et al. (2007)	6	college students	AD ACL	Resistance (weight lifting)	weight lifting video
Bartholomew et al. (2001)	6	college students	EFI	Resistance (weight lifting)	body composition measurements
Bartholomew et al. (2005)	3	depressed patients	POMS	Aerobic (treadmill walking)	quiet rest
Dishman et al. (2010)	6	fatigued students	POMS	Aerobic (cycle ergometry)	sit on cycle ergometer
Focht & Koltyn (1999)	10	college students	POMS	Resistance (weight lifting)	weight lifting video
Glazer & O'Connor (1992)	4	bulimic patients	POMS	Aerobic (walking)	quiet rest or reading
Hansen et al. (2001)	3	college students	POMS	Aerobic (cycle ergometry)	quiet sitting facing a window
Herring & O'Connor (2009)	4	fatigued students	POMS	Resistance (weight lifting)	sitting on exercise machine
Johansson et al. (2008)	1	Qigong participants	POMS	Aerobic (qigong)	lecture
Plante et al. (2003)	2	university workers	AD ACL	Aerobic (cycle ergometry)	cycling video game
" "	2	" "	" "	Aerobic (cycle ergometry + video game)	" "
Rejeski et al. (1995)	3	college students	EFI	Aerobic (cycle ergometry)	took blood pressure
Roth (1989)	1	college students	POMS	Aerobic (cycle ergometry)	quiet sitting
Roth et al. (1990)	1	college students	POMS	Aerobic (cycle ergometry)	quiet sitting
Szabo et al. (1993)	1	healthy males	POMS	Aerobic (cycle ergometry)	video watching
Treasure & Newbery (1998)	2	college students	EFI	Aerobic (cycle ergometry)	quiet rest or reading
Zervas et al. (1993)	3	college students	POMS	Aerobic (aerobic dance)	lecture

Table 3.1 cont.

Authors	Physical Activity History	Intensity	Duration (mins.)	Post-Exercise Measurement Time (mins.)
Arent et al. (2007)	> 1 year weight training	50% 1RM	30	5, 15, 30, 60, 90, 120
Bartholomew et al. (2001)	weight training class	50%, 80% 1RM	30	10, 25, 40
Bartholomew et al. (2005)	< 2 exercise bouts/week	60-70% age predicted HR max	30	5, 30, 60
Dishman et al. (2010)	>½ SD below 7-day Kcal expenditure norms	40%, 75% VO_2 peak	30	10
Focht & Koltyn (1999)	physical activity class participants	50%, 80% 1RM	30	0, 20, 60, 120, 180
Glazer & O'Connor (1992)		70% VO_2 peak	20	10, 20
Hansen et al. (2001)		60% estimated VO_2 max	10, 20, 30	
Herring & O'Connor (2009)	< 2 exercise bouts/week	15%, 70% 1RM	35	20, 30
Johansson et al. (2008)	regular Qigong exercisers		30	0
Plante et al. (2003)		60-70% age predicted HR max	30	0
" "		" "	" "	0
Rejeski et al. (1995)	600 Kcal/week moderate-to-vigorous	70% HR reserve	10, 25, 40	20
Roth (1989)		HR 115-135 beats/min	20	15
Roth et al. (1990)			10	9
Szabo et al. (1993)	mean estimated VO_2 = 40 ml/kg/min	60% VO_2 max	30	
Treasure & Newbery (1998)	> 6 months no regular exercise	70-75% HR reserve	15	15
Zervas et al. (1993)	aerobic dance class	40%, 60%, 80% HR reserve	30	

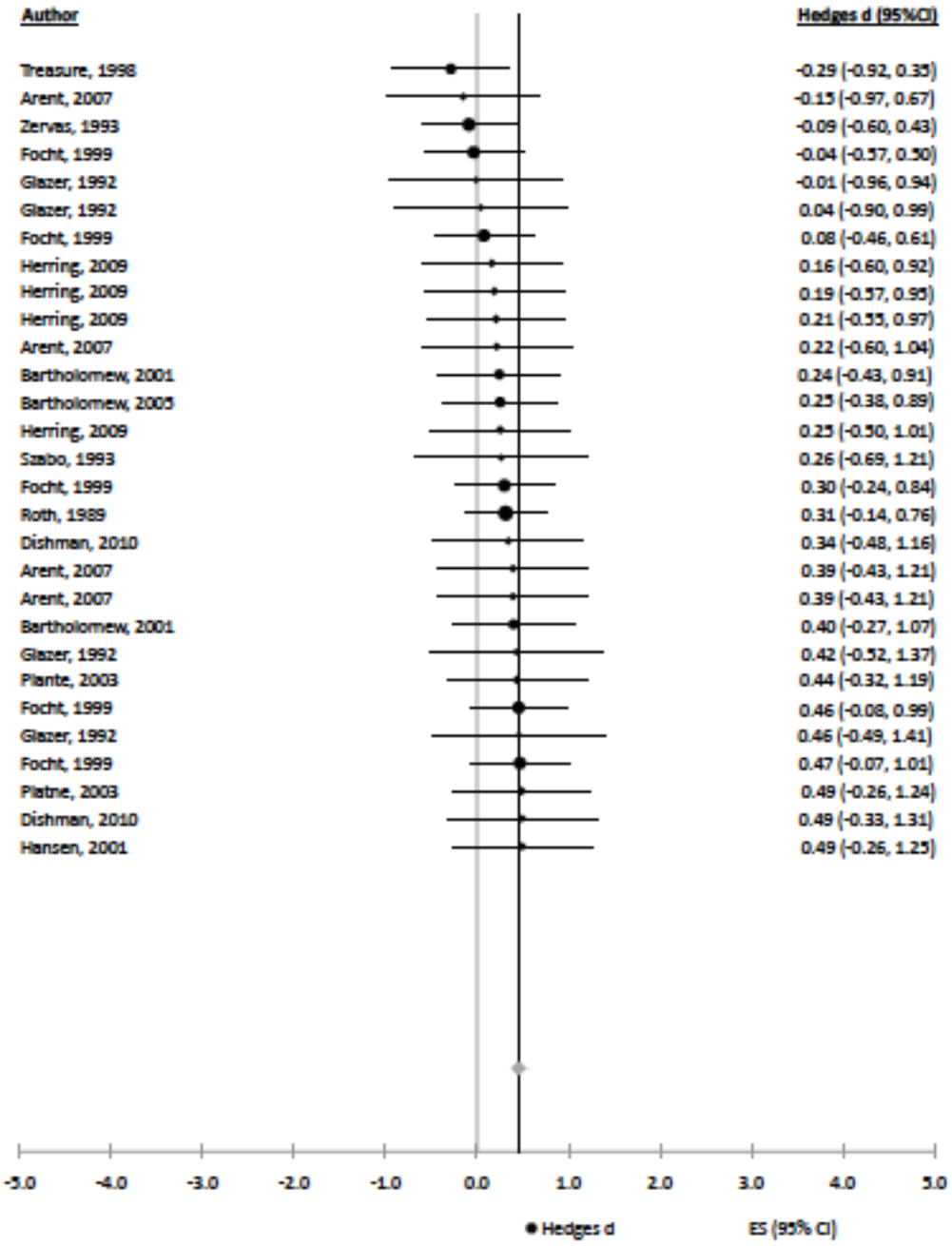
Table 3.2

Univariate results for Fatigue Moderator Variables

Effect Moderator	Number of Effects	Effect Size *d* (95% CI)	*P* Value
Participant Variables			
Pre-Exercise T-Score			
< 40	4	-0.5577 (-0.8425 to -0.2730)[bc]	0.0001
40-60	50	0.0857 (-0.0183 to 0.1896)[b]	
> 60	4	0.1829 (-0.1582 to 0.5240)[c]	
Physical Activity History			
< ACSM Guidelines	15	0.0601 (-0.1690 to 0.2891)	0.5895
≥ ACSM Guidelines	30	-0.0148 (-0.1617 to 0.1320)	
Characteristics of the Exercise Stimulus			
Intensity			
Very Light to Light	5	0.2554 (-0.1346 to 0.6454)	0.4132
Moderate	31	-0.0083 (-0.1454 to 0.1287)	
Vigorous	20	-0.0290 (-0.2013 to 0.1433)	
Duration (minutes)			
1-20	11	-0.0903 (-0.3478 to 0.1673)	0.3124
21-40	47	0.0555 (-0.0615 to 0.1726)	
Mode			
Aerobic	32	0.0104 (-0.1373 to 0.1581)	0.6946
Resistance	26	0.0533 (-0.1019 to 0.2086)	
Features of the Research Design			
Measurement Time after Exercise (minutes)			
0-9	13	-0.0353 (-0.2470 to 0.1765)	0.3517
10-30	29	0.0210 (-0.1337 to 0.1758)	
31-180	12	0.1791 (-0.0394 to 0.3976)	
Control Condition			
Exercise Equipment	6	0.1724 (-0.2031 to 0.5478)	0.5999
Daily Living Activity	9	0.0970 (-0.1650 to 0.3589)	
Quiet Rest/Reading	18	0.0101 (-0.1884 to 0.2086)	
Lecture/Video	21	-0.0613 (-0.2248 to 0.1022)	

Note. [b, c] moderator levels with a common superscript differ significantly. *P* value reported is for *Q* between

Figure 3.1. Forest plot of energy effect sizes. Negative values represent larger increases in energy after control conditions and positive values represent larger increases in energy after exercise.



