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Effect of Osmolality on *in vitro* Basal and Angiotensin II-Stimulated Aldosterone Secretion by Bovine Adrenal Glomerulosa Cells[1]

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= Abstract =We observed the effect of changes in Na concentration and the associated changes in the osmolality of incubation media on aldosterone secretion by acutely dispersed isolated bovine glomerulosa cells. We also examined whether this effect is due to changes in Na concentration or to changes in osmolality.

When we increased Na concentration and osmolality by addition of NaCl, basal aldosterone secretion was inversely related to the Na concentration and osmolality of the incubation medium. However angiotensin II stimulation increased aldosterone secretion in Low and Normal Na (130 and 149 mM) and osmolality (261 and 297 Osm) media more than in Lower Na (103 mM) and osmolality (210 mOsm) medium.

In addition, when osmolality of the medium was increased by addition of NaCl, sucrose and glucose, basal aldosterone secretion was inhibited to a similar extent and increment in aldosterone above basal levels by angiotensin II stimulation was similar, whereas urea addition had no effect.

From these results, we conclude that changes in Na concentration affect aldosterone secretion by a mechanism sensitive to the osmolality rather than to the Na concentration. Moreover, since increased osmolality of the incubation medium caused by urea addition has no effect on basal aldosterone levels and increment in aldosterone above basal levels by angiotensin II stimulation, changes in intracellular volume or composition appear to be an important modulator of aldosterone secretion.

Key words: ***Glomerulosa cells, Na concentration, Osmolality, Basal, Angiotensin II (AII), Aldosterone***

INTRODUCTION

It is well recognized that aldosterone secretion by adrenal glomerulosa cells is regulated by three well defined systems, such as renin-angiotensin system, potassium ion concentration and adrenocorticotropin(ACTH) (William and Dulhy 1987).

In addition, the unique part of the regulation of aldosterone secretion is the impact of prior dietary sodium and potassium intake on the respone of the adrenal gland to its secretagogues (William and Dulhy 1987). Dietary sodium restriction markedly enhances adrenal aldosterone secretory response to angiotensin II (AII), minimally so to potassium and ACTH without significant changes in plasma sodium concentration (William *et al.* 1976; Carley *et al.* 1978).

While it is generally believed that small changes in extracellular sodium concentration do not influence aldosterone secretion (Schneider *et al.* 1984; Enyedi and Spät 1981) there is some evidence that changes in plasma sodium concentration may induce direct alterations in aldosterone secretion (Tuck *et al.* 1974;

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Childers and Schneider 1981).

On the other hand, in in vitro experiments using glomerulosa cell preparation, there were no consistent effects of sodium chloride concentration on aldosterone secretion (Saruta *et al.* 1972; Lobo *et al.* 1978; Enyedi and Spät 1981).

Recent studies by Schneider *et al.* (1984, 1985, 1986) and Taylor *et al.* (1987) showed that aldosterone secretion by the isolated, arterially perfused canine adrenal gland or primary cultures of bovine adrenal glomerulosa cells varies inversely with small chanes in sodium chloride concentration in the perfusion or incubation medium by mechanisms that are dependent on osmotic rather than ionic changes.

The purpose of this study is to observe effects of changes in sodium concentration in incubation medium on in vitro aldosterone secretion by acutely dispersed isolated glomerulosa cells, and to examine whether this effect is due to changes in sodium concentration or to changes in osmolality.

MATERIALS AND METHODS

Glomerulosa cells preparation

Glomerulosa cells were prepared from bovine adrenal gland by collagenase digestion and mechanical dispersion according to Elliott's methods with slight modification (Elliott and Goodfriend 1981). In brief, fresh bovine adrenal glands were obtained in cold buffer solution at the slaughter house. This buffer contained 137 mM NaCl, 3.6 mM KCl, 1 mM $MgSO_4$, 1.25 mM $CaCl_2$, 20 mM Hepes (pH 7.4).

In the laboratory, each adrenal gland was freed of most of its surrounding tissues, and prepared by peeling off the capsule, bisecting and scraping away the medulla and the zonas fasciculata and reticularies. Tissue was cut into small pieces and placed into a vial containing 1.5 ml of a modified Krebs-Ringer bicarbonate solution containing 0.1% bovine serum albumin(BSA), 10 mM glucose, L-glutamin, essential and non-essential amino acid mixtures with the potassium concentration adjusted to 3.5 mM (KRBGA).

