The Intriguing Role of Histamine in Exercise Responses

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LUTTRELL, M.J. and J.R. HALLIWILL. The intriguing role of histamine in exercise responses. *Exerc. Sport Sci. Rev.*, Vol. 45, No. 1, pp. 16–23, 2017. *In humans, histamine is a molecular transducer of physical activity responses, and antihistamines modify more than 25% of the genes responding to exercise. Although the upstream signal that results in release of histamine within exercising skeletal muscle remains to be identified, it is likely a fundamental exercise response and not an allergic reaction.* **Key Words:** endurance exercise, gene expression, histamine, antihistamines, receptors, molecular transducers of physical activity, recovery from exercise

Key Points

- Aerobic exercise results in activation of histamine H_1 and H_2 receptors within the previously exercised muscle, triggering vasodilation and a broad range of responses to exercise.
- Histamine affects the availability of glucose to skeletal muscle, glucose uptake by skeletal muscle, and insulin sensitivity after exercise.
- Histamine contributes to the sensations of pain and discomfort as well as loss of muscle strength associated with delayed-onset muscle soreness.
- Histamine exerts a profound influence on the human transcriptome response to exercise, modifying more than 25% of the genes responding to exercise, including ones involved in such physiological domains as inflammation, vascular function, metabolism, and cellular maintenance.
- The histamine released during exercise seems to result from mast cell degranulation as well as *de novo* synthesis of histamine. This response, a fundamental element of exercise, seems to comprise an anaphylactoid reaction and not an allergic reaction to exercise.

INTRODUCTION

Histamine is a primordial signaling molecule with important physiological functions. At low evolutionary levels, such as the unicellular eukaryote *Tetrahymena pyriformis*, histamine is critical for organism survival, playing key roles in phagocytosis, cell growth, glucose metabolism, and chemotaxis (7). In humans, histamine is more commonly associated with allergic reactions and gastric acid secretion as well as inflammation and immune responses (26). However, an emerging area of research is the study of molecular transducers of physical activity, and mounting evidence supports the view that histamine is an important molecular transducer triggered by aerobic exercise. When suggesting that histamine plays an important role in exercise responses, questions arise, such as "are you saying people are allergic to exercise?" In the process of considering this question, we focus on recent research investigating the intriguing role of histamine in exercise responses. We define exercise responses as the coordinated physiological response to the disruption of homeostasis caused by exercise, both acutely and adaptively (24).

EARLY OBSERVATIONS OF HISTAMINE IN EXERCISE RESPONSES

In 1935, Anrep and Barsoum (2) demonstrated that, in dogs, the concentration of histamine in venous blood increased in response to tetanic muscle contractions and was dependent on both the intensity and duration of the contractions. Two decades later, Duner and Penrow (11) showed that the circulating concentration of histamine in humans increased after a bout of cycle ergometer exercise. Around this same time, Duff *et al.* (9) demonstrated the potent vasodilator effect of histamine in the human forearm and hand arterial system. This dilator action of histamine could be blocked with first-generation H_1 receptor antagonists (10). H_2 receptor antagonists would not be developed until the mid-1960s and would not be available for use in research settings until the 1970s. In 1977, Morganroth *et al.* (22) demonstrated a potential role for histamine H_1 receptors in the prolonged vasodilation after flow-restricted muscle contractions in dogs. A few years later, however, Daniel and Honig (8) found no effect of combined histamine H_1/H_2-receptor blockade on vasodilation during flow-restricted muscle contractions in dogs. Collectively, these results suggested that

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histamine could play a role in exercise recovery as a vasodilator (at least after flow-restricted contractions), but that histamine was not a necessary signal for exercise hyperemia as assessed with these models.

HISTAMINE'S RESURGENCE

Since those early days, the potential involvement of histamine during exercise has produced variable results in humans. Interpretation of findings often was complicated by factors such as measurement times (during vs after exercise), measurement methods (histamine concentrations in whole blood vs plasma), and the use of heterogeneous exercise durations and intensities. However, two recent lines of research have revitalized interest in the role of histamine during exercise and recovery from exercise. First, Endo *et al.* (3,14,36) initiated a series of studies to explore the possible contribution of histamine in the hyperalgesia of muscle overuse syndromes such as temporomandibular disorder. Second, our research group began exploring whether histamine could explain the sustained vasodilation that underlies postexercise hypotension (16). Although the geneses of these two lines of research seem disparate, they have provided a unifying understanding of novel physiology and a resurgence of interest in histamine as it relates to exercise and recovery.

