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Effect of Levonorgestrel and Ethinyloestradiol on Vasoconstriction in Rat Isolated Vasculature

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Abstract—Female Sprague-Dawley rats were injected s.c. with 0·2 μg day^{-1} ethinyloestradiol (EE_2) or 2·0 μg day^{-1} levonorgestrel (NG), procedures previously shown to increase systolic blood pressure. Increases in perfusion pressure to clonidine, phenylephrine, noradrenaline (NA) and angiotensin II (AII) were observed in rat isolated tail arteries, and to NA in the isolated mesenteric vasculature from steroid and vehicle-treated rats. NG treatment for four weeks produced increases in sensitivity to phenylephrine and NA in rat tail arteries; at 6 weeks the increases in sensitivity had largely disappeared but the maximum responses to clonidine and phenylephrine were increased. No change in sensitivity to AII was observed with NG. In contrast, EE_2 treatment for six weeks produced increases in sensitivity to AII, and a decrease in sensitivity and maximum response to clonidine but not to phenylephrine or NA, in tail arteries. Responses to NA in the mesenteric vasculature were increased after 6 weeks NG treatment but unaffected after 12 weeks EE_2 treatment. It is concluded that NG treatment stimulates α-adrenoceptor number, affinity or receptor-linked Ca^{2+} events which may contribute to its previously demonstrated hypertensive effect. The increased responsiveness to AII but not the decrease in α_2-adrenoceptor responsiveness may be associated with the chronic hypertension induced by EE_2.

Mild hypertension is one side-effect of oral contraceptive use in women (Khaw & Peart 1982). Contraceptive steroids administered to rats also cause hypertension (Saruta et al 1975; Fowler et al 1985). In both species, the oestrogen component of the contraceptive steroids appears to be the major cause of this hypertensive effect (Wilson et al 1984), and has been linked with a stimulation of the renin-angiotensin system (Weir et al 1970; Cain et al 1971). Few reports of progestagen-induced hypertension have been made. Progestagen-only preparations have failed to induce hypertension in women (Spellacy & Birk 1972; Hawkins & Benster 1977) and in rats (Fowler et al 1985), although, in one study, experimental hypertension was induced by 19-nor-progesterone treatment in rats (Komanicky & Melby 1981).

Previous results from our laboratory (Geraghty et al 1984) have demonstrated that both levonorgestrel (NG) and ethinyloestradiol (EE_2) induce hypertension in female Sprague Dawley rats, injected daily with NG and/or EE_2, at doses comparable on a weight-to-weight basis to those used in women (Geraghty et al 1984). NG produces a sharp, transient increase in systolic blood pressure, peaking at 6 weeks of treatment and returning towards control levels by about 12 weeks. EE_2, in contrast, produces an increase in systolic blood pressure slower in onset, beginning at six weeks, but sustained for at least 12 weeks of treatment (Geraghty et al 1984; Byrne et al unpublished). In our rat model, EE_2-induced hypertension is associated with an increased activity of the renin-angiotensin system (Byrne et al 1985) and with a decreased number of renal α_2-adrenoceptors (Geraghty & Burcher 1986). However, no changes in these parameters were observed as a result of NG treatment, suggesting that its transient hypertensive effect may be due to another mechanism.

In these experiments, we investigated the effect of NG and EE_2 pre-treatment on responses to vasoconstrictors in the rat tail artery, to determine whether NG- or perhaps EE_2-induced hypertension may be related to increased vascular responsiveness. The rat mesenteric artery was also used to confirm that the changes observed were not confined to one vessel type. We report that responses to both α_1- and α_2-adrenoceptor agonists in blood vessels from the NG-treated animals were greatly enhanced compared with controls. In contrast, EE_2 caused a decrease in response to the α_2-adrenoceptor agonist clonidine but an increase in response to AII.

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Materials and Methods

Perfused tail arteries

Female Sprague-Dawley rats, 180–220 g, were injected s.c. with either 0·2 μg EE_2 (for 6 weeks), 2·0 μg NG (for 4 and 6 weeks) or vehicle (0·2 mL, 5% ethanol: 0·9% saline) (for 4 and 6 weeks), six days per week. Animals had free access to Clark King pellets and tap water. They were housed 5 animals per cage at 26°C, and illuminated for 12 h daily.

