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Influence of Hydrocortisone on Histamine-Evoked Catecholamine Secretion from the Isolated Rat Adrenal Medulla

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ABSTRACT

The present study was designed to determine the effect of hydrocortisone on CA secretion evoked by histamine from the isolated perfused rat adrenal glands. Histamine (150 ug) given into an adrenal vein produced significantly CA secretion from the rat adrenal medulla. This histamine-evoked CA secretion was enhanced markedly by the pretreatment with the natural glucocorticoid hydrocortisone (30 uM) or the synthetic glucocorticoid dexamethasone 30(uM) for 20 min, respectively. Hydrocortisone-induced potentiation of CA secretion evoked by histamine was inhibited by preloading with heparin (3.56 U/ml), an IP_3 receptor antagonist while more enhanced by forskolin (0.2 uM), a potent stimulator of adenylate cyclase.

From the experiment result taken together, it is thought that hydrocortisone (glucocorticoids) can enhance the releasing effect of CA evoked by histamine from the isolated perfused rat adrenal medulla, which seems to be associated to accumulation of inositol phosphate as well as cyclic AMP in the rat adrenomedullary chromaffin cells.

Key Words: Hydrocortisone, Histamine, Catecholamine Secretion, Adrenal Gland

INTRODUCTION

It has been found the histamine injected or infused directly into the adrenal gland in situ or in the isolated perfused gland of the rat and the cat produces the increase in CA secretion (Szczygielski, 1932; Smith and Ribinson, 1970; Yoshizake, 1973). Histamine is also known to evoke CA secretion from the adrenal gland of the dog (Schaepdryver, 1959; Narita, 1971), the bovine adrenal medulla (Shima *et al.*, 1979), the bovine adrenal medullary chromaffin cells (Noble *et al.*, 1988; Livett and Marley, 1986; Goh and Kurosawa, 1991), and the perfused rat adrenal gland (Lim *et al.*, 1993).

Histamine not only stimulates CA secretion but also promotes the activation of phospholipase C and the accumulation of inositol phosphates in chromaffin cells (Noble *et al.*, 1986). Recently, Choi and his coworkers (1993) have shown that glucocorticoids enhance histamine-stimulated inositol phosphate accumulation in chromaffin cells. In general, chromaffin cells are known to contain the glucocorticoid, or type II, corticosteroid receptor (Kelner and Pollard, 1985; Betito *et al.*, 1992). Glucocorticoids and CA interact in multiple ways to maintain homeostasis (Ramey and Goldstein, 1957). Hinson and his colleagues (1989) have reported that histamine stimulates the release of glucocorticoids from the adrenal cortex. Aikawa and his coworkers (1986), using a hypophysectomized, nephrectomized dog adrenal

preparation, found that histamine stimulated both cortisol and aldosterone secretion. It has been also previously shown that the corticosterone secretion rate is closely dependent on the rate of flow of perfusion medium through the adrenal gland. Increasing the flow rate through the gland, either mechanically or by the use of a vasodilator, results in increased corticosterone secretion rates (Hinson *et al.*, 1986a)

In the present study, an attempt was made to investigate the effect of hydrocortisone on histamine-evoked CA secretion in the isolated perfused rat adrenal medulla.

MATERIALS AND METHODS

Experimental animals

Mature male Sprague-Dawley rats, weighing 180~300 grams, were anesthetized with ether. The adrenal gland was isolated as described previously by Wakade (1981a). The abdomen was opened by a midline incision, and the left adrenal gland and surrounding area were exposed by placing three hook retractors. The stomach, intestine and portion of the liver were not removed, but pushed over to the right side and covered by saline-soaked gauge pads and urine in bladder was removed in order to obtain enough working space for tying blood vessels and cannulations.

A cannula, used for perfusion of the adrenal gland, was inserted into the distal end of the renal vein after all branches of adrenal vein (if any), vena cava and aorta were ligated. Heparin (400 IU/ml) was injected into vena cava to prevent blood coagulation before ligating vessels and cannulations.

A small slit was made into the adrenal cortex just opposite entrance of adrenal vein. Perfusion of the gland was started, making sure that no leakage was present and the perfusion fluid escaped only from the slit made in adrenal cortex. Then the adrenal gland, along with ligated blood vessels and the cannula, was carefully removed from the animal and placed on a platform of a leucite chamber. The chamber was continuously circulated with water heated at 37±1℃.

