Regulation of the Angiotensinogen Gene by Estrogens in Rat Liver and Different Brain Regions (43624)

LY Q. HONG-BROWN AND C. F. DESCHEPPER[1]
Department of Physiology, University of California at San Francisco, San Francisco, California 94143-0444

Abstract. **Estrogens regulate the production of angiotensinogen (AOG) in liver and other tissues. However, evidence suggests that the effect is tissue specific and that it may depend on a variety of factors. We have tested the effects of ethynylestradiol (EE) on liver AOG mRNA and plasma AOG in intact male and ovariectomized female rats, as well as in hypophysectomized male rats. EE stimulated both variables to a comparable extent and in a dose-dependent manner. However, its effect on plasma AOG was significantly higher in female than in male rats. In addition, there was no response in hypophysectomized male rats; however, responsiveness was restored by pretreatment of the animals with prolactin. AOG mRNA concentration was also affected by EE in brain, but there were striking time- and region-specific differences. These results indicate that cell-specific factors also modulate the response of the AOG gene to EE in extrahepatic tissues.** [P.S.E.B.M. 1993, Vol 203]

Angiotensinogen (AOG) is the glycoprotein precursor of the angiotensin peptides. It is cleaved by renin to yield the decapeptide angiotensin I; angiotensin-converting enzyme then removes a dipeptide from the C-terminal end of angiotensin I to form the physiologically active octapeptide angiotensin II (Ang II). Both renin and AOG are rate-limiting factors in the generation of Ang II (1–3). *In vivo*, the concentration of Ang II in plasma is primarily controlled by renin (4). However, it is clear that AOG also plays an important role, since injections of monoclonal antibodies against AOG result in a drop in blood pressure (5), and transgenic mice carrying the rat angiotensinogen gene become hypertensive and display elevated levels of plasma Ang II (6). Liver is the tissue where AOG is produced most abundantly. However, it is produced in other tissues as well, including brain and adipose tissue (4, 7). Although the significance of extrahepatic production of AOG is not entirely clear, recent experiments in transgenic mice indicate that these sites may be important in the expression of the hypertensive phenotype (6).

A variety of hormones, including glucocorticoids, thyroid hormones, sex steroids, and interleukins, regulate the expression of the angiotensinogen gene (for reviews, see Refs. 4, 8–10). The effect of estrogens is of particular interest. Thus, a rise in plasma AOG has been observed in humans treated with medications that contain estrogens (11–15). In many of these cases, this effect is accompanied by elevated plasma levels of renin and Ang II (11–13, 15), along with an Ang II-dependent reduction in renal blood flow (12). Additional studies have been performed in rats (16–20). Yet, the mechanisms of action of estrogens on the production of AOG have been studied in less detail than those of other hormones. In particular, there is evidence that the effects of estrogens may be partly dependent on the endocrine status of the animals. For instance, it has been reported that estrogens do not stimulate liver AOG in hypophysectomized (HYPOX) rats (21–23). This suggests that the effect of estrogens on AOG is partly dependent on the presence of other pituitary hormones. However, the identity of such hormones has not been elucidated yet.

Many of the hormones that regulate liver AOG can also affect its production in extrahepatic tissues. However, the effect is often tissue specific as well (7, 24–26).

[1] To whom correspondence and requests for reprints should be addressed at Clinical Research Institute of Montreal, 110, Pine Avenue West, Montreal, PQ H2W 1R7 Canada.

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Some authors have reported differences in the effects of estrogens on AOG mRNA in various tissues (27–29). However, there are also discrepancies in the results reported in these various studies, in particular concerning the effects of estrogens on brain AOG mRNA. Such discrepancies may result from differences in sampling protocols, although this has not been tested yet.

To investigate the actions of estrogens in further detail, we have tested the effects of ethynylestradiol (EE) on both liver AOG mRNA and plasma AOG in intact male and female rats, as well as in HYPOX male rats. Different time points and doses of EE were tested. In addition, we have investigated the effects of EE on AOG mRNA concentration in different brain regions, looking at different time points after the injection.