Animals were anaesthetized with sodium pentobarbitone (60 mg kg^{-1} i.p.). A proximal section of caudal artery (1–2 cm in length) was removed into warm modified Krebs solution (composition NaCl 118, KCl 4·7, $NaHCO_3$ 25, $MgSO_4$ 0·45, KH_2PO_4 1·03, $CaCl_2$ 2·5, D-(+)-glucose 11·1, NaEDTA 0·067 mmols L^{-1}) and cannulated at the proximal end. The prepared artery was mounted vertically, with the distal end uppermost, under a tension of 0·5 g. The artery was perfused with the modified Krebs solution, gassed with 5% CO_2 in 95% O_2 at 37°C at constant flow (4mL min^{-1}) using a Gilson pump. The solution first perfused the lumen and then superfused the outside of the artery (Medgett & Rajanayagam 1984).

Perfusion pressure (PP) was recorded via a Bell & Howell (USA) physiological pressure transducer connected to a Grass polygraph. A stabilization period of 20–30 min was allowed, during which time the pressure fell from approximately 80 to 20 mmHg, where it remained fairly constant. A standard response to KCl (60 mmol L^{-1}) was obtained at the beginning and the end of the experimental session, to monitor the viability of the artery. The artery was perfused

for a further 15 min, before responses to the drugs were obtained. Responses to the agonists were then obtained by momentarily stopping perfusion with Krebs and immediately replacing it with Krebs containing the required concentration of drug for 1–2 min until a consistent response was obtained, after which the artery was reperfused with plain modified Krebs.

Perfused mesenteric vasculature

Four groups of weight and age-matched female Sprague-Dawley rats (180–220 g) were used. Each group of animals was injected s.c. with either 0·2 μg EE_2 for 12 weeks, 2 μg NG for 6 weeks or the vehicle (0·2 mL, 5% ethanol: 0·9% saline) for 6 and 12 weeks. At the end of the drug and appropriate control treatments the animals were anaesthetized with pentobarbitone (60 mg kg^{-1} i.p.) and the mesenteric vasculature was isolated according to McGregor (1965). The blood vessels were perfused with Krebs-Henseleit solution containing added glucose (NaCl 118, KCl 4·3, $NaHCO_3$ 25, $MgSO_4$ 1·2, KH_2PO_4 1·2, $CaCl_2$ 2·5, D-(+)-glucose 11·1, mmol L^{-1}). The solution was gassed with 5% CO_2 in O_2, maintained at 37°C and perfused at 2 mL min^{-1}. The inlet tubing to the peristaltic pump (Cole-Palmer) was divided into two equal lengths attached via a Y-piece to allow changing solution reservoirs without altering the baseline pressure. Changes in PP were recorded via a Statham P23Db pressure transducer connected to a Grass polygraph.

Statistics

Comparison between the dose-response curves of tissues taken from drug and vehicle treated animals was carried out using one-way analysis of variance. Student's unpaired *t*-test was used to assess whether the differences between treatment means and their controls were statistically significant. All data are expressed as mean ± s.e.m.; with n = number of animals. Means were considered significantly different if $P < 0.05$.

Materials

NG was obtained from Wyeth. EE_2, phenylephrine, noradrenaline bitartrate and AII were all obtained from Sigma. Clonidine was a gift from Boehringer Ingelheim. All other reagents were of analytical grade.

Results

Perfused tail arteries

Experimental protocols were designed such that both groups of steroid-injected rats were run in parallel with their vehicle-injected group. Dose-response curves to clonidine, phenylephrine and NA were obtained in one group of arteries, while responses to AII were obtained in another group.

Clonidine produced small increases in perfusion pressure, with similar maximum responses (approximately 65 mmHg) being obtained in both the four and six week vehicle control groups (Fig. 1). EE_2 treatment for 6 weeks produced a marked decrease in sensitivity to clonidine, and the maximum response was reduced to 33% of vehicle control ($P < 0.05$). In contrast, treatment of animals with NG usually increased responses to clonidine. Arteries from NG-treated rats (4 weeks) showed no significant increase in sensitivity with no change in maximum response. After six weeks NG treatment, the maximum response was increased by 77% ($P < 0.05$), without change in sensitivity.

Phenylephrine produced larger responses than clonidine in both vehicle-treated groups (Fig. 2), confirming earlier data that α_1-adrenoceptors are more numerous than α_2-adrenoceptors in this preparation (Medgett & Langer 1984). EE_2 did not alter the maximum response and produced no change in sensitivity to phenylephrine. In contrast, NG caused an increase ($P < 0.05$) in sensitivity at four weeks, with little change in maximum response. At six weeks, with NG treatment the sensitivity was identical with control, but there was a 58% increase in maximum response ($P < 0.05$).

