Anesthesiology
V 41, No 2, Aug 1974

# *Effects of Local Anesthetics, Antihistamines, and Glucocorticoids on Peripheral Blood Flow and Vascular Smooth Muscle*

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THE ANESTHESIOLOGIST'S RESOURCES include many adjuvant drugs which not only have complex effects on the autonomic and central nervous systems, but also modify tissue blood flow. Transport of any substance or drug from one region of the body to another, a distance which may be a few microns or more than a meter, must obviously be accomplished by way of the circulatory system. Since the sites of action of some of these adjuvant drugs may be partially or entirely on the blood vessel walls, directly or indirectly affecting their vascular smooth muscle, these agents can literally influence their own distribution and metabolism through their vasomotor effects on blood flow. It is therefore important for the clinician to understand precisely the primary or secondary actions which the adjuvant drugs he uses may have on peripheral blood vessels and tissue perfusion.

Only a limited number of adjuvant drugs can be adequately discussed in the space allocated for this review; the selection and orientation of the selected subject matter reflects our own prejudices and preoccupation. Fortunately, during the past few years a number of excellent reviews of particular aspects of this extensive subject have become available. Vasopressor, adrenergic and vasodilator drugs have been intensively covered.[11,14,38,48,86,148,150,176] The peripheral vascular actions of angiotensin and prostaglandins have also been reviewed recently.[48,51,86,119,122,150,164,176] In view of these excellent sources of information, the present review is limited to a discussion of adjuvant drugs other than the foregoing.

The maintenance of circulatory homeostasis depends to a large extent on the responsiveness of the peripheral blood vessels to the sympathetic nervous system and circulating neurohumoral substances. Certain drugs which can interfere with these normal responses can seriously affect blood pressure, tissue blood flow, and cardiac output, expecially in patients subjected to anesthesia and stress. We have focused on the peripheral vascular effects of local anesthetics, antihistamines, and glucocorticoids in this review, since these three classes of structurally different molecules 1) share certain common physiologic and pharmacologic properties which are probably important in relation to their actions on peripheral vessels—namely, potentiation of the constrictor actions of catecholamines[15,150] and stabilization of cell membranes[58,146]; 2) have not heretofore been compared with respect to their actions on blood vessels and flow.

## Local Anesthetics

### In-vivo Actions on Regional Blood Flow and Microcirculation

In general, local anesthetics stabilize cell membranes.[58,132,146] It is this action on excitable membranes of nerves and muscles[132,146] which is thought to account for the analgesic actions of these drugs. It is now well established that local anesthetics block propagation of the nerve impulse by altering ionic conductance, thus stabilizing the axon membrane.[132] Although intravenous local anesthetics are regularly used in the treatment of ventricular arrhythmias, they must be administered judiciously, since one of their common side

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TABLE 1. Comparative Effects of Local Anesthetics on Peripheral Blood Flow in Mammals and Man

| Local Anesthetic | Relative Potency* | Regional Blood Flow† | Microcirculatory Flow | References |
|---|---|---|---|---|
| Procaine | 1 | ↑↓ | ↑ | 6,30,44,110,136, 138,149,160 |
| Lidocaine | 4 | ↑↓ | ↑ | 6,30,37,56,63, 89,120,168 |
| Mepivacaine | 4 | ↑↓ | ↑↓ | 1,15,62,63, 94,125 |
| Tetracaine | 25 | ↑ | ↑↓ | 15,85,101 |

* Based on *in-vitro* analgesic properties of local anesthetics in the isolated frog sciatic-nerve preparation.

† ↑ = Vasodilatation and/or increased blood flow (decreased peripheral resistance); ↓ = vasoconstriction and/or decreased blood flow (increased peripheral resistance). Size of arrow indicates relative dominance of effect.

effects is hypotension. Procaine is currently being used much less frequently than lidocaine for this purpose because it is prone to induce much greater hypotension.[14] Procaine administered intravenously is thought to exert a profound depressant effect on peripheral blood vessels.[58] It is generally believed, but by no means certain, that most local anesthetics (except cocaine and mepivacaine) relax vascular smooth muscle[58,95,150] and can produce peripheral vasodilatation (table 1). Direct observations of the living microvascular system indicate that local anesthetics such as procaine and lidocaine, when applied topically to mammalian blood vessels, do indeed promote relaxation or dilatation of arterioles, metarterioles, and precapillary sphincters, whereas mepivacaine and tetracaine have mixed or biphasic effects which are dose-dependent.[6,15,30] Although lidocaine, where investigated, has been demonstrated to exert predominantly peripheral vasodilator actions,[6,15,58,150] there is one report suggesting that it can produce constriction of lobar venous vessels of the lung in intact dogs.[89] It should be stressed that the latter effect was found in venous smooth muscle; this investigator could not demonstrate such a contractile effect on the intact pulmonary arteries.[89] These contractions, where they occur, could be indirect, since certain local anesthetics such as lidocaine have been demonstrated to potentiate the responses of vascular smooth muscle to catecholamines.[6,150]

