PROPRANOLOL-BLOCKADE OF VASOPRESSIN INDUCED INCREASE IN PLASMA PROGESTERONE IN EARLY HUMAN PREGNANCY

By

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ABSTRACT

Following continuous dilation of the uterine cervix or intravenous infusion of vasopressin during the first trimester of human pregnancy, a marked increase in the peripheral plasma progesterone levels was observed. This effect was blocked by simultaneous administration of propranolol (Inderal®, a β-blocking agent. It is suggested that both these stimulating and inhibiting effects might be related to 3', 5'-adenosine monophosphate (cyclic AMP). The results indicate the existence of β-receptors in steroid producing tissues.

Dilation of the uterine cervix or vasopressin infusion has been shown to increase the plasma progesterone levels during the first trimester of human pregnancy (Fylling & Norman 1970; Fylling 1971). It was suggested that the effect might be mediated by 3', 5'-adenosine monophosphate (cyclic AMP). According to Robison et al. (1967) it seems likely that the β-receptor might be equivalent to the adenylyl cyclase in the tissues. Catecholamines are reported to depress and β-receptor blocking agents to increase uterine activity in pregnant women (Hendricks et al. 1961; Eskes et al. 1965; Stander 1967; Wansbrough et al. 1968). Adrenaline increases the synthesis of cyclic AMP in pigeon erythrocytes and this effect is blocked by β-blocking agents (Davoren & Sutherland 1963). Hence, it might be expected that the stimulating effect of cervical dilation or vasopres-

* The following abbreviations and trivial names are used:
Progesterone: pregn-4-ene-3, 20-dione.
sd: standard deviation.
sin infusion on the plasma progesterone levels would be inhibited by propranolol, a $\beta$-blocking agent.

The present investigation demonstrates that the increase in the plasma progesterone levels following cervical dilation and vasopressin infusion, is inhibited by the simultaneous administration of propranolol.

**MATERIAL AND METHODS**

*Subjects*

Twenty-one healthy women, 18 to 26 years old, were included in the present investigation. They were hospitalized for legal abortion at a gestational age of between 10 and 12 weeks.

**Experimental procedure**

Five of the patients in the first series ($n = 11$) received orally, 40 mg of propranolol Inderal® (»I.C. I.«) 30 minutes before the insertion of the dilator. Six patients without pretreatment with propranolol, served as controls. The dilator and its insertion have been described previously (Fylling & Norman 1970). Blood samples were drawn immediately before insertion of the dilating instrument (zero time) and 1 and 3 hours respectively later.

In the second series ($n = 10$) 5 patients received vasopressin (Pitressin®, »Parke-Davis«) and 5 received vasopressin combined with propranolol (Inderal®). The infusion experiments are listed in Table 1. The infusion period was 3 hours, and blood samples were drawn before and at the end of the infusion period.

The side effects observed in some of the women in both series were slight headache and diarrhoea.

The blood samples were drawn and stored as described previously (Fylling 1970; Fylling & Norman 1970).

**Progesterone assay procedure**

Duplicate measurements of progesterone in 0.25 ml plasma samples were performed by the rapid protein binding technique described by Johansson (1969) with minor modification (Fylling 1970). The values presented are not corrected for procedural losses.