NA induced responses greater than both clonidine or phenylephrine (Fig. 3) and the maximum responses obtained

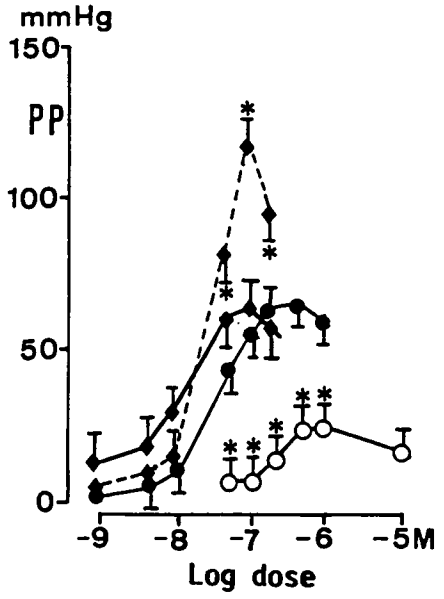

FIG. 1. Dose-response curve for clonidine in perfused tail arteries from control 6 weeks (●), EE_2 6 weeks (○), NG 4 weeks (♦), and NG 6 weeks-treated rats (♦, dashed line). * $P < 0.05$ compared with control. There was no significant difference in the responses of 4 and 6 week controls, therefore, the 4 week control has been omitted for clarity.

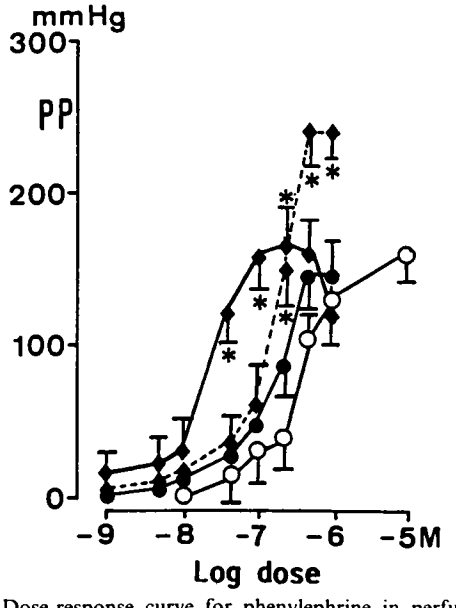

FIG. 2. Dose-response curve for phenylephrine in perfused tail arteries from control 6 weeks (●), EE_2 6 weeks (○), NG 4 weeks (♦) and NG 6 weeks-treated rats (♦, dashed line), * $P < 0.05$ compared with control.

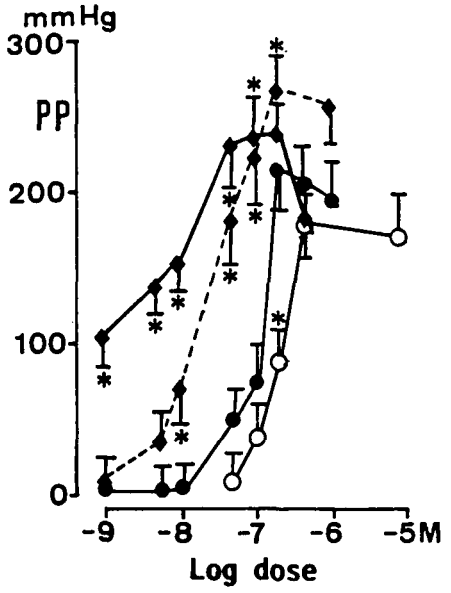

FIG. 3. Dose-response curve for noradrenaline in perfused tail arteries from control 6 weeks (●), EE_2 6 weeks (○), NG 4 weeks (♦), and NG 6 weeks-treated rats (♦, dashed line). * $P<0.05$ compared with control.

in vehicle-treated rats were approximately equal to the sum of those obtained for clonidine and phenylephrine combined. Responses after EE_2 treatment were reduced in sensitivity, but the maximum response was unchanged. NG treatment after four weeks produced a large (approximately 100-fold) increase in sensitivity to NA, particularly at lower concentrations, without significant change in maximum response. After six weeks NG treatment, sensitivity to NA was still enhanced, but to a lesser extent than at four weeks. The maximum response was slightly increased by 26%.