Modified Krebs-Ringer Bicarbonate solution contained 117 mM NaCl, 2.5 mM KCl, 1 mM KH_2PO_4, 1.25 mM $CaCl_2$, 1 mM $MgSO_4$ and 24 mM $NaHCO_3$. An 8.5 ml aliquot of crude collagenase solution was added to each vial (total 10 ml enzyme solution: 3.5 mg collagenase/ml for two adrenal glands in each vial). Tissue in each vial was incubated at 37°C in a Dubnoff metabolic shaking incubator (100 rotations/min) for one hour under a stream of 95% O_2/5% CO_2 and the contents of each vial were mixed at 30 minute intervals by pipetting up and down 30-35 times through a wide-mouth 5 ml pipette tip. At the end of one hour, the digested tissue was filtered through nylon mesh into cornical tube and centrifuged at 900 r.p.m. for ten minutes, the supernatant was discarded and the pellet was washed twice with sufficient volume of KRBGA.

Cells were counted in a hemocytometer and cell viability was monitored by observing exclusion of trypan blue dye. Over 90% of glomerulosa cells excluded trypan blue in this cell preparation.

Experimental procedures

Cells were incubated under one of the four different media: 1) Lower Na and osmolality medium (102-104 mM, 209-211 mOsm) 2) Low osmolality medium (259-261 mOsm) 3) Normal osmolality medium (295-300 mOsm), and 4) High osmolality medium (335-340 mOsm). These media were prepared by adding the appropriate quantity of NaCl, sucrose, urea, choline chloride and glucose to an aliquot of Lower Na and osmolality medium.

Lower Na and osmolality medium contained 75 mM-80 mM NaCl, 2.5 mM KCl, 1 mM KH_2PO_4, 1.25 mM $CaCl_2$, 1 mM $MgSO_4$, 24 mM $NaHCO_3$, 10 mM glucose, L-glutamin, essential and non-essential amino acid mixtures and 0.1% BSA (Lower Na and osmolality KRBGA). Thus all media used in a given experiment came from the same parent solution.

Angiotensin II(5-isoleucine AII, Beckman Inc.) solution was prepared daily by diluting aliquots of frozen stock solutions with Lower Na and osmolality medium, and the same volume of Lower Na and osmolality medium was added to incubation tubes for basal aldosterone secretion. After glomeurlosa cells were prepared, cell suspension was preincubated in KRBGA for one hour at 37°C under a stream of 95% O_2/5% CO_2. The tubes were again centrifuged and the pellets were washed once with Lower Na and osmolality medium. The final cell suspension

was made by mixing cell pellets with the desired volume of Lower Na and osmolality medium.

An aliquot of the cell suspension was pipetted into tubes containing 0.05 ml of AII solution or the same volume of Lower Na and osmolality medium, and the appropriate quantity of NaCl, sucrose, urea, choline chloride and glucose (total incubation volume $\fallingdotseq$ 0.5 ml). The tubes were incubated at 37°C in a Dubnoff metabolic shaking incubator for 90 minutes under a stream of 95% O_2/5% CO_2.

At the end of incubation the tubes were centrifuged and supernatants were stored at −20°C until assayed for aldosterone.

Analytic methods

The sodium and potassium concentrations were measured by flame photometry and osmolality was measured by freezing point depression. Aldosterone level was measured in duplicate directly, using commercial RIA kit (Diagnostic products; Los Angeles CA).

Data analysis

All values in the figures are presented as Mean ± 1 S.E.M. Statistical analysis was performed using linear regression analysis and one-way or two-way analysis of variance (ANOVA) and multiple comparison tests between groups were done using Scheffe's method. In all tests p-value below 0.05 was regarded as significant. The interexperiment variation was minimized by determining absolute levels (ng/10^6 cells), dividing absolute levels by basal levels, AII-stimulated levels and increment in aldosterone above basal levels by AII stimulation in Lower Na and osmolality medium for each experiment and multiplying by 100 to obtain % of basal, AII-stimulated levels and increment in Lower Na and osmolality medium, e.g.