PRIMORDIAL ORIGINS OF HISTAMINE AND HISTAMINE RECEPTORS

When suggesting that histamine plays an important role in exercise responses, it is worth investigating the natural history of histamine. The existence of histamine as a signaling molecule capable of activating cells in autocrine or paracrine fashion via specific cell-surface receptors seems to predate the origins of multi-cellular organisms (7). As evidence, *Tehrahymena* (Fig. 1) expresses the same gene for histidine decarboxylase (HDC, the enzyme that produces histamine) as do mammals, with a high degree of conservation in the genetic sequence between humans and *Tetrahymena* (17). This suggests it evolved before multi-cellular organisms but after the divergence of eukaryotes from prokaryotes.

Mast cells, which are capable of synthesizing, storing, and releasing histamine, arose later than histaminergic signaling in unicellular organisms but are likely to be more than 500 million years old, predating the chordates (31). Test cells in invertebrates such as *Ciona intestinalis* (Fig. 1) may have had a common ancestor with mast cells. Mast cells have been found in all vertebrate species (6), and, to date, there is no documented case of a human lacking mast cells (37). This is one indication that they have physiological importance beyond the allergic response.

It is clear that histamine and histamine receptors predate the development of innate and adaptive immunity (and therefore allergies). In *Tetrahymena*, histamine can stimulate a number of cell functions, including phagocytosis, chemosensory behavior, glucose uptake, and cell division via histamine H_1 and H_2 receptor activation (7,17). Thus, histamine has a long natural history and serves various functions that may include a role in the fundamental physiology of exercise responses in humans.

SYNTHESIS, DEGRADATION, AND ACTIONS OF HISTAMINE

There are a number of reviews that provide a broad perspective of histamine pharmacology and physiology (26).