Materials and Methods

Experimental Treatments. Male and female Sprague-Dawley rats weighing 180–220 g (Bantin and Kingman, Fremont, CA) were housed individually and maintained at 20–22°C in a 14:10 photoperiod environment. Hypophysectomized rats were purchased from Charles Rivers (Wilmington, MA). A bilateral ovariectomy was performed on the female rats 7 days before steroid treatments.

Hormonal treatments were performed as follows. Groups of six rats received single subcutaneous injections of 17α-ethynylestradiol (EE; 0.2 or 3 mg/kg body wt; dissolved in polypropylene glycol diluted with saline). Control animals received subcutaneous injections of saline. In certain groups of animals, hypothyroidism was induced by addition of propylthiouracil (0.5 g/liter) to the drinking water for 10 days. As published previously, this treatment induced a marked decrease in circulating levels of triiodothyronine and thyroxine (25). Purified ovine prolactin (PRL; gift of Harold Papkoff) was dissolved in saline and administered to rats (1 mg/day sc) for 3 consecutive days before administration of EE (30). The animals were sacrificed by decapitation at various time after the injection of EE. Five ml of trunk blood were collected in chilled tubes containing 0.5 ml of 0.3 *M* EDTA. Plasma was obtained by centrifugation at 4°C. Cerebellum, brain stem (essentially pons and medulla), and diencephalon were dissected from rat brains as described previously (31). All tissues were immediately frozen in liquid nitrogen and stored at -80°C until further processed. Experimental groups contained no more than six animals on any particular day. However, results from replication experiments were sometimes pooled; in consequence, the final *n* is sometimes greater than 6 in presented data sets.

Analytical Procedures. Plasma AOG was determined by incubating the samples with excess porcine renin and measuring by radioimmunoassay the angiotensin I that was generated, as described previously (26). Total RNA was prepared from tissue by disruption in buffer containing 5 *M* guanidine monothiocyanate and subsequent ultracentrifugation on a cushion of 5.7 *M* cesium chloride. Ten μg of each sample were analyzed by Northern blot, as published previously (25). For quantitation, the intensity of the autoradiogram bands (expressed as arbitrary optical density units) was determined by scanning the film with an Ultrascan XL laser densitometer (LKB Bromma, Northwich, Cheshire, England). To verify that equal amounts of RNA were present in each sample, the 18S and 28S ribosomal bands were visualized by ethidium bromide staining of the gel and photographed. The negative image of the picture was scanned by densitometry, as described above.

All data are expressed as means ± SE. In some experiments, all values were divided by the mean value of the control group, and expressed as percentage of control. Statistical analyses were performed on an IBM-compatible computer, using the NCSS software (written by Dr. J. L. Hintze, Kaysville, UT). Significant differences between groups were tested by one-way analysis of variance followed by Newman-Keuls multiple comparison post hoc tests, using $P < 0.05$.

Results

In preliminary experiments, we measured plasma AOG and liver AOG mRNA concentration in intact male rats at different times after a single injection of EE (3 mg/kg body wt). Four hours after the injection, liver AOG mRNA was statistically higher than control; peak levels were reached by 8 hr and maintained at the same level at 24 hr (Fig. 1). Likewise, there was a progressive rise over time of plasma AOG, although it lagged slightly behind the AOG mRNA response. Thus, plasma AOG was statistically higher than control at the 8-hr time point, and reached maximal levels at 24 hr. At that time, the amplitudes of the two responses (plasma AOG and liver AOG mRNA) were similar,