Perfusion of adrenal gland

The adrenal glands were perfused by means of a ISCO pump (WIZ Co.) at a rate of 0.31 ml/min. The perfusion was carried out with Krebs-bicarbonate solution of following composition (mM): NaCl, 118.4; KCl, 4.7; $CaCl_2$ 2.5; $MgCl_2$, 1.18; $NaHCO_3$, 25; KH_2PO_4, 1.2; glucose, 11.7.

The solution was constantly bubbled with 95% O_2+5% CO_2 and the final pH of the solution was maintained at 7.4±0.1. The solution contained disodium EDTA (10 ug/ml) and ascorbic acid (100 ug/ml) to prevent oxidation of catecholamine.

Drug administration

Single injection of histamine (150 ug) or Ach (50 ug) in a volume of 0.05 ml were made into perfusion stream via a three way stopcock. In the preliminary experiments it was found that upon administration of the above drugs, secretory responses to Ach and histamine returned to preinjection level in about 4 min. Generally, the adrenal glands were perfused with normal Krebs solution for about one hour before the experimental protocols are initiated.

Collection of perfusate

The adrenal perfusate was collected in chilled tubes.

As a rule, prior to each stimulation with histamine or Ach samples were collected (4 min) to determine the spontaneous secretion of CA ("background sample"). Immediately after the collection of the "background sample", collection of the perfusate was continued in another tube as soon as the perfusion medium containing the stimulatory agent reached the adrenal gland. Each perfusate was collected for 4 min. The amounts secreted in the "background sample" have been subtracted from those secreted in the "stimulated sample" to obtain the net secretion value of CA, which is shown in all of the figures and tables.

To study of effects of a test agent on the spontaneous and drug-evoked secretion, the adrenal gland was perfused with Krebs solution containing the agent for 20~30 min, then the perfusate was collected for a specific time period ("background sample"), and then the medium was changed to the one containing the test agent and the perfusate was collected for the same period as that for the "background sample".

Measurement of catecholamines

CA content of perfusate was measured directly by the flurometric method of Anton and Sayre (1962) without the intermediate purification alumina for the reasons described earlier (Wakade, 1981), using fluorospectrophotometer (Shimadzu Co., Japan). A volume of 0.2 ml of the perfusate was used for the reaction.

The CA content in the perfusate of stimulated glands by Ach or histamine was high enough to obtain readings several-fold greater than the reading of control samples (unstimulated). The sample blanks were also lowest for perfusates of stimulated and non-stimulated samples.

The content of CA in the perfusate was expressed in terms of norepinephrine (base) equivalents. All data are presented as means with their standard erros.

Drugs and their sources

The following drugs were used: histamine chloride, acetylcholine chloride, norepinephine bitartrate, forskolin and heparin from Sigma Chemical Co., U.S.A. Drugs were dissolved in distilled water (stock) and added to the normal Krebs solution as required. Concentrations of all drugs used are expressed in terms of molar base except for the case of histamine or Ach in ug.

Statistical analysis

The statistical significance between groups was determined by utilizing the Student's t-test. A P-value of less than 0.05 was considered to represent statistical significant changes unless specifically noted in the text. Values given in the text refer to means with standard errors of the mean (S.E.M.).

The statistical analysis of the present experimental results was made by computer program of statistics described previously by Tallarida and Murray (1987).

RESULTS

The effect of hydrocortisone on histamine-evoked secretory response of CA from the isolated perfused rat adrenal gland.

The resting (basal) CA secretion from the perfused rat adrenal glands reaches a steady state after the perfusion with normal Krebs solution for 60 min before the experimental protocol is initiated. The secretory responses of the isolated perfused rat adrenal gland to the initial injection of a range of doses of histamine (37.5~150 ug) are shown in a nearly complete dose-response relationship (data not shown) as in the previous study (Lim *et al.*, 1993). These observations are identical to those reported previously (Smith and Robinson, 1970; Schaepdryver, 1959; Narita, 1971; Schneider, 1969, Shima *et al.*, 1976; Kilpatrick, 1984; Noble *et al.*, 1988). When Ach (50 ug) was given into the perfusion stream via a threeway stopcock, CA secretion was 958±121 ng for 4 min from 8 rat adrenal glands. Since the tachyphylaxis to releasing effects of CA evoked by histamine from the perfused adrenal medulla of the cat (Smith and Robinson, 1970) and the rat (Lim *et al.*, 1993) has been found, in all subsequent experiments, 150 ug-dose only of histamine was used along with 50 ug ACh in order to compare each other in CA secretion. In the present work, histamine (150 ug) injected into an adrenal vein caused the increased CA secretion of 289±12 ng for 4 min from 8 rat adrenal glands. However, in the presence of 30 uM hydrocortisone which is preloaded for 20 min, histamine-induced CA secretory response amounted to 327±11 ng/4 min which is 113% of the control. There was a statistical significance ($P<0.05$) in histamine-induced CA release between before and after pretreatment with hydrocortisone. The present results are consistent to the previous reports (Choi *et al.*, 1993; 1995).