## IN-VITRO ACTIONS ON BLOOD VESSELS

Both procaine and lidocaine can contract isolated segments of cat and rat anterior mesenteric veins.[136a] Since these contractions could not be abolished by specific cholinergic-, adrenergic-, histaminergic-, or serotoninergic-blocking agents,[136a] it would appear that procaine and lidocaine may induce contraction of some venous smooth muscles by a direct action. It has been suggested that some or all of these contractile actions in *venous* smooth muscle are not only concentration- but tone-dependent[1,2]; low concentrations increase tension and/or spike frequency, while high concentrations induce relaxation. Although we have examined a number of relaxed, isolated *arteries* from dogs, rats, rabbits, and cats (*e.g.*, carotids, femorals, mesenterics, renals, aortas), none that would contract in the presence of procaine, lidocaine, hexylcaine, or even mepivacaine in concentrations to 250 μg/ml could be found.[19,20] These agents can, however, exert effects on hormone- and drug-induced contractions of these isolated mammalian blood vessels.[15,20,68,150] A variety of drug- and hormone-induced contractions, including depolarizing concentrations of potassium chloride, of isolated as well as intact vessels can be dose-dependently relaxed by a variety of local anesthetics (*i.e.*, procaine, lidocaine, tetracaine, mepivacaine) in concentrations equal to or greater than 0.5 μg/ml, the thresholds and magnitudes being dependent

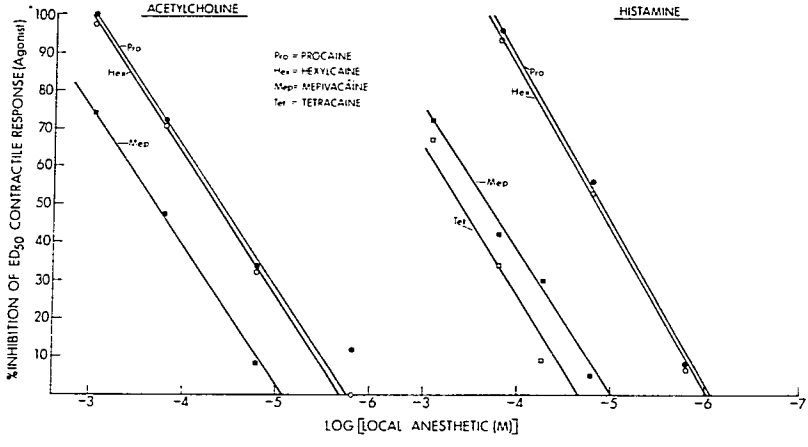


FIG. 1. Log concentration–effect curves of the percentage inhibition to $ED_{50}$ isometric contractile responses of acetylcholine and histamine in rabbit aortic strips produced by different local anesthetics (procaine, ●; hexylcaine, ○; mepivacaine, ■; tetracaine, □). All of the local anesthetics used were hydrochloride salts.

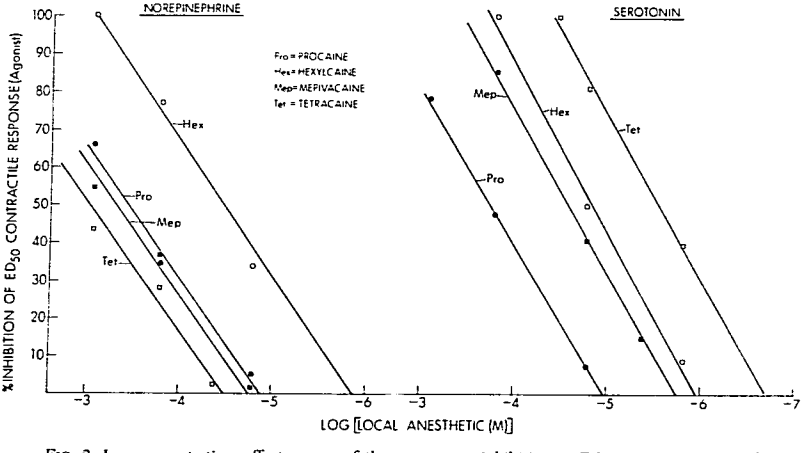


FIG. 2. Log concentration–effect curves of the percentage inhibition to $ED_{50}$ isometric contractile responses of norepinephrine and serotonin in rabbit aortic strips produced by different local anesthetics (procaine, ●; hexylcaine, ○; mepivacaine, ■; tetracaine □).

upon type of vasoactive stimulant and local anesthetic. Similar actions were found in all types of isolated arteries investigated to date.[20] These observations support previous findings of others[150] and, in addition, indicate that such vascular effects may not be species-dependent.

