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The effect of histamine on changes in mental energy and fatigue after a single bout of exercise

Bryan D. Loy *, Patrick J. O'Connor

Department of Kinesiology, University of Georgia, Athens, Georgia

HIGHLIGHTS

- Histamine H_1 binding was tested as a mechanism of post-exercise fatigue reduction.
- H_1 receptor antagonism blocked exercise reductions in feelings of mental fatigue.
- Physical energy increased after exercise for both H_1 antagonism and placebo.
- Histamine influences exercise-induced fatigue reductions but not energy increases.

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ABSTRACT

The purpose of this research was to determine if histamine, acting on brain H_1 receptors, influences changes in feelings of energy and fatigue or cognitive test performance after acute exercise. Women ($n = 20$) with low vigor and high fatigue were administered the H_1 antagonist drug doxepin hydrocholoride (6 mg) in tomato juice and tomato juice alone (placebo) in a randomized, double-blinded, cross-over experiment before performing 30 min of light intensity cycling exercise and completing energy, fatigue, sleepiness, and motivation scales, and cognitive tasks. After exercise, mental fatigue increased for the doxepin condition ($p = 0.014$) but not placebo ($p = 0.700$), while mental energy decreased for both PLA and DOX ($p < 0.001$) and cognitive task performance was unaffected. It is inferred that histamine binding to H_1 receptors in the brain has a role in exercise-induced reductions in mental fatigue, but not increases in energy.

1. 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 and lasts at least 20 min [56]. The neurobiological reasons for changes in energy and fatigue with acute exercise are unclear and the biological basis of energy and fatigue is unknown [17]. However, a substantial body of literature links energy and fatigue symptoms to several neurotransmitters including adenosine, dopamine, norepinephrine, serotonin, and histamine [25,89].

Histamine is a neurotransmitter with an established role in promoting alertness [37,38,69]. Histaminergic neurons originate only in the tuberomammillary nucleus but have widespread projections throughout the brain [70], 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. The histamine system, in part through its actions on monoaminergic neurons, can influence energy and fatigue symptoms, and attention [83,103]. A smaller body of research has found that histamine plays a role in motivation and reward mechanisms in the brain [2,42].

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 [83], and sleep can influence mental energy [66] and cognitive performance [73]. Drugs that cross the blood–brain barrier and act as antagonists or inverse agonists on H_1 receptors can reduce alertness and cognitive function [6,59]. 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

* Corresponding author at: Department of Kinesiology, University of Georgia, 330 River Road, Athens, GA 30602-6554.
E-mail address: bloy@uga.edu (B.D. Loy).

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attributed solely to H_1 receptor antagonism [85]. Doxepin hydrochloride is over 100 times more selective for H_1 receptors than any other examined receptor (i.e., 5-HTT, muscarinic$_1$, alpha1-adrenergic, alphal2-adrenergic, $5HT_{1A}$, $5HT_2$, dopamine D_2) [22,90], does not bind in H_1 receptor knockout mice [46], is efficacious at low doses (≤6 mg) [77,84], and is used in positron emission tomography studies to image H_1 receptors [102,104].

Acute exercise can influence performance on tasks requiring sustained attention [50], 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 [39,55,58] and elevations in brain ATP and ADP can promote histamine release from the tuberomammillary nucleus [31]. 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 [5,74]. 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 [67]. It is also known that exercise training alters the expression of H_1 receptors in the nucleus tractus solitariii [7,98,99]. There is a need for investigations that document the effects of acute exercise on brain histamine and determine 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 test 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 mental work [66]. 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.

2. Methods

2.1. 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.

2.2. 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 [43]. This was done to minimize possible ceiling effects and because a larger effect of light intensity exercise on exercise-induced fatigue reductions occurs when baseline fatigue is elevated from normative values [56]. Only females were recruited to minimize potential confounding due to sex differences in H_1 receptor density [105]. 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 [92].

2.3. Outcome measures

The primary outcomes selected to be consistent with a model of mental energy [66], 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 [66].

2.3.1. Mood states

The Mental and Physical State Energy and Fatigue Scales (SEF) were used to measure four perceived 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 [65]. Published data support the validity of the SEF for measuring physical and mental energy and fatigue states and for assessing change in these variables [34,48,57].

2.3.2. 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 [3,54,57]. The Bakan was selected here because it can be influenced by acute exercise [62] and because antihistamines acting on H_1 receptors impair working memory and vigilance performance [96]. The locus coeruleus and the anterior cingulate cortex have a role in alerting and inhibition, respectively [72], and the locus coeruleus and tuberomammillary nucleus are networked via several pathways that influence alertness [83].

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 the 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 (RT), and the number of false alarms for each task were recorded. A total of 960 numbers were presented during each 16 min Bakan task, which always included 8 primary targets and 96 secondary targets. The task was scored using an index [$P(\bar{A})$] [35] 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 1.0 indicate a greater probability of correctly identifying both hits and false alarms [35].

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 [21,44]. 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].