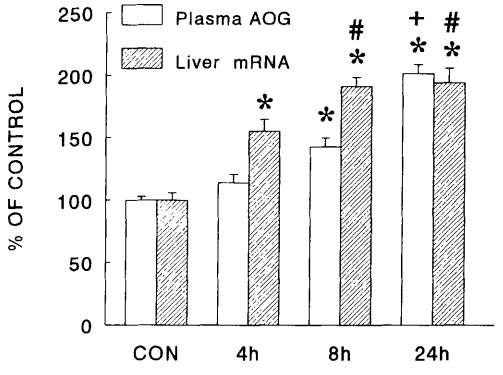

Figure 1. Time course of the effect of EE on plasma AOG and AOG liver mRNA. Male rats received a subcutaneous injection of EE (3 mg/kg body wt) and were sacrificed at various times after the injection. Results are means ± SE; $n = 18$ in control groups, and $n = 10$–12 in EE-treated groups. $^{*}P < 0.05$ vs control; $^{\#}P < 0.05$ vs the 4-hr time point; $^{+}P < 0.05$ vs the 8-hr time point.

and no statistical difference was detected between the two.

In subsequent experiments, we examined the effects of two different doses of EE on plasma AOG and liver AOG mRNA concentration in either intact male or ovariectomized (OVX) female rats (Figs. 2 and 3). A representative Northern blot example is shown in Figure 2. All rats were sacrificed 24 hr after the injection, since maximal effects had been observed previously at that time point. In both males and females, there was a dose-dependent increase of both variables. In addition, there were no statistical differences between the amplitudes of the responses of AOG mRNA and plasma AOG. This was in agreement with results we have obtained previously in male rats treated with EE, since we have reported that there was a 1:1 correlation between changes in plasma AOG and liver AOG mRNA in such animals (32). Consequently, we performed additional analyses on only one of the two variables, i.e., plasma AOG. Statistical analysis of the absolute values of plasma AOG revealed that EE (at either dose) stimulated plasma AOG to a greater extent in female than in male rats (Table I). At the highest dose of EE, there was a 3-fold increase of plasma AOG, as compared with only a 2-fold increase in males.

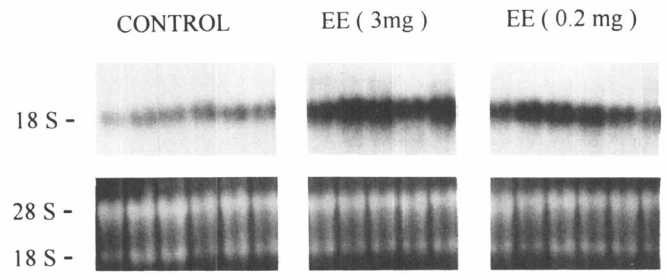

Figure 2. Autoradiogram of a representative Northern blot analysis of liver extracts from three groups of OVX female rats. All animals were sacrificed 24 hr after injection of either saline (control), EE 3 mg/kg body wt, or EE 0.2 mg/kg body wt. Ten μg of total liver RNA from each sample were loaded in each lane. Ethidium bromide-stained ribosomal RNA is shown in the bottom part of the figure. The migration positions of 28S and 18S ribosomal RNA are as indicated.

We then examined the effect of EE (3 mg/kg) in HYPOX male rats. In contrast to intact male rats, EE had no effect on either plasma AOG or liver AOG mRNA (Fig. 4). Further experiments were performed to determine which endocrine defect may underlie the nonresponsiveness of AOG to EE in HYPOX rats. In propylthiouracil-treated hypothyroid rats, basal levels of plasma AOG were significantly lower than control (Fig. 5A); however, administration of EE increased plasma AOG to the same extent both in control or hypothyroid rats. In HYPOX rats, basal levels of plasma AOG were also lower than control and similar to what was observed in hypothyroid rats (Fig. 5B); indeed, it has been shown previously that the thyroid hormone deficit is responsible for the low levels of plasma AOG in HYPOX rats (33). Neither EE nor PRL had any statistically significant effect on plasma AOG in HYPOX rats. However, PRL treatment partially restored the responsiveness of AOG to EE (Fig. 5B).

