Mechanisms of histamine-induced relaxation in bovine small adrenal cortical arteries

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Zhang, David X., Kathryn M. Gauthier, and William B. Campbell. Mechanisms of histamine-induced relaxation in bovine small adrenal cortical arteries. Am J Physiol Endocrinol Metab 289: E1058–E1063, 2005. First published August 2, 2005; doi:10.1152/ajpendo.00162.2005.—Adrenal steroidogenesis is closely correlated with increases in adrenal blood flow. Many reports have studied the regulation of adrenal blood flow in vivo and in perfused glands, but until recently few studies have been conducted on isolated adrenal arteries. The present study examined vasomotor responses of isolated bovine small adrenal cortical arteries to histamine, an endogenous vasoactive compound, and its mechanism of action. In U-46619-precontracted arteries, histamine (10^{-5}–5 \times 10^{-8} \text{M}) elicited concentration-dependent relaxations. The relaxations were blocked by the H_{1} receptor antagonists diphenhydramine (10 \text{ M}) or mepyramine (1 \text{ M}) (maximal relaxations of 18 \pm 6 and 22 \pm 6\%, respectively, vs. 55 \pm 5\% of control) but only partially inhibited by the H_{2} receptor antagonist cimetidine (10 \text{ M}) and the H_{3} receptor antagonist thioperamide (1 \text{ M}). Histamine-induced relaxations were also blocked by the nitric oxide synthase inhibitor N-nitro-L-arginine (L-NA, 30 \text{ M; maximal relaxation of 13 \pm 7\%}) and eliminated by endothelial removal or L-NA combined with the cyclooxygenase inhibitor indomethacin (10 \text{ M}). In the presence of adrenal zona glomerulosa (ZG) cells, histamine did not induce further relaxations compared with histamine alone. Histamine (10^{-7}–10^{-5} \text{M}) concentration-dependently increased aldosterone production by adrenal ZG cells. Compound 48/80 (10 \mu{\text{g}}/\text{ml}), a mast cell degranulator, induced significant relaxations (93 \pm 0.6\%) which were blocked by L-NA plus indomethacin or endothelium removal, partially inhibited by the combination of the H_{1}, H_{2}, and H_{3} receptor antagonists, but not affected by the mast cell stabilizer sodium cromoglycate (1 \text{ mM}). These results demonstrate that histamine causes direct relaxation of small adrenal cortical arteries, which is largely mediated by endothelial NO and prostaglandins via H_{1} receptors. The potential role of histamine in linking adrenal vascular events and steroid secretion requires further investigation.

In addition to stimulating steroidogenesis, ACTH causes marked vasodilation in vivo as reflected by increased adrenal blood flow (8, 12, 27, 35). ACTH also increases flow in vitro in perfused adrenals (6, 15, 16, 25, 31). Studies into the mechanism of ACTH-induced dilation have suggested a role for mast cell-derived histamine and serotonin (15, 16). Mast cells have been identified in the rat adrenal gland, primarily located in the walls of arterioles at the point where they penetrate the connective tissue of the capsule (16). Stimulation of histamine and serotonin release with compound 48/80, a mast cell degranulator, mimics the ACTH-induced increase in adrenal blood flow and steroidogenesis. Sodium cromoglycate, a mast cell stabilizer, blocks the effects of ACTH. Thus histamine and serotonin release from mast cells may mediate ACTH-induced increase in adrenal blood flow (16). However, histamine and serotonin antagonists were not tested in these studies. In addition, most of our understanding of these potential mediators comes from in vivo studies and the perfused adrenal gland, not from isolated arterial preparations.

Recently, we reported an in vitro model of isolated small cortical arteries from the bovine adrenal gland. We found that these small arteries are highly responsive to various vasoactive compounds such as endothelin-1, serotonin, angiotensin II, and acetylcholine (11, 37, 38). Serotonin is a vasoconstrictor of isolated adrenal cortical arteries; therefore, it is unlikely to mediate the relaxations to ACTH. In the present study, we examined the responses of these arteries to histamine, the other potential mediator of ACTH-induced dilation (15, 16). We also explored the mechanisms of action of histamine, including the specific histamine receptors involved, the role of endothelium-derived relaxing factors such as NO and prostaglandins, and the possible interaction of adrenal steroidogenic cells and adrenal vessels.