Fig. 1 shows that hydrocortisone increases the CA secretory response evoked by histamine in the rat adrenal glands.

The effects of heparin and forskolin on hydrocortisone-Induced potentiation of CA secretion evoked by histamine

Since it has been found that the H_2 receptors on chromaffin cells, like those in the tissue, are coupled to phospholipase C (Abdel-Latif, 1986), activation of these receptors leads to hydrolysis of inositol-containing phospholipids, the accumulation of inositol phosphate, and a rise in intracellular Ca^{2+} (Nobel *et al.*, 1986; Plevin and Boarder, 1988; Bunn *et al.*, 1990; Stauderman and Pruss,

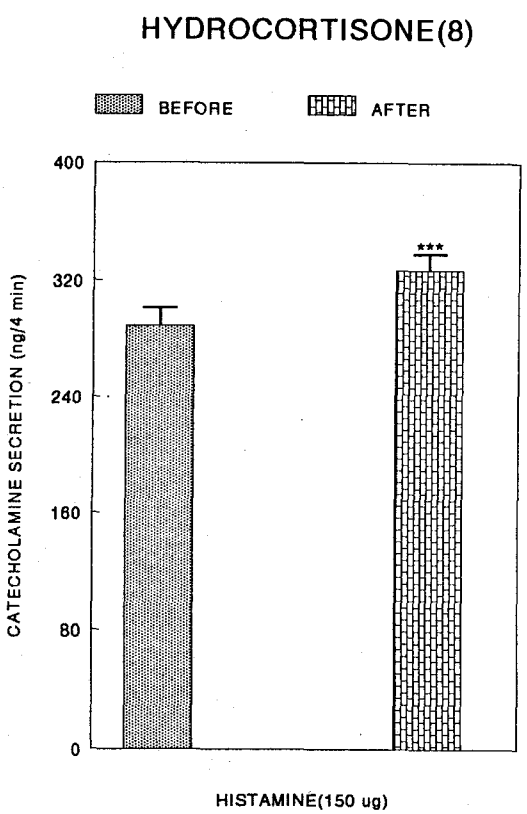

Fig. 1. Influence of hydrocortisone on histamine-stimulated catecholamine (CA) secretion from the isolated perfused rat adrenal glands. CA secretion was induced by a single injection of histamine (150 ug) after perfusion with normal Krebs solution for one hour prior to initiation of the expermental protocol. "BEFORE" and "AFTER" denote CA secretion evoked by histamine before and after preloading with 30 uM hydrocortisone for 20 min, respectively. Number in the parenthesis indicates number of experimental rat adrenal glands. Verti-cal bars represent the standard error of the mean (S. E.M.). Ordinate: the amounts of CA secreted from the adrenal gland in ng. Abscissa: histamine (150 ug). Statistical difference was obtained by comparing the control with the pretreated group. Each perfusate was collected for 4 minutes. ***: $P<0.01$

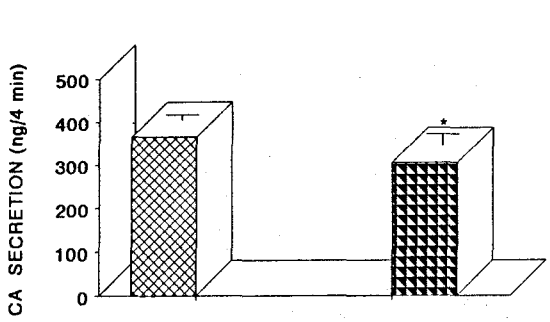

Fig. 2. Effect of hydrocortisone in the presence of heparin on histamine-evoked CA release. Histamine (150 ug) was induced before and after preloading with 30 uM hydrocortisone plus heparin (3.56 Units/ml) for 20 min. Other legends are the same as in Fig. 2. Cortisone: hydrocortisone, H: heparin. *: $P<0.05$

1990) it was exciting to examine the effect of heparin on hydrocortisone-induced potentiation of CA secretion evoked by histamine.

