Histamine and a Possible Unity of Autonomous Microcirculatory Dilator Responses*

Histamine and Autonomous Dilatation

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Introduction

In two previous papers I have presented a microcirculation-based unified theory of glucocorticoid action (Schayer, 1964, 1967). To link the microcirculation to the major effects of these hormones requires the reasonable postulate that autonomous dilator responses result from a well-defined intrinsic mechanism, not from haphazard formation of "dilator metabolites" in other tissues.

In this paper I will try to show how the proposed intrinsic dilator mechanism may, with due allowance for a variety of modifying factors, underlie the dilator phases of reactive hyperemia, post-exercise hyperemia, hyperemia due to local warmth, autoregulation, vasomotion, inflammation, and shock.

These ideas are based on histamine studies (Schayer, 1962, 1963, 1966). However, since there is much misunderstanding about histamine, and since the theory can be largely developed without need to identify the dilator, this paper will be presented in two parts. First, interpretation of the above phenomena in terms of an intrinsic dilator mechanism will be attempted. Second, evidence supporting histamine as the dilator will be given.

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Requirements for an Intrinsic Dilator Mechanism

The theory requires that the dilator be continuously produced within microvascular smooth muscle cells by an inducible enzyme system, and that it act primarily on intracellular "intrinsic" receptors.

It is obvious that the microcirculation requires means for adaptation; this may be accomplished through alteration of enzyme activities. An intrinsic site of formation and action is supported by repeated failure to find dilator activity in fluids from dilated tissues, and by the inability of any blood-borne substance to mimic natural dilator phenomena (Alexander, 1963; Barcroft, 1963; Folkow, 1949, 1964; Hilton, 1962; Zweifach, 1953).

Normal Distribution of Intrinsic Dilator Molecules

If a dilator were continuously synthesized within microvascular smooth muscle cells, it would be distributed into three distinct categories. (1) Intracellular: Some molecules would remain free in the cytoplasm of the smooth muscle cells. Since intrinsic receptors are stimulated, the intracellular concentration of dilator would determine the magnitude of the dilator action. (2) Loosely Bound: As dilator molecules diffuse from the cell, some are loosely bound in the cell wall. (3) Extracellular: Dilator molecules reaching the lumen of the vessel will be washed away when blood is flowing, or accumulate if flow is blocked. Dilator molecules in the blood stream, because of dilution or inactivation, are of no further significance.

The autonomous microcirculatory phenomena listed in the Introduction may all relate to this distribution of dilator, or to modifications of it.

Reactive Hyperemia

When blood flow is mechanically blocked, dilator molecules accumulate extracellularly. There follows a gradual increase in dilator concentration—first, in the cell wall, then intracellularly, and, finally, at intrinsic receptor sites. When the obstruction to flow is removed, muscle immediately relaxes to a degree roughly proportional to the time of occlusion. As extracellular dilator is washed away, the intracellular concentration gradually drops to normal.

Interpretation of a number of key experiments relating to reactive hyperemia is shown in Table 1.

Vasomotion

This periodic opening and closing of precapillary sphincters, said

to provide the most precise adjustment of nutritive blood flow, may arise as follows: In the sphincter of a closed capillary, dilator accumulates until relaxation occurs and blood flows. As extracellular dilator molecules wash away, the intracellular concentration gradually decreases. When constrictor forces (intrinsic "tone force" plus circulating constrictors) again predominate, the sphincter closes and the cycle is complete.

The process of vasomotion can adjust to environmental requirements through an adaptive resetting of the rate of intrinsic dilator synthesis.

Post-Exercise Hyperemia

The rapid production of heat in working skeletal muscle causes a local increase in tissue temperature. Intrinsic dilator production is immediately increased as a result of the temperature effect on enzymes. Precapillary sphincters immediately open, thus initiating a "conducted vasodilatation" of arterioles and arteries (Hilton, 1962). Presumably, moderate warming of a tissue by any means could have a similar effect; on the other hand, moderate cooling, by reducing intrinsic dilator production, could lead to the observed vasoconstriction.

Autoregulation

In an isolated perfused tissue, a moderate increase in perfusion pressure may increase flow through precapillaries, expedite washout of extracellular dilator, reduce the intracellular concentration, cause sphincters to close more rapidly than they normally would, and thus increase resistance to flow.