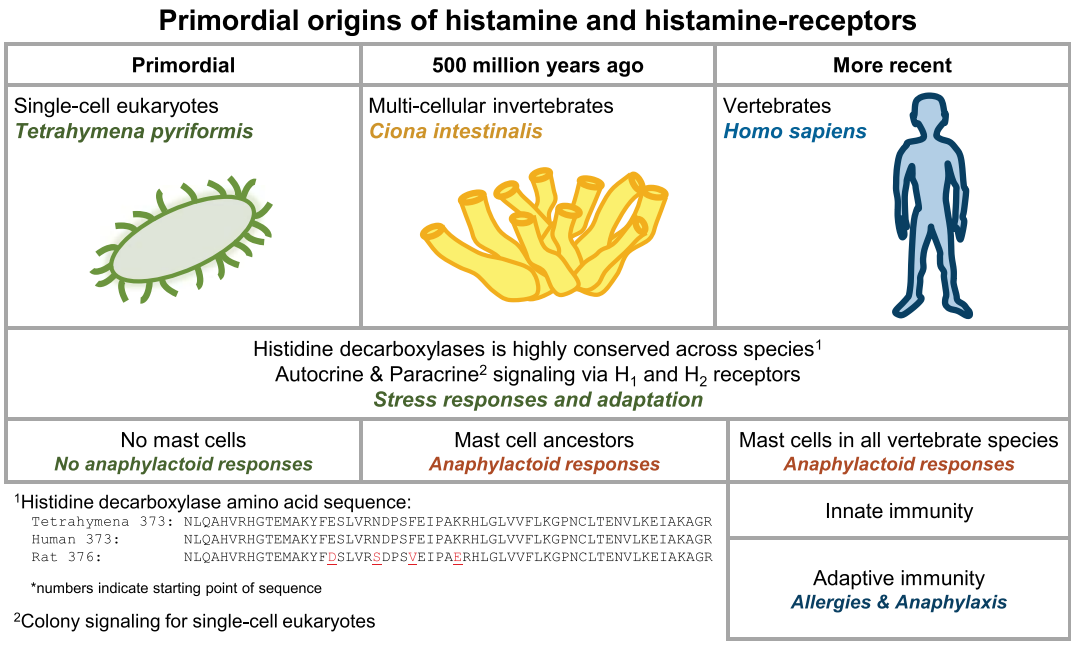

Figure 1. The primordial origins of histamine and its receptors. The existence of histamine as a signaling molecule, capable of activating cells in autocrine or paracrine fashion via specific cell-surface receptors, seems to predate the origins of multi-cellular organisms. As evidence, the ciliated protozoa *Tehrahymena pyriformis* expresses the same gene for *histidine decarboxylase* (the enzyme that produces histamine) as do mammals, with a high degree of conservation in the genetic sequence between humans and *Tetrahymena*. Histamine seems to have evolved before multi-cellular organisms, but after the divergence of eukaryotes from prokaryotes. Mast cells arose later than histaminergic signaling, but are likely to be more than 500 million years old, predating the chordates. Test cells in invertebrates such as *C. intestinalis* may have had a common ancestor with mast cells. Mast cells have been found in all vertebrate species. Histamine and histamine receptors predate the development of innate and adaptive immunity. In *Tetrahymena*, histamine can stimulate a variety of cell functions including phagocytosis, chemosensory behavior, glucose uptake, and cell division working through H_1 and H_2-receptors. Amino acid sequence reproduced from the study of Hegyesi *et al.* (17).

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Histamine is synthesized by the decarboxylation of the amino acid L-histidine by a single enzyme, HDC. As previously mentioned (see also Fig. 1), the DNA and amino acid sequences of HDC are highly homologous between single-cell organisms and humans, suggesting that HDC is a highly conserved enzyme among eukaryotes (17). The presence of HDC has been reported in many human cell types, including mast cells, basophils, gastric parietal cells, and neurons. There also is evidence suggesting that this enzyme is likely present in vascular and lymphatic endothelial cells, pericytes, smooth muscle cells, and platelets. Although histamine has a short half-life *in vivo*, because of rapid enzymatic degradation by either diamine oxidase or by histamine-N-methyltransferase, it can be stored in cytoplasmic granules within mast cells and basophils after it has been synthesized, to be subsequently released by degranulation.

Histamine can act as either a paracrine or autocrine signal, binding with four known histamine receptor subtypes (H_1-H_4), all of which are G protein–coupled receptors but signaling through different second messenger systems (26). Of these, H_1 and H_2 receptors are the most highly characterized in terms of both their pharmacology and physiological effects. Although we now know that these histamine receptors are widely distributed throughout many human cell types, as shown in Figure 2, important locations for H_1 and H_2 receptors within skeletal muscle include endothelial cells, vascular smooth muscle cells, nociceptive afferent neurons, and perhaps other cell types. In contrast, H_3 receptors may be limited to the central nervous system and peripheral nerves, and the recently identified H_4 receptors may be limited to the central nervous system and immune system.

PHYSIOLOGY OF HISTAMINE DURING AND AFTER EXERCISE

Studies in humans and in animal models have provided strong evidence that histamine is an important mediator of postexercise hypotension and sustained postexercise vasodilation. These vascular effects may explain how histamine also is involved in glucose delivery and uptake; however, nonvascular effects also may be important. Although histamine has long been linked to inflammation in other contexts, newer work ties it to inflammation and nociception in response to exercise. Lastly, emerging evidence suggests that histamine also contributes to the transcriptome response to exercise.

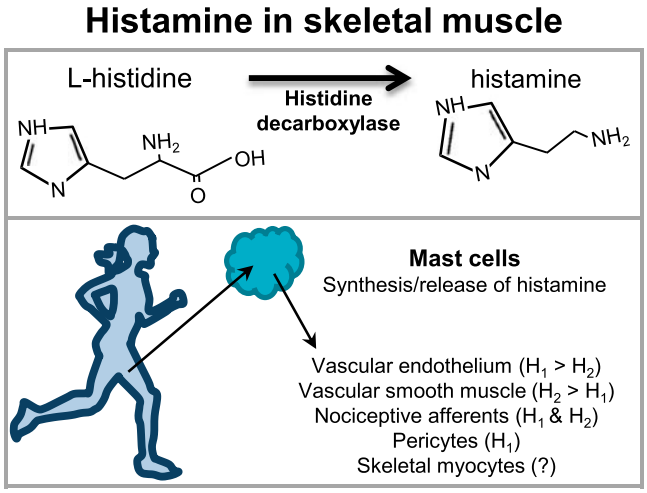

Figure 2. Histamine pathway in skeletal muscle. Histamine is synthesized by the enzyme histidine decarboxylase from the precursor L-histidine. When synthesized and released by mast cells embedded within skeletal muscle, it can bind to several histamine receptor subtypes that are preferentially expressed on a range of cell types. The presence of receptor subtypes is poorly characterized for many cell types with skeletal muscle tissue.