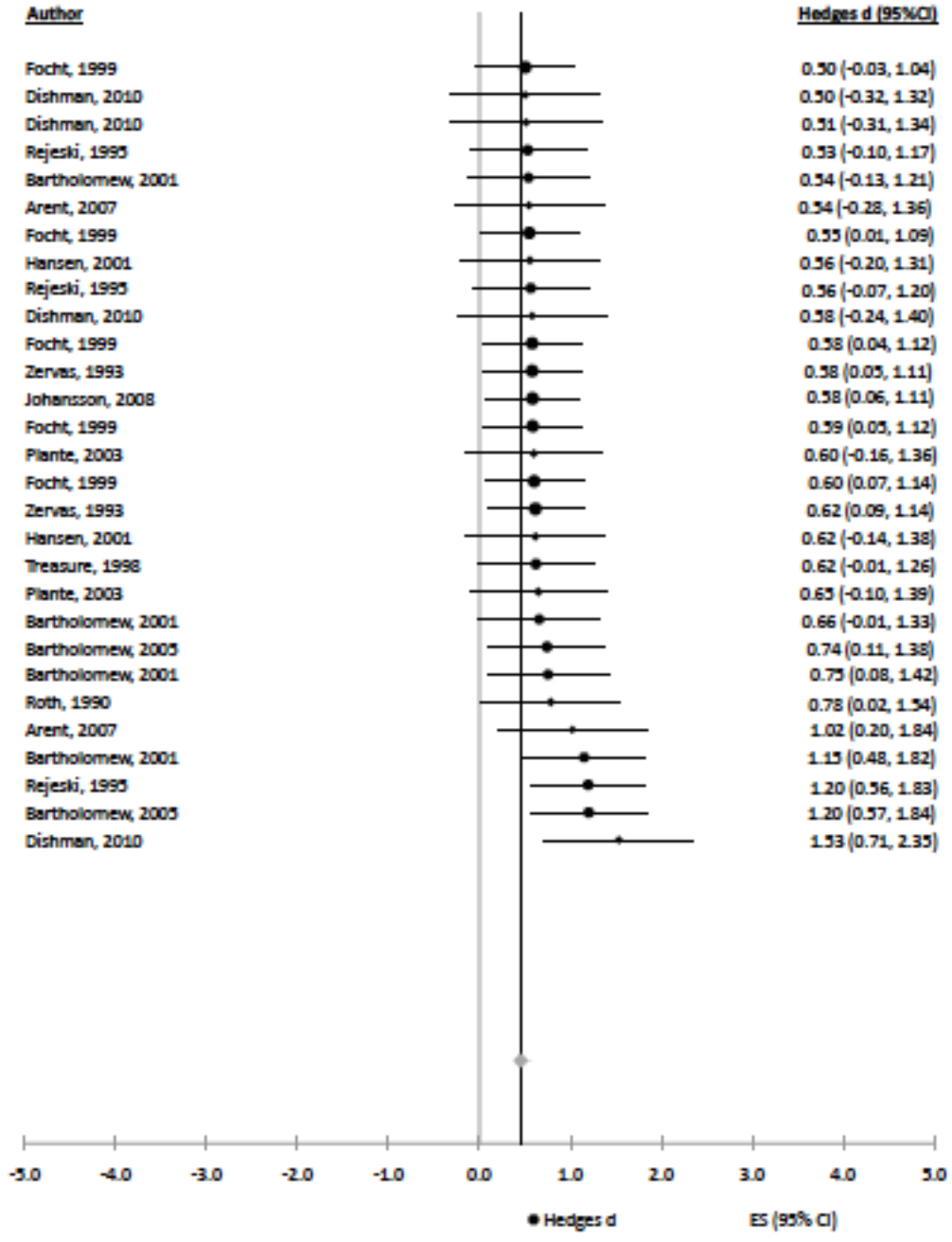
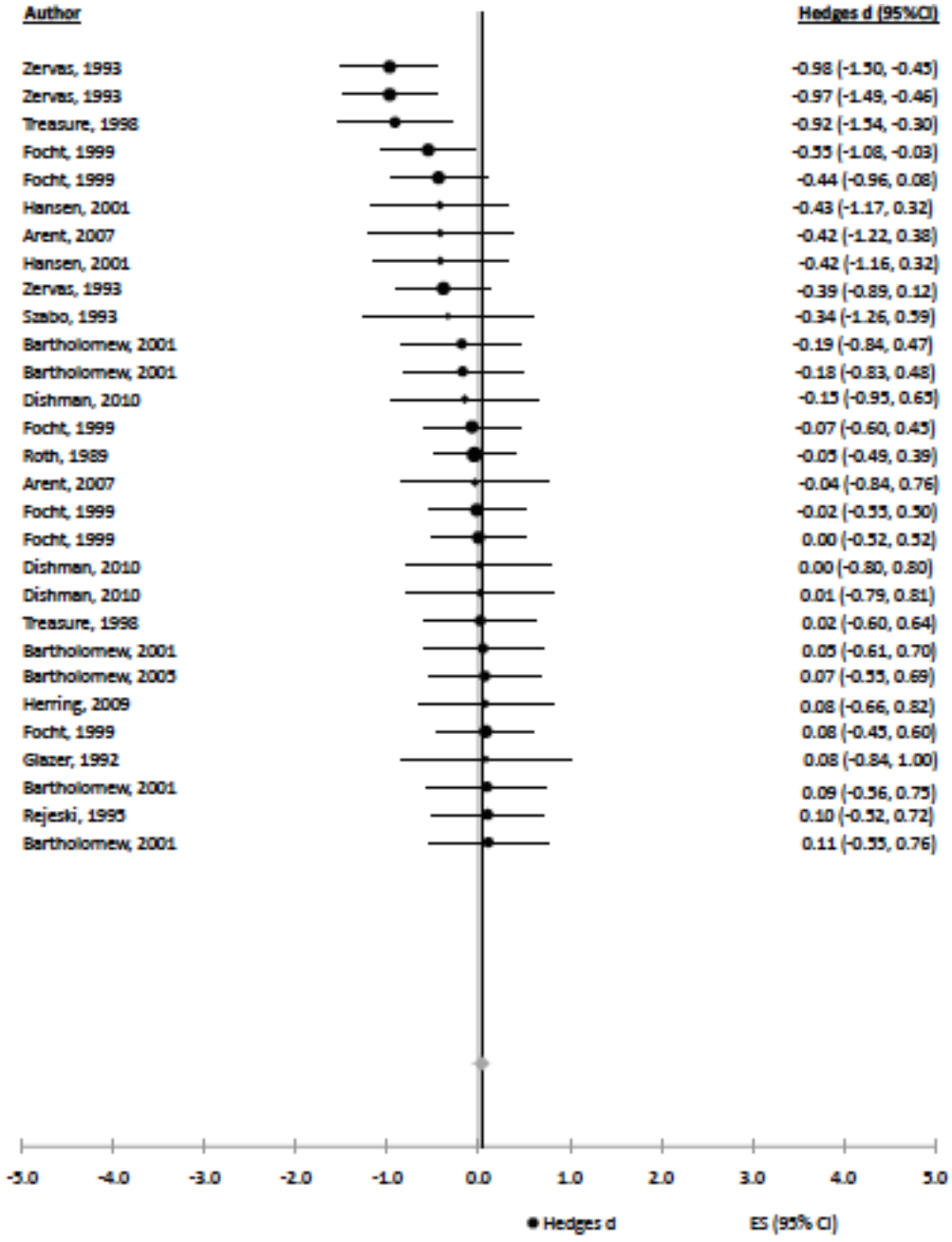
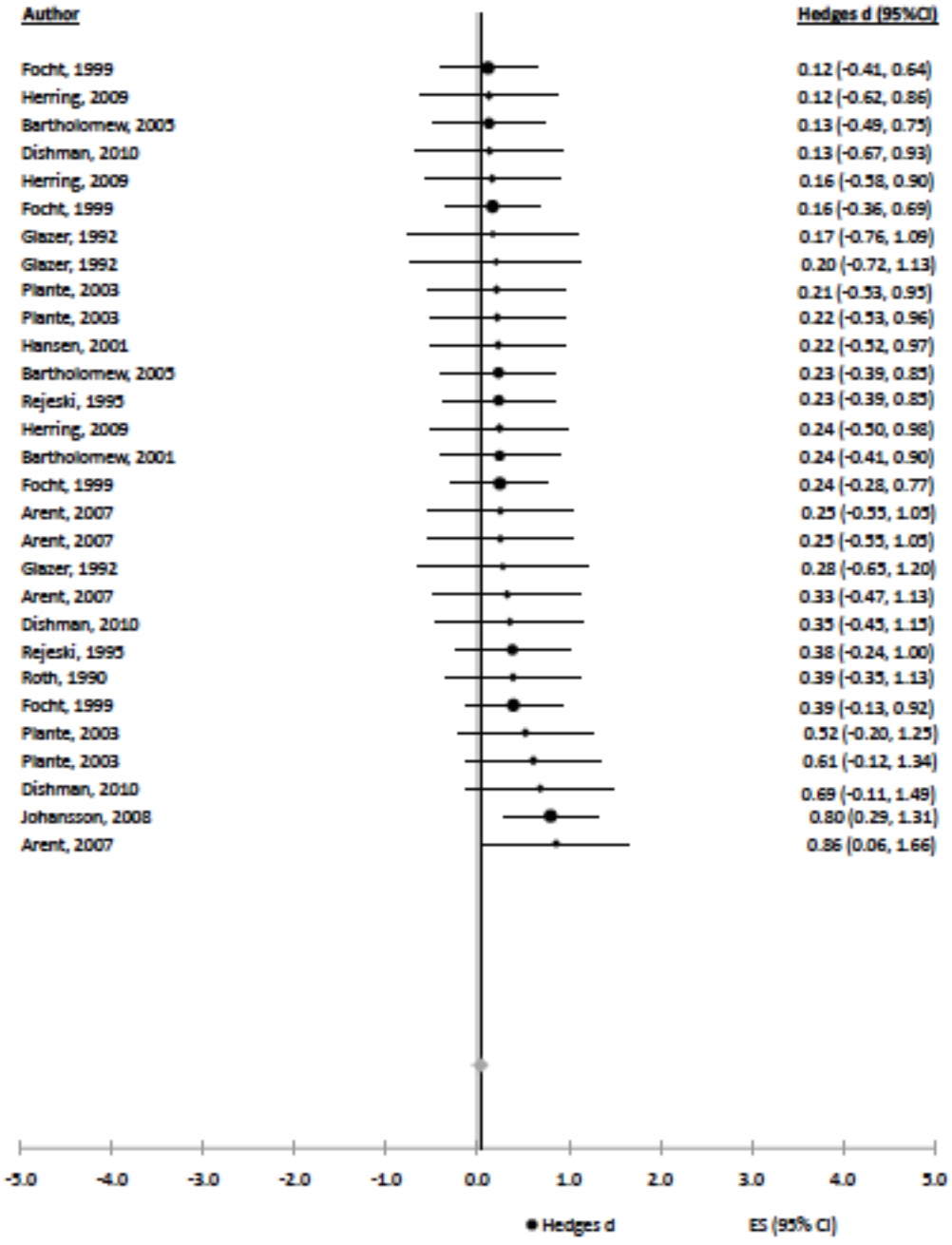

Author
Hedges d (95%CI)
Focht, 1999 0.50 (-0.03, 1.04)
Dishman, 2010 0.50 (-0.32, 1.32)
Dishman, 2010 0.51 (-0.31, 1.34)
Rejeski, 1995 0.53 (-0.10, 1.17)
Bartholomew, 2001 0.54 (-0.13, 1.21)
Arent, 2007 0.54 (-0.28, 1.36)
Focht, 1999 0.55 (0.01, 1.09)
Hansen, 2001 0.56 (-0.20, 1.31)
Rejeski, 1995 0.56 (-0.07, 1.20)
Dishman, 2010 0.58 (-0.24, 1.40)
Focht, 1999 0.58 (0.04, 1.12)
Zervas, 1993 0.58 (0.05, 1.11)
Johansson, 2008 0.58 (0.06, 1.11)
Focht, 1999 0.59 (0.05, 1.12)
Plante, 2003 0.60 (-0.16, 1.36)
Focht, 1999 0.60 (0.07, 1.14)
Zervas, 1993 0.62 (0.09, 1.14)
Hansen, 2001 0.62 (-0.14, 1.38)
Treasure, 1998 0.62 (-0.01, 1.26)
Plante, 2003 0.65 (-0.10, 1.39)
Bartholomew, 2001 0.66 (-0.01, 1.33)
Bartholomew, 2005 0.74 (0.11, 1.38)
Bartholomew, 2001 0.75 (0.08, 1.42)
Roth, 1990 0.78 (0.02, 1.54)
Arent, 2007 1.02 (0.20, 1.84)
Bartholomew, 2001 1.15 (0.48, 1.82)
Rejeski, 1995 1.20 (0.56, 1.83)
Bartholomew, 2005 1.20 (0.57, 1.84)
Dishman, 2010 1.53 (0.71, 2.35)
-5.0
-4.0
-3.0
-2.0
-1.0
0.0
1.0
2.0
3.0
4.0
5.0
Hedges d
ES (95% CI)

Figure 3.2. Forest plot of fatigue effect sizes. Negative values represent larger decreases in fatigue after control conditions and positive values represent larger decreases in fatigue after exercise.




Author
Hedges d (95%CI)
Focht, 1999
0.12 (-0.41, 0.64)
Herring, 2009
0.12 (-0.62, 0.86)
Bartholomew, 2005
0.13 (-0.49, 0.75)
Dishman, 2010
0.13 (-0.67, 0.93)
Herring, 2009
0.16 (-0.58, 0.90)
Focht, 1999
0.16 (-0.36, 0.69)
Glazer, 1992
0.17 (-0.76, 1.09)
Glazer, 1992
0.20 (-0.72, 1.13)
Plante, 2003
0.21 (-0.53, 0.95)
Plante, 2003
0.22 (-0.53, 0.96)
Hansen, 2001
0.22 (-0.52, 0.97)
Bartholomew, 2005
0.23 (-0.39, 0.85)
Rejeski, 1995
0.23 (-0.39, 0.85)
Herring, 2009
0.24 (-0.50, 0.98)
Bartholomew, 2001
0.24 (-0.41, 0.90)
Focht, 1999
0.24 (-0.28, 0.77)
Arent, 2007
0.25 (-0.55, 1.05)
Arent, 2007
0.25 (-0.55, 1.05)
Glazer, 1992
0.28 (-0.65, 1.20)
Arent, 2007
0.33 (-0.47, 1.13)
Dishman, 2010
0.35 (-0.45, 1.15)
Rejeski, 1995
0.38 (-0.24, 1.00)
Roth, 1990
0.39 (-0.35, 1.13)
Focht, 1999
0.39 (-0.13, 0.92)
Plante, 2003
0.52 (-0.20, 1.25)
Plante, 2003
0.61 (-0.12, 1.34)
Dishman, 2010
0.69 (-0.11, 1.49)
Johansson, 2008
0.80 (0.29, 1.31)
Arent, 2007
0.86 (0.06, 1.66)
-5.0
-4.0
-3.0
-2.0
-1.0
0.0
1.0
2.0
3.0
4.0
5.0
Hedges d
ES (95% CI)

CHAPTER 4

THE EFFECT OF HISTAMINE ON CHANGES IN MENTAL ENERGY AND FATIGUE AFTER A SINGLE BOUT OF EXERCISE[2]

[2] Loy B.D. & O'Connor P.J. To be submitted to *Medicine and Science in Sports and Exercise*.