Conversely, a drop in perfusion pressure, by reducing the rate of dilator washout, would permit

TABLE 1

Reactive Hyperemia in Muscle and Skin
Compatibility of Intrinsic Dilator Mechanism with Experimental Findings

Observation	*Comment*
1. In isolated gastrocnemius of cat, 30 seconds of artery occlusion and 30 seconds of maximal exercise gave approximately the same increase in flow. However, after ischemia, flow subsided more quickly (Hilton, 1953).	1. In both cases, removal of excess dilator would depend on diffusion from cell. However, after exercise, the rate of dilator synthesis remains elevated until muscle temperature returns to normal.
2. Reactive hyperemia in skeletal muscle is soon lost during perfusion with saline (Folkow and Löfving, 1956).	2. Production of an intrinsic dilator would be reduced as substrate and co-factors were removed.
3. The longer the period of circulatory arrest, the greater the subsequent hyperemia. The increase is mainly in duration of high flows, the peak value being relatively little increased (Patterson and Whelan, 1955).	3. Accumulation of intrinsic dilator should relate to time of occlusion. After the concentration required to cause maximal dilation is reached, further accumulation should, following release, prolong the period of high flow.
4. Reactive hyperemia is most readily demonstrated when a limb is warm.	4. Dilator synthesis is temperature dependent, and accumulation should occur more rapidly in a warm tissue.
5. Reactive hyperemia is reduced if forearm is packed with blood during period of arrest (Duff, Patterson, and Whelan, 1955).	5. Packing would provide additional blood into which the dilator could diffuse; intracellular accumulation would be reduced.
6. In reactive hyperemia in the human leg, the rate of return of flow to initial levels was exponential (Dornhorst and Whelan, 1953).	6. The rate of loss of accumulated intrinsic dilator molecules should be roughly proportional to the number remaining and, therefore, exponential.
7. From studying effect of reduced arterial pressure on reactive hyperemia and post-exercise hyperemia, Dornhorst and Whelan (1953) concluded that in both cases the vasodilation could be due to an intracellular metabolite, the removal of which from the vessel wall is limited more critically by its diffusion gradient than by the rate of blood flow through the tissue lumen.	7. The interpretation of Dornhorst and Whelan indicates that an intrinsic dilator best explains the findings of these experiments.
8. In the forearm, after a five-minute period of arrest, circulation was released, but flow kept from rising above the resting level for an additional five minutes by compressing the brachial artery. There was no reactive hyperemia when the artery was released (Blair, Glover, and Roddie, 1961).	8. Accumulated intrinsic dilator molecules can presumably diffuse from smooth muscle cells and be washed away by normal blood flows within five minutes.

sphincters to remain open for a longer than normal period and thus reduce resistance to flow.

Slowly Developing Dilator Responses

If the mechanism for intrinsic dilator production is adaptive and is normally required for coping with minor, everyday, environmental changes, then a marked increase in production, caused by drastic local or systemic stimuli, could lead to the slowly developing microvascular dilatation observed in inflammation and shock, respectively.

Many authors have emphasized the similarities between inflammation and shock in this respect (Lewis, 1927; Moon, 1938). According to Zweifach (1961), the development of shock seems to involve progressive activation of a mechanism primarily concerned with local blood flow.

As evidence that microvascular opening in inflammation and shock may be exaggerated manifestations of the normal intrinsic dilator mechanism, I cite the ability of this concept to provide a reasonable unification of glucocorticoid effects (Schayer, 1964a, 1967). If these hormones function by moderating the action of the microcirculatory dilator, their vital stress role and their anti-inflammatory effect could relate to antagonism of the increased dilator influence in stress and inflammation; the metabolic effects of glucocorticoids could be derived from suppression of the normal dilator influence in vasomotion. The microcirculatory effect of glucocorticoids is their earliest known action; it is a tendency to potentiate effects of vasoconstrictors. The glucocorticoid-intrinsic dilator relationship will be mentioned in a later section.

In inflammation, endothelial changes also occur; this fact causes no difficulties in interpretation, provided that histamine is the intrinsic dilator (Schayer, 1964b).

Other Factors in Microcirculatory Dilatation

Numerous substances or conditions have been proposed to account for opening of small vessels in vasomotion, hyperemia, autoregulation, inflammation, and shock. It is not denied that some may be of significance, particularly in brain, heart and kidney. However, preoccupation with a variety of mechanisms seems to have led to the unsatisfactory conclusion that there is no process inherent within microvascular smooth muscle cells which is an obligatory participant in their response to every stimulus. I believe this process involves continuous production of traces of histamine, catalyzed by an inducible, environment-responsive form of histidine decarboxylase. Since many pitfalls may be encountered in the experimental testing of this concept, the next section will be devoted to some of them.

Comments on Experimental Testing of the Histamine-Microcirculation Theory

Histamine metabolism is a very complex field whose facts are often inaccessible to available experimental procedures. It is obvious that, if experimentation on histamine led to unequivocal results, it should not have required 50 years to find a reasonable physiological role.

The complexities of the field may be illustrated by considering the significance of quantitative analyses for histamine.