Postexercise Hypotension and Sustained Postexercise Vasodilation

In a series of studies aimed at uncovering the mechanisms of postexercise hypotension in humans, our laboratory determined that exercise generates a sustained postexercise vasodilation within the vascular beds of previously active skeletal muscle (16). In these investigations, we demonstrated that activation of both histamine H_1 and H_2 receptors contributes to postexercise hypotension in young adults by elevating leg muscle vascular conductance for up to 90 min after moderate-intensity (60% $V\cdot O_{2peak}$) cycling exercise. The combined histamine H_1/H_2-receptor antagonists (540 mg fexofenadine and 300 mg ranitidine) blocked 80% of the sustained postexercise vasodilation after whole-body cycling exercise, both in sedentary and in endurance-trained individuals (16). The remaining 20% can be attributed to decreases in sympathetic vasoconstriction (16). Moreover, there were no changes in circulating histamine concentrations, which suggests that the actions of histamine are paracrine and confined within the previously active skeletal muscle. Moving to a single-leg dynamic knee-extension exercise model in which the sympathoinhibitory influence of postexercise hypotension is absent (5), we then showed that combined histamine H_1/H_2-receptor blockade fully inhibits the sustained postexercise vasodilation (4), consistent with the histamine response being localized to the exercising muscle groups (*i.e.*, it is not present in the contralateral resting leg).

Although studies from our laboratory have focused on the sustained postexercise vasodilation, which is driven by histamine, it seems that histamine is one of several factors that are responsible for the immediate postexercise hyperemia (16). By extension, it remains possible that histamine contributes to exercise hyperemia during prolonged physical activity (25), but this has not been tested.

Skeletal Muscle Glucose and Glycogen

As reviewed previously (16), activation of histamine receptors after exercise modifies the delivery of glucose to recovering muscle groups. Our laboratory locally administered histamine H_1- and H_2-receptor antagonists via intramuscular microdialysis, which successfully reduced local skeletal muscle perfusion and lowered the interstitial skeletal muscle glucose concentration during recovery from a 60-min bout of cycling exercise (30). This effect is likely mediated by the influence of changes in muscle perfusion on glucose delivery, but there also could be a contribution from blocking histamine-mediated increases in capillary permeability. Although we found that systemic blockade of H_1 and H_2 receptors reduced skeletal muscle glucose delivery after exercise, it did not consistently reduce glucose uptake because of high interindividual variability in skeletal muscle glucose uptake (13). A correlation analysis of these data suggests that there may be an absolute work rate threshold that needs to be exceeded before the influence of histamine on skeletal muscle glucose uptake is evident. As such, it remains likely

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that the histamine response to exercise plays a role in skeletal muscle glycogen resynthesis during recovery, particularly in highly trained endurance athletes who can attain the workloads required to exceed the threshold. Consistent with this possibility, Niijima-Yaoita *et al.* (25) found that histamine-receptor blockade in a mouse model leads to greater glycogen depletion and reduced exercise performance. These findings suggest that histamine can play a role in blood flow and glucose delivery during prolonged exercise.

Mediator of Inflammation and Nociception

Much of the research regarding the role of histamine in mediating exercise responses has been focused on the cardiovascular and hemodynamic effects. Given the known role of histamine in mediating acute inflammation, however, there may be overlap between exercise-induced histamine release and the inflammatory consequences of muscle damage.

One mechanism by which histamine may influence the inflammatory response to exercise is via its action on microvascular endothelial and pericyte cells, which results in an increased capillary permeability. This exercise-induced increase in capillary permeability may facilitate macrophage and leukocyte migration from the microcirculation to the skeletal muscle extravascular space. Consistent with this possibility, muscle damage and delayed-onset muscle soreness (DOMS) are associated with leukocyte recruitment and actions within skeletal muscle as an early contributor to the skeletal muscle repair process. It is unclear which signal initiates this process (28), but histamine, with its natural history of chemotaxis, could contribute to recovery from exercise.

As mentioned previously, the work of Endo *et al.* (3,14,36) on the role of histamine in the hyperalgesia of muscle overuse syndromes helped create our current histamine resurgence. We asked a similar question regarding a possible role of histamine in DOMS associated with downhill running (12). We showed that histamine-receptor blockade attenuated postexercise blood flow after muscle-damaging exercise, but had no effect on the response of inflammatory markers, and may have even increased muscle damage by unknown mechanisms (12). However, antihistamines had a beneficial effect on preservation of muscle strength and reduced pain perception, most notably at 24 h after the end of exercise. Of note, the pain and strength responses lasted longer than the duration of histamine-receptor blockade, indicating that histamine influences a pathway that generates a lasting influence on nociceptive nerve fibers or the pathways involved in pain perception. Postexercise inflammation has been associated with an elevation of neural growth factor (NGF) and glial-derived nerve factor (GDNF), which likely contribute to the sensitization of type III and IV afferent fibers in skeletal muscle (23,35). Consistent with this possibility, these two transcripts were among the many that exhibited reduced expression at 3 h postexercise in individuals taking combined histamine H_1/H_2-receptor antagonists relative to control conditions (33). This intriguing finding may explain part of the reduced pain sensitization and preservation of strength reported by Ely *et al.* (12).