MATERIALS AND METHODS

Wire myograph. Fresh bovine adrenals were obtained from a local abattoir, placed in ice-cold HEPES solution containing (in mM) 150 NaCl, 5.0 KCl, 1.8 CaCl\textsubscript{2}, 1.0 MgCl\textsubscript{2}, 10 HEPES, and 5.5 glucose, pH 7.4, and transported immediately to the laboratory. Small adrenal cortical arteries closely attached to the adrenal surface (200–300 \mu{\text{m}}) were carefully dissected and cleaned of connective tissues. Isolated arterial segments were threaded on two stainless steel wires (40 \mu{\text{m}} diameter) and mounted on a four-channel wire myograph (model 610M, Danish Myo Technology), as we described previously (38). Briefly, arteries were set to an initial luminal diameter at which passive tension was first measurable and equilibrated in physiological saline solution (PSS) containing (in mM) 119 NaCl, 4.7 KCl, 2.5 CaCl\textsubscript{2}, 1.17 MgSO\textsubscript{4}, 24 NaHCO\textsubscript{3}, 1.18 KH\textsubscript{2}PO\textsubscript{4}, 0.026 EDTA, and 0.8 \text{mM} calcium chloride.

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5.5 glucose, bubbled with 95% O₂-5% CO₂ at 37°C for 30 min. Arteries were then gradually stretched to a resting tension of 1 millinewton (mN) during an additional 30-min equilibration period. Thereafter, the arteries were stimulated two times with KCl (60 mM) plus U-46619 (100 nM) for 3–5 min at 10-min intervals. Arteries were then allowed to equilibrate for another 30 min before the initiation of experimental protocols.

Cumulative concentration-responses to histamine (10⁻⁹-5 × 10⁻⁶ M) were first assessed on the basal tension. To evaluate relaxation responses to histamine, a submaximal concentration of the thromboxane A₂ mimetic U-46619 (100–300 nM) was added to the bath to preconstrict the arteries to 50–75% of maximal KCl contraction. Cumulative concentrations of histamine were then added. To identify specific receptors involved in vascular responses of histamine, arteries were pretreated for 15–30 min with diphenhydramine (H₁ receptor antagonist, 10 μM), mepyramine (H₁ receptor antagonist, 1 μM), cimetidine (H₂ receptor antagonist, 10 μM), or thioperaimide (H₃ receptor antagonist, 1 μM) alone or in combination, and concentration responses were repeated. To examine the possible role of nitric oxide (NO) and prostaglandins in vascular responses of histamine, arteries were pretreated for 15 min with t-NA (30 μM), an endothelial NO synthase (NOS) inhibitor, or indomethacin (10 μM), a cyclooxygenase inhibitor, alone or in combination. To examine the potential indirect effect of histamine on vascular tone via the release of hormones by adrenal steroidogenic cells, freshly isolated zona glomerulosa (ZG) cells (0.5–1.0 × 10⁶ cells in 5–10 μl; see below for the preparation) were added to U-46619-pretreated arteries pretreated with t-NA and indomethacin, followed by the determination of concentration responses to histamine. To assess the role of endogenous histamine in the regulation of vascular tone, vascular responses of compound 48/80 (0.1–10 μg/ml), a mast cell histamine releaser, were determined in the absence or presence of the phospholipase C inhibitor U-73122 (10 μM), the mast stabilizer sodium cromoglycate (1 mM), a combination of diphenhydramine, cimetidine, and thioperaimide, t-NA plus indomethacin, the epoxycisatroenonic acid (EET) antagonist 14,15-EEZE (2 μM), the cytochrome P-450 epoxysenase inhibitor SKF 525A (10 μM), high K⁺ (60 mM), and the large-conductance Ca²⁺-activated K⁺ channel (BKCa) blocker iberiotoxin (IbTX, 100 nM).

Experiments were performed on arteries with intact endothelium. Where indicated, the endothelium was removed by gently rubbing the intimal surface of the vessel with a human scalpel hair while a small, passive tension (0.2 mN) was applied (24). The endothelium was considered intact if acetylcholine (1 μM) caused >80% relaxation of arteries precontracted with U-46619 and effectively removed (denuded) if acetylcholine induced <10% relaxation.