Finally, we examined the effects of estrogen on AOG mRNA concentration in different brain regions (Figs. 6 and 7). A representative Northern blot example is shown is Figure 6. Intact male rats were injected with EE (3 mg/kg body wt) and sacrificed at various times after the injection. Estrogens had no effect on AOG mRNA in cerebellum at any time point. In diencephalon, there was a time-dependent effect of EE; however, the effect was opposite of what had been observed in liver, since AOG mRNA was statistically lower than control at the 24-hr time point. In brain stem, AOG was statistically higher than control at the 8-hr time point, and returned to control levels after 24 hr.

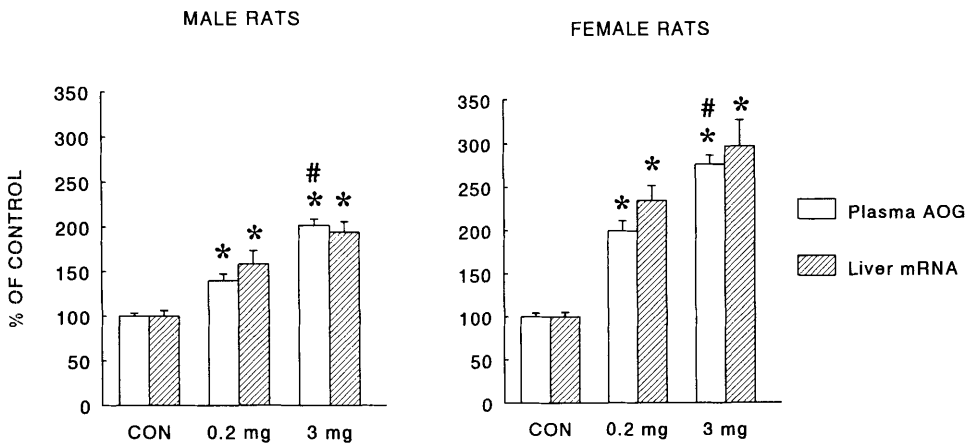

Figure 3. Effects of two doses of EE (0.2 mg/kg body wt and 3 mg/kg body wt) on plasma AOG and liver AOG mRNA, either in intact male or OVX female rats. All rats were sacrificed 24 hr after the administration of EE. Results are means ± SE; n = 6–12/group. *$P < 0.05$ vs control; #$P < 0.05$ vs the 0.2-mg dose.

Table I. Effects of EE on Plasma AOG in Male and Ovariectomized Female Rats[a]

	CON	EE	
		0.2 mg/kg body wt	3 mg/kg body wt
Males (n = 12)	1024 ± 34	1435 ± 88[b]	2068 ± 72[b,c]
OVX females (n = 6)	1003 ± 25	1927 ± 249[b,c]	2879 ± 176[b,d,e]

[a] Values are fmol/ml, and represent means ± SE. The groups are rats injected with either saline (CON) or EE (0.2 or 3 mg/kg body wt). Statistical differences were evaluated by analysis of variance followed by post hoc Newman-Keuls analysis.
[b] $P < 0.05$ vs CON.
[c] $P < 0.05$ vs males injected with EE 0.2 mg/kg body wt.
[d] $P < 0.05$ vs females injected with EE 0.2 mg/kg body wt.
[e] $P < 0.05$ vs males injected with EE 3 mg/kg body wt.

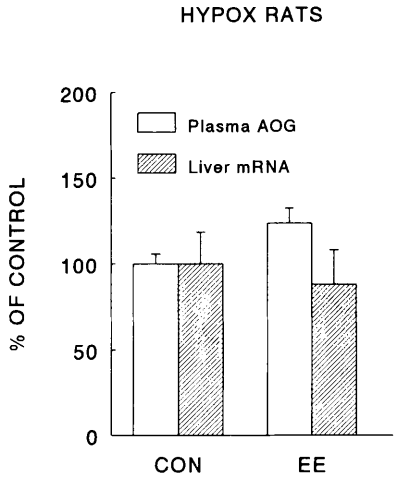

Figure 4. Effects of EE (3 mg/kg body wt) on plasma AOG and liver AOG mRNA in HYPOX male rats. The animals were sacrificed 24 hr after the injection of EE. Results are mean ± SE; n = 6–12/group. No significant differences were detected between either group.

