THE STIMULATION OF PROLACTIN SECRETION
BY SULPIRIDE IN “ADOLESCENT GYNAECOMASTIA”

By
R. D’Agata¹), S. Andó, S. Gulizia, L. Condorelli,
C. Paci²), U. Scapagnini³) and P. Polosa

ABSTRACT

In order to evaluate the function of the hypothalamic-pituitary-prolactin axis in “adolescent gynaecomastia” (AG), sulpiride was administered to 7 normal boys and 7 boys with AG. The maximum increase in serum prolactin (PRL) above the mean baseline level ($\Delta_{\text{max}}$) was used as index of response. The sulpiride induced a greater PRL release in boys with gynaecomastia than in the controls. Our data indicate that boys with gynaecomastia may have a greater pituitary prolactin pool. The results also illustrate the usefulness of specific neurotrophic agents such as sulpiride as important tools for evaluating the function of the hypothalamic-pituitary-PRL axis.

“Adolescent gynaecomastia” (AG) is a well defined phenomenon which occurs in many boys at the time of puberty. However, the pathogenesis of this syndrome is unknown and several facets of clinico-pathological correlations remain undefined (Goldfine et al. 1971; Bannayan & Hajdu 1972).

¹) Address reprint requests to Centro Endocrino, Istituto di Patologia Medica II, Ospedale Garibaldi, Catania, Italy.
Present address: National Institutes of Health-Bldg. 10 Rm.6B04, Bethesda, 20014 Maryland, USA.
²) Department of Psychiatry, University of Catania.
In view of their morphogenetic effects on the breast, oestrogens, testosterone and prolactin have been suggested for the induction of AG (Paulsen 1974). However, conflicting findings in this field do not support a well established relationship between AG and the actual plasma levels of these hormones (Hall 1959; Levy et al. 1964; Goldfine et al. 1971; Lee 1975).

The present study was undertaken in order to evaluate the prolactin component in dynamic conditions, to reveal possible alterations in the hypothalamic-pituitary-prolactin axis in AG.

It is increasingly evident that biogenic amines play an important part in regulating prolactin secretion. Dopamine (DA) release by tubero-infundibular neurons (TIDA) (Carlsson et al. 1962; Fuxe 1964; Hökfelt & Fuxe 1970) is considered to play the major inhibitory role in prolactin secretion either by inhibiting prolactin release directly at the level of the anterior pituitary (MacLeod 1969; Birge et al. 1970) or stimulating at the hypothalamic level the release of PIF (Kamberi et al. 1971). The removal of the tonic dopaminergic inhibition on PRL secretion by DA antagonists results in a prompt release of the hormone in several species including man (Frohman & Stachura 1975; Besser & Mortimer 1976; MacLeod 1976). Thus, the use of DA antagonists can be utilized as a stimulating test for the prolactin cell secretory capacity (Thorner et al. 1974; Mancini et al. 1976).

In this investigation we studied the effect of sulpiride, a major tranquilizer (Justine-Besacon et al. 1976) on prolactin secretion in normal and AG boys.

**MATERIALS AND METHODS**

Sulpiride induction of prolactin release was studied in 14 male subjects ranging from 14–19 years of age. All subjects had normal puberal development and were considered post-puberal (P3) according to Tanner’s classification (Tanner 1962).

Seven out of the 14 subjects were healthy boys who served as controls, whereas the remaining 7 were boys with bilateral gynaecomastia. In the latter group gynaecomastia occurred around the time of puberty and was generally present without associated aetiological factors (“adolescent gynaecomastia”). None of them had any illness or were taking any medication known or suspected to influence breast development as no abnormalities were observed by routine laboratory tests including radiological examination of the sella turcica. Repeated buccal smears were chromatin negative. A visible breast enlargement was present in each boy. Both hyperplastic breasts had an adolescent female consistency. Macroscopically the configuration of the gynaecomastia was divided into two types (Bannayan & Hajdu 1972): a diffuse form in which the hyperplastic breast tissue had ill defined margins merging with the surrounding tissue; a discrete form in which the hyperplastic tissue was well circumscribed with well defined margins (see Table 1). Mass size ranged from 3 cm to 7 cm in diameter (see Table 1). There were no nipple or areola changes. The subjects of the control group were chosen so that the boys were matched in weight, age and stage of sexual development with those of the AG group. In all 14 subjects for a period of three
months multiple blood specimens were obtained. Gonadotrophins, testosterone and oestradiol were within the normal range of our assays in all samples. The weight of the 14 boys was found to be within the theoretical range expected.