(1) Basal levels or AII-stimulated levels in other media

$$\frac{\text{Basal or AII-stimulated levels in Lower Na and osmolality medium}}{\text{in other media}} \times 100 = \%\ \text{of basal or AII-stimulated levels in Lower Na and osmolality medium}$$

(2) AII-stimulated aldosterone levels minus basal levels in other media

$$\frac{\text{AII-stimulated aldosterone levels minus basal levels in Lower Na and osmolality medium}}{\text{Lower Na and osmolality medium}} \times 100 = \%\ \text{of increment in aldosterone above basal levels in Lower Na and osmolality medium}$$

RESULTS

In this experiment, 10^{-7}M concentration of angiotensin II was used for stimulation of aldosterone secretion. aldosterone secretion by isolated bovine adrenal cells in KRBGA was maximally stimulated as concentration of angiotensin II reached 10^{-7}M (data not shown).

Effects of different Na concentrations or osmolalities in the media on basal and angiotensin II-stimulated aldosterone secretion are shown in Fig. 1.

There was a remarkable decrease in basal aldosterone secretion as the sodium concentration and osmolality was increased from Lower to High Na and osmolality medium. Correlation between basal aldosterone secretion and Na concentration or osmolality is highly significant ($r = -0.91$, -0.90, $p<0.001$).

There was nc significant difference in angiotensin II-stimulated aldosterone secretion between Lower, Low and Normal Na and osmolality media ($p>0.1$), but a significant decrease in angiotensin II-stimulated aldosterone secretion was observed in High Na and osmolality medium ($p<0.05$).

In comparison with Lower Na and osmolality medium, increment in aldosterone above basal levels by angiotensin II stimulation was significantly high in Low and Normal Na and osmolality media ($p<0.01$) even though there was no difference in total angiotensin II-stimulated aldosterone secretion between them.

Fig. 2 depicts a comparison of the effects on basal aldosterone secretion of increasing osmolality by the addition of Nacl, sucrose, and urea to Lower Na and osmolality medium.

A similar inhibition of basal aldosterone secretion occurred when media osmolality was increased by addition of NaCl and sucrose. In contrast, basal aldosterone secretion was not affected when media osmolality was increased by addition of a membrane permeable solute,