In view of the findings suggesting that local anesthetics induce nonspecific inhibition of vascular tone, it was of interest to determine whether local anesthetics, in general, could affect a variety of pharmacologic receptor systems in vascular smooth muscle.[15,20,68] Figures 1 and 2 demonstrate that a variety of local anesthetics can inhibit drug-induced contractions of blood vessels. However, such data indicate that 1) relatively high anesthetic concentrations ($>10^{-5}$M) are needed; 2) the relative potencies for these inhibitory actions do not seem to be related to the true local anesthetic potencies, as assessed by classic techniques; 3) contractions induced by different agonists are differentially inhibited by local anesthetics. It is of great interest (figs. 1 and 2) that the regression lines for all of the local anesthetic-induced inhibitory effects are parallel, suggesting that different local anesthetics may be acting on vascular muscle by the same mechanism. Figures 3 and 4 show the typical effects that increasing anesthetic concentrations exert on amine- and peptide-induced contractions of isolated vascular smooth muscle. Such data, which have been found by others as well,[68] indicate that low concentrations of a variety of local anesthetics (*e.g.*, procaine, lidocaine, mepivacaine, and tetracaine) seem to produce parallel shifts to the right of the amine- and peptide-induced contractile responses, while higher concentrations produce shallowing of the sigmoid log concentration–effect curves concomitant with reductions in maximum response. The former effect has been attributed by some workers to changes in the affinities of the various agonists for their respective receptive sites in vascular smooth muscle,[68] while the latter has been hypothesized to be due to an effect of local anesthetics on mobilization of calcium ions.[68] Local anesthetics have been shown to exert significant antagonistic effects on movement of calcium ions in a variety of cell types,[33,43,46,49,64,102,113,153] including smooth muscle.[65,88,121] However, since alterations of vascular smooth muscle cell metabolism can also produce parallel shifts of drug-induced responses,[13,16,34] local anesthetics may be inducing these apparent changes in drug-receptor kinetics by acting on events beyond the agonist receptor sites: local anesthetics have been shown not only to penetrate cell membranes,[43,132,146] but also to depress intracellular oxidation of glucose in brain homogenates[163] and uptake of oxygen in cultured cells.[66]

## Antihistamines

Antihistamines are widely prescribed in the treatment of motion sickness, urticaria and other allergic skin conditions, hay fever, vasomotor rhinitis, and other diseases where an allergic background may be suspected. They are also administered to treat allergic manifestations prior to or during anesthesia and widely used as preoperative sedatives. Some antihistamines have been advocated for the treatment of parkinsonism. The latter two indications for antihistamines are probably related to the ability of some of these molecules to induce depression of the CNS and muscle relaxation, respectively.[173] Antihistamines comprise a group of drugs which counteract or prevent the pharmacologic actions specific to histamine. These agents are thus not thought to produce direct pharmacologic agonist effects which are categorically opposite to those of histamine, as does epinephrine, which will relax intestinal or bronchiolar smooth muscle contractions induced by histamine by a direct pharmacologic action.

### Specificity of Antihistamines

The diamine, histamine, is a powerful stimulant of smooth muscle from many organs, such as the already mentioned intestine and bronchioles, as well as arterial and venous smooth muscle. Normally, the latter vascular actions can be attenuated by low concentrations of various classic, clinically available antihistaminic compounds such as diphenhydramine (Benadryl), chlorpheniramine (Chlor-Trimeton), pyrilamine (Neoantergan), promethazine (Phenergan), and tripelennamine (Pyribenzamine). Other pharmacologic effects induced by histamine, such as stimulation of

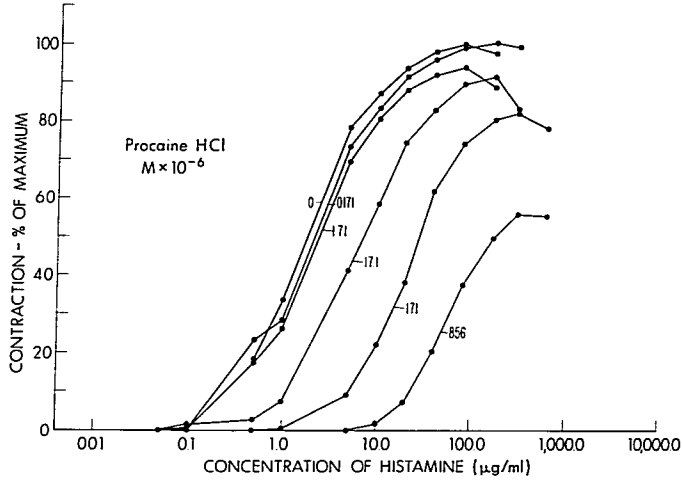


FIG. 3. Effect of procaine on concentration–effect curves of histamine in rabbit aortic strips. 0 = control. Procaine was incubated with tissue for 15 minutes prior to obtaining cumulative dose–response curves.

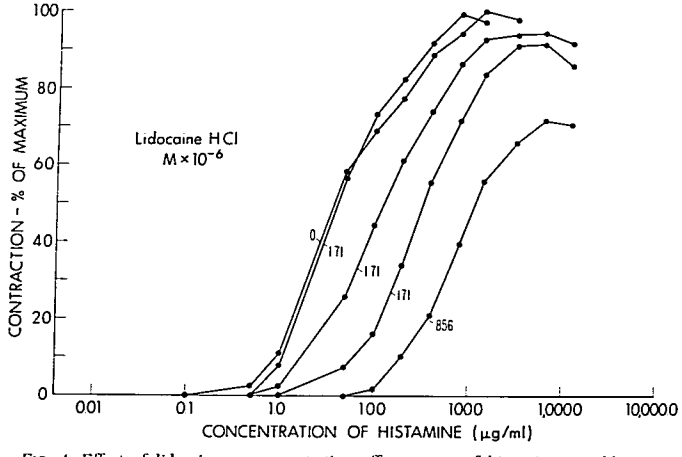


FIG. 4. Effect of lidocaine on concentration–effect curves of histamine in rabbit aortic strips. 0 = control. Lidocaine was incubated with tissue for 15 minutes prior to obtaining cumulative dose-response curves.