Preparation of ZG cells. Bovine adrenal ZG cells were prepared by enzymatic dissociation of adrenal cortical slices as previously described (26). Briefly, 8–12 glands were trimmed of fat and bisected. A Stadie-Riggs microtome (Thomas Scientific, Swedesboro, NJ) was used to cut sequential 500-μm slices of tissue from the outer surface of the gland. The tissue was finely minced and digested for 30–45 min at 37°C in Earle’s balanced salt solution (EBSS) buffer containing collagenase (1.8 mg/ml), hyaluronidase (0.75 mg/ml), dispase (1 mg/ml), fatty acid-free BSA (1 mg/ml), and DNase (0.2 mg/ml). Cells from four or five digestion cycles were pooled, rinsed in HEPES, and stored on ice until use. Cells were 95–98% ZG cells and 2–5% zona fasciculata (ZF) cells. For some experiments, ZG cells were plated at a density of 200,000 cells/well in Falcon 24-well tissue culture-treated plates (Becton-Dickinson, Lincoln Park, NJ) and maintained in culture for 2–5 days. Cells were fed daily with Ham’s F-12 medium supplemented with 14 mM NaCl, 14 mM NaHCO₃, 2% fetal bovine serum, 50 μM butylated hydroxyanisole, 1.2 μM α-tocopherol, 100 μM sodium ascorbate, 50 mM sodium selenite, 0.15 μM glutathione, 20 nM insulin, 10 μg/ml transferrin, 5 μM metyrapone, 200 U/ml penicillin, 200 μg/ml streptomycin, 3 μg/ml gentamicin, 3 U/ml nystatin, and 2.5 μg/ml fungizone.

Aldosterone assay. Cultured adrenal ZG cells were washed twice with 0.5 ml of steroidogenic medium 1 (SM1), consisting of Ham’s F-12 medium supplemented with 14 mM NaCl, 14 mM NaHCO₃, and 1 mg/ml BSA, and incubated for 2 h at 37°C. The buffer was then replaced with 0.5 ml of steroidogenic medium 2 (SM2), consisting of Ham’s F-12 medium, 14 mM NaCl, 14 mM NaHCO₃, 1.8 mM CaCl₂, and 2 mg/ml BSA. Histamine (10⁻⁷-10⁻⁵ M) or corresponding vehicle control was added, and the incubation was continued for 2 h at 37°C. The incubation was stopped by transferring the SM2 buffer to plastic tubes and freezing at -40°C. Aldosterone was measured by enzyme-linked immunosorbant assay (ELISA), as previously described (14). The assay system included a primary mouse monoclonal antibody against aldosterone, a goat anti-mouse, Fc fragment-specific secondary antibody (Jackson ImmunoResearch), an aldosterone-horseradish peroxidase conjugate (provided by Dr. C. E. Gomez-Sanchez, Truman V. A. Medical Center, Columbia, MO), and 2,2'-azino-bis-(3-ethylbenzothiazoline-6-sulfonic acid) (Sigma) as a color reagent. Aldosterone was quantified by colorimetric measurement using an automated plate reader (Bio-Tek model EL309) with a 490-nm filter.

Data analysis. Contractile responses to an agonist are expressed as the percentage of the maximal contraction induced by U-46619. Relaxations are expressed as percent relaxation relative to U-46619-precontraction, with 100% relaxation representing basal tension. Data are presented as means ± SE. Significance of mean values between and within multiple groups was evaluated by ANOVA followed by the Student-Newman-Keuls multiple comparison test. A value of P < 0.05 was considered statistically significant.

RESULTS

Vascular responses to histamine. We first examined the effects of histamine on basal tone of small adrenal cortical arteries and on arteries contracted with U-46619 and the contribution of specific histamine receptors to these responses. As shown in Fig. 1A, histamine (10⁻⁹-5 × 10⁻⁶ M) had no significant effects on arteries under basal tone. In U-46619-precontracted arteries, histamine elicited concentration-dependent relaxations with a maximal response at 5 × 10⁻⁶ M of 55 ± 5% (Fig. 1B). Higher concentrations of histamine (10⁻⁵-10⁻⁴ M) resulted in reduced relaxations and tachyphylaxis (data not shown). Histamine-induced relaxations were markedly inhibited by two structurally unrelated H₁ receptor antagonists diphenhydramine (10 μM) and mepyramine (1 μM) (maximal relaxations of 18 ± 6 and 22 ± 8%, respectively). Treatment of arteries with the H₂ receptor antagonist cimetidine (10 μM) or the H₃ antagonist thioperaimide (1 μM) caused a rightward shift of the concentration-response curve to histamine without effect on maximal relaxations (Fig. 1, C and D). Compared with diphenhydramine alone, the combination of the above three antagonists resulted in a further small (but not statistically significant) reduction of histamine-induced relaxations (maximal relaxation of 10 ± 4%).