Discussion

Many hormones have been shown to regulate AOG (4, 8–10). Among these, estrogens may be of particular importance since they may be partly responsible for some of the blood pressure disorders observed in women taking contraceptives or during pregnancy (11, 13, 34, 35). However, the effects of estrogens on AOG have been studied in less detail than in other hormones. In particular, a comparison of the effects of estradiol on plasma AOG and liver AOG mRNA has been published only very recently (20).

In the present study, we have compared the effects of two doses of EE on AOG mRNA and plasma AOG, either in intact male or OVX female rats. In a time-course experiment, we determined that both liver AOG mRNA and plasma AOG were maximally stimulated 24 hr after injection. However, the effect on AOG mRNA preceded that of plasma AOG by a few hours. This time difference in the onset of the effect may reflect the time needed by the hepatocytes to manufacture and secrete proteins from *de novo* synthesized mRNA. This observation is in good agreement with results published recently by others (20).

Most of the reported effects of estrogens occur at the level of gene transcription (36). However, they may also act at the level of translation, independently of

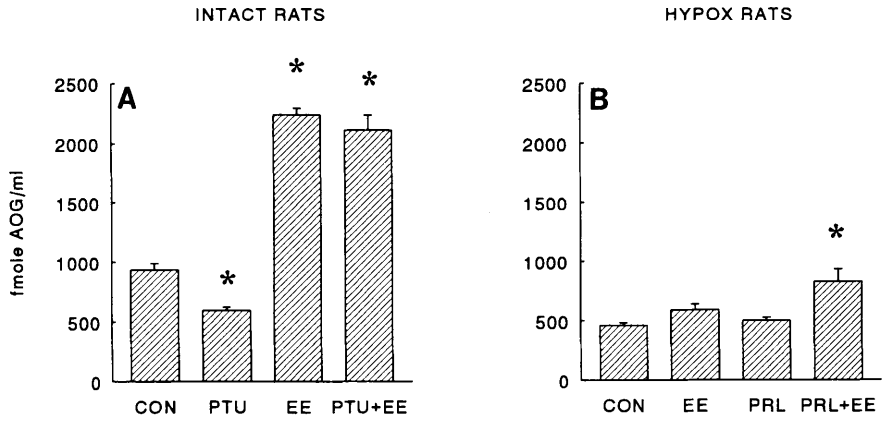

Figure 5. Effects of EE (3 mg/kg body wt) on plasma AOG. (A) Intact male rats. The groups were control (CON; normal water, saline injection), propylthiouracil (PTU; PTU water, saline injection), EE (normal water, EE injection), and PTU + EE (PTU water, EE injection). All rats were sacrificed 24 hr after the injection. Results are mean ± SE; n = 6/group. *$P < 0.05$ vs control. (B) HYPOX rats. The groups were CON (saline pretreatment, saline treatment), EE (saline pretreatment, EE treatment), PRL (PRL pretreatment, saline treatment), or PRL + EE (PRL pretreatment, EE treatment). *$P < 0.05$ vs control.