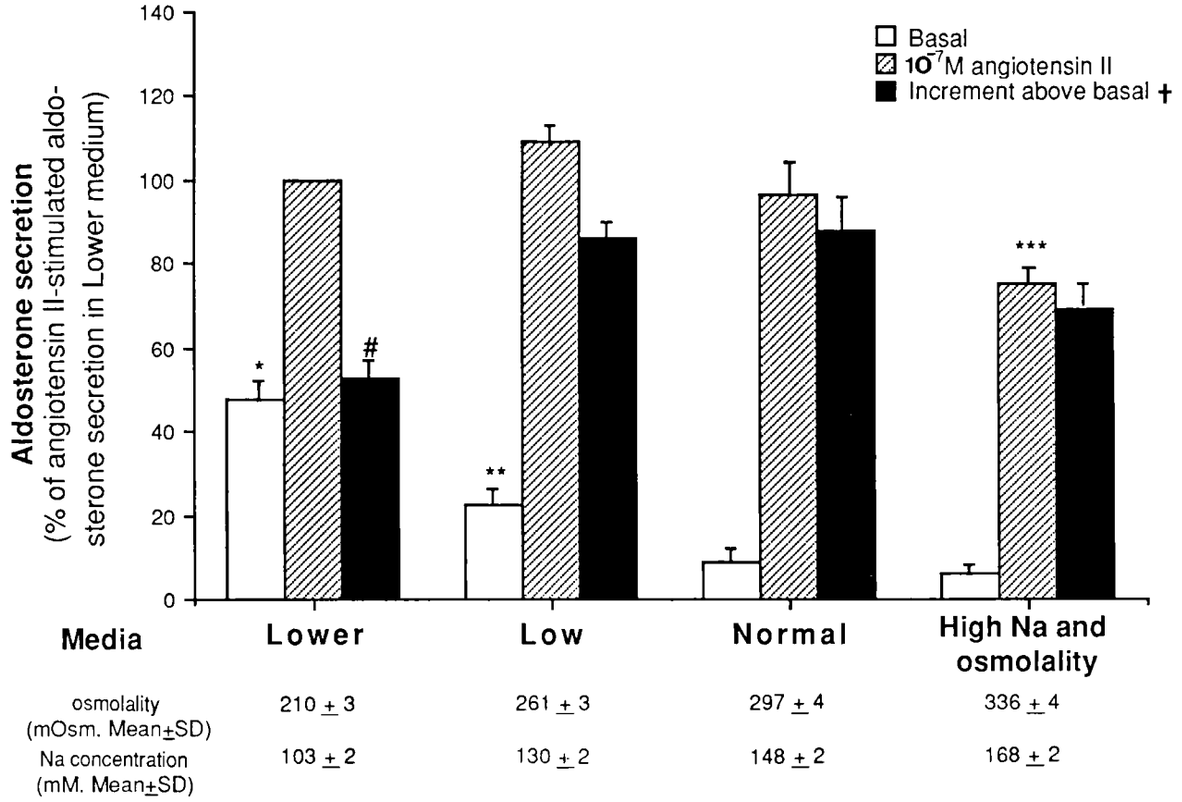

Fig. 1. Effect on basal and angiotensin II(10^{-7}M)-stimulated aldosterone secretion of increasing Na and osmolality by addition of NaCl to Lower Na (103 mM) and osmolality (210 mOsm) medium.

Each bar represents the mean ± 1 S.E.M. of 7 experiments. All data are converted to % of angiotensin II(10^{-7}M)-stimulated aldosterone secretion in Lower Na and osmolality medium (angiotensin II-stimulated aldosterone secretion in Lower Na and osmolality medium = 100%)

†Increment in aldosterone above basal level is determined by substracting basal level from angiotensin II-stimulated aldosterone level.

*$p<0.01$ vs. in Low, Normal and High media

**$p<0.01$ vs. in Normal and High media

***$p<0.01$ vs. in Lower and Low media, $p<0.05$ vs. in Normal Medium

#$p<0.01$ vs. in Low and Normal media

urea.

In Fig. 3, increment in aldosterone above basal levels by angiotensin II stimulation is greater with added NaCl than with added urea, but the effect of sucrose was not different from those of NaCl and urea. When medium osmolality was increased by addition of urea, increment in aldosterone above basal levels by angiotensin II stimulation was not affected at any osmolality, as in basal aldosterone secretion (Fig. 2).

Fig. 4 shows a comparison of the effect on basal aldosterone secretion of increasing osmolality by addition of ionic solutes, NaCl and choline Cl, and a nonionic solute, glucose.

Basal aldosterone secretion was inhibited to a similar extent when the medium osmolality was increased by the addition of NaCl and glucose, but at any given osmolality, basal aldosterone secretion was greater with added choline Cl than with added NaCl and glucose.

In Fig. 5 there were no significant differences in increment in aldosterone above basal levels by angiotensin II stimulation when medium osmolality was made iso-osmotic by addition of NaCl, choline Cl and glucose. Owing to the number of experiments ($n=2-3$) and large deviation of data, clear results could not be elucidated.

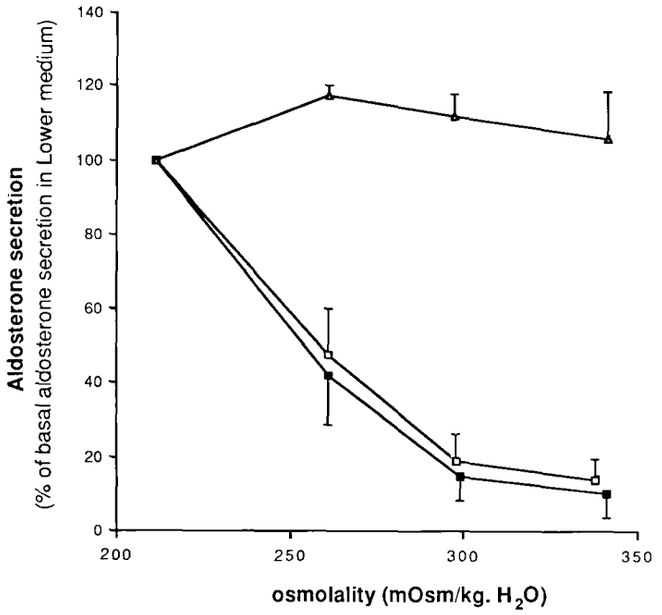

Fig. 2. Effect on basal aldosterone secretion of increasing osmolality by addition of NaCl (□-□), sucrose(■-■) and urea (△-△) to Lower Na (104 mM) and osmolality (211 mOsm) medium.
Each point represents the mean±I.S.E.M. of 3-4 experiments. All data are cenverted to % of basal aldosterone secretion in Lower Na and osmolality medium (basal aldosterone secretion in Lower Na and osmolality medium =100%).
Addition of urea did not have significant effect on basal aldosterone secretion when tested with one-way ANOVA ($p>0.1$) and the effect of urea was different from those of NaCl and sucrose when tested with two-way ANOVA ($p<0.001$).