**RESULTS**

The results of the dilator experiments are shown in Fig. 1. The initial value ($0 = \text{zero time}$) in each case is set to 100 per cent and the following values are expressed as percentage changes from the zero time values. The mean values with $\text{SD}$ are plotted. As shown in Fig. 1, a marked increase in the plasma levels was observed after insertion of the dilator in the control group. This effect was similar to that described previously (Fylling & Norman 1970). However, following pretreatment with propranolol (Inderal®), the effect on the plasma progesterone levels 1 hour after insertion of the instrument was abolished ($P < 0.01$). The difference between the propranolol group and the control group
Table 1.
Progesterone levels in peripheral plasma of women between 10 and 12 weeks of gestation, before (No. 1) and after (No. 2) 3 hours infusion of vasopressin and vasopressin + propranolol (Inderal®). Prog. = progesterone.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Infusion medium</th>
<th>Dosage</th>
<th>ng prog./ml plasma</th>
<th>Per cent of control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>No. 1</td>
<td>No. 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>21.2</td>
<td>26.5</td>
</tr>
<tr>
<td>B. E.</td>
<td>Vasopressin in saline</td>
<td>70 mU/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K. A.</td>
<td>Vasopressin in saline</td>
<td>80 mU/min</td>
<td>28.8</td>
<td>39.5</td>
</tr>
<tr>
<td>J. M.</td>
<td>Vasopressin in saline</td>
<td>114 mU/min</td>
<td>30.0</td>
<td>38.4</td>
</tr>
<tr>
<td>G. N.</td>
<td>Vasopressin in saline</td>
<td>133 mU/min</td>
<td>27.5</td>
<td>39.7</td>
</tr>
<tr>
<td>E. K.</td>
<td>Vasopressin in saline</td>
<td>144 mU/min</td>
<td>17.2</td>
<td>25.7</td>
</tr>
<tr>
<td>M. P.</td>
<td>Vasopressin (V) + propranolol (P) in saline</td>
<td>111 mU/min (V)</td>
<td>26.7</td>
<td>26.0</td>
</tr>
<tr>
<td>I. H.</td>
<td>Vasopressin (V) + propranolol (P) in saline</td>
<td>70 µg/min (P)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. H.</td>
<td>Vasopressin (V) + propranolol (P) in saline</td>
<td>160 mU/min (V)</td>
<td>17.5</td>
<td>16.8</td>
</tr>
<tr>
<td>E. Kj.</td>
<td>Vasopressin (V) + propranolol (P) in saline</td>
<td>100 µg/min (P)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. U.</td>
<td>Vasopressin (V) + propranolol (P) in saline</td>
<td>165 mU/min (V)</td>
<td>32.7</td>
<td>27.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>66 µg/min (P)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>166 mU/min (V)</td>
<td>29.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>140 µg/min (P)</td>
<td>29.7</td>
</tr>
</tbody>
</table>
Fig. 1.

Changes in the peripheral plasma progesterone levels during continuous dilation of the uterine cervix. Without pretreatment (●-●, mean and sd, n = 6), and following pretreatment with propranolol (○-○, mean and sd, n = 5). The values at >0« (zero time) are set at 100 per cent and the following values are expressed as a per cent of these values.

1 hour after zero time was significant \( P < 0.01 \), but less marked and not significant \( 0.2 > P > 0.1 \) after 3 hours.

The results of the infusion experiments with vasopressin and vasopressin combined with propranolol are listed in Table 1. Vasopressin alone increased the plasma progesterone level in all the patients \( 0.05 > P > 0.01 \), in agreement with previous results \( (Fylling 1971) \). When propranolol was added to the infusion medium, however, the increase in the progesterone levels was blocked in all the patients.

**DISCUSSION**

The effect of cervical dilation and vasopressin infusion on the progesterone levels in peripheral plasma are consistent with the findings reported previously \( (Fylling & Norman 1970; Fylling 1971) \). In good agreement with the hypothesis put forward in the introduction, the increase in peripheral plasma progesterone levels by these stimuli can be inhibited by the \( \beta \)-blocking agent propranolol. The reduced difference between the propranolol group and the control group 3 hours after zero time in the first series may be explained by a diminution of the drug effect with time.

The mechanism underlying the effect of cervical dilation on uterine contractility has, so far, not been defined \( (Wansbrough et al. 1968; Fylling & Norman 1970) \). It has been suggested that the adrenergic nerves act as the efferent pathway during cervical dilation, and that this effect can be blocked by epi-
ducal anaesthesia (Sala et al. 1970). It has also been demonstrated that β-adrenergic drugs are able to depress myometrial activity in women (Hendricks et al. 1961; Wansbrough et al. 1968; Gamissans et al. 1969) and in rat (Sethi & Chaudhury 1970; Triner et al. 1970).

Evidence is accumulating that β-receptors are closely related to the adenyl cyclase system (reviewed by Robison et al. 1967). The effect of β-receptor stimulating agents on the synthesis and release of cyclic AMP has, so far, been shown to be inhibited by β-blocking agents like propranolol in the heart, aortic strips, uterus, liver and erythrocytes (Murad et al. 1962; Davoren & Sutherland 1963; Bartelstone et al. 1964; Bartelstone & Nasmyth 1965; Levine & Vogel 1965; Dobbs & Robison 1968).

The present experiments seem to justify the conclusion that the stimulation of progesterone secretion in the foeto-placental unit caused by cervical dilation or vasopressin infusion act via β-receptors. This might indicate the presence of a β-receptor like system in a steroid forming organ. The findings reported in the present paper, might form the basis of new approaches to the diagnosis and treatment of functional disturbances of the foeto-placental unit.

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REFERENCES


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