Abstract

Introduction: Acute exercise increases feelings of energy and can reduce fatigue symptoms, but the neurobiological cause for these effects is unknown. The purpose of this research is to determine if histamine, acting on CNS H_1 receptors, influences changes in energy and fatigue or performance on objective cognitive tests related to mental fatigue after acute exercise.

Methods: Women (n = 20) with low vigor and high fatigue were administered the H_1 antagonist drug doxepin hydrocholoride (6 mg) and placebo in a randomized, double-blinded, cross-over experiment. On the first visit, participants practiced cognitive tests and performed a cycling $\dot{V}O_{2peak}$ test. On the second and third visits, participants received either doxepin (DOX; mixed in tomato juice) or placebo (PLA; tomato juice only), performed 30 minutes of light intensity cycling, and completed energy, fatigue, sleepiness, and motivation scales, and cognitive tasks three times: before the drinks, 90 minutes after the drinks, and immediately after exercise.

Results: DOX induced increases in sleepiness and reductions in cognitive task performance. After exercise, mental fatigue increased for the DOX condition but not PLA, while mental energy decreased for both PLA and DOX. After exercise, changes in sustained attention, visual perceptual processing efficiency, and motor speed did not differ between DOX and PLA despite reductions in mental task motivation induced by DOX.

Conclusion: Treatment with DOX blocks expected decreases in mental fatigue and increases in motivation for cognitive work after acute exercise, but does not strongly influence exercise-induced changes in energy, sustained attention, visual perceptual processing efficiency, or motor speed. It is inferred that histamine binding to H_1 receptors in the central nervous system has a role in exercise-induced reductions in mental fatigue and motivation to perform cognitive tasks.

Keywords: attention, doxepin, cognition, vigor, motivation, sleep

Introduction

A systematic review and meta-analysis reported that a single session of exercise consistently increases feelings of energy, but only reduces feelings of fatigue when concurrent increases in energy are moderately large and exercise is of low or moderate intensity lasting for at least 20 minutes (53). The neurobiological reasons for changes in energy and fatigue with acute exercise are unclear and the biological basis of energy and fatigue is unknown (16). However, a substantial body of literature links energy and fatigue symptoms to several neurotransmitters including adenosine, dopamine, norepinephrine, serotonin, and histamine (16, 23, 85).

Histamine is a neurotransmitter with an established role in promoting alertness (81). Histaminergic neurons originate only in the tuberomammillary nucleus but have widespread projections throughout the brain (67), including synapses on dopaminergic neurons originating in the ventral tegmental area, serotonergic neurons originating in the dorsal and median raphe nuclei, and norepinephrine neurons from the locus coeruleus. Thus, the histamine system, in part through its actions on monoaminergic neurons, can plausibly influence energy and fatigue symptoms, and attention (79, 97). A smaller body of research has found that histamine plays a role in motivation and reward mechanisms in the brain (2, 40).

Histamine binds to four receptors H_1, H_2, H_3 and H_4 but the alerting effects of histamine are thought to be primarily mediated by H_1 receptors. Histamine binding to H_1 receptors can influence sleep and wake states (79), and sleep can influence mental energy (63) and cognitive performance (70). Drugs that cross the blood-brain barrier and act as antagonists or inverse agonists on H_1 receptors reduce alertness and cognitive function (6, 56). A meta-analysis of 18 experiments examining the effects of diphenhydramine, a centrally acting H_1 receptor inverse

agonist, reported significant impairments in alertness with the largest effects found for reductions in performance on attention tasks and increases in self-reported fatigue and sleepiness (6). While diphenhydramine binds primarily to H_1 receptors it also binds to the other histaminergic or cholinergic receptors, consequently, its effects cannot be attributed solely to H_1 receptor antagonism (80). Doxepin hydrochloride, in low doses, has the highest known selectivity for H_1 receptors, therefore it is used in positron emission tomography studies to image H_1 receptors (97).

Acute exercise can influence performance on tasks requiring sustained attention (47), but whether these are effects on cognition per se or cognition related processes such as visual perception or the motivation to complete cognitive tasks is unknown, as are the effects of acute exercise on brain histamine. It is known that histamine increases peripherally in response to acute exercise to aid in vasodilation (37, 52, 55) and elevations in brain ATP and ADP can promote histamine release from the tuberomammillary nucleus (29). Histaminergic neurons also innervate brain structures involved in cardiovascular regulation (5), and blood pressure and heart rate can be altered via stimulation of central histamine receptors (5, 71). Histamine receptors may also promote vasodilation and contribute to improved circulation within the brain, although it is uncertain if this is mediated by H_1 or H_2 receptors (64). It is also known that exercise training alters the expression of H_1 receptors in the nucleus tractus solitariii (7, 92, 93). There is a need for investigations aimed at documenting the effects of acute exercise on brain histamine and if such responses are linked to psychological outcomes known to be associated with the brain histamine system.

The purpose of the research summarized here was to determine if brain histamine, binding at the H_1 receptor, is a mechanism that influences changes in “mental energy” after a

single session of exercise. Mental energy has been conceptualized as involving three dimensions: energy and fatigue perceptions, cognitive performance on tasks that require sustained attention, and motivation to perform work (63). Expected improvements in all three dimensions of mental energy after low intensity cycling exercise in a placebo condition performed by adults reporting symptoms of low energy and high fatigue were hypothesized to be blocked by the pre-exercise administration of the histamine H_1 receptor antagonist doxepin.

Methods

Design and Ethics

The investigation was a randomized, placebo-controlled cross-over experiment. All methods were approved by the University Institutional Review Board before the experiment began.

Participants

Participants were recruited using listservs, flyers, and verbal announcements in academic classes. Included were females aged 18-34 years with both low vigor (< 11) and high fatigue (> 7) during the prior week, based on scores on the Profile of Mood States questionnaire. Females alone were recruited to minimize potential confounding due to sex differences in H_1 receptor density (98). Exclusion criteria were: a) participant concerns about health risks of doxepin use, b) medical conditions that could make doxepin use unsafe (e.g., glaucoma, liver disease), c) a history of a mental disorder, d) physician instructions to avoid antihistamines, e) pregnancy or trying to become pregnant, f) prescription medication use (not including oral contraceptives), g) regular use (> 1 time/week) of over-the-counter antihistamines, supplements or energy drinks, h) regular use (> 2 servings/week) of grapefruit or grapefruit juice, and i) contraindications to exercise as assessed using the Physical Activity Readiness Questionnaire.

Outcome Measures

The primary outcomes selected to be consistent with a model of mental energy (63), involved measures of energy and fatigue states, three objective cognitive tests, and one measure of motivation to perform the cognitive tests. The model proposes that mental energy is composed of a cognitive, mood, and motivation dimension and that each dimension can be influenced by other variables such as sleep and health status (63).

Mood States

The Mental and Physical State Energy and Fatigue Scales (SEF) were used to measure four perceived psychological states: mental energy, physical energy, mental fatigue and physical fatigue. The SEF consists of 12-items, three items per scale. The energy items are energy, vigor and pep while the fatigue items are fatigue, exhaustion and being worn out. Participants rate their current ("right now") intensity of feelings in relation to their perceived capacity to perform either typical physical activities or typical mental activities. Each item is a 10-cm visual analog scale (VAS) anchored by wording designed to capture the full range of intensity from as low as possible (e.g., "I feel I have no energy") to as high as possible (e.g., "strongest feelings of energy ever felt"). Scoring followed procedures described in a manual (62). Published data support the validity of the SEF for measuring physical and mental energy and fatigue states and for assessing change in these variables (32, 45, 54).

Cognitive Tasks

The Bakan task is often described as a measure of sustained attention though accurate performance also involves adequate vision and short-term memory, the ability to inhibit prepotent responses, and the ability to generate a correct and fast motor response (3, 90). The

Bakan was selected here because it can be influenced by acute exercise (59) and because antihistamines acting on H_1 receptors impair working memory and vigilance performance (90). The locus coeruleus and the anterior cingulate cortex have a role in alerting and inhibition, respectively (69), and the locus coeruleus and tuberomammillary nucleus are networked via several pathways that influence alertness (79).

Participants were presented with a continuous string of numbers (1-9; Tahoma Regular font, size 20) for 1000 ms each, during which time the participant had two tasks (primary and secondary). The primary task was to detect the presentation of three successive odd and different numbers (e.g., 5-9-3). The secondary task was to identify the specific number 6. The participants pressed a key with the right index finger to indicate presence of 3 successive odd numbers, and a different key with the left index finger to indicate when a 6 was observed. The number of primary and secondary targets correctly detected (hits), the average reaction time for correct detection of each target, and the number of false alarms for each task were recorded. A total of 960 numbers were presented during each 16 minute Bakan task, which always included 8 primary targets and 96 secondary targets. The task was scored using a index [$P(\bar{A})$](33) based on signal detection theory (1) that reflects each participant's probability of hits and false alarms, and possible values of the index range from 0.5 to 1.0. Values closer to one indicate a greater probability of correctly identifying both hits and false alarms (33).

The critical flicker-fusion (CFF) threshold was used to assess changes in visual perceptual processing efficiency. Antihistamines, including those that act on H_1 receptors consistently reduce the CFF threshold while stimulants, including high intensity exercise, increase the CFF threshold. Because of these and other experimental observations the CFF threshold at times has been described generally as a measure of central nervous system (CNS)

arousal (20, 42). More recently it has been shown that light sensitive retinal cells transmit information about ambient light to the CNS where flicker perception is associated with the activation of the bilateral frontal and left parietal cortex while fusion perception is associated with the activation of the occipital cortex (14). Thus, the efficiency of interactions among brain regions involved in these types of visual perceptual processes is a more specific hypothesis as to what the CFF threshold assesses (75). In the absence of an experimental treatment the CFF threshold has high short-term stability (within a single testing session) (68).

Critical flicker-fusion threshold was determined using a Lafayette Instrument 12021 Flicker Fusion device. The participant was instructed to press a response button in the dominant hand when steady lights appear to begin flickering (descending presentations - Flicker) or when flickering lights appeared to fuse into a steady beam (ascending presentations - Fusion). The participant placed her face into the mask of the device and viewed two round simultaneous light beams (left and right eye) presented 2.75” apart at a distance of 15” and at a viewing angle of 1.9 degrees. The luminance was set at 100%. The frequency of the target was increased and decreased in 0.1 Hz steps. Participants completed 6 ascending and 6 descending trials at each measurement occasion. The average of the flicker and fusion frequency yielded a single CFF threshold value (20, 48).

The finger tapping task (FTT) was used to assess changes in sensorimotor speed (74). A keyboard was placed directly in front of the participant’s dominant hand and the participant was told to press down completely on the space bar key with the index finger as many times as possible during a 10-sec trial without lifting the wrist. A computer recorded the number of taps completed in 10-sec. Both finger tapping and acute whole body exercise increase blood flow in

the motor cortex (82), and non-specific antihistamines consistently impair psychomotor task performance (90).

Motivation

Motivation to complete the cognitive tasks was assessed using a numerical 0-10 scale anchored from "No motivation" (rating of 0) to "Highest motivation imaginable" (rating of 10). This scale can detect both reductions in motivation for performing cognitive tasks, induced by completing tasks of sustained attention repeatedly over several hours, and increases in motivation for performing cognitive tests induced by caffeine (51, 54). While poorly understood, it has been hypothesized that circuits involving the ventral tegmental area, nucleus accumbens, anterior cingulate cortex and the prefrontal cortex are involved in regulating effort-related decisions (77) and brain histamine acts directly and indirectly to influence approach and avoidance behaviors (36).