These findings indicate that histamine may play multiple roles in mediating inflammatory responses during recovery from exercise. Blocking histamine receptors may impair this process by delaying the migration of immune cells to the damaged muscle tissue, thus prolonging the exercise recovery and remodeling associated with exercise adaptation. Although nociception may be impaired by H_1/H_2 receptor antagonism during or after an acute bout of strenuous exercise, more research is needed to identify the underlying mechanisms and determine if antagonism modifies exercise training adaptations.

Broader Effects via Transcriptional Influences

We recently investigated the contribution of histamine, acting via H_1 and H_2 receptors, on the transcriptome response to exercise. Skeletal muscle biopsies were taken from the *vastus lateralis* before, immediately after, and 3 h after a 1-h bout of dynamic knee-extension exercise. By comparing the changes in mRNA in response to exercise, under control conditions versus when histamine H_1 and H_2 receptors had been blocked, we were able to uncover the substantial footprint of histamine on the exercise transcriptome (Fig. 3). These data reveal that release of histamine and activation of H_1 and H_2 receptors during recovery from exercise seems to upregulate pathways related to inflammation, endothelial and vascular function, metabolism, and cell maintenance. These transcriptome-level changes suggest that there is indeed cross-talk between histaminergic and inflammatory signaling, and also many other systems within skeletal muscle (*e.g.*, metabolism, cell maintenance, vascular function) in response to a bout of aerobic exercise. Whether these transcriptome changes translate to altered protein abundance or enzyme activity in specific skeletal muscle cell types is unknown but is critically important to unraveling the complex role of histamine in exercise responses.

APPLICATIONS FOR HISTAMINE IN HUMAN HEALTH AND PERFORMANCE

Athletes take antihistamine medications at a higher rate than the general population, likely because of the interaction of a number of factors including greater exposure to environmental allergens, and exercise-induced asthma and urticaria

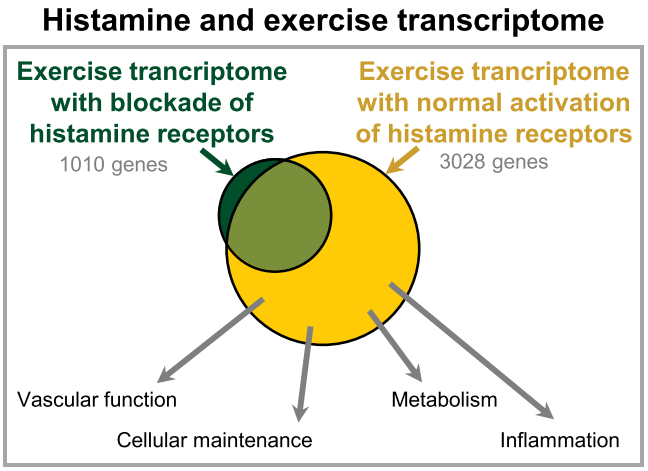

Figure 3. The location of histamine on the human transcriptome response to exercise. A single bout of exercise alters the expression, either upregulating or downregulating, of thousands of protein-coding genes (represented by yellow circle). Much of this response depends on the activation of H_1 or H_2 receptors by histamine because combined histamine H_1/H_2-receptor blockade markedly reduces the transcriptome response to exercise (represented by green circle). Histamine can modulate many cellular functions, including vascular function, metabolism, inflammation, and cellular maintenance. Based on data from the study of Romero *et al.* (33).

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(1), as well as for treatment of exercise-associated gastroesophageal reflux disease (GERD) symptoms. Although the influence of antihistamine medications on athletic performance has been reviewed previously (20), this topic warrants an update.

Impact on Athletic Performance

Using a first-generation histamine H_1-receptor antagonist (50 mg diphenhydramine) that is able to cross the blood-brain barrier and a second-generation H_1-receptor antagonist (60 mg terfenadine) that has no central nervous system effects, Montgomery and Deuster (19,21) (1991, 1992) found no influence of these acutely administered low doses of antihistamines on measures of skeletal muscle strength, VO_{2max}, or repeated sprints to task failure. Studies on later generations of antihistamine medications have generally found negligible effects on athletic performance in laboratory settings. An important consideration is whether chronic use of these medications, as for the treatment of chronic allergies or GERD, influences these shorter-duration measures of athletic performance.

