Modulation of Postinhibitory Increase in Plasma Prolactin by Domperidone in Patients with Prolactin Secreting Adenoma

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Abstract

To evaluate the PRL secretory mechanism in patients with PRL-secreting adenoma (PRL-oma), plasma PRL responses to dopamine (DA) were studied in these cases and in normal subjects. Plasma PRL values showed clear decreases during the infusion of DA (5 μg/kg/min for 90 min) in both 6 normal and 7 PRL-oma subjects (%decrease: 43.8±3.9% vs. 53.9±5.6%; NS) and postinhibitory increases after the termination. However, the postinhibitory increase occurred more promptly and markedly in PRL-oma patients than in normal subjects, i.e. the postinhibitory increase exceeded the basal level 45 min after the termination of DA infusion in PRL-oma patients, whereas the increase in normal subjects did not exceed the basal level even 90 min after the infusion. When domperidone was injected at the termination of DA infusion, the postinhibitory increases were significantly enhanced in either PRL-oma or normal subjects. The maximal increments in plasma PRL in the combination test of DA plus domperidone were significantly larger in PRL-oma patients, but were almost the same in normal controls, compared to the single domperidone test. In contrast, TRH did not modify the postinhibitory rises in 9 PRL-oma patients. These results indicate that the secretory properties and the sensitivities of lactotrophs to decreasing action of DA might be different between PRL-oma patients and normal controls. Further, the postinhibitory rebound phenomenon in PRL-oma patients is possibly determined by an overshoot of PRL storage concomitantly with a decreasing DA action. The PRL secretory properties of lactotrophs and the hypothalamic DA might play important roles in the postinhibitory increases in PRL secretion in patients with PRL-oma.

Usually, pituitary hormones show rebound rises exceeding the basal levels after the administration of inhibitory agents (Hall et al., 1973; Leblank et al., 1976; Leebaw et al., 1978; Kaptein et al., 1980; Hanew et al., 1984). The postinhibitory rebound rises are considered to be a mechanism for maintaining the homeostatic hormone secretion.

In patients with prolactin (PRL) secreting pituitary adenoma (PRL-oma), defects in hypothalamic dopamine (DA) neurons and in DA receptors of tumor lactotrophs have been indicated (Fine and Frohman 1978; Bansal et al., 1981). However, as the postinhibitory rebound increases in PRL secretion...
are also observed in PRL-oma patients (Leblanc et al., 1976; Genazzani et al., 1983), the homeostatic PRL secretion might be present in such a pathologic state. Although PRL secretion in man may be mainly regulated by hypothalamic DA (Owens et al., 1984), it is not clear whether DA plays a role in the postinhibitory rebound phenomenon in patients with PRL-oma. Further, the role of endogenous PRL releasing factors, e.g. TRH and VIP (vasoactive intestinal peptide), in the suppressed state of PRL secretion is a matter to be clarified (Owens et al., 1984), although PRL-oma patients are less responsive in the basal state in their release of PRL following exogenous TRH, VIP, and DA-antagonists (Charpentier et al., 1982; Crosignani et al., 1984).

To study the PRL secretory mechanisms in PRL-oma patients, postinhibitory rises in PRL secretion induced by DA were studied in these cases and in normal subjects. Additionally, domperidone (DA D₂-receptor blocker), which does not cross the blood brain barrier (Laduron and Leysen, 1979; Lazareno and Nahorsky, 1982), and TRH were employed whether or not the rebound phenomenon in PRL-oma was modified by these agents.

Materials and Methods

Sixteen patients with PRL secreting pituitary adenoma (PRL-oma), 1 male and 15 females, aged 17 to 41 years, were studied. Every case showed hyperprolactinemia (Mean±SEM of plasma PRL levels: 672±210 ng/ml, range: 132–3496 ng/ml; normal range 3–18 ng/ml), and showed evidence of pituitary adenoma by tomography of the sella turcica and by computed tomographic scanning. Twelve cases had macroadenomas and four had microadenomas according to the criteria of Hardy (1979). Each case complained of amenorrhea-galactorrhea or loss of libido. The pituitary-adrenal and thyroidal functions were normal in all cases. These cases received several tests at 0800 h to 0900 h after an overnight fast with an interval of more than two days between tests. As PRL-oma patients exhibit a hypoestrogenic state (Jacobs et al., 1976), 6 normal male subjects (aged 21 to 27 years) were used as controls. Informed consent was obtained from every normal or PRL-oma subject. All subjects received the DA infusion test, and 7 of 16 cases (#1–7) received either a single domperidone test or the combination test of DA plus domperidone. The other 9 cases (#8–16) received a single TRH test and the DA plus TRH test. Dopamine (Kyowa Hakko, Tokyo) was infused intravenously at a rate of 5 µg/kg/min for 90 min with or without subsequent iv injections of 10 mg domperidone (Kyowa Hakko, Tokyo) or 500 µg TRH (Tanabe, Osaka). Blood specimens were collected at −30 min, immediately before and at 15 min intervals over 180 min after DA infusion test, and −30 min, immediately before and 15, 30, 45, 60, 90 min after domperidone and TRH injections. As a control study for each test, fluctuations in plasma PRL levels in the basal state were examined in 14 PRL-oma and 6 normal subjects, where blood samples were obtained every 15 or 30 min for 3 hrs during the slow infusion of physiological saline. As basal PRL values varied according to the individual, the percent values of the basal PRL were used for comparison in the several tests. Plasma samples obtained were kept frozen at −20°C until assayed. Plasma PRL was measured in duplicate according to the previous method (Hanew et al., 1980). Wilcoxon's nonparametric analysis or Student's t-test was performed for statistical analysis, and the variation from the mean was expressed as S.E.M.