Sleepiness

Antihistamines can induce sleepiness (6) and sleepiness can impair cognitive performance (86). Acute sleepiness was measured using the Stanford Sleepiness scale (SSS). The SSS is a single item scale. Participants rated sleepiness "at that moment" with the SSS which ranges from 1 (Feeling active and vital; alert; wide awake) to 7 (Almost in reverie; sleep onset soon; lost struggle to remain awake) (43). The scale has been used frequently in clinical and research settings and to assess the effects of antihistamines on sleepiness (56, 60, 91).

Procedure

On the first visit, informed consent was obtained using a paper form and widely used baseline questionnaires of health status, the SF-36 Health Survey (94), sleep quality, the Pittsburgh Sleep Quality Index (13) and physical activity, the Godin Leisure Time Exercise

Questionnaire (31), used to characterize the sample were completed on a desktop computer using qualtrics.com. Participants were instructed on, and practiced, all the cognitive tasks. A maximal exercise test using an electronically braked cycle ergometer (Excalibur Sport, Lode, Groningen, The Netherlands) was completed to measure $\dot{V}O_{2peak}$ so that the exercise workload of 40% $\dot{V}O_{2peak}$ could be assigned on subsequent visits. Light intensity exercise was chosen based on a literature review suggesting that light intensity would be most likely to increase feelings of energy, reduce feelings of fatigue and favorably impact cognitive performance in the placebo condition among people reporting low energy and high fatigue symptoms (53).

The computerized indirect calorimetry system (ParvoMedics TrueOne Metabolic System, Sandy, UT) was turned on 30 min before the O_2 and CO_2 analyzers and flowmeter were calibrated. The protocol was described and participants were fitted with a mouthpiece and nose plug for gas collection and the cycle seat was adjusted. The test started with a 5-min warm-up at 25 W at a self-selected cadence > 30 revolutions per minute (RPM). Work rate then increased every 2 min by 25 W until volitional exhaustion was indicated or the cadence decreased to < 30 RPM. Heart rate, using a Polar Vantage XL heart rate monitor (Polar Electro Oy, Kempele, Finland), ratings of perceived exertion (RPE), using Borg's 6-20 RPE scale (10), and pain intensity in the quadriceps muscles, using a 0-10 category rating scale (18), were measured at the end of every 2-min stage. The highest VO_2 value recorded ($\dot{V}O_{2peak}$) was used to determine workload on visits 2 and 3. Participants were scheduled for their second and third visits to occur i) each at the same time of day (± 2 hours) and ii) at least 48 hours apart from each other to allow time for washout of doxepin.

Prior to the second and third visit participants were required to i) obtain a normal amount of sleep the previous night (± 2 hours of usual sleep duration, see appendix), ii) refrain from

using caffeine for 4 hours prior to the beginning of each study session, iii) avoid using prescription (besides birth control) or over-the-counter medication for 24 hours prior to the study testing time, iv) avoid exercise, and v) report no plans of driving until the next day. Compliance was checked using a questionnaire (see appendix), and participants were rescheduled as necessary (n = 1). The outcomes were measured and the participant was then administered 6 ounces of tomato juice (to mask the bitter taste of doxepin; R.W. Knudsen Organic) with 6 mg doxepin hydrochloride (DOX) added or without (placebo, PLA). DOX and PLA were administered using a double-blind, cross-over design. The treatment order was block randomized in blocks of two. An investigator (PJO) not involved in daily testing determined the administration order using Research Randomizer (www.randomizer.org) and prepared the PLA and DOX drinks. For the DOX drinks, 0.6 mL of an oral solution of doxepin hydrochloride with a concentration of 10 mg/mL was pipetted into a plastic drink cup containing tomato juice, mixed gently with the pipette tip, tightly capped and refrigerated for 1-24 h prior to consumption. Neither the researcher conducting testing (BDL) nor the participants knew the drink contents. After the participant consumed the tomato drink the they immediately guessed the contents (DOX or PLA) and rested quietly for 90 min while watching a space exploration documentary to allow time for the drug to become bioavailable (95, 96). The outcome measures were completed a second time to quantify the effects of DOX. Participants then completed 30 min of exercise on a cycle ergometer at W eliciting 40% of VO_2 peak. Heart rate, RPE and leg muscle pain were assessed every 5 minutes during exercise. Immediately after exercise, the outcomes were completed a third time, followed by a second administration of the “What I Think I Got” questionnaire. Before being released from the laboratory, the participants were instructed to not

drive, operate dangerous equipment or drink alcohol until the next day because they may have received DOX.

Visit three was identical to visit two, except the condition (DOX, PLA) was reversed. The timing of the study procedures is illustrated in Table 4.1.

Statistical Analysis

Preliminary

An a priori power analysis (21) with 20 participants, correlations of $r = 0.85$ between repeated measures, and an expected effect size of $\Delta = 0.50$ (53) resulted in statistical power ≥ 0.80 to test for a condition X time interaction effect using a two-tailed repeated-measures ANOVA with $\alpha = .05$. All statistical analyses were performed before the blind was broken. Data were entered twice by 2 research assistants, compared for agreement and accuracy, and errors were corrected. All data were analyzed using SPSS 20.0 (IBM Corp., Armonk, NY). Missing data (< .01% of the total data obtained) were imputed using the last value carried forward procedure. The reliability of pre-treatment repeated cognitive measures (FTT, CFF) was assessed across the three time points (T1, T2, T3) for each condition (DOX, PLA) using intraclass correlation coefficients with a two-way mixed model for consistency. The reliability of all cognitive measures at each time point was high ($\alpha \geq .90$). The average of the 5 FTT and the 6 CFF trials were used as the criterion measures in subsequent analyses. Data were checked for outliers (> 3 SDs from the mean) and normality using histograms and Kolmogorov-Smirnov tests. Outlying values on the FTT (n=2) or CFF (n=2) were transformed to the next highest score plus one. Four participants had outlying values that could not be transformed (i.e., zero correct responses for the Bakan primary task) and were removed before the primary analysis. Three of these cases (75%) occurred during the DOX condition. A reverse log transformation was applied

to remaining data to yield a normal distribution. All other data were normally distributed. A series of 2 condition (DOX, PLA) x 4 time (10 min, 15 min, 20 min, 25 min) RMANOVAs were used to determine if cardiac (heart rate) and perceptual (RPE, pain) responses during exercise were the same in both conditions.

Primary

A series of 2 condition (DOX, PLA) x 3 time (baseline, post-treatment, post-exercise time) repeated-measures analyses of covariance (RMANCOVA), controlling for the difference in prior night's sleep between experimental days, were used to test for the hypothesized interactions on the SEF subscales, cognitive tasks (i.e. FTT, CFF, Bakan), Stanford Sleepiness scale, and motivation to complete mental work scale. Significant condition-by-time interactions were decomposed using separate (for each condition) one-way RMANCOVAs and simple contrasts, which test if the size of the difference between conditions at one time point is different than at the contrasted time point (28, 44, 65). If the sphericity assumption was violated, adjustments were made using Huynh-Feldt epsilon. Hedges' *g* was also calculated to provide a measure of the size of the effects for all variables and *g*-values ≥ 0.80 are conventionally described as large effects.

Results

Preliminary Analysis

Participant flow through the experiment is shown in Figure 4.1

Sensitivity Analysis

One participant expressed a strong distaste for tomato juice after the first visit (PLA) and was given orange juice for the second visit (DOX). The participant was included in the dataset

because a sensitivity analysis with the participant removed resulted in no change in the significance of statistical tests.

Order Effect

Drink administration order (DOX first, PLA first) was tested using RMANOVAs and no significant effects ($p > .05$) were detected.

Blinding

Immediately after drink administration, 11 participants (55%) correctly guessed they had received DOX and 55% correctly guessed PLA. At the end of the visits, 75% correctly guessed they had received PLA and 60% correctly guessed DOX. Participants were not told the study hypotheses or the expected effects of DOX before the study began.

Prior Night's Sleep

Participants reported getting 6.6 (± 1.4) h sleep the night before the DOX visit and 7.1 (± 1.0) h before PLA.

Exercise Responses

Descriptive statistics (M, SD) for the sample and $\dot{V}O_{2peak}$ test results are reported in Table 4.2. Participants were assigned a mean of 37 (± 8.9) watts (range 25-55) and pedaled at 65 (± 11.9) revolutions per minute (range 42-87). There was a significant effect of time for heart rate, $F(3,19) = 21.74$, $p < 0.001$, *partial* $\eta^2 = .63$, RPE $F(3,19) = 36.69$, $p < 0.001$, *partial* $\eta^2 = .66$, and quadriceps pain, $F(3,19) = 12.86$, $p < 0.001$, *partial* $\eta^2 = .40$. The condition and the condition X time interaction effects were not statistically significant (all $p > .32$). Heart rate increased from 108.3 (± 9.9) beats per minute (BPM) to 115.8 (± 13.3) BPM, RPE increased from 8.5 (± 1.3) to 10.6 (± 2.0), and quadriceps pain intensity increased from 0.3 (± 0.4) to 1.1 (± 1.2).

Psychological Outcomes

Descriptive statistics (*M*, *SD*) for the PSQI and SF-36 data are presented in Table 4.2. Descriptive statistics of energy and fatigue states, sleepiness, motivation, and cognitive tasks are reported in Table 4.3. Effect sizes (Hedges' *g*) calculated using unadjusted means are presented in Table 4.4.

Primary Analysis

Energy and Fatigue Ratings

The condition-by-time interaction for mental fatigue was statistically significant, $F(2,36) = 4.07$, $p = 0.025$, *partial* $\eta^2 = 0.18$. The one-way RMANCOVA for DOX was significant $F(1.97,35.37) = 4.90$, $p = 0.014$, *partial* $\eta^2 = 0.21$,while PLA had no change over time, ($p = 0.700$). Simple contrasts indicated a difference for DOX between baseline and post-exercise, $F(1,18) = 6.17$, $p = 0.023$, *partial* $\eta^2 = 0.26$. At post-exercise, mental fatigue was increased from baseline for DOX but not PLA (Fig 4.2, Panel A). Inspection of unadjusted individual data (not presented here) showed mental fatigue was reduced post-exercise for 10 participants after PLA, and 6 participants after DOX.

The condition-by-time interaction for mental energy was not significant ($p = 0.27$) and the main effect for condition was not significant ($p = .147$). The main effect for time was significant, $F(2,36) = 9.36$, $p = 0.00$, *partial* $\eta^2 = 0.34$. Simple contrasts showed a difference between baseline and post-drink, $F(1,18) = 22.60$, $p = 0.00$, *partial* $\eta^2 = 0.56$, and baseline and post-exercise, $F(1,18) = 10.10$, $p = 0.00$, *partial* $\eta^2 = 0.36$. Figure 4.2 Panel B shows lower mental energy after exercise compared to baseline for both DOX and PLA.

The condition-by-time interaction for physical energy was not significant ($p = 0.392$). The main effect for condition was not statistically significant ($p = 0.091$), but the main effect for

time was significant, $F(2,36) = 6.24$, $p = 0.00$, *partial* $\eta^2 = 0.26$. Simple contrasts showed a difference between baseline and post-drink, $F(1,18) = 11.56$, $p = 0.003$, *partial* $\eta^2 = 0.39$, and post-drink and post-exercise, $F(1,18) = 7.01$, $p = 0.02$, *partial* $\eta^2 = 0.28$. For both DOX and PLA, there was a post-drink decrease in physical energy followed an increase after exercise (Table 4.3).

For physical fatigue, the condition-by-time interaction was not statistically significant ($p = 0.157$) nor was the main effect for time ($p = 0.225$). The main effect for condition was significant, $F(1,18) = 10.94$, $p = 0.00$, *partial* $\eta^2 = 0.37$ with greater physical fatigue for DOX than PLA.