Current evidence from animal models suggests that antihistamines may modify athletic performance, but only in long-duration events on the order of a few hours or longer. First, in a mouse model of voluntary masseter muscle activity (gnawing to escape restraint), Yoneda *et al.* (38) found that skeletal muscle activity during a 4-h period was reduced by a histamine H_1-receptor antagonist. Although this study was not designed to evaluate the influence of histamine on exercise performance *per se*, it suggested a role of histamine in supporting prolonged skeletal muscle activity. Second, in a mouse model of involuntary walking for up to 5 h, Niijima-Yaoita *et al.* (25) demonstrated that histamine H_1-receptor antagonism (fexofenadine), histamine H_1-receptor knock out, inhibition of HDC (reducing *de novo* histamine formation), and HDC knock out all reduced walking time by half. Histamine H_2-receptor antagonism (ranitidine) also tended to reduce prolonged exercise performance, whereas neither H_3- nor H_4-receptor blockade had an influence on this model of endurance exercise (25). Extrapolating from these studies to humans, it is reasonable to expect that histamine could provide an ergogenic benefit (perhaps via changes in blood flow or sparing of muscle glycogen) during longer-duration athletic performances, and that acute antihistamine administration could undermine this benefit. This hypothesis remains to be tested.

However, there also is evidence that histamine directly sensitizes type III and IV afferent fibers in skeletal muscle as well as upregulates several hyperalgesic factors (*e.g.*, NGF and GDNF). Thus, histamine may increase the sensitivity of nociceptive skeletal muscle afferents to stimuli during prolonged exercise, and in the days after muscle-damaging exercise (12). Therefore, blocking the action of histamine may be beneficial during longer-duration athletic performances (*e.g.*, marathon), multievent, or multiday athletic events, when development of muscle soreness and the concurrent loss of muscle strength may otherwise impair athletic performance. At present, most governing bodies in athletics do not ban antihistamines, but the lists of banned substances are updated frequently.

Despite the dogma that antihistamines do not impact athletic performance, recent studies have provided a fresh perspective and scintillating possibilities to be tested.

Potential Role in Recovery and Adaptation

An important consideration is whether chronic use of antihistamines, such as for the treatment of chronic allergies or GERD, influences long-term exercise training adaptations, and if so, which exercise modalities are impacted? Peake *et al.* (27) have elegantly explored this issue, using the lens of hormesis, to examine how most of the therapies that are used to minimize the inflammatory response to exercise have been proven to be counterproductive because they generally reduce the positive adaptations of exercise training.

The balance between beneficial and detrimental influences of inflammation in response to exercise remains unclear, but evidence suggests some aspects of this process are necessary for muscle repair and remodeling. The emerging evidence on histamine and exercise is that much of the early inflammatory response to exercise may be driven by this primordial signal molecule (33). What is currently unknown is whether this histaminergic component of postexercise inflammation is necessary or permissive for exercise recovery broadly, or muscle repair specifically. We can only speculate that the acute ergogenic benefit associated with antihistamine use is likely an acute phenomenon. Given the role of histamine as an inflammatory mediator, there is a possibility that histaminergic signaling is an important component for the adaptive responses to strenuous exercise training. As an agent of hormesis, the heritage of histamine in exercise may extend back to the cycle of stress and adaptation in single-cell organisms such as *Tetrahynena*.

Clinical Translation

Our interest in histamine began within the context of postexercise hypotension. There is evidence that histamine H_1-receptor blockade can protect against postexercise syncope. Our research group subjected healthy humans to a head-up tilt test (an orthostatic challenge) after moderate-intensity dynamic exercise in the heat (18). When subjects had taken an oral dose of 540 mg fexofenadine before exercise, postexercise mean arterial pressure during a head-up tilt was maintained compared with the control condition (no histamine-receptor blockade). Thus, in healthy individuals prone to postexercise syncope or participating in prolonged exercise in the heat, histamine-receptor blockade may be a pharmacological alternative to other methods of preventing syncope or reducing presyncopal symptoms.