TABLE 2. Important Pharmacologic Properties of Antihistamines Which Can Affect Peripheral Blood Vessels and Flow

| Pharmacologic Property | References |
|---|---|
| Local anesthetic action | 60,83,116,146 |
| Analgesic action | 87,104 |
| Quinidine-like action | 53,60 |
| Anticholinergic effects | 53,111 |
| Anti-adrenergic effects | 53,61,67,111 |
| Anti-serotonin effects | 53,167 |
| Histamine liberation | 53,123,162 |
| Inhibit ion transport | 96,97,127,146 |
| Depolarize nerve and muscle membranes | 57,112,118 |
| Potentiate cardiovascular effects of catecholamines | 4,10,29,30,75, 90,114 |
| Effects on cell metabolism | 78,96,97,127 |
| Partial inhibition of reflex vasodilatation | 75,79,108, 158,159 |

acid secretion by the stomach, increased heart rate, or inhibition of (rat) uterine contractions cannot be antagonized by the aforementioned antihistamines. Recently, an antagonist, burimamide, which will selectively block the effects of histamine on acid secretion, heart rate, and uterine contractions has been synthesized.[45] This development has given added support to the idea that histamine can act through more than one type of receptor.[35] Histamine receptors blocked by the classic antihistamines have been termed "$H_1$ receptors," while those blocked by burimamide have been termed "$H_2$ receptors."[35,45] Depressor responses to intravenous injection of histamine are not completely blocked by either $H_1$ or $H_2$ receptor blockers, but seem to require a combination of both types of antihistamines.[45] It has therefore been suggested by Black and co-workers[45] that the cardiovascular effects of histamine are subserved by both $H_1$ and $H_2$ receptors.

## Microvascular Effects

Complete antagonism of the microcirculatory actions induced by histamine, *i.e.*, vasodilatation of terminal arterioles, metarterioles, precapillary sphincters, and muscular venules, requires relatively high concentrations of either the classic $H_1$ blockers or burimamide (>10 mg/kg).[15,29] But these and even lower antihistaminic concentrations (2–5 mg/kg) have a dose-dependent constrictor action on various muscular components of the microvasculature in a variety of regional vascular beds (including the cutaneous circulation) in rodents as well as all other mammalian species thus far investigated.[8,11,15,29–31,41,84,134] These, and other observations,[7,9,10,12,15,18,19,30] have led us to conclude that most antihistamines ($H_1$ and $H_2$ receptor blockers) have direct musculotropic effects as well as other pharmacologic effects on vascular smooth muscle exclusive of their antagonism of histamine. For those who use these drugs it is important to be aware of some recently reported direct and indirect vascular actions of antihistaminic compounds, particularly those which affect vessel tone and reactivity (table 2).

Most antihistamines not only induce direct contraction of regional microvessels in blood concentrations of the order attained by usual oral or parenteral doses,[8,10,173] but in addition, potentiate the constrictor and pressor actions of catecholamines.[29,75,90,114] The latter phenomenon is thought to be due to the cocaine-like effects of these compounds on the neuronal uptake of norepinephrine.[75,90] It is of interest that certain drugs such as corticosteroids and beta-adrenergic blockers, in pathologic states such as endotoxemia, can profoundly potentiate the microvascular constriction induced by antihistaminics.[10] Therefore, caution should be exercised in using antihistaminics in these circumstances.

The ability of antihistaminics to induce microvascular contraction does not appear to be quantitatively related to their true antihistaminic potencies.[10] Although a parallel relationship between epinephrine-, norepinephrine-, and antihistamine-induced contractions exists in many experimental situations, a common receptor site is not involved.[10] However, an accessory (binding) alpha-adrenergic receptor site may be involved in antihistamine-induced microvascular constrictions.[10]

## Macrovascular Effects

Recent *in vitro* studies, performed on a variety of arteries (from rabbits, cats, dogs, man),[7,18–20] indicate that most types of anti-

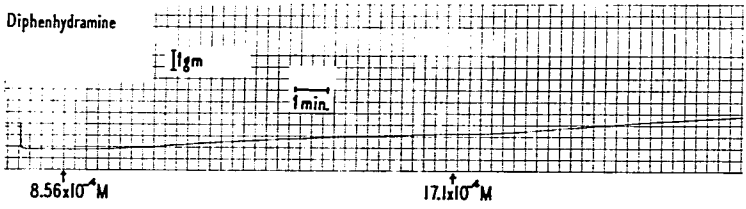


FIG. 5. Representative tracing of the dose-dependent contractile action of diphenhydramine on a rabbit aortic strip.

histaminics (*e.g.*, promethazine, diphenhydramine, chlorpheniramine, pyrilamine, and tripelennamine) induce dose-dependent contractile responses in these isolated mammalian blood vessels (fig. 5). These data, therefore, lend support to the hypothesis that many antihistaminics induce contraction of vascular smooth muscle by a direct action, *i.e.*, possibly by depolarization of the smooth muscle cell membrane coupled with a release of bound calcium ions. That these agents can exert a direct contractile action on microcirculatory blood vessels may help to explain their inhibitory actions against mediators other than histamine in inflammatory states.[10,133]