Finger Tapping Test (FTT)

The FTT condition-by-time interaction was statistically significant, $F(1.92,34.51) = 6.63$, $p < 0.001$, *partial* $\eta^2 = 0.27$. The one-way RMANCOVA for DOX was significant $F(1.51,27.16) = 13.39$ $p < 0.001$, *partial* $\eta^2 = 0.43$,while PLA had no change over time, ($p = 0.218$). Simple contrasts indicated a difference for DOX between baseline and post-drink, $F(1,18) = 14.65$, $p = 0.001$, *partial* $\eta^2 = 0.45$, and baseline and post-exercise, $F(1,18) = 15.55$, $p = 0.001$, *partial* $\eta^2 = 0.46$. Figure 4.3 shows that DOX caused a decrease in FTT, but there was no change for PLA. DOX caused a decrease in FTT for 16 participants by a mean of 4.5 (± 3.2) taps, whereas PLA caused 12 participants to decrease by a mean of 2.3 (± 1.4) taps.

Critical Flicker Fusion (CFF) Threshold

The CFF condition-by-time interaction was not significant ($p = 0.10$) nor was the main effect for condition ($p = 0.07$). The main effect for time was significant, $F(2,36) = 7.37$, $p < 0.001$, *partial* $\eta^2 = 0.29$. Simple contrasts showed a difference between baseline and post-drink, $F(1,18) = 6.00$, $p = 0.025$, *partial* $\eta^2 = 0.25$, and baseline and post-exercise, $F(1,18) = 11.76$, $p <$

0.001, *partial* $\eta^2 = 0.40$. Both the DOX and PLA conditions had decreases in CFF throughout the experiment (Table 4.3).

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The condition-by-time interaction for P(Ā)-Primary was not significant ($p = 0.68$) nor was the main effect for condition ($p = 0.23$) or time ($p = 0.40$). For the primary task RT, the condition-by-time interaction was not significant ($p = 0.28$) and the main effect for condition was not significant, ($p = 0.34$). The main effect for time was significant, $F(2,28) = 4.21$, $p = 0.025$, *partial* $\eta^2 = 0.23$, with contrasts showing a decrease in RT from baseline to post-exercise, $F(1,14) = 8.75$, $p = 0.01$, *partial* $\eta^2 = 0.39$, and from post-drink to post-exercise, $F(1,14) = 5.41$, $p = 0.04$, *partial* $\eta^2 = 0.28$.

The condition-by-time interaction for P(Ā)-Secondary was not significant ($p = 0.62$) nor was the main effect for time ($p = 0.64$). There was a significant main effect for condition, $F(1,14) = 5.09$, $p = 0.00$, *partial* $\eta^2 = 0.53$, with greater signal detection sensitivity for PLA than DOX (Table 4.3). The condition-by-time interaction for secondary task RT was not significant ($p = 0.80$) but the main effects were significant for condition, $F(1,14) = 9.70$, $p = 0.00$, *partial* $\eta^2 = 0.41$, and time, $F(2,28) = 8.94$, $p = 0.025$, *partial* $\eta^2 = 0.39$. Contrasts revealed RT was reduced from baseline to post-drink drink, $F(1,14) = 8.84$, $p = 0.01$, *partial* $\eta^2 = 0.39$, and from baseline to post-exercise, $F(1,14) = 14.56$, $p = 0.00$, *partial* $\eta^2 = 0.51$, and was lower for PLA than DOX, $F(1,14) = 9.70$, $p = 0.00$, *partial* $\eta^2 = 0.41$ (Table 4.3).

Motivation

The condition-by-time interaction was statistically significant, $F(2,36) = 3.98$, $p = 0.028$, *partial* $\eta^2 = 0.18$. The one-way RMANCOVA for DOX was significant $F(2,36) = 12.60$, $p < 0.001$, *partial* $\eta^2 = 0.41$,while the PLA condition did not significantly change over time, ($p =$

0.080). Simple contrasts showed a difference between baseline and post-drink and $F(1,18) = 18.99$, $p < 0.001$, *partial* $\eta^2 = 0.51$ and baseline and post-exercise, $F(1,18) = 18.96$, $p < 0.001$, *partial* $\eta^2 = 0.51$. Motivation decreased for both conditions from baseline to post-exercise, although the change was statistically significant for DOX and not PLA (Fig 4.4). Inspection of individual data (not shown here) revealed that, after exercise compared to baseline, 70% taking DOX and 40% taking PLA had a decrease in motivation to perform mental tasks.

Sleepiness

The condition-by-time interaction for sleepiness was statistically significant, $F(2,36) = 4.13$, $p = 0.024$, *partial* $\eta^2 = 0.19$. The one-way RMANCOVA for DOX was significant $F(1.52,27.40) = 8.49$, $p = 0.003$, *partial* $\eta^2 = 0.32$. Simple contrasts for DOX showed a difference between baseline and post-drink, $F(1,18) = 27.36$, $p < 0.001$, *partial* $\eta^2 = 0.60$ and baseline and post-exercise, $F(1,18) = 5.53$, $p = 0.030$, *partial* $\eta^2 = 0.24$. The PLA condition also significantly changed over time, $F(2,36) = 3.74$, $p = 0.033$, *partial* $\eta^2 = 0.17$. Simple contrasts for PLA revealed a difference between post-drink and post-exercise, $F(1,18) = 7.31$, $p = 0.015$, *partial* $\eta^2 = 0.29$. Sleepiness increased after the drink for DOX but not PLA, and

exercise after PLA resulted in a decrease in sleepiness (Table 4.3). Individual data (not shown) revealed that 7 participants taking DOX had post-exercise increases in sleepiness, while only 1 participant taking PLA had an increase in sleepiness.

Discussion

The primary finding of this investigation is that mental fatigue increased post-exercise after DOX, but not PLA, when adjusting for differences in the prior night's sleep. In contrast, in both the DOX and PLA conditions exercise had similar effects on energy. Perceptions of physical energy were increased in both the DOX and PLA conditions, and the size of the effect

was consistent with previous research documenting energy responses to acute exercise (53). Although histamine has been hypothesized to influence changes in energy and fatigue (85), this is the first study to suggest that brain histamine mediates exercise-induced fatigue reductions, with less effect on energy symptoms.

Brain histamine has been implicated in sleep-wake states (35, 79), but others have suggested that changes in adenosine, norepinephrine, serotonin and dopamine influence energy, fatigue, and motivation states (85). While the key novel findings here are that blocking histamine influences fatigue, sleepiness, and motivation to perform cognitive work, this does not suggest that other neurotransmitters have no role in fatigue or motivation changes. Around 80% of noradrenergic neurons in the locus coeruleus can be excited by histamine H_1 receptor activity (36) and H_1 binding promotes serotonergic activity in the dorsal raphe nucleus (12, 66). Histaminergic neurons from the tuberomammillary nucleus also innervate the stratium, but only the H_2 and H_3 receptors influence dopaminergic activity (26). There are H_1 receptors within the nucleus accumbens and dopamine release within the accumbens may have a role in energy, fatigue, and motivation (78). Blocking H_1 receptors also reduces dopamine release in the accumbens (30), which can decrease behaviors indicative of higher energy and motivation, or reduced fatigue (78, 87). The locus coeruleus, dorsal raphe, striatum, and nucleus accumbens have potential roles in fatigue changes (39). Since changes in energy were not as strongly influenced by DOX in the present study, it is possible that dopamine has a greater role in energy, and not fatigue, changes, but this hypothesis remains to be directly tested. In sum, norepinephrine, serotonin, dopamine and histamine could all be involved in exercise-induced fatigue or energy state changes, but may depend on histamine H_1 receptor binding.

Fatigue during exercise may also occur due to reductions in cholinergic activity (17, 22) and histamine binding to H_1 receptors can increase central acetylcholine release (15, 66) to induce wakefulness (79). On the other hand, histamine binding to H_3 receptors can also induce acetylcholine release (66), particularly in the anterior cingulate cortex (84) and prefrontal cortex (15). The H_3 receptor serves as a autoreceptor or a heteroreceptor to regulate neurotransmitter release from non-histaminergic neurons (66). Histaminergic binding to H_3 receptors may improve cognitive performance (27), but could have less role in fatigue than H_1 receptor binding (61). Although the histamine system may more strongly mediate cholinergic activity via H_3 than H_1 binding (8, 9), it is not known exactly how histamine interacts with acetylcholine or other neurotransmitter systems to influence ratings of mental fatigue in humans.

It is also possible that fatigue increased post-exercise in the DOX condition due reductions in brain blood flow caused by H_1 receptor blockade. H_1 receptors are present within cerebral blood vessels (25) and rats administered a H_1 antagonist drug have reduced cerebral blood flow (34). H_1 antagonist drugs also can reduce blood flow during attention tasks as measured by near-infrared spectroscopy (46, 88). Reductions in cerebral oxygenation, which occur at high intensity exercise, may result in exercise fatigue that leads to reduced performance or complete cessation of exercise (38, 73). Changes in blood flow may be related to fatigue changes that occur in response to cognitive work (19) and a single bout of exercise (58), but additional research is needed before strong conclusions can be drawn about the relationship between brain oxygenated blood flow and self-reported fatigue. In this study, it is also not possible to separate the possible effects of H_1 blockade in the vasculature from neuronal receptor antagonism.

The effect of acute exercise on mental task motivation was small and positive in the PLA condition (g = 0.16), but negative in the DOX condition (g = -0.15). This was novel because the effect of acute exercise on mental task motivation has not been quantified. Animal models suggest that histamine has a role in motivation and there is reduced H_1 receptor binding in disorders (e.g., depression, schizophrenia) where reduced motivation or drive is common (87). There are H_1 receptors located in the nucleus accumbens (11), which has a role in motivation (76), but the influence of acute exercise on the nucleus accumbens is uncertain (24). The pattern of motivation changes was similar to that of mental energy, and previous models have suggested that motivation influences mental energy (63). Future studies should measure motivation for mental tasks in order to consider the role that exercise or psychoactive drugs may have on motivation to perform cognitive work.

Cognitive tasks are not often used to assess changes in mental energy and fatigue, although cognitive tasks are sometimes considered objective measures of mental energy or fatigue (63). DOX was expected to impair cognitive performance (90), and acute cycling exercise was expected to result in improvements (50), but this did not occur. Psychomotor speed (FFT) was reduced by DOX, but not improved by exercise in either condition. Visual perception efficiency (CFF threshold) decreased over time in both conditions and was not influenced by exercise. Previous studies have reported that acute exercise increases CFF (49), although the exercise intensity was higher than completed in the present study. DOX and exercise also did not strongly influence sustained attention, measured using the Bakan, which may have occurred for several reasons. First, participants may have still been learning the task as evidenced by decreases in secondary task RT that occurred throughout each visit for both DOX and PLA. It was expected that acute exercise would decrease RT, but the drop in RT from baseline to post-

drink was not hypothesized. However, practice on the cognitive tasks was included to minimize practice effects and there were no significant visit order effects on baseline performance, which would be hypothesized if task learning were occurring across testing days.

It is also possible that significant results were not obtained due to ceiling and floor effects. Bakan data were skewed and transformations were necessary to meet parametric statistical assumptions, and outliers (n = 4) with data that could not be transformed were eliminated. Specifically, data for four participants with zero correct primary targets were eliminated, but three of those cases occurred during the DOX condition. Considering only the individual responses of all 20 participants (not reported here) it does appear that DOX reduces sustained attention. Deleting four cases resulted in a loss of statistical power, specifically of three participants who may have been responding strongly to the manipulation (DOX) on the Bakan, which underscores the usefulness of selecting cognitive tests that yield data that approximate a normal distribution.

It is worth noting that several of the significant condition X time interactions reported here did not reach statistical significance until variance associated with differences in prior night's sleep was considered. Participants were required to sleep within ± 2 h of normal for testing to continue on any given day. Some participants slept more than normal on one visit and less than normal on another visit, which yielded a net difference which was sometimes larger than 2 h. Most previous studies examining changes in fatigue and cognitive performance have not controlled for, or measured, sleep and have reported that a single bout of exercise does not reduce fatigue states (4, 57, 89). A recent meta-analytic review of the literature also noted how few studies have measured sleep, such that sleep could not be considered as a moderator (53). Future researchers should account for differences in sleep when seeking to answer questions

related to the effect of manipulations (e.g., exercise, psychoactive drugs, supplements, bright light) on energy and fatigue states or cognitive performance.

