Prolactin Release in Polycystic Ovarian Syndrome

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Abstracts

To evaluate the prevalence of hyperprolactinemia in patients with polycystic ovarian syndrome (PCO), 72 patients with oligo- or anovulation were studied. All of the patients had persisting elevated LH (>25 mIU/ml), normal FSH, high LH/FSH ratio (>2.5), and exaggerated LH responses to LHRH. Mean testosterone and androstenedione concentrations were appreciably increased in these patients. Out of 171 samples for prolactin (PRL) determination from these 72 patients, only 5 patients had a PRL value above 30 ng/ml during the first sampling. The next sampling from these same 5 women disclosed that they were transiently hyperprolactinemic because the next samples showed a normal PRL value. To further investigate the PRL secretory capacity 500 μ g of TRH and 10 mg of metoclopramide (MCP) were administered to these 72 and 44 patients, respectively. The PRL response to MCP was significantly blunted in these patients compared to normal women while the PRL response to TRH in these patients was not indistinguishable from that in normal women. These results indicate that the true prevalence rate of hyperprolactinemia in PCO may be low rather than high and the association of hyperprolactinemia with PCO may be coincidental rather than a pathogenically related phenomenon.

Basal serum PRL levels have been reported to be elevated in one-third of patients with PCO (Alger *et al.*, 1980, Carmina *et al.*, 1984., Duignan 1976, Luciano *et al.*, 1984). One of the postulated mechanisms which associates elevated PRL with PCO is an abnormal central neurotransmitter, particularly in the dopaminergic control of PRL release (Corenblum and Taylor 1982, Luciano *et al.*, 1984). Hypothalamic dopamine is known to be the major factor inhibiting PRL secretion. Since LH

has also been reported to be suppressed by dopamine (Ferrari *et al.*, 1981, Leblanc *et al.*, 1976, Pehrson *et al.*, 1983), dopamine deficiency may result in hyperprolactinemia and an increase in LH. However, it was demonstrated recently that dopamine can stimulate *in vitro* release of GnRH from the adult human hypothalamus (Rasmussen *et al.*, 1986). Further, dopamine antagonist metoclopramide (MCP) was shown to reduce LH in rhesus monkeys (Kaufman *et al.*, 1985). Since these observations indicate the stimulatory role of dopamine in LH release, they are clearly against the hypothesis that deficient hypothalamic dopamine may play a role in the high prevalence of hyper-

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prolactinemia in PCO. We undertook to reevaluate the secretory capacity of PRL in PCO patients.

Materials and Methods

Seventy-two patients with an established clinical and laboratory diagnosis of PCO were studied. Their ages were between 18 and 36 years. The condition was diagnosed on the basis of infrequent or absent ovulation. In addition, all of the patients included in this study persistent elevated LH (>25 mIU/ml), normal FSH, a high LH/FSH ratio (>2.5) and exaggerated LH responses to LHRH. The 56 healthy and regularly menstruating women served as the control.

Basal LH, FSH, testosterone, androstenedione and PRL secretion

Random serum LH, FSH, testosterone (T'sterone), androstenedione (A'dione) and PRL were evaluated 189, 189, 93, 86 and 171 times, respectively, in 72 patients with PCO. These T'sterone and A'dione concentrations were compared with those, determined randomly in 52 normal women. Basal PRL was compared with that in 11 normal women throughout their 11 cycles.

LH and FSH responses to LHRH

A 100 μ g of LHRH test (intramuscularly) was performed in 72 patients with PCO. These results were compared with those in 25 normal women examined in the mid-follicular phase.

PRL stimulation tests

500 μ g of TRH was administered intramuscularly to 72 patients with PCO. These results were compared with those obtained in 18 normal women examined in the mid-follicular phase. In addition, an intravenous 10 mg of MCP test was performed in 44 out of 72 patients with PCO. These results were compared with those obtained in 12 normal women examined in the mid-follicular phase and 16 normal women examined in the mid-luteal phase.