The histamine content of a tissue is a composite value which includes some or all of the following: (a) histamine ingested in the diet; (b) histamine formed in the intestine by bacteria and then absorbed; (c) histamine formed by another tissue, e.g., stomach, which produces relatively large amounts of histamine concerned with gastric secretion; (d) histamine formed locally in mast cells and bound in them, in inactive form, in enormous concentrations; (e) histamine released from mast cells; (f) histamine associated with "non-mast cell" binding sites; (g) histamine of microvascular origin which is "on its way out"; and (h) the relatively minute quantities of histamine of microvascular origin still in a physiologically strategic position. Obviously, there is no simple means of measuring (h) in the presence of the other pools, particularly when concentrations fluctuate in accordance with many factors, often poorly defined. Plasma histamine assays also give composite values which are often meaningless or misleading.

Measurements of histidine decarboxylase activity are preferable, but here, too, there are problems. Histidine decarboxylase is found not only in microvascular cells but also in mast cells, stomach, and in certain specialized cells; each may vary in activity in response to its own specific stimuli and tend to obscure changes in microvascular histidine decarboxylase activity. Other difficulties in evaluating the physiological role of histamine have been presented elsewhere (Schayer, 1963, 1966).

For the most part, my findings on histamine have been confirmed in other laboratories (Graham, Kahlson and Rosengren, 1964; Graham and Schild, 1967; Johansson and Wetterqvist, 1963; Kahlson and Rosengren, 1964, 1968; Kahlson, Rosengren and Thunberg, 1966; Pearlman and Waton, 1966). The single exception is experiments reported by Burton Altura (Altura and Zweifach, 1965a, b; 1967); he feels that some results are compatible with the theory, while others are not. A detailed discussion of these experiments would require too much space, but I am confident that Altura's "negative" findings can be readily explained. Some of his experiments are too long and too complicated for clear interpretation. In others, histamine levels of tissue determined in other lab-

oratories under different conditions were used for evaluation. Still others are based on a misinterpretation of the significance of the theory.

Experimental evidence and arguments, which I believe provide important support for the histamine concept, are listed in the next section.

Evidence Supporting Histamine as an Intrinsic Microcirculatory Dilator

Ability of Histamine to Mimic Natural Microcirculatory Dilation

Histamine dilates microvascular smooth muscle; at higher concentrations it affects endothelial cells. It also can initiate reflex dilatation of arterioles. If histamine were formed within these cells, there is no evident reason why it could not underlie the phenomena under discussion.

Adaptive Nature of Histamine Formation

It is now known that adaptation often involves induction of enzymes in cell types which require them. Histidine decarboxylase is inducible to activity many times the normal level but, under certain circumstances, can be reduced to subnormal levels; its activity is clearly responsive to changes in internal and external environment.

Vascular Locus of Histamine Formation

Histidine decarboxylase is present in arteries and veins and can be activated in them (Kahlson et al., 1966; Schayer, 1962). These vessels contain no significant number of cells other than smooth muscle and endothelium. Further, the inducible form of histidine decarboxylase has been found in all tested tissues of the commonly studied species. This widespread distribution, a rigorous requirement for a microvascular regulatory mechanism, has not been shown for any other inducible enzyme.

Autonomy of Histamine Production

Small vessels can dilate due to a local mechanism; histidine decarboxylase activation can also be local. Neither process requires any known nervous or endocrine mechanism or the presence of any dispensible tissue.

Time Course of Increased Histamine Production

Following a stimulus, local or systemic, histidine decarboxylase undergoes gradual activation, becoming first detectable in roughly 30 to 60 minutes and reaching near-maximum activity in three to four hours. The duration of the activated state depends on the persistence of the stimulus; activity may return to near normal in 12 to 24 hours (as after injection of catecholamines) or may remain elevated for at least ten days, the longest period tested (in turpentine-injected rat paws). The rate of activation is indistinguishable from the rate of development of the delayed phase of inflammation (Schayer, 1963, 1964b; Spector and Willoughby, 1963) and, allowing for constrictor effects of released catecholamines, activation parallels the gradual reopening of the small vessels in shock (Chambers, Zweifach, and Lowenstein, 1944; Schayer, 1961; Zweifach et al., 1957).

Effect of Inhibition of Histidine Decarboxylase Activation

The only drugs known to block activation of histidine decarboxylase are inhibitors of protein synthesis, e.g., puromycin, actidione (cycloheximide), and tenuazonic acid (Shigeura and Gordon, 1963). Actinomycin D, which inhibits synthesis of RNA, and, thus, indirectly blocks activation of most known inducible enzymes, fails to block histidine decarboxylase activation (Schayer, 1968). When these compounds were tested on turpentine inflammation in rat paw (a violent reaction virtually unaffected by cortisol or indomethacin), those drugs which blocked histidine decarboxylase activation also showed an extraordinarily great anti-inflammatory action. Actinomycin D failed to suppress either histidine decarboxylase activation or inflammation; in fact, under certain experimental conditions, it enhanced both processes. Since this drug indirectly blocks activation of many enzymes, the findings are strong evidence for a crucial role of histamine in slowly-developing inflammation.