Role of endothelium in histamine responses. The role of two major endothelium-derived relaxing factors, i.e., NO and prostacyclin, in histamine-induced relaxations was examined (Fig. 2A). Pretreatment of arteries with t-NA (30 μM) caused a marked inhibition of the relaxation response to histamine. Maximal relaxations in control and t-NA-treated arteries were 50 ± 5 and 13 ± 7%, respectively. Indomethacin (10 μM) also inhibited histamine-induced relaxations (maximal relaxation of 30 ± 4%). The combination of t-NA and indomethacin abol-
ished the relaxations to histamine. To confirm that histamine responses were endothelium dependent, experiments were repeated in endothelium-denuded arteries. As shown in Fig. 2B, endothelium removal eliminated the histamine-induced relaxations.

**Effect of ZG cells on histamine responses.** Because small adrenal cortical arteries are in close contact with adrenal steroidogenic cells in vivo, we assessed the possible indirect effect of histamine on vascular tone through the release of a relaxing factor(s) from adrenal cells. Arteries were pretreated with L-NA and indomethacin or the endothelium was removed to eliminate direct relaxing responses to histamine. Arteries were then contracted with U-46619, and freshly isolated adrenal ZG cells (0.5–1.0 × 10^6 cells) were added into the bath. ZG cells alone did not cause relaxation of U-46619-contracted arteries. Subsequent addition of histamine on top of the ZG cell addition also failed to elicit significant relaxation (data not shown).

To confirm that the negative effect of adrenal ZG cells on histamine responses was not due to lack of stimulation, we examined the effect of histamine on aldosterone release by these cells. Isolated adrenal ZG cells were incubated with histamine (10^{-7}–10^{-5} M) for 2 h, and the production of aldosterone was measured (Fig. 3). Histamine concentration-dependently increased aldosterone release from ZG cells. Histamine caused a twofold increase at 10^{-5} M. As a control, angiotensin II (10^{-8} M) caused over a 10-fold increase in aldosterone release (data not shown). These data confirm that histamine stimulates the release of aldosterone but not relaxing factors from isolated bovine ZG cells.

**Vascular responses to compound 48/80.** We also examined the effect of endogenous histamine on vascular tone of small adrenal cortical arteries by use of the mast cell degranulator compound 48/80. In U-46619-precontracted arteries, addition of compound 48/80 induced a concentration-dependent relaxation with maximal response of 93 ± 0.6% (Fig. 4A). The maximal relaxation to compound 48/80 (93 ± 0.6%) was significantly greater than the maximal response to histamine (55 ± 5% at 5 × 10^{-6} M, *P < 0.05; Fig. 1B). The relaxation to compound 48/80 (10 μg/ml) was not affected by the phospholipase C inhibitor U-73122 (10 μM) or the mast cell stabilizer sodium cromoglycate (1 mM) and was only partially inhibited by the combination of the histamine receptor antagonists diphenhydramine (10 μM), cimetidine (10 μM), and thioperamide (1 μM). In contrast, L-NA (30 μM) plus indomethacin (10 μM) or removal of the endothelium largely inhibited or eliminated the relaxations to compound 48/80 (Fig. 4B). The remaining relaxations in the presence of L-NA and indomethacin were blocked by high K^+ (60 mM) and the BKCa channel blocker IbTX (100 nM) but were not affected by the EET antagonist 14,15-EEZE (2 μM), or the cytochrome P-450 epoxygenase inhibitor SKF 525A (10 μM) (Fig. 4C).

**DISCUSSION**

Previous studies have shown that histamine causes concentration-dependent increases in adrenal blood flow in vivo and in the perfused adrenal gland (16, 36). However, mechanisms of action of histamine are unclear. The present study characterized the vascular responses to histamine in isolated small cortical arteries from bovine adrenal glands. We have demonstrated that histamine is a direct vasodilator of small adrenal cortical arteries, and this action is mediated by endothelial NO and prostaglandins via H1 receptor activation.