Apart from direct vascular actions of these compounds, data are accumulating to indicate that most, if not all, of the classic $H_1$-receptor blockers may not be *specific* antagonists of histamine even in macrovascular smooth muscle (*e.g.*, arteries and veins).[7,12,15] *In-vitro* studies performed in our laboratory on a variety of arterial vessels from different mammals, including man, indicate that 1) True competitive antagonism (*i.e.* parallel right shifts of dose–response curves with no reduction in maximum response) exists over very limited antihistaminic dose ranges (see, *e.g.*, figs. 6–8); 2) Non-competitive histamine antagonism (*i.e.*, shallowing of dose–response curves concomitant with reduction in maximum response) is seen over rather wide antihistaminic dose ranges (figs. 6–8); 3) Certain antihistamines such as tripelennamine, which has been used in studies involving reflex vasodilatation (to unmask histamine),[75,79,108,158,159] appear to act noncompetitively with histamine on certain types of arterial smooth muscle[15] exclusively; 4) Most of the antihistamines (*e.g.*, promethazine, chlorpheniramine, diphenhydramine, pyrilamine, tripelennamine), although somewhat more potent against histamine than other vasotropic agonists,[7,12,15] can also effectively antagonize, both competitively and noncompetitively, agonists such as catecholamines, serotonin, and acetylcholine (see, *e.g.*, figs. 9 and 10). This antagonism of agonists other than histamine appears to be related to their well known antiadrenergic, antiserotoninergic and anticholinergic properties (table 2); (5) Antihistaminics can dose-dependently relax drug-induced contractions of a variety of mammalian blood vessels.[7,12,-15,67,174]

Since antihistaminics share with local anesthetics the ability to stabilize cell membranes[146] and to inhibit the movement of $Ca^{++}$,[76,146] it is probably these properties which are responsible for inhibition and reversal of drug-induced contractions of regional blood vessels. However, some of the other properties of the antihistaminics listed in table 2 may also have roles in the inhibitory actions observed in peripheral blood vessels.

Overall, the studies reviewed here emphasize that antihistaminics may have important effects on peripheral blood vessels and blood flow in addition to the principal action for which they are usually given. These vasomotor actions must be considered in their clinical use and when used as experimental tools to define a physiologic or pharmacologic response as being histaminic or otherwise in the cardiovascular system.

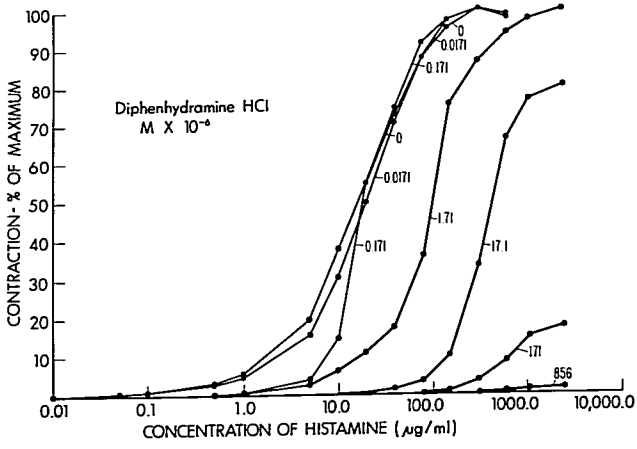


FIG. 6. Effect of diphenhydramine on concentration–effect curves of histamine in rabbit aortic strips. 0 = control. Antagonist was incubated with tissue here (and in figures 7–10) for 15 minutes prior to obtaining cumulative dose–response curves.

## Glucocorticoids

The adrenal cortex synthesizes two major types of steroids, corticosteroids and androgens. There are two types of corticosteroid hormones, glucocorticoids and mineralocorticoids. Since the amount of stored corticosteroids in the adrenal cortex is insufficient to support normal body functions, these hormones must be synthesized at a turnover rate of several times per day.[77] The rate of secretion of the corticosteroids is dependent upon the rate of biosynthesis, which in turn is under the regulatory influence of hormones such as ACTH, angiotensin II and cyclic adenosine 3′,5′-monophosphate (cyclic AMP).[77] Stressful situations such as systemic infections, trauma, blood loss, and circulatory shock, among others, stimulate increased corticosteroid secretion.

The adrenal cortex, with its corticosteroid hormones, is considered by many investigators to be the pivotal organ in the maintenance of homeostasis. So, too, the natural and synthetic adrenal steroids have become a major therapeutic resource in augmenting many of the body's defense mechanisms against stress. Although the subject of homeostasis and host defense merits further discussion, the remaining space in this section is limited to the circulatory actions of the glucocorticoids, their related cellular actions, and their role and use in disease states associated with altered blood flow. Nor is an attempt made to review here all of the reported physiologic and pharmacologic effects of the glucocorticoid hormones. This information can be found in many excellent articles and monographs.[40,50,55,77,93,157]

Many reports in the literature conclude or infer that glucocorticoids have important actions on peripheral blood vessels, blood flow, endothelial cells, and the formed elements of the blood (table 3). Despite this common impression, however, it should be clearly stated that there is no convincing evidence that either physiologic or pharmacologic concentrations of glucocorticoids can directly alter vessel diameters or peripheral blood flow.[4,10,11,21–23,82,98,107,142,144,150,152] A more likely interpretation is that although physiologic concentrations of the glucocorticoid hor-