An indwelling catheter was inserted at 8.30 a.m. into an antecubital vein, 25 mg sulpiride (Dogmatil®, Delagrange, Paris) was administered intravenously at 9.30 a.m. (time 0) as a bolus and blood samples were collected before and 15, 30, 60, 90 and 120 min following the 0 time. Serum prolactin (PRL) was determined by a double antibody homologous radioimmunoassay technique (Kit supplied by Serono Immunochemicals, Roma, Italy) with slight modifications, by the use of ¹²⁵I-labelled human prolactin and rabbit antihuman prolactin antibodies. As standard, we used human serum PRL; 100 ng of this serum is equivalent to 4 mUI of 71/222 WHO standard reference preparations. Results were expressed in ng/ml. Intra- and between-assay variations were 4.8% and 7.8%, respectively. The assay had an adequate sensitivity (lowest detectable level 0.5 ng/ml) and a satisfactory accuracy, as demonstrated by the consistent parallelism between the standard curve and the progressive dilutions of hyperprolactinaemic sera.

Table 1.

<table>
<thead>
<tr>
<th>Patient age (years)</th>
<th>Size or breast mass (diameter) cm</th>
<th>PRL (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Basal value</td>
</tr>
<tr>
<td>1 *D. G. 14</td>
<td></td>
<td>9.4</td>
</tr>
<tr>
<td>2 *D. F. 14</td>
<td></td>
<td>10.6</td>
</tr>
<tr>
<td>3 *P. L. 14</td>
<td></td>
<td>6.9</td>
</tr>
<tr>
<td>4 *R. C. 15</td>
<td></td>
<td>8.8</td>
</tr>
<tr>
<td>5 *R. A. 17</td>
<td></td>
<td>4.8</td>
</tr>
<tr>
<td>6 *M. U. 18</td>
<td></td>
<td>14.6</td>
</tr>
<tr>
<td>7 *B. G. 19</td>
<td></td>
<td>13.3</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 °N. S. ↓ 14</td>
<td></td>
<td>9.8</td>
</tr>
<tr>
<td>9 °I. M. ↓ 14</td>
<td></td>
<td>9.4</td>
</tr>
<tr>
<td>10 °M. O. ↑ 14</td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>11 °C. A. ↑ 15</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>12 °G. O. ↑ 15</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>13 °C. G. ↑ 16</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>14 °A. S. ↓ 17</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Normal male basal values - PRL (ng/ml) 3–18.
* Control boys.
° Boys with gynaecomastia.
Form of gynaecomastia: diffuse (↑), discrete (↓) (see Materials and Methods).
RESULTS

The mean basal prolactin concentration in boys with gynaecomastia did not differ from the basal values of the controls (Table 1). As can be seen in Fig. 1 sulpiride induced an immediate increase in serum prolactin levels in all subjects tested. Peak values were observed from 15 to 30 min after drug injection \((P < 0.05\) compared to mean basal values). At 120 min PRL remained significantly higher than the control values \((P < 0.05\). A comparison of the post-stimulated PRL values between control and AG groups showed significant differences at each time throughout the entire experimental period \((P < 0.05\). The \(\Delta_{\text{max}}\) response to sulpiride have been calculated for each subject and are reported in Table 1. As can be seen from Table 1, the mean \(\Delta_{\text{max}}\) in boys with AG is significantly higher than in the control group \((P < 0.05\); the single PRL \(\Delta_{\text{max}}\) are closely matched in each group tested (Table 1).

DISCUSSION

Our findings show that PRL resting levels of boys with AG overlap those in normal subjects. Whereas, the PRL release induced by sulpiride, a DA receptor blocker, is greater in AG subjects than in normal boys.

One obvious conclusion which can be drawn from these results is the existence of a larger pool of acutely releasable prolactin in AG. This increased
releasable pool is unmasked by sulpiride which acts by removing the well-known tonic inhibitory control of DA (Van Maanen & Smelik 1968; Hökfelt & Fuxe 1970). Although the site of action of sulpiride (hypothalamic and/or pituitary) is still unsettled, it is well known that this drug acts as a dopaminergic antagonist at receptor sites. Hence, considering the mode of action of the drug, the higher response observed in AG could reflect a greater displacement of catecholamines from the receptor sites.

From our data no answer can be given to the question of whether PRL is involved in the induction of AG, either acting on the PRL specific receptor containing cells or by interfering with the receptors and/or metabolism of androgens, as has been recently shown in breast cancer (Miller 1976; Shafie & Brooks 1977). However, based on our findings one should consider the possibility that all physiological, hormonal and psychological factors which act on PRL secretion by interfering with DA tone (Meites 1973) result in AG candidates or patients in an episodically increased release of prolactin.

In conclusion the present study emphasizes the importance of using specific neurotrophic agents, such as sulpiride, to reveal changes on the neuroendocrine PRL regulatory mechanism and to evaluate the size of the pituitary pool in the endocrine disease.

REFERENCES

Frohman L. A. & Stachura M. E.: Metabolism 24 (1975) 211.
Fuxe K.: Z. Zellforsch. 61 (1964) 710.

Received on October 4th, 1976.