Serum was removed and frozen until assayed. Serum LH, FSH, and PRL were determined by radioimmunoassay as previously described (Minakami *et al.*, 1984, 1986). Intra-

and interassay coefficients of variation for LH, FSH, and PRL did not exceed 7% and 11%, respectively. Testosterone (T'sterone) and androstenedione (A'dione) levels were determined by radioimmunoassay at Special Reference Lab. (Japan). Intra- and interassay coefficients of variation for T'sterone were 4.1% and 12.2%, respectively. Those for A'dione were 9.0% and 10.9%, respectively. Statistical analyses were performed by means of Student's *t*-test.

Results

Fig. 1 shows the basal LH and FSH levels in 72 patients with PCO. The mean ($\pm$ SD) basal levels of LH and FSH were 41.5 ± 13.2 and 11.6 ± 2.6 mIU/ml, respectively.

LH and FSH responses after a 100 μ g intramuscular injection of LHRH are shown in Fig. 2. The mean LH ($\pm$ SE) concentrations before and after LHRH administration were significantly elevated ($p < 0.001$) in the 72 patients with PCO while the FSH concentrations were indistinguishable from those found in 25 normal women.

Basal T'sterone and A'dione concentrations are shown in Fig. 3. A considerable number of patients had high T'sterone and/or A'dione. Consequently, the mean ($\pm$ SD) concentrations of T'sterone (1.06 ± 0.51 ng/ml) and A'dione (1.44 ± 0.81 ng/ml) in PCO were significantly higher than those (0.80 ± 2.4 ng/ml and 0.82 ± 0.41 ng/ml) found in normal women.

Fig. 4 shows basal PRL in patients with PCO and normal women. Eighty and ninety-seven determinations of PRL during the follicular and luteal phases of 11 apparently normal women served as the control. Even in normal women, 8.5 per cent of the samples collected throughout the entire menstrual cycle showed high PRL (>30 ng/ml). In contrast, only 5 out of 171 samples (2.9%) showed a PRL concentration above 30 ng/ml in PCO. Further, these mild hy-

Fig. 1. One-hundred and eighty-nine determinations of basal LH and FSH in 72 PCO patients.

Fig. 2. LH and FSH responses after an administration of 100 μ g of LHRH in 72 patients with PCO and 25 normal women.

Fig. 3. Serum testosterone and androstenedione in 72 PCO patients are contrasted to those in 52 normal women.

Fig. 4. One-hundred and seventy-one determinations of PRL in 72 PCO patients are contrasted with 80 and 97 determinations for PRL sampled during the follicular phase and the luteal phase during 11 cycles of 11 normal women. F refers to the follicular phase and L to the luteal phase.

Fig. 5. PRL response after an intravenous administration of 10 mg of metoclopramide (MCP) and an intramuscular administration of 500 μ g of TRH in patients with PCO and normal women. F refers to the follicular phase and L to the luteal phase.

perprolactinemia cases were transient because the next 5 samples from these 5 women showed normal PRL.

The response of PRL to lactotrope stimulating agents MCP and TRH is shown in Fig. 5. A blunted PRL response after a 10 mg intravenous MCP administration was observed in PCO patients when compared to normal women, while the PRL response to TRH in PCO patients was indistinguishable from that in normal women. When compared with the control group examined in the luteal phase, the PRL concentrations after MCP administration in PCO were significantly ($p < 0.001$) low at any time. When compared with the control group examined in the follicular phase, the PRL values at 30, 60, and 90 minutes after MCP administration in PCO patients were significantly low at $p < 0.02$, $p < 0.05$, and $p < 0.02$, respectively.