Local production and release of histamine from mast cells contribute to the regulation of vascular resistance in the mi-
croscirculation. Three distinct subtypes of histamine receptors, namely H₁, H₂, and H₃, have been identified either functionally or at the molecular level (20). In the present study, we found that histamine-induced relaxation is mediated largely by H₁ receptors in bovine adrenal arteries. These results are in agree-

Fig. 2. Effect of N-nitro-l-arginine (L-NA), indomethacin, and endothelial removal on histamine-induced relaxations of bovine small adrenal cortical arteries. A: arteries were pretreated with L-NA (30 μM) and indomethacin (10 μM) alone or in combination. B: responses were determined before (control) and after endothelium removal. *P < 0.05 vs. control. All values are means ± SE (n = 8–20).

Fig. 3. Effect of histamine on aldosterone secretion by bovine zona glomerulosa cells. Cells were stimulated with increasing concentrations of histamine for 2 h at 37°C. *P < 0.05 vs. control. All values are means ± SE (n = 5–6).

Fig. 4. Compound 48/80-induced relaxations of bovine small adrenal cortical arteries. A: concentration-response curve for compound 48/80. B: arteries were pretreated with phospholipase C inhibitor U-73122 (10 μM), mast cell stabilizer sodium cromoglycate (1 mM), a combination of diphenhydramine (Diphen, 10 μM), cimetidine (cimet, 10 μM), and thioperamide (thioper, 1 μM), L-NA (30 μM) plus indomethacin (10 μM), or the endothelium was removed. C: experiments were performed in the presence of L-NA and indomethacin, and arteries were pretreated with epoxyeicosatrienoic acid (EET) antagonist 14,15-EEZE (2 μM), cytochrome P-450 epoxygenase inhibitor SKF 525A (10 μM), or Ca²⁺-activated K⁺ (BKCa) channel blocker iberiotoxin (IbTX, 100 nM), or were precontracted with 60 mM KCl. For B and C, 10 μg/ml compound 48/80 was used. Arteries were contracted with U-46619 unless otherwise indicated. *P < 0.05 vs. control. All values are means ± SE (n = 4–12).
ment with previous studies showing that relaxation responses to histamine are mediated predominantly via the activation of endothelial H1 receptors in a number of vascular preparations (17, 28, 30, 32). In the small adrenal arteries of this study, H2 and H3 receptor antagonists also partially inhibited the relaxations to histamine. This occurred only with a low concentration of histamine. This indicates that H2 and H3 receptors, to a smaller extent, may also be involved in relaxation responses of histamine. Compared with the H1 receptor antagonist alone, the combination of H1, H2, and H3 antagonists did not further inhibit histamine-induced relaxations in a statistically significant manner, although a small reduction was noted. The reasons for this are not clear and may be due to some cross-reactivity and interference of these receptor antagonists. Previous studies have shown that H2 and H1 receptor-mediated vasomotor responses are less consistent and may vary depending on species and vascular beds investigated. In some preparations, activation of smooth muscle H2 receptors is coupled with adenylyl cyclase, and the subsequent increase in cAMP contributes to histamine-induced relaxations (17, 30). Other studies of canine spinal and human cerebral arteries indicated that histamine produces relaxation through stimulation of endothelial H2 receptors (18, 29). Similarly, the H3 receptor mediates histamine-induced relaxation of rabbit middle cerebral arteries but not other cranial blood vessels (9, 17).

Removal of the endothelium abolished the relaxations to histamine, indicating that the relaxations are endothelium dependent. Three major endothelium-derived relaxing factors include NO, prostaglandin I2, and endothelium-derived hyperpolarizing factors (EDHFs) that include cytochrome P-450 metabolites of arachidonic acid (i.e., EETs) (7, 10, 22). In the current study, the NOS inhibitor l-NA significantly inhibited histamine-induced relaxations. The cyclooxygenase inhibitor indomethacin, to a smaller extent, also inhibited relaxation responses to histamine. The combination of l-NA and indomethacin abolished the relaxations to histamine. These results indicate that histamine-induced relaxations are mediated by NO and prostaglandins in small bovine adrenal arteries. The mediators involved in the histamine responses are somewhat different from other vasodilators that we reported previously (11, 38). For example, endothelin-1- and acetylcholine-induced relaxations are mediated by NO and cytochrome P-450 metabolites of arachidonic acid, whereas the relaxation responses to low concentrations of angiotensin II are entirely mediated by NO. These differences may be due to different intracellular coupling mechanisms activated by the specific receptors.