Histamine and a Unified Theory of Glucocorticoid Action

If it is postulated that the principal target of glucocorticoids is the microvascular smooth muscle cell and that these hormones function to reduce the dilator action of histamine, one can derive a simple interpretation for the stress function of glucocorticoids, their anti-inflammatory effect, and their widespread influence on metabolic processes and body economy. This theory seems to be compatible with most of the major in vivo observations on glucocorticoid physiology and pharmacology (Schayer, 1964a, 1967). The histamine-microcirculation theory may also help clarify the metabolic and developmental effects of thyroid hormone (Schayer, 1969).

Lack of an Alternative to Histamine

If one accepts the existence of an intrinsic microcirculatory dilator, it is necessary to consider the alternatives to histamine. To my knowledge, the only other substance seriously proposed as a "universal" dilator is bradykinin (Rocha e Silva, 1963).

The case for bradykinin is extremely fragile, and I have listed many objections to it (Schayer, 1963). Recently Webster, Skinner, and Powell (1967) have reported experiments which virtually elimi-

nate bradykinin as the dilator of skeletal muscle. The repeated failures to implicate bradykinin can not be attributed to an "intrinsic" site of formation, for the substrate of bradykininogen exists in plasma, not in cells. In contrast, free L-histidine is abundant in all cells and all body fluids.

Effect of Antihistamines on the Microcirculation

Topical application of antihistamines to microcirculatory preparations causes constriction of the small vessels; in this test antihistamines behave like catecholamines (Altura and Zweifach, 1965a, b; Conard, 1951; Haley and Andem, 1950; Haley and Harris, 1949). The constrictor effect is produced by antihistamines of many basic structures but is not shown by anti-serotonin, anti-acetylcholine, or local anesthetic drugs as groups. The effective concentrations of antihistamines are high, but this is expected for antagonism of intrinsic histamine.

The most recent work in this field has been done by Dr. Altura; he has concluded that antihistamines are direct vasoconstrictors (oral communication, 1968) and cites their contractile effect on uterine (Rocha e Silva, 1955) and bronchiolar (Hawkins, 1955) smooth muscle in vitro as evidence of direct action (Altura and Zweifach, 1965b).

Since I reject this conclusion and regard the constrictor effect of antihistamines as near proof for the reality of microvascular histamine, it is essential to consider these two conflicting views in detail.

First, antihistamines are drugs of various structures which attach to histamine receptors and block virtually all histamine actions in vitro and in vivo; as a group they have no other identity. All antihistamines have side effects, but these vary in kind and degree.

Second, antihistamines have no catecholamine-like actions in vitro (Goodman and Gilman, 1965).

Third, since antihistamines are selected for their ability to occupy histamine receptors, it is not surprising that many can release histamine by displacing it from binding sites (Mota and da Silva, 1960). The stimulatory action of antihistamines on uterine and bronchiolar smooth muscle is believed due to release of bound "intrinsic" histamine (Rocha e Silva, 1955; Hawkins, 1955). This stimulatory effect resembles that of histamine, not catecholamines. The anomalous relaxing effect of histamine on rat uterus (Altura and Zweifach, 1965a) mentioned by Altura is due to released catecholamines (Tozzi and Roth, 1967).

In conclusion, Altura's view implies that antihistamines, a large group of variously-structured compounds selected solely for ability to block histamine actions, also invariably possess a histamine-unrelated property of direct vasoconstriction. If true, this would be a most remarkable coincidence. The conservative interpretation suggests that microvascular smooth muscle cells are under the continual dilator influence of histamine produced within them.

Summary

Evidence based on recent research on histamine metabolism supports the following views:

(a) Microvascular smooth muscle cells are under the continuous dilator influence of minute quantities of histamine formed within them.

(b) This histamine is produced by action of an inducible form of histidine decarboxylase and acts on intracellular "intrinsic" receptors.

(c) Autonomous dilator activities of the microcirculation, e.g., vasomotion, reactive and post-exercise hyperemia and autoregulation, may all involve this intrinsic dilator.

(d) Adaptation of the microcirculation to environmental changes may be accomplished, in part, by readjustment of the rate of histamine formation.

(e) Drastic stimuli which cause a marked increase in histamine output, locally or systemically, may lead to the microvascular changes in inflammation and shock, respectively.

(f) The proposed intrinsic dilator mechanism permits a reasonable unification of the major effects of the glucocorticoids in terms of a primary interaction of hormone molecules with microvascular smooth muscle cells.

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