Discussion

Earlier, many authors observed the higher incidences of hyperprolactinemia in patients with PCO (Alger *et al.*, 1980, Carmina *et*

al., 1984, Duignan 1976, Luciano *et al.*, 1984). In the present study, we demonstrated that none of the 72 PCO patients had persistently increased basal PRL. One explanation for this discrepancy may be patient selection. There is an inconsistency in the diagnosis of PCO. Sometimes in clinical and biochemical PCO there is no ovary enlargement (Goldzieher 1981, Yeh *et al.*, 1987). On the other hand, multifollicularity of the ovary is sometimes found in anovulatory patients who are apparently different from PCO cases (Adams *et al.*, 1985, Givens 1984). Givens (1984) insisted that morphological polycystic ovary was the final expression of several specific entities and thus was a sign and not a specific diagnosis. Therefore the detection of enlarged ovary by palpation or ultrasonography may not be essential to diagnosis as Goldzieher (1981) says. Despite the difference in diagnostic criteria, similarities in the hormonal profile found in our PCO patients with other studies indicate that we are dealing with the same pathology. Even taking into account an inclusion of a heterogeneous group of oligo-anovulation in this study, our result shows that none of

the patients studied were complicated by persisting hyperprolactinemia which suggests that hyperprolactinemia may be seldom found in PCO. Similar findings were obtained recently by Murdoch *et al.*, (1986). It is also of interest to note that MCP caused a more blunted increase in PRL in PCO than in normal woman while the PRL responses to TRH did not differ in PCO and normal women.

Although both PRL and thyrotropin (TSH) are known to be suppressed by dopamine (Morley, 1981), it has been reported that the PRL response to MCP was decreased while at the same time the TSH response was increased in patients who were considered to have increased central dopamine activity (DeMarinis *et al.*, 1984). Further, there are several reports which indicate an association between increased dopamine activity and attenuated PRL response to a dopamine receptor blockade (Quigley *et al.*, 1979, Scanlon *et al.*, 1981). Recently, Agner *et al.*, (1986) reported that the infusion of dopamine reduced the PRL response to MCP in normal menstruating women in the follicular phase. The pathophysiological importance of their report is that their experiments may provide evidence of an association between increased dopamine activity and diminished PRL responses to a dopamine receptor blockade. If this is the case, central dopamine activity may be high rather than low in PCO and the reportedly high prevalence of hyperprolactinemia in PCO could not be explained by the deficient central dopamine. In addition, it might be speculated that long-standing increased central dopamine activity may selectively decrease the amount of PRL which should be released in response to dopamine receptor blocking agents.

The concept of a suppressive role of central dopamine in the control of LH release has been supported by the observation that peripherally administered dopamine reduced basal LH in normal and hypo-

gonadal women (Ferrari *et al.*, 1981, Leblanc *et al.*, 1976, Pehrson *et al.*, 1983). These effects of dopamine have been believed to act via LHRH suppression because LH response to LHRH was unchanged during dopamine infusion (Pehrson *et al.*, 1983). The exaggerated decrease in serum LH after dopamine administration observed in PCO by Quigley *et al.*, (1981) further supported the theory of a central dopamine deficiency as a cause of an increase in LH in PCO. However, it was reported by Kaufman *et al.*, (1985) that the dopaminergic blocking agent MCP reduced the frequency of LHRH pulse generator activity, resulting in decreased LH in rhesus monkeys. Kaufman's report (1985) indicates that endogenous dopamine may play a facilitory role in the control of pulsatile LH release. In PCO patients, the frequency of LH pulses is reportedly increased, resulting in an increase in LH (Rebar *et al.*, 1976). The high frequency of LH pulses found in PCO (Rebar *et al.*, 1976) may result from augmented central dopamine activity. In addition, dopamine was recently reported to stimulate *in vitro* release of LHRH from the adult human hypothalamus by a dopamine receptor mediated mechanism (Rasmussen *et al.*, 1986). Since these reports strongly suggest a facilitory role of central dopamine in the LH release by the LHRH mediated mechanism, it is difficult to accept the hypothesis that central dopamine deficiency causes an increase in LH secretion in PCO.

On the basis of our findings and the abovementioned reports, we believe that central dopamine is present and active rather than deficient in PCO patients and therefore the actual incidence of hyperprolactinemia in PCO may be low as observed in this study. The association of hyperprolactinemia with PCO may be a coincidence rather than a pathophysiologically related phenomenon.

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