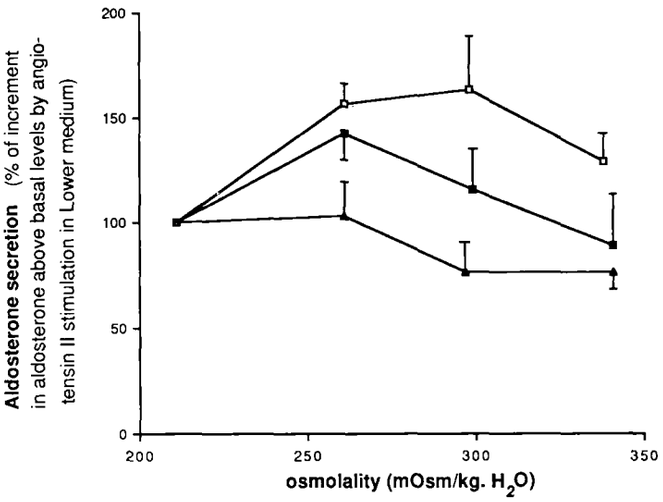

Fig. 3. Effect on angiotensin II(10^{-7}M)-stimulated aldosterone secretion of increasing osmolality by addition of NaCl(□-□), sucrose (■-■) and urea (△-△) to Lower Na(104 mM) and osmolality (211 mOsm) medium. Each point represents the mean±I.S.E.M. of 3-4 experiments.
All data are converted to % of increment in aldosterone above basal levels by angiotensin II(10^{-7}M) stimulation in Lower Na and osmolality medium (increment in Lower Na and osmolality medium=100%). Addition of urea did not have significant effect on angiotensin II-stimulated aldosterone secretion when tested with one-way ANOVA ($p>0.1$) and the effects of urea and NaCl were different when tested with two-way ANOVA ($p<0.001$).

DISCUSSION

The present study shows an inverse correlation between basal aldosterone secretion and Na concentration or osmolality of the incubation medium. Furthermore this study demonstrates that changes in Na concentration from 102 mM to 168 mM appear to act by a mechanism sensitive to osmolality rather than to the concentration of Na or Cl ions.

In this study, the low limit of Na concentration and osmolality was arbitrarily decided as 102-104 mM and 209-212 mOsm respectively, owing to possibility that cells may be lysed in an incubation medium with a sodium concentration and osmolality less than 100 mM and 200 mOsm, respectively.

Saruta *et al.* (1972) reported that decreased sodium concentration stimulated aldosterone synthesis of outer bovine adrenal slice. Lobo *et al.* (1978) have demonstrated that small decreases in NaCl concentration without changes in osmolality stimulated basal aldosterone secretion, but at different Na concentrations, addition of AII (1 μg/ml) to glomerulosa cells increased aldosterone secretion to similar levels. Thus they concluded that Na concentrations did not affect the response of the glomerulosa cells to AII. Enyedi and Spät (1981) failed to find any effect of Na concentration on AII-stimulated aldosterone secretion.