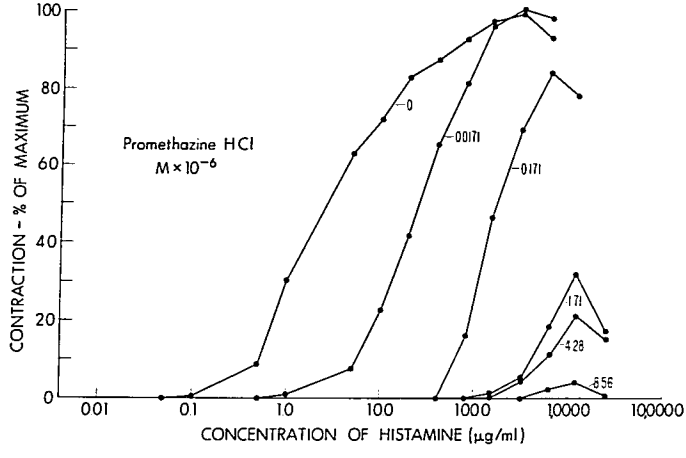


FIG. 7. Effect of promethazine on concentration–effect curves of histamine in rabbit aortic strips.

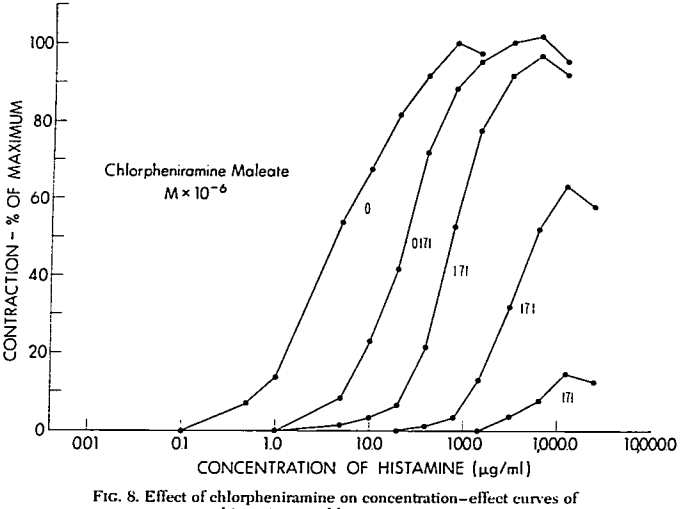


FIG. 8. Effect of chlorpheniramine on concentration–effect curves of histamine in rabbit aortic strips.

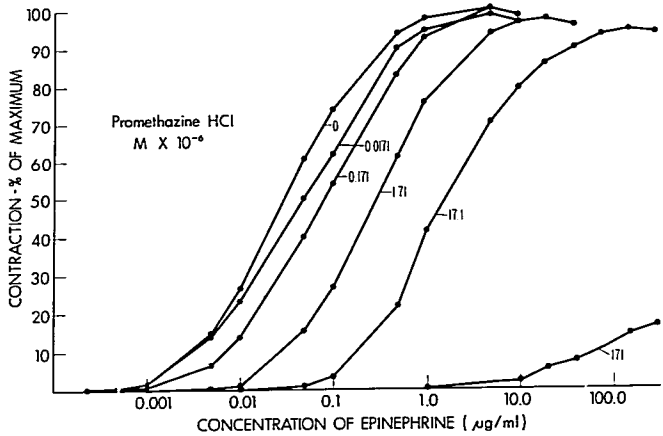


FIG. 9. Effect of promethazine on concentration–effect curves of epinephrine in rabbit aortic strips.

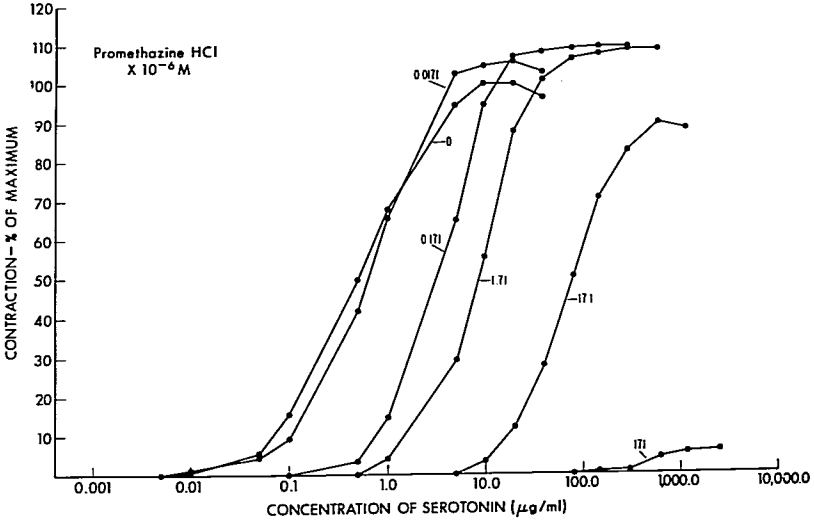


FIG. 10. Effect of promethazine on concentration–effect curves of serotonin in rabbit aortic strips.