Results

1) Comparisons of plasma PRL responses to DA, domperidone, and DA plus domperidone in normal controls and PRL-oma patients

The fluctuations in plasma PRL in the basal state in normal and PRL-oma subjects were minimal, i.e. the mean maximal %increase and %decrease from the initial (0 min) value were +9.2±5.3% (M±SEM) and −8.8±2.1% in normal subjects (N= 6), and +13.4±3.2% and −9.5±1.6% in PRL-oma patients (N=14) (data not shown). Following DA infusion, normal controls showed a prompt decrease in plasma PRL
The minimal value following the infusion (4.1 ± 0.4 ng/ml) was significantly lower than the basal value (10.9 ± 0.7 ng/ml; P < 0.001). After the termination of DA infusions, plasma PRL levels showed postinhibitory increases, but did not exceed the basal levels. In PRL-oma patients, plasma PRL levels also decreased promptly from 465.4 ± 163.4 ng/ml to 228.3 ± 104.4 ng/ml, although the difference was not statistically significant due to the wide range of basal and nadir PRL values, and showed a rebound increase exceeding the basal levels after the termination of the infusion (Fig. 1). In Fig. 1 mean (SEM) values expressed as a percent of each basal value are shown. Although the maximal percent decreases caused by DA were not different between controls and PRL-oma patients (43.8 ± 3.9% vs 53.9 ± 5.6%; P = NS), the postinhibitory rises occurred more quickly in PRL-oma patients than in controls (Fig. 1). Namely, after the cessation of the infusion, PRL levels returned to the basal levels within 45 min in PRL-oma patients, whereas PRL levels were still lower than the basal levels in controls at 90 min after the infusion. The postinhibitory increase was significantly greater in PRL-oma patients than in normal subjects (P < 0.01 at 135–180 min).

In contrast, normal controls showed remarkable responses to a single administration of domperidone, having the peak value at 30 min after the injection, whereas PRL-oma patients showed no response. When domperidone was administered at the termi-
nation of DA infusion (at 90 min), normal controls showed a much faster and greater increase (vs single infusion: P<0.01 at 105-180 min) despite similar PRL inhibition during the DA infusions, and the peak was almost the same as that of the single domperidone test (624.3±27.7% vs 664.5±36.7%). Similarly, PRL-oma patients showed a much faster and greater postinhibitory rebound phenomenon after the additional injection of domperidone (vs single DA infusion: P<0.01 at 105, 120 min, P<0.05 at 135 min). The maximal PRL increments in the combination test of DA plus domperidone (419.2±123.9 ng/ml) were far larger than those of the single domperidone test (59.7±23.1 ng/ml) (P<0.002).

2) Plasma PRL responses to DA, TRH, and DA plus TRH in 9 patients with PRL-oma

Nine patients received a single injection of 500 µg TRH, and showed a slight increase, having the peak value at 30 min after the injection (Fig. 2). Unlike domperidone, TRH did not enhance the postinhibitory PRL rises induced by DA. The peak value in this combination test of DA plus TRH appeared 30 min later than in the single TRH test.

The mean minimal value of PRL during the DA infusion in all above 16 PRL-oma subjects was 47.6±13.3%, and the mean maximal rebound increase was 125.6±2.5%. There was no significant correlation between the maximal inhibition and the maximal
inhibitory PRL rises in PRL-oma patients than in normal controls. Also, it was evident that the postinhibitory PRL rises were enhanced by a DA antagonist, domperidone, and were not modified by TRH.