An unexpected finding of the investigation is that significant group X time interactions did not emerge between baseline and post-drink (except for sensorimotor speed) or post-drink and post-exercise, but did occur between baseline and post-exercise. There are at least two reasons this may have occurred. First, it appears the experimental protocol itself may have reduced energy. Physical energy declined in both conditions from baseline to post-drink, and mental energy and CFF decreased during both visits. Reductions in energy could have occurred in part due to the length of the visit (~4 h) and the cognitive tasks that were completed, as previous investigators have reported decreases in energy with mental work (59). Participants were also sitting for ~3 hours before exercise began, and extended sedentary time may lead to reduced energy or increased fatigue. In a study of workers with sedentary jobs, removal of a standing workstation increased time spent sitting and reduced vigor (72). Data reported in a meta-analysis of 16 studies also suggests that control conditions in exercise studies, consisting largely of sedentary activities (e.g., watching videos, sitting on exercise equipment, reading), led to larger decreases in energy and little change in fatigue. For energy, T-scores before and after exercise were 53.4 and 51.2 (Δ = -2.2), while respective T-scores for fatigue were 47.3 and 47.0 (Δ = -0.3) (53). There is a paucity of data that directly examines effects of short-term sitting on psychological states, but it appears here (especially for PLA) that sitting time had a greater effect on energy than fatigue.

Another possibility is that peak doxepin availability (C_{max}) may not have been reached at the post-drink measurement time point. The median C_{max} for oral doxepin is 3 h (95) in fasted participants, but higher C_{max} can be obtained if the drug is administered with a food or beverage

(96), as was done in this study. Post-drink measurements were made at 1.5 h after DOX was taken, but post-exercise measures were administered 2 h 40 min after drink administration. Thus, it is possible that C_{max} may have been obtained in more participants by post-exercise than at post-drink. Exercise itself may have also helped more participants reach C_{max}, particularly in the brain, by increasing blood flow to the frontal cortex (73, 83). This may account for why significant interactions occurred between baseline and post-exercise, but not baseline and post-drink time points.

A strength of the study was measurement of physical and mental energy and fatigue. Although energy and fatigue are often conceptualized as existing on a single bipolar continuum (94), factor analysis (41) and differently sized effects of exercise (53) suggest that energy and fatigue are separate states with distinct neurobiology. In addition, studies that measure both physical and mental energy and fatigue often report different effects of manipulations on energy or fatigue. Completing cognitive work may reduce mental energy but have a non-significant effect on mental fatigue (47) and caffeine is reported to increase mental energy, but not reduce mental fatigue (54). On the other hand, differences in macronutrient content in recovery beverages consumed after cycling exercise did not result in significantly different energy or fatigue effects (32), and swimming performance is similarly correlated with physical fatigue, mental energy, and mental fatigue (45). Here, antagonizing H_1 receptors blocked exercise-induced reductions in mental fatigue but did not strongly influence increases in physical energy. Future investigators should continue to conceptualize and measure mental and physical energy and fatigue as four separate, but related, constructs.

Most studies have limitations and the present study is not an exception. First, no physiological measures of blood levels of doxepin or doxepin binding (e.g. PET) were obtained.

Consequently, drug bioavailability and presence in the brain were not directly confirmed. Nevertheless, doxepin is well-characterized (95, 97), and expected reductions in sleepiness and sensorimotor speed were reported here that suggest doxepin was bioavailable and producing a brain-based effect. A different drug delivery method (e.g., injection, inhalation) could have also been used which may have shortened the time to C_{max}. However, low-dose doxepin has most often been delivered orally (95) and the side-effect profile or exact time to C_{max} using a different method is uncertain. It is also unknown if acute exercise of the intensity and duration used here was adequate to stimulate the release of CNS histamine.

The results of this investigation support that histamine release and binding at the H_1 receptor mediates exercise-induced reductions in fatigue and motivation to complete cognitive work, but has less influence on energy states, sustained attention, visual perceptual processing efficiency and motor speed. Additional studies should investigate the role of histamine in medical conditions marked by elevated fatigue such as chronic fatigue syndrome/myalgic encephalitis/chronic exertional intolerance disease, multiple sclerosis, and depression. In addition, investigators should determine if H_1 receptor antagonist drugs used to treat other conditions block the expected fatigue-reducing effect of light-intensity exercise as was shown here.

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Figure Captions

Fig 4.1. Participant flow through the experiment. Of those who declined participation in Visit 1, 6 cited the time commitment of the study and 18 did not respond to emails to schedule a visit. Of those who dropped out after the first visit, 2 participants cited the time commitment and 3 did not respond to follow-up emails.

Fig 4.2. Panel A. Effect of doxepin hydrochloride and placebo on ratings of mental energy using the State Mental Energy Scale. The population norm for females is 161.9 (SD = 56.8) (O'Connor, 2006). Mental energy was significantly reduced from baseline at post-drink ($p < 0.001$) and was significantly lower post-exercise than baseline ($p < 0.001$).

Panel B. Effect of doxepin hydrochloride and placebo on ratings of mental fatigue using the State Mental Fatigue Scale. The population norm for females is 132.9 (SD = 64.1) (O'Connor, 2006). Fatigue was reduced from baseline at post-exercise for placebo, but not doxepin ($p < 0.001$). Points correspond to the mean value of 20 participants adjusted for differences in prior night's sleep. Bars are standard errors.

Fig 4.3. Average number of finger taps in 10 seconds in doxepin hydrochloride and placebo conditions across experimental phases. Taps were reduced at post-drink for doxepin but not placebo ($p = 0.009$). Points correspond to the mean value of 20 participants adjusted for differences in prior night's sleep. Bars are standard errors.

Fig 4.4. Effect of doxepin hydrochloride and placebo on mental task motivation across phases of the experiment. Ratings were completed using a 0-10 motivation scale with higher scores indicating greater motivation. There was a significant reduction in motivation from baseline at

post-exercise for doxepin but not placebo (p =0.016). Points correspond to the mean value of 20 participants adjusted for differences in prior night's sleep. Bars are standard errors.

Table 4.1
Timing of Study Procedures

Time (hours:mins)	Task	Test Phase
Visit 1		
0:00 – 0:02	Greet participant	Practice
0:02 – 0:10	Participant completes informed consent	Practice
0:10 – 0:20	Baseline questionnaires (PSQI, SF-36)	Practice
0:20 – 0:30	Practice finger tapping test	Practice
0:30 – 0:40	Practice critical flicker fusion	Practice
0:40 - 1:00	Practice bakan vigilance task	Practice
1:10 – 1:30	Perform ($\dot{V}O_{2peak}$) test	Practice
1:30 - 1:31	Schedule visits 2 and 3	Practice
Visit 2		
0:00 – 0:02	Greet participant	
0:02 – 0:05	Confirm compliance to test procedures	
0:05 – 0:10	SEF and SSS questionnaires	Baseline
0:10 – 0:11	Motivation to complete mental work	Baseline
0:11 – 0:20	Finger tapping test	Baseline
0:25 – 0:30	Critical flicker fusion	Baseline
0:30 – 0:46	Bakan vigilance task	Baseline
0:46 - 0:50	Consume tomato juice w/ doxepin or placebo	Treatment/bioavailability
0:50 – 0:51	What I think I got questionnaire	Treatment/bioavailability
0:51 – 2:20	Quiet rest	Treatment/bioavailability
2:20 – 2:25	SEF and SSS questionnaires	Post-drug
2:25 – 2:26	Motivation to complete mental work	Post-drug
2:26 – 2:35	Finger tapping test	Post-drug
2:35 – 2:40	Critical flicker fusion	Post-drug
2:40 – 2:56	Bakan vigilance task	Post-drug
2:56 – 3:30	Cycling exercise (30 minutes at 40% $\dot{V}O_{2peak}$)	
3:30 – 3:35	SEF and SSS questionnaires	Post-exercise
3:35 – 3:36	Motivation to complete mental work	Post-exercise
3:36 – 3:45	Finger tapping test	Post-exercise
3:45 – 3:50	Critical flicker fusion	Post-exercise
3:50 – 4:06	Bakan vigilance task	Post-exercise
4:06 – 4:07	What I think I got questionnaire	
Visit 3		
	Repeat Visit 2 procedures with other treatment (doxepin or placebo)	

PSQI = Pittsburgh Sleep Quality Index

SF-36 = SF-36 Health Survey

SEF = State Physical and Mental Energy and Fatigue

SSS = Stanford Sleepiness Scale

Table 4.2
Descriptive Sample, $\dot{V}O_{2peak}$, PSQI, and SF-36 Data

Measure		Mean	SD	Range
Sample Characteristics:	Age (years)	21.00	3.88	18-33
	Height (cm)	165.12	5.10	149.86-170.82
	Weight (kg)	62.15	8.89	45.81-84.82
	Body Mass Index ($kg \cdot m^2$)	22.80	3.14	17.72-30.18
$\dot{V}O_{2peak}$ Test:	$\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	28.41	5.98	18.9-44.7
	$Power_{peak}$ (W)	153.35	30.82	100-225
	$Heart\ Rate_{peak}$ (BPM)	184.45	7.53	166-198
	RER_{peak} ($VCO_2/\dot{V}O_2$)	1.22	0.09	1.10-1.43
	RPE_{peak} (6-20)	17.60	1.67	13-20
	$Pain_{peak}$ (0-10)	5.60	2.81	0.5-10
Godin Leisure-Time Exercise				
	Strenuous	1.98	1.44	0-5
	Moderate	2.75	2.22	0-7
	Mild	4.25	3.31	0-14
	Total Score	44.28	20.88	0-86
Pittsburgh Sleep-Quality Index:	Total	5.70	1.78	3-9
	Sleep quality	1.35	0.49	1-2
	Sleep latency	1.55	0.83	0-3
	Sleep duration	0.30	0.57	0-2
	Habitual sleep efficiency	0.00	0.00	0-0
	Sleep disturbance	1.05	0.22	1-2
	Use of sleeping medication	0.15	0.49	0-2
	Daytime dysfunction	1.30	0.57	0-2
SF-36 – Physical:	Physical functioning	93.25	9.50	70-100
	Role-physical	78.75	23.33	25-100
	Bodily pain	86.75	14.12	55-100
	General health	59	18.89	25-95
SF-36 – Mental:	Vitality	43.75	12.45	15-65
	Social functioning	77.60	19.09	32-100
	Role-emotional	45	37.89	0-100

Note. $\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$) = peak volume of oxygen consumed (milliliters of oxygen per kilogram of body weight per minute). W = watts. BPM = beats per minute. RER = respiratory exchange ratio. RPE = rating of perceived exertion. Higher scores (max = 100) on the SF-36 indicate less disability.

Table 4.3
Means and Standard Deviations for Mood, Sleepiness, Motivation and Cognitive Measures

	Doxepin			Placebo		
Measure	Baseline	Post-drink	Post-exercise	Baseline	Post-drink	Post-exercise
State Energy and Fatigue Scales						
Physical Energy	119.3 ± 48.6	98.0 ± 53.6	106.5 ± 63.0	128.0 ± 55.0	106.5 ± 56.4	129.5 ± 52.6
Physical Fatigue	153.8 ± 48.8	176.8 ± 44.6	169.6 ± 48.5	139.1 ± 55.3	150.0 ± 55.5	123.3 ± 61.1
Mental Energy	128.0 ± 51.2	104.8 ± 58.2	101.0 ± 57.6	146.3 ± 49.0	112.6 ± 52.8	128.8 ± 53.1
Mental Fatigue	158.8 ± 52.4	182.1 ± 46.1	181.6 ± 51.9	142.8 ± 53.6	149.3 ± 54.3	136.9 ± 55.2
Stanford Sleepiness Scale	3.5 ± 1.2	4.5 ± 1.2	4.0 ± 1.4	3.1 ± 0.9	3.6 ± 1.3	2.9 ± 0.9
Mental Task Motivation	5.7 ± 1.9	4.5 ± 1.8	4.2 ± 2.2	6.3 ± 1.7	5.3 ± 1.7	5.6 ± 2.1
Finger Tapping	57.2 ± 3.7	53.2 ± 5.0	53.8 ± 4.2	58.1 ± 4.4	57.6 ± 4.7	57.6 ± 4.2
Critical Flicker Fusion Threshold	38.0 ± 3.6	36.6 ± 3.2	36.1 ± 2.9	38.3 ± 2.9	37.7 ± 2.4	37.6 ± 2.0
Bakan Vigilance Task						
P(Ā)-Primary	0.94 ± 0.06	0.92 ± 0.06	0.94 ± 0.05	0.95 ± 0.06	0.95 ± 0.05	0.95 ± 0.04
RT-Primary	624.9 ± 67.6	637.2 ± 66.7	621.4 ± 62.4	657.0 ± 69.7	643.1 ± 82.1	614.1 ± 54.9
P(Ā)-Secondary	0.99 ± 0.00	0.98 ± 0.02	0.97 ± 0.04	0.99 ± 0.01	0.99 ± 0.01	0.99 ± 0.01
RT-Secondary	652.5 ± 47.9	641.2 ± 44.4	632.3 ± 48.5	630.0 ± 37.9	611.5 ± 33.7	605.9 ± 36.2

Note. N = 20 except for the Bakan Viglance Task (N = 16). P(Ā) reflects sensitivity for detecting targets relative to non-targets and is computed using a published formula (Grier, 1971). RT = reaction time. Primary = primary task of detecting 3 successive odd and different numbers. Secondary = secondary task of identifying the number 6. Means are unadjusted.