TABLE 3. Important Physiologic and Pharmacologic Actions of Glucocorticoids Which Can Affect Peripheral Blood Vessels, Blood Flow, Endothelium and Formed Blood Elements

| Cellular Effect | References |
|---|---|
| Potentiation of constrictor and pressor actions of catecholamines* | 4,10,11,21,23,36,42,69,70,100, 103,105,131,142,180 |
| Attenuation of certain vasodilator actions* | 4,154,177,179 |
| Restoration of vascular reactivity in stress*† | 4,70,177,179,180 |
| Inhibition of histamine binding to tissues*† | 139,141,156,175 |
| Inhibition of histamine synthesis and alteration of its metabolism*† | 54,130,139,156 |
| Stabilization of endothelial and cell membranes*† | 146,177,179,180 |
| Enzyme induction and various metabolic actions*† | 40,77,93,157 |
| Inhibition of leukocytic sticking, diapedesis, and accumulation*† | 3,36,80,137 |
| Stimulation and inhibition of reticuloendothelial system function*† | 21,161 |
| Clearance of lysosomal enzymes and toxins from circulation*† | 74,128,172 |
| Inhibition of platelet aggregation† | 115,124 |
| Stabilization of lysosomal membranes† | 72,91,155,166 |
| Attenuation of vasoconstrictor action† | 21–23, 126, 135 |

* These effects can be attained *in vivo* with concentrations of steroid at, near, physiologic.
† These effects can be attained *in vivo* with pharmacologic concentrations of steroid.

mones do not, by themselves, have direct actions on vascular smooth muscle,[4,11,150] they do alter blood-vessel caliber and flow in the microcirculation by indirect actions (*e.g.*, on circulating catecholamines, histamine, and kinins; maintenance of endothelial tone and integrity; maintenance of blood fluidity by acting on the formed elements; maintenance of reticuloendothelial system integrity) (references in table 3).

## Mechanisms of Glucocorticoid Vasotropic Actions

It is generally believed that low (probably physiologic) doses of the steroid hormones substantially and specifically potentiate the contractile actions of catecholamines on micro- and macrovascular smooth muscle.[42,100,140] But the mechanisms are largely uncertain. Besse and Bass suggest that glucocorticoids increase the affinity of adrenergic receptors for catecholamines,[42] but others have found that these steroids have no such effect on the affinity of catecholamines for their receptors in vascular muscle.[81] Kalsner, using rabbit aortic strips, concluded that this steroid-induced potentiation of catecholamines results from inhibition of catechol-O-methyltransferase activity.[100] Other investigators could find no evidence to support the latter hypothesis.[81,169] Williams and Hudgins[169] have recently suggested that the steroid-induced potentiation may be due to a limitation of transmembrane movement of catecholamines. All of the latter studies, however, either employed cortisol (hydrocortisone) exclusively or tested a limited number of vasoactive agents other than epinephrine and norepinephrine. In the context of this experimental background, it has recently been reported that: 1) some glucocorticoids, when given locally and systemically, acutely, can potentiate the constrictor action of antihistamines, serotonin, and methoxamine (noncatecholamines) on rat mesenteric microvessels[4,10,11,39]; 2) multiple doses of glucocorticoids can potentiate the *in-vivo* constrictor actions of vasopressin as well[4]; 3) methylprednisolone, which is almost pure glucocorticoid in action,[77] in contrast to cortisone and hydrocortisone, which have both glucocorticoid and mineralocorticoid properties, fails to potentiate catecholamine or vasopressin constrictor action in the microcirculation over a 10,000-fold change in dose when given either topically or intravenously.[21,23] These findings in the microcirculation could be used to suggest that, physiologically, 1) steroid molecules such as cortisone and hydrocortisone which show mixed glucocorticoid and mineralocorticoid properties[77] *do not* exclusively potentiate the constrictor actions of epinephrine and norepinephrine, as has been heretofore promulgated by some[42,100,140]; 2) the pure glucocorticoid prop-

erties of the steroids *per se may not* be associated with potentiation of the vascular actions of catecholamines,[21,23] as has been suggested previously by others.[42,100,140] Further work, using a variety of blood vessels and pure glucocorticoids (with high glucocorticoid potency) *in vivo* and *in vitro*, will, however, be required before these controversial issues can be clarified.

## The Inflammatory Response and Microcirculatory Effects

Glucocorticoids are widely used, clinically, for their attenuation of many aspects of acute inflammatory responses. They are probably effective in these situations because they can influence, by a variety of their actions (table 3), the cardinal signs of local tissue injury or inflammation which develop in the microvessels (increased microvascular caliber; release of vasoactive mediators such as histamine and kinins; separation of endothelial cells; leukocytic sticking, diapedesis and aggregation; platelet aggregation; release of lysosomal hydrolases). To illustrate: Potentiation by glucocorticoids of the constrictor actions of endogenous catecholamines would attenuate histamine and kinin-induced local vasodilation, as well as modify movement of leukocytes and plasma across the capillary and venular walls. Attenuation of histamine and kinin-induced vasodilation would restore microcirculatory flow toward normal. Inhibition of tissue histamine binding and synthesis by glucocorticoid hormones would prevent further vasodilatation and separation of endothelial cells. (Release of histamine in acute inflammatory conditions is thought to play an important role in inducing capillary permeability changes.[133]) Inhibition of the accumulation of leukocytes by these steroid hormones would tend to prevent the release of other vasoactive mediators and lysosomal hydrolases from the leukocytes, which could exacerbate the local tissue injury, etc.[92] It thus becomes apparent that the amelioration of the acute inflammatory responses by the glucocorticoid hormones can, in one way or another, be attributed to the actions these steroids exert on the various components of the walls of microvessels (smooth muscle cells, endothelial cells) and the formed elements that they contain. Since all of these beneficial actions can occur very rapidly, it appears unlikely that glucocorticoids ameliorate inflammation by virtue of their effects on cell metabolism or cytoplasmic receptors.[157]