Histamine also can impact glucose handling by skeletal muscle. There is evidence that antihistamines may influence whole-body glucose regulation and insulin sensitivity after exercise. When healthy subjects performed an oral glucose tolerance test after an hour-long bout of moderate-intensity cycling exercise, systemic H_1- and H_2-receptor blockade blunted postexercise insulin sensitivity by approximately 25% compared with control conditions (29). It is not clear whether this would impact the therapeutic use of exercise as a mechanism to regulate or improve glucose control in patients with insulin insensitivity, such as type 1 and type 2 diabetes mellitus.

Beyond the effects on hemodynamic stability and glucose transport, the hormetic role of histamine should be exploited for improving some chronic disease conditions. For example, targeting the local skeletal muscle histaminergic system may help improve blood pressure regulation and skeletal muscle perfusion, particularly in individuals with hypertension and

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peripheral artery disease. Histamine contributes to angiogenic responses in contexts such as wound healing, tumor growth, and pregnancy, and there is ample evidence for histamine in the initiation of angiogenic potential *in vitro*, but there are limited data on this process in humans. Whether future therapies derived from this pathway are exercise-based or nonexercise "ergomimetics" requires additional research and may depend on an individual's exercise capability.

SOURCE OF HISTAMINE IN EXERCISE RESPONSES

There is compelling evidence that histamine is released locally within the exercised muscle tissue and is not part of a systemic or generalized response (16). Some studies show a rise in blood or plasma histamine concentrations in response to exercise, but it is not indicative of the local response, which makes it more challenging to investigate the source of histamine during and after exercise and to determine how it is regulated.

There is an increase in HDC enzymatic activity as well as HDC expression in mice after a bout of prolonged walking (15,25). Muscle samples taken at different time points during the course of the exercise protocol suggest that the increase in skeletal muscle HDC varies with time (14). Similarly, Romero *et al.* (33) found that HDC expression in skeletal muscle tissue increased after exercise in humans. In mice subjected to repeated bouts of walking, however, the exercise-induced increase in HDC expression in skeletal muscle tissue was reduced, perhaps because of a training adaptation (14). It is unknown whether the response also becomes blunted with exercise training in humans, or the specific role of this adaptation.

In addition to changes in HDC expression that occur through several hours, there is evidence that factors associated with exercise (*e.g.*, higher skeletal muscle temperature, lower pH) should favor increased HDC enzyme activity (15). Romero *et al.* (34) recently examined the influence of *de novo* histamine formation on the exercise response in humans. In these experiments, an inhibitor of HDC administered into skeletal muscle by intramuscular microdialysis reduced intramuscular histamine concentrations and muscle blood flow responses during exercise and recovery. This finding suggests that *de novo* histamine formation is an important part of the process for the histamine exercise response.

The development of transgenic mice that either do not express HDC or do not have mast cells have yielded novel and intriguing evidence for the source of histamine in exercise-related responses. Although mast cells are recognized as a common source of histamine, many other cell types within skeletal muscle tissue are capable of synthesizing or releasing histamine. Electrical stimulation of skeletal muscle has been used as a model for increasing HDC enzyme activity in mice, but mice lacking mast cells still exhibit this form of HDC upregulation, which suggests that other cell types within skeletal muscle can contribute to histamine synthesis. Nonetheless, the HDC response to exercise is less in mast cell–deficient mice than in wild-type mice.

To examine the cellular source of histamine during exercise in humans, we tested the hypothesis that mast cells within skeletal muscle degranulate during aerobic exercise (34). In these experiments, interstitial tryptase was directly measured as a biomarker of mast cell degranulation via intramuscular microdialysis. Both tryptase and histamine concentrations increased during exercise, supporting the idea that mast cells are an important source of histamine responses to exercise in humans.

The stimulus for the release or synthesis of histamine by specific cells in skeletal muscle in response to dynamic exercise is still unknown. Oxidative stress, heat, vibration, and [H+]/pH are capable of causing mast cell degranulation, resulting in histamine release *in vitro* and in some animal models. To address one of these mechanisms, we investigated the potential contribution of reactive oxygen species to the histaminergic response to exercise (32). Infusion of high-dose N-acetylcysteine, a potent antioxidant, did not block the histamine-mediated sustained vasodilation after exercise, indicating that reactive oxygen species are not a necessary trigger for this response. Interestingly, infusion of ascorbate (vitamin C) blocks the