Only heparin (Ferris *et al.*, 1989; Ehrlich and Watras, 1988; Ghosh *et al.*, 1988) and IP_3 derivatives (Hirata *et al.*, 1989; Prestwich *et al.*, 1991) have been reported to affect the IP_3 receptor, in spite of the importance of IP_3 in various cellular functions, i.e., smooth muscle contractility, secretion, neuronal exciatability, the activation of inflammatory cells, and cell proliferation.

When given into an adrenal vein, a volume of 0. 05 ml, histamine (150 ug)-induced CA secretion in the presence of 30 uM hydrocortisone along with heparin (3.56 units/ml), which was perfused for 20 min, was significantly inhibited to 305 ± 26 ug/4min ($P<0.05$) as compared to the control secretory response of 365 ± 2 ng/4min in the presence of 30 uM hydrocortisone from 6 rat adrenal glands as shown in Fig 2.

Forskolin treatment has been demonstrated to increase intracellular cyclic AMP levels in chromaffin cell cultures by as much as 86 fold within 1 hour (Abou-Domia *et al.*, 1988; Morita *et al.*, 1987a). It was tried to test the effect of forskolin on hydrocortisone-induced potentiation of CA release evoked by histamine.

Histamine (150 ug)-evoked CA secretory response after preloading with Krebs solutin con-

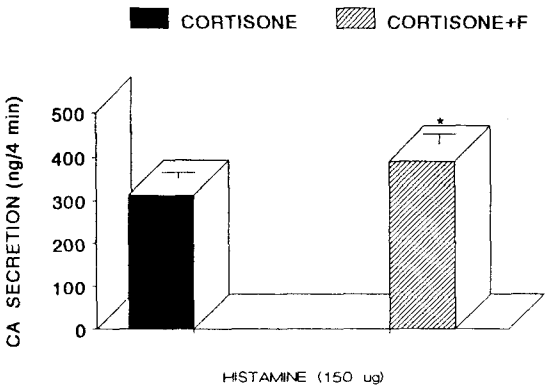

Fig. 3. Effect of hydrocortisone in the presence of forskolin on histamine-evoked CA release. Histamine (150 ug) was induced before and after preloading with 30 uM hydrocortisone plus 0.2 uM forskolin for 20 min. Other legends are the same as in Fig. 2. Cortisone: hydrocortisone, F: forskolin. *: $P<0.05$

taining 30 uM hydrocortisone along with 0.2 uM forskolin for 20 min was clearly enhanced to 390± 22 ng/4min, which is statistically significant as compared to the control release of 312±13 ng/4min in the presence of hydrocortisone effect only from 7 adrenal glands. Figure 3 illustrates that hydrocortisone-induced potentiation of CA secretion evoked by histamine is enhanced by the pretreatment with forskolin.

The effect of dexamethasone on histamine-evoked secretory response of CA from the isolated perfused rat adrenal gland

It has been shown that the synthetic glucocorticoid dexamethasone, which is the same as prednisolone except for an α-F in position 9 and α-CH3 in position 16 (9α-fluoro-16α-methylprednisolone), enhances histamine-evoked CA secretion from cultured bovine chromaffine cells (Choi *et al.*, 1995), it is likely of particular to examine the effect of dexamethasone on histamine-evoked CA secretory response from the perfused rat adrenal medulla.

In the presence of 30 uM dexamethasone which was preloaded for 20min, histamine (150 ug) produced the increased CA secretion to 409±34 ng/4min as compared to the corresponding control release of 354±36 ng/4min from 8 adrenal glands.