The results cited above are consistent with

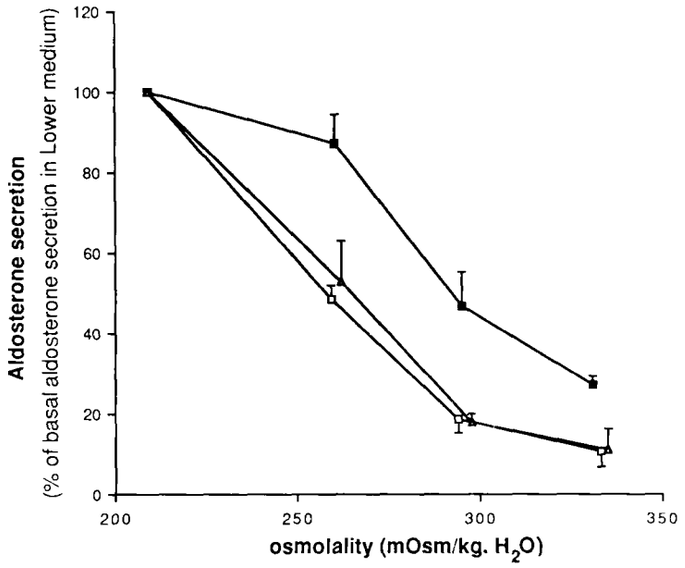

Fig. 4. Effect on basal aldosterone secretion of increasing osmolality by addition of ionic solutes, NaCl(□-□), and choline Cl(■-■), and nonionic solute, glucose(△-△) to Lower Na(102 mM) and osmolality(209 mOsm)) medium.
Each point represents the Mean±I.S.E.M. of 2-3 experiments. All data are converted to % of basal aldosterone secretion in Lower Na and osmolality medium (basal aldosterone secretion in Lower Na and osmolality medium =100%). The effet of choline Cl was different from those of NaCl and glucose when tested with two-way ANOVA ($p<0.001$, $p<0.001$ respectively)

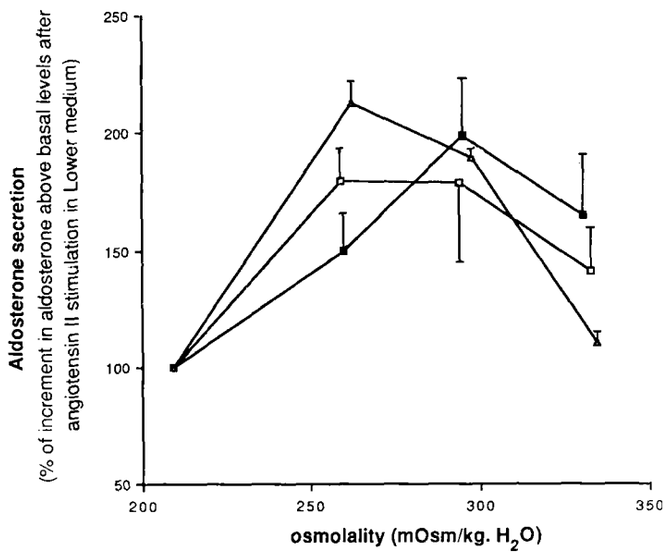

Fig. 5. Effect on angiotensin II(10^{-7}M)-stimulated aldosterone secretion of increasing osmolality by addition of ionic solutes, NaCl(□-□) and choline Cl(■-■), and nonionic solute, glucose(△-△) to Lower Na(102 mM) and osmolality(209 mOsm) medium.
Each point represents the mean±I.S.E.M. of 2-3 experiments. All data are converted to % of increment in aldosterone above basal level by angiotensin II stimulation in Lower Na and osmolality medium (increment in Lower Na and osmolality medium=100%). There were no significant differences between effects of NaCl, choline Cl and glucose when tested with two-way ANOVA ($p>0.1$)

those of the present study, but the first two investigators postulated that Na concentration rather than osmolality of incubation medium affected basal aldosterone secretion.

In contrast to the studies cited above, Schneider *et al.* (1984, 1985, 1986) and Taylor *et al.* (1987) reported that AII-stimulated aldosterone secretion by the isolated, arterially perfused canine adrenal gland or primary cultures of bovine adrenal glomerulosa cells varies inversely with NaCl concentration by mechanisms that are dependent on changes of osmolality rather than changes of NaCl concentration, while basal aldosterone secretion was unaffected.

The reason for this discrepancy is not readily apparent, but may be related to differences in species and isolation procedures, and consequently to the responsiveness of glomerulosa cells (rat, dog vs. calf, in vivo vs. in vitro, or acutely dispersed cells vs. cultured cells), or perhaps to the concentration of AII employed (submaximal vs. maximal dose).

Our findings that NaCl, sucrose and glucose were equally effective as osmotic particles demonstrated that osmolality rather than NaCl concentration of the incubation medium affects aldosterone secretion and are consistent with those of studies by Schneider *et al.* (1986).

Labella *et al.* (1975) reported that release of hormones from bovine anterior pituitary tissue in vitro was inversely related to the osmolarity of the incubation medium, and that the sensitivity of the response to osmotic changes suggests a possible role of body osmolarity in the regulation of adrenohypophysial secretion. In contrast, Chen *et al.* (1987) reported that hyperosmolality stimulated parathyroid hormone secretion in dispersed parathyroid cells. These studies suggest

that the effect of osmolality on hormone secretion may occur in a different manner.