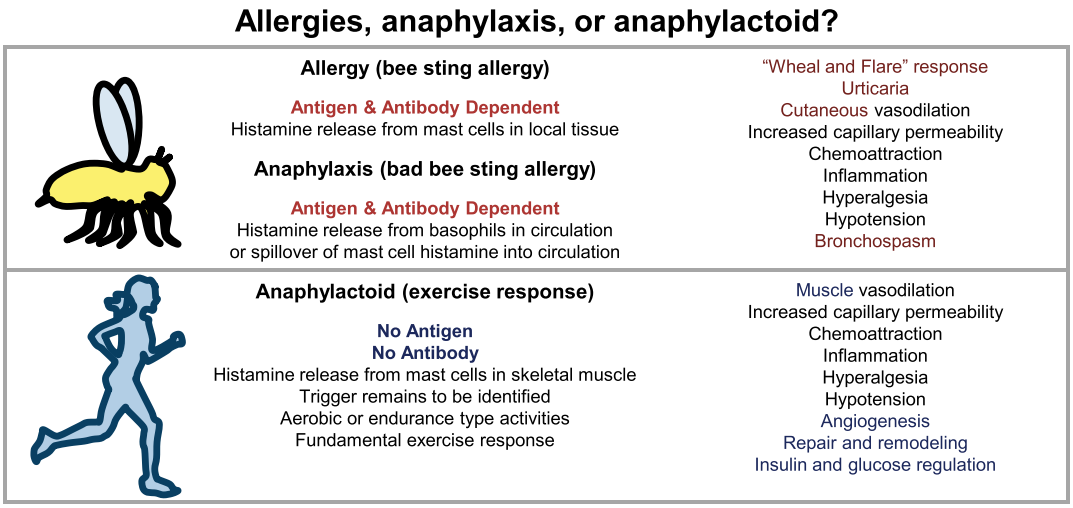

Figure 4. Allergies, anaphylaxis, or anaphylactoid? Allergic and anaphylactic reactions share a common signaling pathway in which an antigen, such as bee venom, becomes bound to an IgE antibody that is specific to that antigen. Recognition of the antibody-antigen complex triggers mast cell or basophil degranulation and release of histamine, along with other inflammatory mediators. Signs, symptoms, and responses are stereotyped based on the location of the reaction, whether it remains localized (allergic reaction) or becomes systemic (anaphylaxis). In contrast, anaphylactoid reactions occur in the absence of an antibody-antigen complex, but do generate mast cell (or basophil) degranulation, and many of the same signs, symptoms, and responses, depending on location. Aerobic or endurance-type exercise seems to generate a localized anaphylactoid reaction within the exercised skeletal muscle tissue.

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vasodilation, apparently by its ability to catalyze the breakdown of histamine.

THE EXERCISE RESPONSE IS NOT AN ALLERGY

It is important to distinguish between the role of histamine in pathological conditions and its role as a molecular transducer of exercise adaptations. In an allergic or anaphylactic reaction, an acute immune insult, represented as an identifiable antigen, triggers the release of inflammatory mediators, including histamine. This effect is mediated by IgE antibody binding the antigen and recognition of that antibody-antigen complex by cognate receptors on immune cells (*e.g.*, mast cells and basophils), which release histamine and generate the hypersensitivity response. Signs, symptoms, and responses are stereotyped based on the location of the reaction, whether it remains localized (allergic reaction) or becomes systemic (anaphylaxis). In contrast, anaphylactoid reactions occur in the absence of an antibody-antigen complex, but do generate mast cell (or basophil) degranulation and many of the same signs, symptoms, and responses, depending on location. Many adverse reactions to drugs, or drug hypersensitivities, are actually anaphylactoid reactions and not true allergies. The preponderance of evidence indicates that aerobic or endurance exercise produces a degranulation of mast cells and release of histamine within the exercising skeletal muscle tissue, and there does not seem to be an exercise antigen. Thus, exercise satisfies the criteria for being a localized anaphylactoid reaction within the exercised skeletal muscle tissue rather than an allergic reaction (Fig. 4).

SUMMARY

The full scope of histamine-mediated exercise responses is only beginning to be understood, but likely represents a distinct response from typical anaphylactic responses associated with allergies. The role of histamine in various exercise responses is localized within the previously active skeletal muscle and may have a range of effects beyond its contribution to sustained postexercise vasodilation. Potential and intriguing roles for histamine in response to exercise include acute inflammatory signaling, angiogenic signaling, changes in glucose regulation, and modulation of nociception. Major gaps in our knowledge include the degree of overlap between the acute histaminergic signaling triggered by a single bout of exercise and the hormetic adaptations of exercise training. Despite recent advances in determining the role of histamine in exercise responses, relatively little is known about this molecule in the context of exercise physiology, but it seems to be a fundamental component of exercise responses in humans.

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