Table 4.3
Effect Size (Hedges *g*) of Treatment and Exercise

Task	After Drink			Exercise Change from Post-Drink			Post-Exercise Change from Baseline		
	DOX	PLA	|DIFF|	DOX	PLA	|DIFF|	DOX	PLA	|DIFF|
State Energy and Fatigue Scales									
Physical Energy	-0.42	-0.39	|0.03|	0.15	0.42	|0.27|	-0.23	0.01	|0.24|
Physical Fatigue	0.49	0.20	|0.29|	-0.15	-0.46	|0.31|	0.32	-0.27	|0.59|
Mental Energy	-0.42	-0.66	|0.24|	-0.07	0.31	|0.38|	-0.50	-0.34	|0.16|
Mental Fatigue	0.47	0.12	|0.35|	-0.01	-0.23	|0.22|	0.44	-0.11	|0.55|
Stanford Sleepiness Scale	0.87	0.38	|0.49|	-0.50	-0.84	|0.34|	0.32	-0.52	|0.84|
Mental Task Motivation	-0.65	-0.59	|0.06|	-0.15	0.16	|0.10|	-0.73	-0.37	|0.36|
Finger Tapping									
Dominant Hand	-0.91	-0.11	|0.80|	0.13	0.00	|0.13|	-0.86	-0.12	|0.74|
Non-dominant Hand	-0.71	-0.13	|0.58|	0.11	0.11	|0.00|	-0.67	-0.02	|0.65|
Critical Flicker Fusion Threshold	-0.41	-0.23	|0.18|	-0.16	-0.05	|0.11|	-0.58	-0.28	|0.30|
Bakan Vigilance Task									
P(Ā)-Primary	-0.33	0.00	|0.33|	0.36	0.00	|0.36|	0.00	0.00	|0.00|
RT-Primary	0.18	-0.18	|0.00|	-0.24	-0.42	|0.18|	-0.05	-0.68	|0.63|
P(Ā)-Secondary	-0.71	0.00	|0.71|	-0.32	0.00	|0.32|	-0.71	0.00	|0.71|
RT-Secondary	-0.24	-0.52	|0.28|	-0.19	-0.16	|0.03|	-0.42	-0.65	|0.23|

Note. DOX= Doxepin. PLA = Placebo. |DIFF| = Absolute difference between DOX and PLA. P(Ā) reflects sensitivity for detecting targets relative to non-targets and is computed using a published formula (Grier, 1971).After Drink formula for Hedges *g*: (90 min post Drink – baseline) / Pooled SD. After Exercise formula for Hedges *g*: (After exercise – 90 min post Drink) / Pooled SD. Exercise Change from Baseline formula for Hedges *g*: (After exercise – baseline) / Pooled SD. Negative effect sizes represent a larger change for PLA compared to DOX. Effect sizes are calculated using unadjusted means and standard deviations.

Figure 4.1

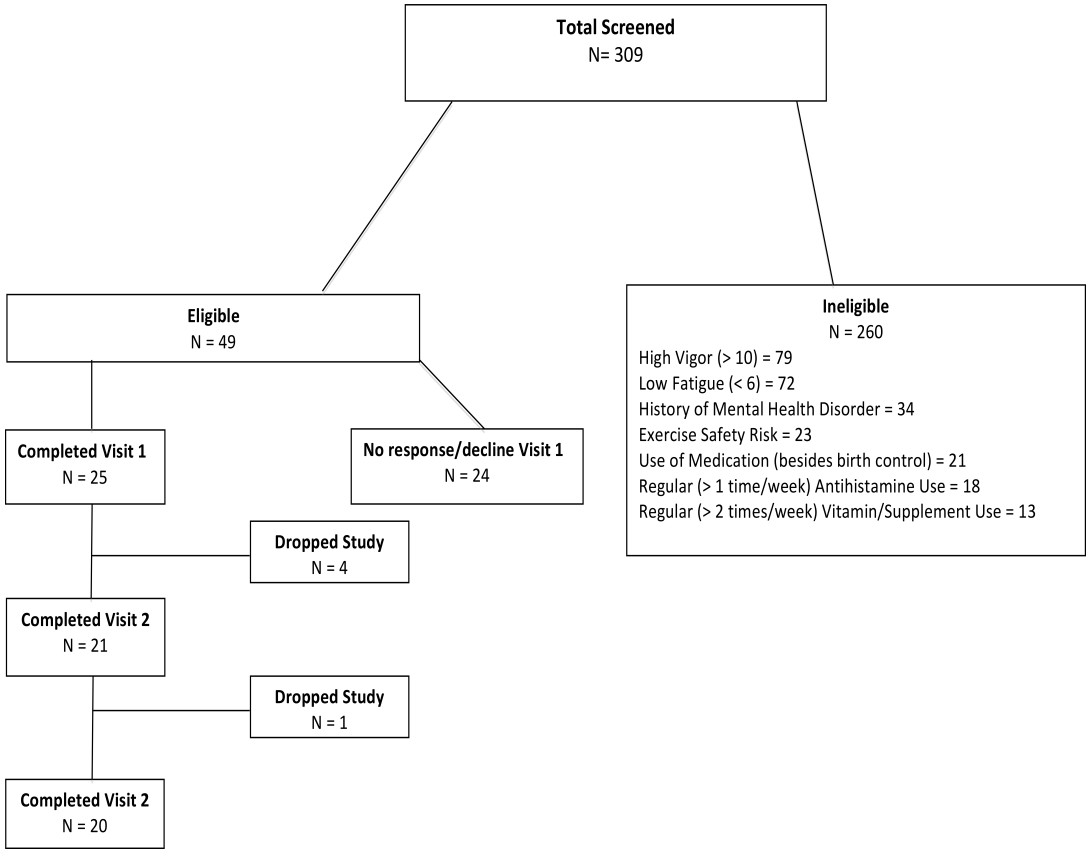
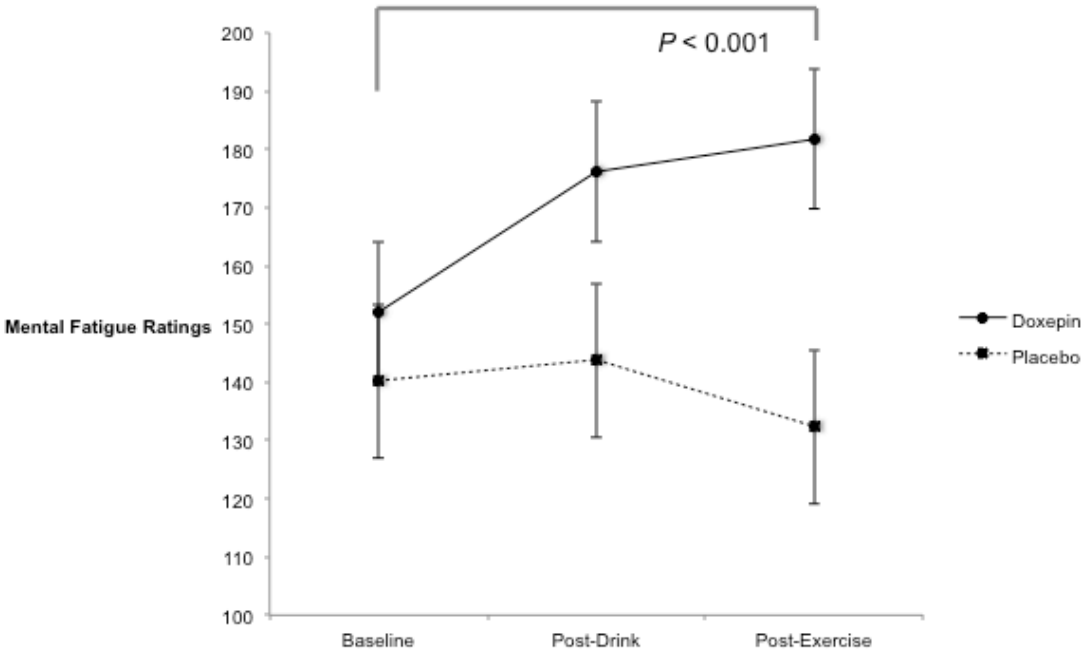

Total Screened
N= 309
Eligible
N = 49
Ineligible
N = 260
High Vigor (> 10) = 79
Low Fatigue (< 6) = 72
History of Mental Health Disorder = 34
Exercise Safety Risk = 23
Use of Medication (besides birth control) = 21
Regular (> 1 time/week) Antihistamine Use = 18
Regular (> 2 times/week) Vitamin/Supplement Use = 13
Completed Visit 1
N = 25
No response/decline Visit 1
N = 24
Dropped Study
N = 4
Completed Visit 2
N = 21
Dropped Study
N = 1
Completed Visit 2
N = 20