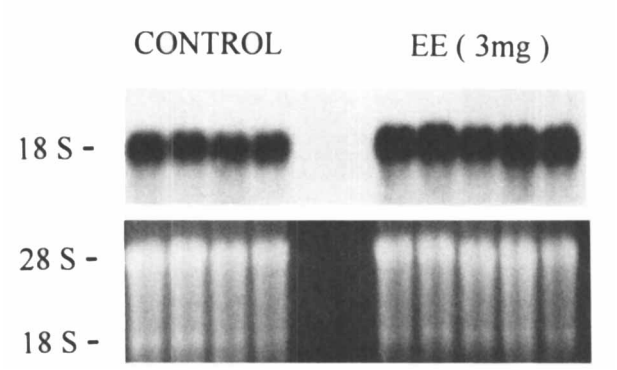

Figure 6. Autoradiogram of a representative Northern blot analysis of brain extracts. All samples originated from brain stem; ten μg of total RNA from each sample were loaded in each lane. The rats were injected (8 hr before decapitation) either with saline (control) or with EE (3 mg/kg body wt). Ethidium bromide-stained ribosomal RNA is shown in the bottom part of the figure. The migration positions of 28S and 18S ribosomal RNA are as indicated.

their effects upon transcription (37). In the case of AOG, we always observed an excellent correlation between AOG mRNA concentration and plasma AOG 24 hr after injection of EE, which suggests that there is little or no effect of EE on the translation of the AOG protein. Increased mRNA concentration may result from an increase in transcription rate or a decrease in mRNA degradation. However, it is likely that estrogens increase the transcriptional rate of the AOG gene, since they have been shown to upregulate the expression of a minigene containing 0.75 kb of 5′-flanking sequence of the AOG gene in cognate transgenic mice (38).

The effects of EE also appeared to be modulated by the endocrine status of the animal. For instance, the response of plasma AOG to two different doses of EE was greater in female than in male rats. In addition, no response was observed in HYPOX male rats. These findings are in agreement with the observations of others (21–23). Since the changes in liver AOG mRNA and plasma AOG were always of similar magnitude, it is unlikely that these variations in the amplitude of the response result from differences in the translation rate of the AOG transcript. However, variations in the amounts of liver estrogen receptors may partly explain the observed differences in responsiveness. Indeed, liver estrogen receptors are much more abundant in OVX female rats than in intact male rats (22); likewise, liver estrogen receptors are almost undetectable in HYPOX rats (22, 30).

To date, it has not been verified directly that a treatment that affects the levels of liver estrogen receptors also affects the response of AOG to estrogens in a similar fashion. Since treatment of HYPOX rats with PRL has been shown to partially restore the expression of liver estrogen receptors (30), we tested the effect of such treatment on plasma AOG. PRL had no effect by itself, but it restored the response of plasma AOG to EE. In contrast, there was no alteration of the responsiveness of plasma AOG to EE in either hypothyroid rats (Fig. 4) or adrenalectomized rats (23). Of note, PRL restored the response of plasma AOG to EE only partially. However, the effect of PRL on liver estrogen receptors was only partial too (30). Three alternative explanations may account for this observation: (i) rat PRL (as opposed to ovine PRL) may be required for full restoration of liver estrogen receptors; (ii) a different regimen of administration of PRL may be required; and (iii) PRL may exert its full effect only in the presence of additional (not yet identified) pituitary factors. In any event, the magnitude of the effect of PRL on the response of plasma AOG to EE was similar to that of the effect of PRL on liver estrogen receptors.

Our data in HYPOX rats suggest that the nonresponsiveness of plasma AOG to EE in such animals is not a consequence of a deficit in either thyroid or glucocorticoid hormones. Instead, hormones such as PRL may play a permissive role by controlling the amounts of estrogen receptors present in hepatic cells. Others have recently confirmed the importance of these receptors. Thus, the AOG response of rat hepatoma cells is strictly dependent on the presence of estrogen receptors, as demonstrated by transfection of these cells