Our findings that in comparison with normo-osmotic or hyperosmotic media, basal aldosterone was increased and increment in aldosterone above basal levels by AII stimulation was decreased in hypoosmotic media while total AII-stimulated aldosterone secretion was similar between them (Fig. 1) suggest that aldosterone secretion appears to be already stimulated in hypoosmotic media presumably by mechanism similar to that of AII on aldosterone secretion.

The precise cellular mechanism responsible for translating changes in osmolality of incubation media to changes in aldosterone secretion can not be determined from this study. Based on our findings that urea which is permeable across most cell membranes was not an effective modulator of basal and AII-stimulated aldosterone secretion (Fig. 2,3), it appears that a change in intracellular osmolality is not responsible. Rather a change in cellular volume or intracellular composition may be involved.

Since AII is thought to stimulate aldosterone secretion, in part, by increasing the intracellular calcium concentration (Capponi *et al.* 1984; Braley *et al.* 1986), changes in osmolality may affect aldosterone secretion by changing the intracellular calcium concentration. However Rink *et al.* (1983) failed to demonstrate increase in intracellular calcium concentration after hypotonic dilution of lymphocytes suspension. Further studies evaluating the mechanism of osmolality effects on aldosterone secretion will be needed.

In the present study, at any given osmolality, basal aldosterone secretion, not AII-stimulated aldosterone secretion, was greater with added ionic solute, choline Cl than with ionic solute, NaCl and nonionic solute, glucose (Fig. 4). One possible explanation may be considered for the more effective stimulation of basal aldosterone secretion occurring when osmolality was increased by addition of choline Cl. Extracellular choline is a constituent of acetylcholine and may act as an acetylcholine analogue (Lamber *et al.* 1974), which has been found to stimulate aldosterone secretion by isolated bovine glomerulosa cells through action similar to that of AII on glomerulosa cells (Kojima *et al.* 1986).

It was also reported that choline, like acetylcholine can participate in phosphatidylinositol turnover (Schacht and Agranoff 1972, 1974) which is regarded as the main membrane signal transduction mechanism utilized by AII in stimulating aldosterone secretion (Hunyady *et al.* 1982).

In conclusion, the present results clearly demonstrated that glomerulosa cells are sensitive to changes in osmolality of incubation medium, supporting the contention that plasma osmolality is an important modulator of aldosterone production in vivo.

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= 국문초록 =

Osmolality가 소부신 Glomerulosa Cells에서의 기저 및 Angiotension II 자극 알도스테론 분비에 미치는 영향

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김성연 · 이홍규 · 고창순 · 민헌기

저자들은 소부신 glomerulosa cells을 이용하여 osmolality 변동을 동반한 배양배지의 Na농도 변동이 알도스테론 분비에 미치는 효과를 관찰하였으며 이 증가가 Na농도변동 그 자체 때문인지 혹은 osmolality 변동 때문인지를 알아보고자 하였다. NaCl를 가하여 Na농도와 osmolality를 증가시켰을때 기저 알도스테론 분비는 배양배지의 Na농도 및 osmolality와 역관계를 보였다. 그러나 angiotension II 자극은 매우 낮은 Na (103 mM) 및 osmolality (210 mOsm)보다 좀더 높은 혹은 정상 Na(130, 149 mM) 및 osmolality(261, 297 mOsm)의 배양배지에서 알도스테론 분비를 더 증가시켰다. 또한 배양배지의 osmolality를 NaCl, sucrose, glucose 등을 가하여 증가시켰을 때 기저 알도스테론 분비는 같은 정도로 억제되었으며 angiotensin II 자극에 의한 알도스테론 분비는 비슷하게 증가하였다. 그러나 urea를 가하여 osmolality를 증가시켰을 때는 효과가 없었다.

이러한 결과에서 배양배지의 Na농도의 변동은 Na농도보다 osmolality 변동에 의해 알도스테론 분비에 영향을 미침을 알 수 있었다. 더우기 urea를 가하여 배양배지의 osmolality증가에도 불구하고 기저 및 angiotensin II 자극 알도스테론 분비는 변동이 없어 세포용적 혹은 세포구성성분의 변동이 알도스테론 분비의 중요한 조절인자 인것 같다.