AII caused very small increases in perfusion pressure, approximately 10% of those produced by NA. Tachyphylaxis was observed to higher doses of AII in vehicle and NG-treated rats. Responses to AII in 6 week EE_2-treated rats were enhanced compared with vehicle control, with an increase in sensitivity ($P<0.05$) at lower concentrations and an absence of tachyphylaxis at high concentrations (Fig. 4). There was no change in response to AII in arteries from animals treated with NG for either 4 or 6 weeks.

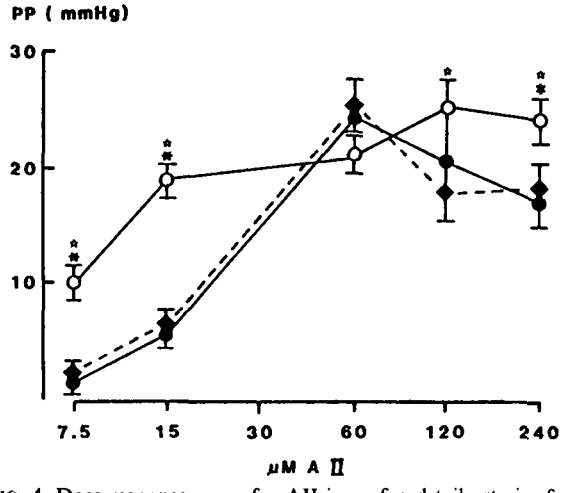

FIG. 4. Dose-response curve for AII in perfused tail arteries from control 6 weeks (●), EE_2 6 weeks (○), and NG 6 weeks-treated rats (♦). * $P<0.05$ compared to control, $P<0.05$ compared with NG.

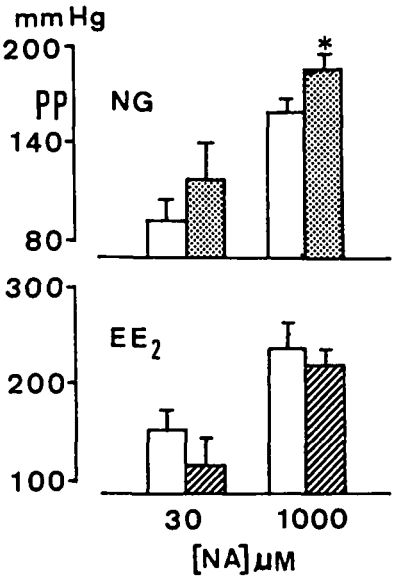

FIG. 5. Rise in perfusion pressure (PP) in mesenteric arteries from both NG 6 weeks (shaded bars) and EE_2 12 weeks-treated rats (lined bars) in response to noradrenaline (NA) at both the EC50 (30 μmol L^{-1}) and maximum concentration (1 mmol L^{-1}). * $P<0.05$ compared with 6 week control (open bars). There was no significant difference between the responses of EE_2-treated tissues and the 12 weeks controls (open bars).

Perfused mesenteric vasculature

NA caused a concentration-related rise in perfusion pressure. The approximate EC50 was 30 μmol L^{-1} and the maximal concentration was 1 mmol L^{-1}. After 12 weeks treatment with EE_2 there was a trend towards decreased sensitivity to NA but the EC50 and maximal responses were not significantly lower than control responses ($P>0.05$).

There was no change in sensitivity to NA in the mesentery of rats treated with NG for 6 weeks, but the maximum response was significantly increased ($P<0.05$), compared with control (Fig. 5).

Discussion

The vascular tissues investigated were the rat tail artery containing α_1- and α_2-adrenoceptors and AII receptors, and the mesenteric vasculature which consists of small resistance vessels having an important function in blood pressure regulation. Earlier data (Medgett & Langer 1984) as well as the present results, show the existence of both α_1- and α_2-adrenoceptors in the proximal region of the rat tail artery. The α_2-adrenoceptors, which are probably the minor subpopulation (Medgett & Langer 1984) are non-innervated post-junctional receptors which are sensitive to both exogenous (Hicks et al 1984; Medgett et al 1984) and circulating catecholamines (Wilfert et al 1982). In contrast, the mesenteric blood vessels of the rat constrict in response to α_1-, but not α_2-agonists (McPherson et al 1984).