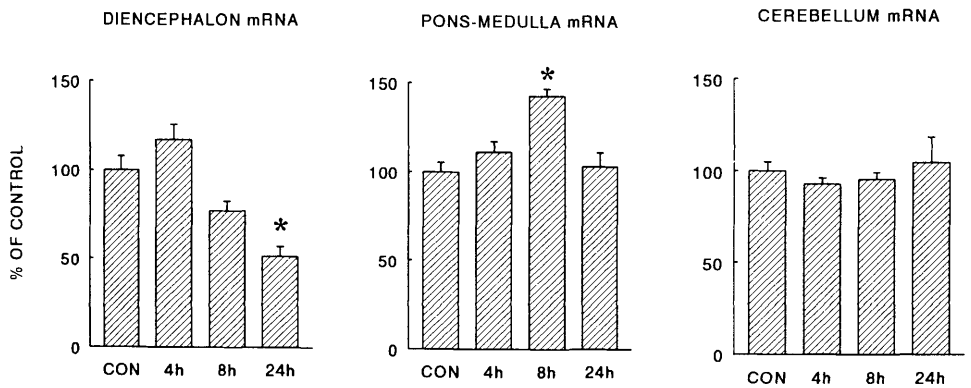

Figure 7. Effects of EE (3 mg/kg body wt) on AOG mRNA in three different brain regions of intact male rats. The animals were sacrificed 4, 8, or 24 hr after the injection of EE. Results are means ± SE; n = 10–12/group. *$P < 0.05$ vs control.

with human estrogen receptors (20). This observation may also have some clinical pertinence. Many studies have reported that plasma AOG was elevated in women taking contraceptives or during pregnancy (11, 13, 34, 35); however, there was also considerable individual variability. It is conceivable that such variability may be partially accounted for by differences in the levels of liver estrogen receptors.

Since brain is one of the nonhepatic tissues that produce AOG most abundantly, we tested the effects of EE on AOG mRNA in different brain regions. We observed striking time- and region-specific differences. In cerebellum, no response was observed. In diencephalon, EE induced a significant decrease in AOG mRNA at 24 hr, an effect that was opposite of what had been observed in liver. In brain stem, we did observe a stimulation of AOG mRNA, but only at an earlier time point. Our results in diencephalon are in agreement with those of Printz *et al.* (39), who reported a decrease in concentration of AOG protein in hypothalamic areas after treatment with estrogens. In contrast, others have reported that AOG mRNA was increased in whole brain extracts 4 hr after administration of EE (27); this is also compatible with our data, but our results indicate that the effect may change according to which brain region or time point is used.

It has been reported previously that the AOG gene responds to hormones in a tissue-specific manner (7, 25–28, 40). More specifically, estrogens have been shown to stimulate the AOG gene in kidney and aorta, but not in cardiac tissue (27, 28). In addition, it has been reported that the time courses of the response of the AOG gene to estrogens were different in distinct tissues (28). We made similar observations in different brain regions. Although variations in the amounts of estrogen receptors may also account for some of the tissue-specific differences, they may not explain the observed differences in the time course or the nature of the effect of estrogens. Those can be explained only on the basis of a modulation of the response by cell-specific factors.

Recently, Healy *et al.* (29) have reported that 4-day implantations of Silastic capsules containing β-estradiol 17-valerate did not affect significantly the concentration of AOG mRNA in brain stem, midbrain cerebellum, or cortex (29). In contrast to our results and those published by others (20, 28), they detected no effect of estrogen on liver AOG mRNA; however, they observed a marked increase of AOG mRNA in the pituitary after the administration of estrogen. The pattern of the effects of chronic administration of estrogen is, therefore, markedly different from that obtained with subacute administration of the steroid. Taken together, these results indicate that the effects of estrogens on expression of the AOG gene in various tissues vary according to the dose, the time of administration, and the target tissue.

Our results show that the responses of both AOG mRNA and plasma AOG to EE vary according to the sex and the endocrine status of the animal. Such variations may partly result from differences in the amounts of liver estrogen receptors. However, there are also some cell-specific differences in the nature of the response in different brain regions. Additional work is needed to determine the importance of the regulation of AOG in extrahepatic tissues and the cellular mechanisms underlying the differences of the responses in different tissues.

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