## Glucocorticoids in Treatment of Shock

Although glucocorticoids also play important roles in growth, immune reactions, cell differentiation, and in the modulation of many hormones,[40,50,55,77,93,157] the remainder of this discussion is limited to the role of these steroids in the therapy of circulatory shock as mediated via their peripheral vascular actions. When administered in massive doses (equivalent to 10–30 mg/kg methylprednisolone), glucocorticoids are widely reported as beneficial in the treatment of various experimental and clinical low-flow states.[21,52,59,71–73,82,91,98,106,107,109,117,165] Several mechanisms have been advanced to account for this protective effect in shock, but at present there is no agreement as to the precise mechanism(s) involved.[59,71,129,141] The more prominent theories include stabilization of lysosomal membranes,[72,73,91,152] metabolic actions,[129,145] increase in cardiac output,[171] inhibition of a myocardial depressant factor (MDF),[73,106] potentiation of the vasoconstrictor action of catecholamines,[52] alpha-adrenergic blockade,[109] and vasodilator action.[109] Very recently, considerable evidence which appears to rule out at least some of the above theories, positive inotropic action, potentiation of catecholamines, or a vasodilator action, as contributing factors to the salutary effects of the steroids in circulatory shock has been accumulating.[21,23,98,129,152] Despite the findings that lysosomal hydrolases can be released in shock and that massive doses of glucocorticoids can prevent this release if given prior to shock,[72,73,91,152,166] several investigators have failed to find an increase in lysosomal enzymes in the sera and tissues of both untreated man and animals.[143,147] Furthermore, administration of lysosomal or acid hydrolases to normal animals does not produce circulatory shock unless the reticuloendothelial system (RES) is blocked or partially excluded from the circulation.[74,129] These observations must of necessity cast doubt on the role stabilization of lysosomal membranes plays in the amelioration of shock

by glucocorticoids. As to specific alpha-adrenergic blockade, there is currently no clear-cut evidence to support this hypothesis, either.

Although there is, at present, no compelling evidence for a hemodynamic basis for glucocorticoid amelioration of shock syndromes, it must be acknowledged that since microcirculatory and vascular smooth muscle dysfunction,[28,170,178] as well as RES phagocytic depression,[24–27] are known to play fundamental roles in the lethality of the shock progression, these entities must also be considered. In this context, there is recent evidence which suggests that glucocorticoids exert certain pharmacologic effects on both vascular smooth muscle and RES function, the nature of which may be important as contributing factors to protection in circulatory shock.[21–23] Briefly, work in our laboratory demonstrated by direct, quantitative *in-vivo* microscopy that massive doses of both hydrocortisone sodium succinate (HC) (300 mg/kg) and methylprednisolone sodium succinate (MP) (30 mg/kg) effectively restored the severely constricted arterioles of rats subjected to hemorrhagic and intestinal-ischemia shock to near normal during, as well as following, intravenous infusion of these steroids.[21–23] Our group also demonstrated that both steroids (*i.e.*, HC and MP in pharmacologic doses) dose-dependently inhibited epinephrine-, norepinephrine-, vasopressin-, serotonin-, and angiotensin-induced contractions, as well as displaced the log dose–response curves of these vasoactive agents, nonspecifically, to the right in studies of arterioles *in vivo* and arterial smooth muscle *in vitro*. HC (300 mg/kg) and MP (30 mg/kg) not only significantly improved survival rates of rats subjected to two types of circulatory shock, when administered after the shock was induced, but effectively restored RES phagocytic function to normal. These findings suggested to us that pharmacologic doses of glucocorticoids may confer protection in shock by: 1) preventing the intense peripheral vasoconstrictor action of the many vasoactive constrictor substances released in shock (*e.g.*, catecholamines, vasopressin, serotonin, angiotensin), and 2) aiding in the restoration of normal RES phagocytic function. This concept, if sustained, could identify a rational hemodynamic basis, at the microcirculatory level, for glucocorticoid therapy in circulatory shock.

## Concluding Comment

We have attempted in this brief review to focus on recent advances in the understanding of physiologic and pharmacologic effects of local anesthetics, antihistamines, and glucocorticoids on peripheral blood vessels. Probably, more questions are raised than answers given. If so, this is likely to be a reflection of the current state of our understanding of this subject. However, it is interesting that many of the more recent studies reviewed have demonstrated that, in addition to potentiating catecholamines and stabilizing cell membranes, these three classes of molecules can, in pharmacologic doses, attenuate contractions of blood vessels induced by a variety of neurohumoral and vasoactive agents. Although substantial progress is being made toward establishing the entire profile of peripheral vascular actions of these classes of molecules, there remain important areas that are frankly controversial or, at best, unclear. These uncertainties are not surprising since vascular smooth muscle is heterogeneous in nature[11,14,20,150] and, as such, can differ in responses to the same drug within adjacent microvascular smooth muscle cells,[11,14] as well as between segments within one and the same bed.[5,17,151]

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