As we have already reported (Hanew and Rennels 1982; Hanew et al., 1984), the rebound could be due to (1) increased hypothalamic releasing factors; (2) decreased hypothalamic inhibiting factors; or (3) an overshoot from the stored pituitary pool (Martin 1976; Judd et al., 1978). At present, DA is believed to be a most important PRL-inhibiting factor, and the DA concentrations in rat or monkey pituitary portal plasma are reported to be 0.25–6.0 ng/ml (Gibbs and Neill 1978; Gudelsky and Porter 1979; Neill et al., 1981). Serri et al. (1983) have reported that small doses of DA infusion (0.02 µg/kg/min) elevate the peripheral plasma free DA to 0.8 ng/ml (within the range of the above pituitary portal concentration), and it can inhibit PRL secretion in normal and PRL-oma subjects. In this study, we used large doses of DA (5 µg/kg/min) and this exogenous DA would make the plasma concentration far higher than the endogenous DA concentration in the basal state (Bansal et al., 1981). Therefore, a decrease in endogenous DA secretion would not seem to be the cause of the rebound phenomenon even taking into consideration the short half life of DA (Benedict et al., 1978; Fitzgerald et al., 1979). Although we could not find a significant correlation between the PRL decrease and the rebound increase induced by DA in PRL-oma patients, the postinhibitory increases were markedly enhanced not only in PRL-oma patients but also in normal controls by a DA antagonist, domperidone. This suggests the importance of the rate of decreasing DA action rather than the stored PRL pool itself in inducing the postinhibitory overshoot. Therefore, the faster and greater postinhibitory PRL rises in PRL-oma patients than in normal controls may indicate the higher responsiveness of the former lactotrophs compared to the latter lactotrophs to decreasing DA action. Unlike with the single domperidone test, PRL-oma patients showed much greater PRL increments during the combination test of DA plus domperidone, whereas normal controls showed quite similar responses. In PRL-oma patients, plasma PRL responses to DA-antagonists are markedly blunted when compared to normal subjects (Crosignani et al., 1984), although the hypothalamic DA tone may be elevated in these patients (Scanlon et al., 1981; Molinatti et al., 1984). Therefore, it seems that the lactotrophs in PRL-omas are less sensitive to endogenous DA. These findings suggest that the decreased sensitivity to DA of tumor lactotrophs was completely overcome by the large doses of DA and resulted in suppression of PRL secretion from the lactotrophs followed by an increase in releasable PRL. The increased storage of PRL in lactotrophs might bring about the rebound phenomenon and the responses of plasma PRL to domperidone.

In contrast, the lactotrophs in normal subjects are very sensitive to endogenous DA and are under the tonic dopaminergic inhibition in basal state, and the blockade of such inhibition by domperidone might cause similar responses of plasma PRL regardless of the DA infusion. Accordingly, PRL secretory properties and sensitivities of lactotrophs to decreasing DA action would be quite different between PRL-oma and normal subjects. However, we should take into consideration the possibility that the differences between plasma PRL dynamics in PRL-oma and normal subjects are somewhat emphasized when distinctly different PRL values are compared as a percent of
Unlike our results, Genazzani et al. (1983) have reported that DA infusion (4 μg/kg/min for 3 hrs) causes much greater rebound rises in PRL in normal female subjects than in PRL-oma patients. In addition, Leblank et al. (1976) demonstrated much greater inhibition and postinhibitory PRL rises after DA infusion in normal women than in agonadal women. However, it is difficult to explain the difference in the rebound rises simply by the difference of estrogen levels since Genazzani et al. (1983) observed a significantly lower postinhibitory rise in postpartum women, who are exposed to chronic hyperestrogenemia, than in normal female or PRL-oma subjects.

In this study, TRH did not modify the postinhibitory rebound rise induced by DA in PRL-oma patients. Also, another PRL-releasing factor, VIP (50 μg, iv), did not modify the rebound phenomenon in these patients (unpublished data). These observations indicate that increased endogenous hypothalamic PRL releasing factors may not participate in the postinhibitory rebound.

In conclusion, the secretory properties and the sensitivities of lactotrophs to decreasing DA action in PRL-oma appear to be different from those of normal subjects. In addition, the postinhibitory rebound phenomenon in PRL-oma patients is possibly determined by the overshoot of the stored PRL pool concomitantly with the disappearance of DA action. The PRL secretory properties of lactotrophs and hypothalamic DA seem to play important roles in the postinhibitory increases in PRL secretion in patients with PRL-omas.

Acknowledgement

The authors are indebted to Dr. Edward G. Rennels, Department of Cellular and Structural Biology, The University of Texas Health Science Center at San Antonio for his valuable criticism in preparing the manuscript. We thank Miss Akiko Kobayashi and Miss Toyoko Naganuma for their expert technical assistance.

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