In the intact adrenal gland, histamine-induced increases in adrenal blood flow could be a direct effect and/or an indirect effect secondary to hormones and metabolites released by adrenal cells (16, 36). In this regard, histamine stimulates aldosterone and cortisol release from adrenal steroidogenic cells in vivo or in situ (1, 16). Consistent with those studies, histamine stimulated aldosterone release in isolated bovine ZG cells. The relaxations to histamine in isolated small adrenal arteries were blocked by l-NA and indomethacin and were not restored by adrenal ZG cells. These results suggest that histamine-induced increases in adrenal blood flow are not secondary to hormones and metabolites released by adrenal cells, but rather from a direct relaxation of adrenal arteries.

Mast cells have been identified in the rat and dog adrenal gland and are located in the capsule or in the walls of small arteries penetrating the capsule. These cells are major sources of histamine (1, 16). We investigated whether this endogenous histamine can affect vascular tone of isolated bovine small adrenal arteries. Compound 48/80, a mast cell degranulator, relaxed small adrenal arteries. Unexpectedly, the relaxations were only partially inhibited by H1, H2, and H3 antagonists. The maximal relaxation response to compound 48/80 exceeded the maximal response to histamine, suggesting that the relaxation mediated by factors or a mechanism in addition to histamine. Furthermore, the mast cell stabilizer sodium cromoglycate was without effect. In contrast, the relaxations were largely inhibited by l-NA and indomethacin and eliminated by endothelium removal. This indicates that the relaxation to compound 48/80 is mediated through NO and prostaglandins and is largely independent of histamine release and histamine receptor activation. Thus compound 48/80 may act directly on vascular endothelial cells to cause relaxation. A recent study has shown that, in human umbilical vein endothelial cells, compound 48/80 is an activator of Gq protein and phospholipase C (13), thus supporting the potential effect of compound 48/80 on endothelial NOS and/or cyclooxygenase. The remaining relaxations to compound 48/80 in the presence of l-NA and indomethacin were blocked by high K+ and IbTX but were not altered by the EET antagonist 14,15-EEZE and the cytochrome P-450 epoxygenase inhibitor SKF 525A. This indicates that some portion of compound 48/80-induced relaxations is mediated by the smooth muscle hyperpolarization via BKCa channel activation. EETs are not likely the mediator for smooth muscle hyperpolarization. Compound 48/80 also releases ATP from endothelial cells (13). ATP relaxed small adrenal cortical arteries and the relaxations were inhibited by xanthine amine congener (XAC), a nonspecific antagonist of the adenosine receptor. However, XAC did not affect compound 48/80-induced relaxations (data not shown). This suggests that relaxations to compound 48/80 are not mediated by ATP release. Therefore, more specific modulators of mast cells are needed for studies of endogenous histamine in the regulation of adrenal blood flow.

As described earlier, ACTH increases adrenal blood flow in vivo and in perfused adrenals (8, 12, 15, 16, 25, 27, 31, 35). Studies by Hinson and colleagues (15, 16) suggested that the increase in blood flow is due to the release of histamine and serotonin from perivascular mast cells and the subsequent vasorelaxation induced by these compounds. We previously reported that serotonin constricts adrenal cortical arteries under basal tone (38) and on U-46619-precontracted arteries (Zhang DX and Campbell WB, unpublished observation), and therefore may not mediate the relaxation responses of ACTH. In the present study, histamine relaxed small adrenal arteries through endothelium-derived NO and prostaglandins. However, ACTH-induced dilation does not involve NO or prostaglandins (6, 12). The reasons for these discrepancies are unclear but may represent species variability. It is also possible that factors other than histamine mediate ACTH-induced dilation in the adrenal gland.

In summary, the present study demonstrates that histamine relaxes small adrenal cortical arteries and stimulates aldosterone release from ZG cells. These direct actions of histamine may explain its stimulatory effect on adrenal blood flow and steroidogenesis in vivo and in perfused glands. The physiological significance of histamine in the adrenal gland remains to be
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determined. In addition to the potential role of histamine in mediating ACTH responses, a previous study has shown that plasma histamine concentration is markedly increased in dogs during anaphylactic shock (1). The increase in histamine may contribute to aldosterone secretion and release into the systemic circulation through direct stimulation of steriogenesis and increasing adrenal blood flow.

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