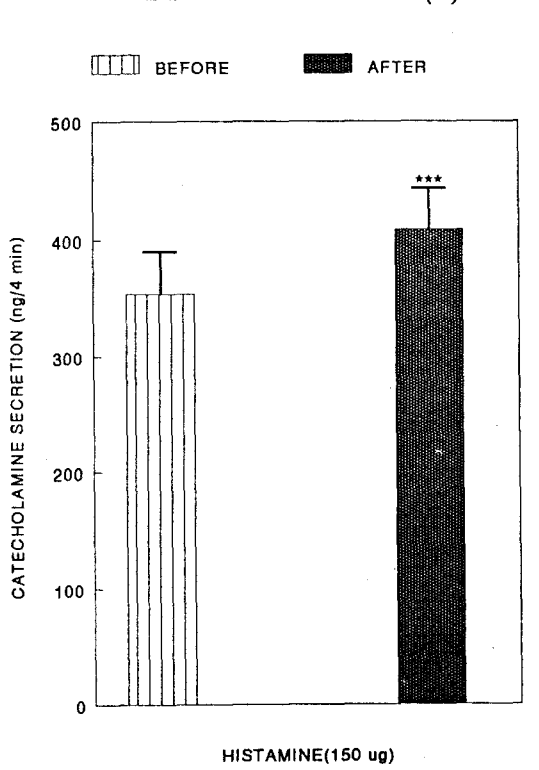

Fig. 4. Influence of dexamethasone on histamine-stimulated catecholamine (CA) secretion from the isolated perfused rat adrenal glands. CA secretion was induced by a single injection of histamine (150 ug) after perfusion with normal Krebs solution for one hour prior to initiation of the experimental protocol. "BEFORE" and "AFTER" denote CA secretion evoked by histamine before and after preloading with 30 uM dexamethasone for 20 min, respectively. Other legends are the same as in Fig. 2. ***: $P<0.01$

Figure 4 shows that pretreatment with dexamethasone potentiates the CA secretory effect evoked by histamine.

DISCUSSION

The present experimental results, taken together, suggest that hydrocortisone as well as a

synthetic glucocorticoid dexamethasone potentiates histamine-evoked CA secretion from the isolated perfused rat adrenal medulla, and that this enhancement appears to be mediated though the increased IP_3 and cyclic AMP in the rat adrenomedullary chromaffin cells. In support of this idea, Aikawa and his coworkers (1986), using a hypophysectomized, nephrectomized dog adrenal preparation, found that histamine stimulated both cortisol and aldosterone secretion. It has been also shown that the corticosterone secretion rate is closely dependent on the rate of flow of perfusion medium through the adrenal gland. Increasing the flow rate through the gland, either mechanically or by the use of a vasodilator, results in increased corticosterone secretion rates (Hinson *et al.*, 1986a). The present results are consistent to that of Choi and his coworkers (1995), in which the synthetic glucocorticoid dexamethasone enhanced histamine-evoked CA secretion from cultured bovine chormaffin cells. Moreover, glucocorticoids are known to enhance histamine-stimulated inositol phosphate accumulation in chromaffin cells (Choi *et al.*, 1993). Hinson and his colleagues (1989) have also found that histamine stimulates the release of glucocorticoids from the adrenal cortex. Glucocorticoids increase the levels of H_1 receptor mRNA in chromaffin cells (Choi *et al.*, 1995).

In the present investigation, the finding that hydrocortisone-induced potentiation of CA secretion evoked by histamine was significantly depressed by the pretreatment with heparin, which is known to be an antagonist of IP_3 receptors, strongly suggest that hydrocortisone may enhance another histamine receptor-mediated process, the activation of phospholipase C, resulting in the increased release of IP_3 into the chromaffin cells which enhances exocytosis of CA.

In support of this facts, it has been reported that glucocorticoids enhance the activation of phospholipase C in bovine chromaffin cells (Choi *et al.*, 1993). In addition, Elliott and Sapolsky (1993) have also found that glucocorticoids increase intracellular Ca^{2+} levels in hippocampal neurons. A similar effect of these hormones on intracellular Ca^{2+} levels in chromaffin cells might contribute to their effect on CA secretion.

Inositol phosphate accumulation is thought to be a direct function of receptor occupancy (Michell and Kirk, 1981); an increase in H_1 receptor expression might also underlie the effects of glucocorticoids on histamine-stimulated inositol phosphate accumulation.