Adrenoceptor changes have been reported in many forms of experimental hypertension in the rat. These changes have been extensively investigated in the myocardium, where a decrease in α- and β-adrenoceptor number occurs in the established phase of hypertension, probably due to agonist-mediated down-regulation (Woodcock & Johnston 1980). In the vasculature, an increased α-adrenoceptor mediated reactivity to NA is a common finding in various forms of experimental hypertension (Hicks et al 1983). Hypertension

in spontaneously hypertensive rats (SHR_s) and induced by DOCA-salt or by renal occlusion is associated with supersensitivity of the mesenteric blood vessels to NA (Finch 1975; Haeusler & Haefely 1970; McLennan & Taylor 1984) and there is an increase in the maximum response but no change in sensitivity to NA in tail arteries from SHRs compared with normotensive WKYs (Medgett et al 1984; Aqel et al 1986).

The present results indicate that NG-induced hypertension is also associated with increased adrenergic responsiveness. Treatment of animals with NG for 4 weeks caused a significant increase in sensitivity to both phenylephrine and NA in tail arteries. This change preceded the well-established, large increase in systolic blood pressure which peaks at 5–6 weeks of NG treatment (Geraghty et al 1984; Byrne et al unpublished), suggesting that the increased sensitivity is not secondary to hypertension produced by other mechanisms. At the time of this peak hypertensive effect (6 weeks) the increase in sensitivity to phenylephrine was attenuated at lower dose levels, but the increased sensitivity to NA persisted. The most striking effect of NG treatment was an increase in maximum response to both α_1- and α_2-adrenoceptor agonists. This change was not confined to the tail artery, as similar, but less pronounced results were seen in the mesenteric vasculature. The increased responsiveness to adrenoceptor stimulation in these two vascular beds may explain the increased systolic blood pressure caused by NG, demonstrated to be independent of changes in the renin-angiotensin system (Byrne et al 1985; unpublished). The lack of NG effect on AII-mediated responses indicates that the increased adrenergic responsiveness was not due to a generalized increase in vascular reactivity, and suggests that an increase in vascular α_1- and perhaps α_2-adrenoceptor number and/or affinity may have occurred. Alternatively, NG-induced hypertension may be associated with post-receptor changes, such as an increased Ca^{2+} sensitivity to α_1-adrenoceptor stimulation, reported by Aqel et al (1986) in spontaneously hypertensive rats.

EE_2 treatment tended to have the opposite effect on α-adrenoceptor-mediated responses, compared with NG. A marked decrease ($P<0.05$) in α_2-adrenoceptor responsiveness was seen in rat tail arteries, compared with vehicle controls, after six weeks, although α_1-adrenoceptor-mediated responses were virtually unaffected. A trend towards decreased sensitivity to NA was seen in both tail artery and mesenteric vasculature. These results with EE_2 are in agreement with previous experiments from rat aortic rings where decreased responsiveness to NA and phenylephrine were reported after mestranol treatment (Shiverick et al 1983), but are in contrast with data from rat mesenteric arteries where 17β-oestradiol is associated with an increase in vascular catecholamine sensitivity and α-adrenoceptor affinity (Colucci et al 1982; Altura 1975). The mestranol data may be of greater relevance to the present study since this steroid is metabolized to EE_2.

In contrast to its inhibitory effects on α_2-adrenoceptor-mediated responses, EE_2 caused an increased sensitivity to AII in the tail artery. Since AII and α_2-agonists decrease intracellular 3′,5′-cyclic AMP in rat tail artery (Volicer & Hynie 1971), a post-receptor effect of EE_2 is unlikely. Thus EE_2 may cause a change in number and/or affinity of α_2- and perhaps AII receptors. This is a feasible hypothesis since much evidence exists showing that oestrogens alter α-adrenoceptor number and responsiveness in a number of tissues. Our laboratory has reported a decrease in the number of α_2-adrenoceptors in the rat kidney during established hypertension after 12 weeks EE_2 treatment (Geraghty & Burcher 1986). Other studies show a decreased number of α_2-adrenoceptors in rabbit platelets (Elliot et al 1980), but an increased number in the uterus (Hoffman et al 1981) and in human platelets (Peters et al 1979) after oestrogens.

The present findings add to the body of literature concerning the regulation of adrenoceptors by oestrogens but offer no direct explanation for the mechanism of EE_2-induced hypertension, already shown to be associated with increases in blood volume and with increased activity of the renin-angiotensin system (Byrne et al 1985; unpublished). In this connection, the increased sensitivity of the tail arteries to AII during EE_2 treatment may be of relevance. In contrast, our data with NG clearly indicate that the increased responsiveness to α_2- and particularly α_1-adrenoceptor agonists precedes and may make a major contribution to the hypertension seen with NG at 6 weeks. It is not clear whether NG exerts its effect by stimulating α-adrenoceptor affinity, number or receptor-linked Ca^{2+} events.

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