Figure 4.2

Panel A



Panel B

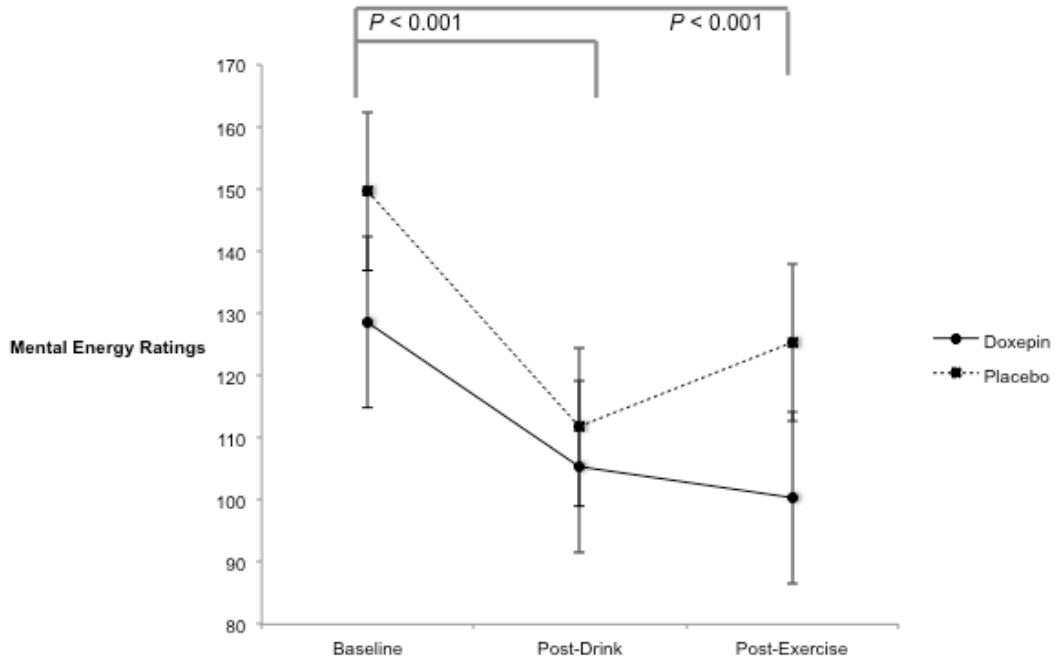


Figure 4.3

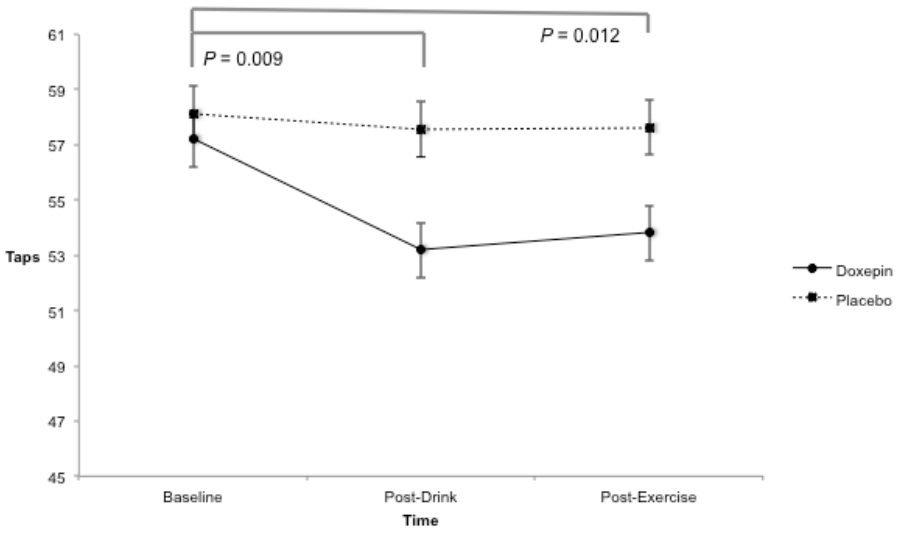
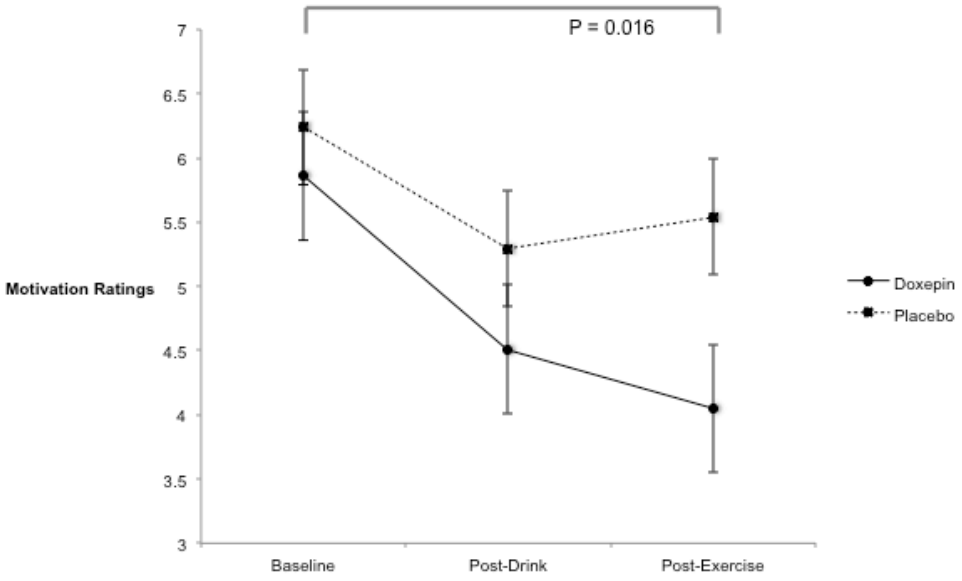

P = 0.012
P = 0.009
61
59
57
55
53
51
49
47
45
Taps
Baseline
Post-Drink
Post-Exercise
Time
Doxepin
Placebo

Figure 4.4


P = 0.016
Motivation Ratings
7
6.5
6
5.5
5
4.5
4
3.5
3
Baseline
Post-Drink
Post-Exercise
Doxepin
Placebo

CHAPTER 5

CONCLUSION

The purpose of this dissertation was to explore the problem of low mental energy and fatigue by determining the effect of a single bout of exercise on energy and fatigue states, and testing if brain histamine acting at the H_1 receptor is a mechanism that may explain the effect of exercise on mental energy or fatigue.

Fatigue is a complaint among 20% of the population (26), and a single session of exercise had been shown in several studies to reduce fatigue and increase energy (2, 7). The first study of the dissertation quantitatively summarized the effect 16 studies that measured both energy and fatigue post-exercise, and concluded that exercise had a moderate and positive effect on increasing energy. The second finding was that exercise had a small effect on reducing fatigue, but only when fatigue scores were elevated at baseline, exercise lasted at least 20 minutes and was performed at a light or moderate intensity, and when changes in energy also occurred. This meta-analysis ran counter to the common belief that acute exercise is likely to cause people to feel increased fatigue afterwards (21). The findings of the meta-analysis also suggest that energy and fatigue are separate feelings with different neurobiology, because feelings of energy and fatigue were differentially impacted by exercise.

The purpose of the experiment in the dissertation was to explore one possible explanation for exercise-induced changes in energy and fatigue. Previous investigators have suggested several neurotransmitters that may have a role in energy and fatigue, including dopamine, histamine, norepinephrine, and serotonin (20). Brain histamine, binding to the H_1 receptor, has an

established role in promoting alertness (9), and was blocked using the H_1 receptor antagonist drug doxepin hydrocholoride before 20 women with elevated fatigue and low energy participated in 30 minutes of light intensity cycling exercise. The main finding was that exercise-induced reductions in mental fatigue were blocked in the doxepin condition. Exercise-induced increases in energy were also smaller in the doxepin condition. Motivation for mental work also decreased across phases of the experiment in the doxepin condition. Cognitive tasks requiring sensorimotor speed were also affected by doxepin, but other tests of arousal and vigilant attention were not. The implication is that histamine binding to the H_1 receptor within the brain has a role in exercise-induced fatigue reductions, but does not influence energy. Dopamine release and binding could plausibly explain exercise-induced increases in energy, but this remains to be tested. The study may be impactful because it further suggests that energy and fatigue are separate states, which may be differentially impacted by different neurobiological mechanisms.

The histaminergic system is also involved in a number of diseases and disorders and the findings here may inform future research questions in those areas. Histamine release in the brain may influence glycogenolysis (18) which suggests a possibility of central histamine disgregulation in diabetes (16). Problems within the histamine system may also have a role in Narcolepsy (17), Multiple Sclerosis, Parkinson's, Alzheimer's, Schizophrenia (15), and addictions (24). While not all diseases and disorders involving the histaminergic system implicate the H_1 receptor, it is clear the histaminergic system can have widespread effects within the brain in health and disease.

On the other hand, neither this dissertation nor other work suggests that changes in central histamine might explain the "runner's high" that still lacks a clear neurobiological explanation (6). One study did report a relationship between opioid binding and euphoria and

happiness in trained males after nearly two hours of running exercise (3). Feelings of energy are increased and fatigue is consistently reduced after single bouts of light intensity exercise that are much shorter in duration than that which may increase opioid binding (12). Taken together, the opioid and histamine bodies of research suggest that exercise can have vastly different effects on the brain that are impacted by exercise duration and intensity. In general, little is understood (especially based on human research) regarding exactly how exercise changes the brain to influence energy and fatigue, mood states, or cognition (5).

The findings here do suggest that taking a centrally-acting H_1 antagonist drug can increase mental fatigue and prevent expected reductions in fatigue that occur after performing a single bout of exercise (12). The type of exercise used here (30 minutes, light intensity) is likely representative of what many people do in their daily lives, but some people may be missing the fatigue-reducing benefit of exercise if they are also taking centrally-acting antihistamines.

Since blocking H_1 receptors increased mental fatigue here, it would seem likely that increasing histaminergic transmission or using H_1 agonist drugs could also reduce mental fatigue without the need for exercise. Giving histamine itself is unlikely to be effective since peripheral histamine does not cross the blood brain barrier (22) and could induce allergic reactions or other side effects (19). Transdermal histamine was reported to be effective for Multiple Sclerosis patients in one trial (8), although the methods of this trial have been criticized. The H_3 receptor was first believed to function as an autoreceptor which made it an attractive target for antagonists, although it is now believed the H_3 receptor functions as a heteroreceptor (15). In general, it may be difficult to administer histaminergic drugs to reduce fatigue without inducing adverse side effects because histamine has widespread roles and functions within the central nervous system (10) and in the periphery (19).

Histaminergic release and binding also varies diurnally (9) and most humans choose to follow a sleep-wake schedule that follows the light cycle. Acute exercise studies have also been performed outside or with the lights on, and no well-controlled acute exercise study has ever measured changes in energy and fatigue without concomitant exposure to light. It is possible that histamine only influences changes in energy and fatigue when exercise is performed in lit conditions. This seems unlikely given that control groups have presumably been exposed to light of the same brightness and do not experience increases in energy or reductions in fatigue of the same magnitude as exercise groups (12). On the other hand, bright light exposure can influence fatigue (1) and it has never been determined that exercise does not interact in some way with light exposure. People also occasionally complete exercise sessions in conditions with very little light and changes in energy and fatigue or other mood states have rarely been examined as a function of light exposure. Further research should determine if the influence of histamine on exercise-induced changes in energy and fatigue is influenced by light exposure.

Preliminary investigations have suggested that histamine has a role in glycogenolysis within the vasculature (18) and previous investigations have also suggested that self-reported energy can be increased by eating a candy bar (23). Glucose obtained from high carbohydrate meals can influence energy, fatigue, mood, and cognitive performance (13) but it is yet unclear how glycogen in the brain, or consumed carbohydrate, may interact with histamine to influence energy and fatigue ratings.

Overall, histamine can have broad and numerous effects within the central nervous system that are still being fully eluctidated (10) and histamine is one of several neurotransmitters that may have a role in energy and fatigue states (20). Reduced energy and elevated fatigue are also commonly reported symptoms in medical practice and may have multiple etiologies (4).

Much of what is known about brain changes in response to exercise is also based on animal research, which presents unique research methodology problems (5). In general, much work remains to be done both on cause of reduced energy and elevated fatigue, and the role that histamine has in changing energy and fatigue states.

The findings of this dissertation research may inform several future research practices and questions. First, researchers measuring energy and fatigue should continue to measure separate but related constructs individually, rather than on a single bipolar continuum (25). Although energy and fatigue are inherently subjective states and are commonly measured by questionnaire (11), future investigators should consider related measures of cognitive performance and motivation to better understand changes in "mental energy" (14). The histamergic system has also been understudied relative to other monoamines (9), but should be examined for it's plausible role in disorders marked by high fatigue. Further inquiry and subsequent investigations will continue to improve understanding of the neurobiological basis of fatigue and further characterize how exercise may be used to overcome the problem of fatigue and low energy.

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APPENDICES

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Pre-Exercise History Questionnaire

1. How do you feel right now? (circle your answer)

Very bad Bad OK Good Very good

2. Have you exercised today? Yes No

    a. If yes, when did you exercise _____

    b. If yes, for how long did you exercise_____

    c. If yes, how intense was the exercise Low Moderate High

3. Have you had anything containing caffeine today? Yes No

    a. If yes, what did you take_____

    b. If yes, when did you take it_____

    c. If yes, what was the dose_____

4. Have you taken any prescription or over-the-counter medications today? Yes No

    a. If yes, what did you take_____

    b. If yes, when did you take it_____

    c. If yes, what was the dose_____

5. Have you consumed any grapefruit or grapefruit juice in the last 24 hours Yes No

    a. If yes, what did you take_____

    b. If yes, when did you take it_____

    c. If yes, what was the dose_____

6. Are you injured or is there any reason why you cannot perform a maximal exercise test today? Yes No

d. If yes, briefly describe the issue

7. When was the last time you drank or ate something (indicate the time to the nearest 5 minutes) _____

8. Will you be required to, or do you have any plans to, do any driving later today or tonight? Yes No

Last Night's Sleep Questionnaire

ID_____ Date_____

Last night I went to bed at _____

Last night I turned out the lights at _____

Last night the number of minutes it took me to fall asleep was _____

Last night the number of times I woke up was _____

Last night the total number of minutes I was awake when I woke up was _____

The time I finally woke up this morning was _____

The number of hours (to the quarter hour, e.g. 7.25) that I sleep on a typical night is _____