In the present study, hydrocortisone-induced potentiation of CA secretory effect evoked by histamine was enhanced by preloading with forskolin in the perfused rat adrenal medulla. It is thought that glucocorticoids may potentiate forskolin-induced facilitation of Ca^{2+} influx into the chromaffin cells. In supprot of this finding, Sasakawa and his coworkers (1986a: 1986b) have shown that pretreatment of the cultured bovine chromaffin cells with phorbol esters can differentially regulate intracellular Ca^{2+} content rises induced by nicotine and high K^+ levels, and studies with PC 12 cells suggest that Ca^{2+} channels may be regulated by PKC activation (Harris *et al.*, 1988). Forkolin has also been shown to enhance agoinst-induced CA secretion and Ca^{2+} uptake in these cells (Morita *et al.*, 1987 a, b). Forskolin is known to be a diterpene that activates the catalytic unit of adenylate cyclase and elevates intracellular cyclic AMP levels (Seamon and Daly, 1981). Moreover, it has been also found that histamine increases cellular cyclic AMP levels in bovine chromaffin cells by three mechanism; by acting H_1 receptors, by acting on H_2 receptors, and by an interaction between H_1 and H_2 receptors (Marley *et al.*, 1991). The H_1 response does not require concomitant activation of H_2 receptors, is fully dependent on extracellular Ca^{2+}, does not depend on secreted chromaffin cell reduction, and is not due to reduced cyclic AMP degradation or export. The H_2 cyclic AMP response is the first functional response reported for H_2 receptors on chromaffin cells, is independent of Ca^{2+}, is not due to reduced cyclic AMP export or degradation, and is likely to be mediated via a direct action through Gs (Marley *et al.*, 1991). The present results that synthetic glucocorticoids dexamethasone also enhances histamine-evoked CA secretory response suggest that glucocorticoids and CA may interact in multiple pathway in their actixon and secretion.

Generally, chromaffin cells apparently have typical glucocorticoid receptors (Kelner and Pollard, 1985; Betito *et al.*, 1992). Because glucocorticoid levels in the adrenal gland have been reported to be up to 100 times higher than those in the

peripheral circulation (Jones *et al.*, 1977), glucocorticoid receptors in chromaffin cells are thought to be largely activated even under resting conditions.

However, the present results do not rule out the possibility that short-term dynamic increase in glucocorticoids to high levels, such as encountered by the adrenal medulla during an acute stress, can cause increases in phenylethanolamine-N-methyltransferase activity, while lower (basal) levels of glucocorticoids function to maintain steady-state phenylethanolamine-N-methyltransferase levels on a long-term basis as previously reported by Betito and his coworkers (1993).

Prolonged stimulation by glucocorticoids might result in a coordinate increase in the expression of H_1-receptors and of phenylethanolamine-N-methyltransferase in the noradrenergic chromaffin cells (Choi *et al.*, 1995); these changes might lead to large increase in epinephrine storage and in histamine-evoked epinephrine secretion.

Anayway, in the present experiment, it is felt that glucocorticoids may play a physiological role in modulating the histamine-evoked CA release from the rat adrenomedullary chromaffin cells.

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=국문초록=

Hydrocortisone이 적출 흰쥐 부신에서 Histamine의 카테콜아민 분비작용에 미치는 영향

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본 연구에서는 Hydrocortisone이 적출 흰쥐 관류 부신에서 histamine에 의한 카테콜아민(CA) 분비작용에 대한 영향을 관찰하고자 시도하였으며, 얻어진 연구 결과는 다음과 같다.

Histamine (150 ug)은 부신정맥내로 주입시 현저한 CA 분비작용을 나타내었다. 이러한 histamine의 CA 분비작용은 천연 글루코콜티코이드인 hydrocortisone (30 uM)이나 합성 글루코콜티코이드인 dexamethasone (30 uM)을 각각 20분간 전처치한 후에 현저히 증강되었다.

Hydrocortisone에 의한 histamine의 CA 분비의 증강작용은 inositol trisphosphate 수용체 억제제인 heparin (3.56 U/ml)으로 전처치시 뚜렷이 억제되었으나 adenylate cyclase의 강력한 활성화제인 forskolin (0.2 uM)으로 전처치시 현저히 강화되었다.

이상과 같은 실험 결과를 종합한 결과, hydrocortisone (글루코콜티코이드)은 흰쥐 적출관류 부신에서 histamine의 CA 유리작용을 증강시킬 수 있으며, 이는 부신수질 크롬친화성 세포에서 inositol phosphate 뿐만 아니라 cyclic AMP의 축적작용과 관련성이 있는것으로 사료된다.